

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and Safety of the Pulsed Electromagnetic Field in Osteoarthritis: A Meta-analysis
AUTHORS	Wu, Ziyang; Ding, Xiang; Lei, Guanghua; Zeng, Chao; Wei, Jie; Li, Jiatian; Li, Hui; Yang, Tuo; Cui, Yang; Xiong, Yilin; Wang, Yilun; Xie, Dongxing

VERSION 1 – REVIEW

REVIEWER	Gianluca Bagnato University of Messina, Italy
REVIEW RETURNED	05-Apr-2018

GENERAL COMMENTS	<p>The authors performed a meta-analysis to assess the efficacy and safety of PEMF in different types of OA. The meta-analysis is well conducted and made according to the PRISMA guidelines.</p> <p>There are some minor concerns:</p> <p>In the methods: please specify in the flow diagram the definition of irrelevant. Please also specify whether articles not in english language were included. Please also specify if the three trials excluded because the full text could not be obtained were RCTs.</p> <p>In the figures: please add the legend for each figure provided, adding enough details to interpret the figure without referring to the main text.</p> <p>Please carefully revise the manuscript for gramamtical errors and typos.</p> <p>In the results provide data and comparison according to duration of PEMF treatment together with the other features (frequency, pulse rate, burst width, wearable, hospital-based...).</p>
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REVIEWER	Fred RT Nelson Henry Ford Hospital, USA
REVIEW RETURNED	10-Apr-2018

GENERAL COMMENTS	<p>Page 5 line 109: Not sure what is meant by “According to Jüni et al.,^{32 33} the higher score one on hierarchy of continuous pain-related outcomes was used if multiple pain scale measured in one study”</p> <p>Page 6 line 127: Albeit time is important, the actual signal has an effect. What was the carrier frequency (when that applies), the intensity, duration of pulse, and duty cycle when that applies?</p> <p>Page 7 line 142: From this point on I have no idea what the units are. It does not match VAS, so what was measured?</p> <p>Page 7 line 157: From this point on I have no idea what the units are.</p> <p>Page 9 line 198: I think that one of the key variables for the neck is that the pain may not be face joint pain, but from some other</p>
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	<p>structure. In the case of the knee and hand, some component of that organ we call a joint may be involved, be it synovium, bone, capsule, or other structure.</p> <p>Page 9 line 211: Morphologic effects as seen on imaging would be, by their very nature, long term, over years.</p> <p>Discussion in general: Suggest discussing the safety of PEMF overall given the wide range of applications such as fracture healing. Also, even if the information is not available, a discussion of the difference fields used would be useful.</p>
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REVIEWER	Deshire Alpizar Rodriguez Hôpitaux Universitaire de Genève, Service du Rhumatologie, Switzerland
REVIEW RETURNED	01-May-2018

GENERAL COMMENTS	<p>This meta-analysis aims to assess the efficacy and safety of the pulsed electromagnetic field therapy in treating osteoarthritis using information from randomized controlled trials. This analysis suggests that PEMF could alleviate pain and improve physical function for knee OA. The strengths of the study are the methodology and clear presentation of information.</p> <p>Major comments The study has some aspects to improve: - Authors could limit their conclusions to knee OA - PEMF effect on pain of hand OA of one clinical trial should not be reported as results in the meta-analysis. This finding on hand OA could be only part of the introduction or discussion.</p> <p>Minor comments 1) Introduction: page 5, line 70, please define PES. 2) Methods: Please specify in page 6, line 105, that adverse events were your safety outcome.</p>
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REVIEWER	Crystal Lynn Keeler Innovations to Wellness, United States
REVIEW RETURNED	28-May-2018

GENERAL COMMENTS	<p>p5 lines 108/109/110 slight wording change . . ".to calculate the change degree" from what to what? More specificity here would be good, from time zero to end of treatment sequence? . . ."the higher score one" not sure what one means, and this sentence should be reworded for better clarity.</p> <p>Pain relief section, p.7 I am interested why the authors chose only to do analysis between sham groups and treatment groups, if in any of these studies they pulled there was a control of no treatment at all (not even sham). It probably would have been too complicated to report additional detail, the study has clean tables with just sham vs. PEMF. However, within acupuncture and other types of energy medicine, the sham groups have a great deal of treatment effect because they are not purely sham. Can the authors respond on their thoughts on how inert PEMF sham seems to be? Are there any functional MRIs of the brain during sham PEMF vs PEMF like there are in acupuncture? This comment should not affect publication, but would be helpful answered.</p>
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	<p>p.7 line 140/151 probably wording "when exposure" should be changed to "with exposure" for better English clarity.</p> <p>p.8 line 172 "et al" should be edited/removed/clarified and "there was no" should be changed to conditional "there were no"</p> <p>p8 Adverse events section: Was their any difference in protocol between the 7 studies that had no AE and the 3 studies that had AE? Also, how many AE? The numbers are usually quite low in AE categories of work of this nature.</p> <p>Discussion: I disagree with their blanket statement of "This study provided a comprehensive assessment on the efficacy and safety of the PEMF therapy in patients with knew, hand and cervical OA. Given that only one study examined OA, the analysis is not comprehensive on OA. Adding the term comprehensive assessment "of the scientific literature" might help smooth out the overgeneralization.</p> <p>p. 8 line 190 there is an extra citation number in the middle of the sentence that should be removed.</p> <p>p. 9 line 198 The discussion of the OA cases is a little strong in generalization and a little weak in possibility of factors affecting. Minor alteration can solve this. as a suggestion. . .The poor efficacy of the treatment for cervical OA may be due to the anatomical factors of cervical spine. . . or the limited number of studies available, the methods used in that particular study, or the sample size used in that study</p> <p>p.9 line 205 grammar, "compression that can lead to"</p> <p>p.9 line 218 Why was the reliability limited? reliability is a statistical word. Do they instead just mean that the conclusions were limited due to small sample size? The authors should be careful not to use a statistical meaning here if none is intended. If they actually mean reliability, in what way was the reliability of those studies limited? The reliability coefficients, etc.</p> <p>p.9 Conclusion is concise and understandable, covers the gist of the article. However, given that people will often read just the abstract and conclusion, it might be worth noting in the conclusion that not enough sample size was available for OA.</p> <p>In the tables, the numbers look well-reported. However, I am curious if the authors performed a subgroup analysis on the number of treatments. No such report was available in the article, the authors reported a different type of subgroup analysis. Many of the articles had 3 or 6 weeks of sessions, for 15-18 sessions. However, others had 84 sessions in six weeks or 30 sessions. Was there a subgroup comparison done between high rate of treatment and low rate of treatment? Did the number of treatments make a difference like the length of time made a difference? I know they ran overall heterogeneity, but I did not see the information on analysis of the number of treatments in the data.</p>
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VERSION 1 – AUTHOR RESPONSE

Replies to Editors:

Comment 1: This was quite a straightforward paper; they cite all the relevant reviews and an update is warranted since the last review by Ryang et al is from 2013. The authors should be able to address all the queries. What transpires from the reviews is that there is perhaps too much prominence given to the hand and cervical osteoarthritis findings when there is just 1 study from hand OA and 1-2 studies for cervical OA, so that should be toned down particularly in the abstract. One of the reviewers even suggests just focusing this review on knee OA only but I think it is probably enough to stress that the hand and cervical OA findings may not be robust enough to inform practice.

Response: Thank you so much for your professional comments.

Comment 2: Please include the original protocol for the study, if one exists, as a supplementary file.

Response: We did not register the protocol, but we conducted this meta-analysis according to a pre-designed protocol. (Appendix 2)

Comment 3: Please revise the formatting of your abstract so that it includes the following sections: Objectives >> Design >> Data Sources >> Eligibility Criteria >> Data extraction and synthesis >> Results >> Conclusions.

Response: Done accordingly. (Page 2 line 19-41)

Replies to Reviewer 1 (Gianluca Bagnato):

Comment 4: In the methods: please specify in the flow diagram the definition of irrelevant. Please also specify whether articles not in English language were included. Please also specify if the three trials excluded because the full text could not be obtained were RCTs.

Response: (1) The word “irrelevant” in the flow diagram including the following aspects: no relevant population, no relevant control, no relevant outcomes. Besides, the word “not OA” means non-OA diseases, and it was classed as “no relevant population” now. And studies involving non PEMF therapy was classed as “no relevant control” now. We have modified some details in the flow chart to avoid misunderstanding.

(2) Studies included in this meta-analysis were not restricted to English language articles.

(3) Three RCTs were excluded because full-text were not available. We have tried to get the full-text through sending an email to corresponding author of each article. Regrettably, we still have not gotten full-text of these three RCTs.

Comment 5: In the figures: please add the legend for each figure provided, adding enough details to interpret the figure without referring to the main text.
Please carefully revise the manuscript for grammatical errors and typos.

Response: Done accordingly. (Page 18)

Comment 6: In the results provide data and comparison according to duration of PEMF treatment together with the other features (frequency, pulse rate, burst width, wearable, hospital-based...).

Response: This issue has been considered in the design of the research protocol, and we have tried to extract relevant data. However, because the number of studies reporting the pulse frequency of PEMF application, pulse intensity and other parameters of PEMF was very limited, we did not conduct a subgroup analysis according to these parameters of PEMF. We have added this issue to the limitation of this study. (Page 10 line 226-228)

Reviewer 2 (Fred RT Nelson):

Comment 7: Page 5 line 109: Not sure what is meant by “According to Jüni et al.,^{32 33} the higher score one on hierarchy of continuous pain-related outcomes was used if multiple pain scale measured in one study”.

Response: Since various scales were used to evaluate pain in different trials, the priority of scale selection is crucial for this meta-analysis. According to the recommended hierarchy of continuous pain-related outcomes used in the meta-analyses, [1] the outcome data that expressed in higher ranking scale was extracted if multiple pain scale measured simultaneously. (Modifications have been made in the methods section. Page 5 line 107-109)

References:

1. Jüni P, Reichenbach S, Dieppe P. Osteoarthritis: rational approach to treating the individual. *Best Practice & Research Clinical Rheumatology* 2006;20(4):721-40.

Comment 8: Page 6 line 127: Albeit time is important, the actual signal has an effect. What was the carrier frequency (when that applies), the intensity, duration of pulse, and duty cycle when that applies?

Response: This issue has been considered in the design of the research protocol, and we have tried to extract relevant data. However, because the number of studies reporting the pulse intensity, duration of pulse, and duty cycle of PEMF was very limited, we did not conduct a subgroup analysis

according to these parameters of PEMF. We have added this issue to the limitation of this study.
(Page 10 line 226-228)

Comment 9: Page 7 line 142: From this point on I have no idea what the units are. It does not match VAS, so what was measured?

Response: Thanks for this comment. Since various scales were used to evaluate pain in different trials, there was a certain problem of inconsistent scale units. This is also a common problem in many previous meta-analysis, we used standardized mean difference (SMD) as previous studies do to solve this issue according to the Cochrane Handbook: section 9.2.3.2.[1,2,3]

Reference:

1. Parkes MJ, Maricar N, Lunt M, et al. Lateral wedge insoles as a conservative treatment for pain in patients with medial knee osteoarthritis: a meta-analysis. *JAMA* 2013;310(7):722-30.
2. Bannuru RR, Schmid CH, Kent DM, et al. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med* 2015;162(1):46-54.
3. Higgins JPT, Green S, Browne KD. Cochrane Handbook for Systematic Reviews of Interventions: A Handbook. Hoboken: John Wiley & Sons, Incorporated, 2010:439.

Comment 10: Page 7 line 157: From this point on I have no idea what the units are.

Response: WOMAC function was preferred measure for function outcome. If a study did not measure or report the WOMAC function, WOMAC total, SF-36 social function score or total score and physician global assessment scores were used in the analysis instead.[1] The similar problem was the inconsistent units in different function scales, and the SMD was used to solve this issue according to the Cochrane Handbook: section 9.2.3.2.[2-4]

Reference:

1. Zeng C, Li H, Yang T, et al. Effectiveness of continuous and pulsed ultrasound for the management of knee osteoarthritis: a systematic review and network meta-analysis. *Osteoarthritis and Cartilage* 2014;22(8):1090-9.
2. Parkes MJ, Maricar N, Lunt M, et al. Lateral wedge insoles as a conservative treatment for pain in patients with medial knee osteoarthritis: a meta-analysis. *JAMA* 2013;310(7):722-30.
3. Bannuru RR, Schmid CH, Kent DM, et al. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med* 2015;162(1):46-54.
4. Higgins JPT, Green S, Browne KD. Cochrane Handbook for Systematic Reviews of Interventions: A Handbook. Hoboken: John Wiley & Sons, Incorporated, 2010:439.

Comment 11: Page 9 line 198: I think that one of the key variables for the neck is that the pain may not be face joint pain, but from some other structure. In the case of the knee and hand, some component of that organ we call a joint may be involved, be it synovium, bone, capsule, or other structure.

Response: We agree with your points. In fact, the points presented in our manuscript is similar to yours. Different components between different organs may be one of the reasons that affect the symptoms and treatment efficacy of OA in different sites.

Comment 12: Page 9 line 211: Morphologic effects as seen on imaging would be, by their very nature, long term, over years.

Response: Thank you for your comment. Morphological effects are meaningful in assessing the therapeutic effects of OA, but it requires longer observation intervals and more effort than pain and function outcomes. However, the follow-up time of the included studies was relatively short and no observation was made. Future researches could focus on this area.

Comment 13: Discussion in general: Suggest discussing the safety of PEMF overall given the wide range of applications such as fracture healing. Also, even if the information is not available, a discussion of the difference fields used would be useful.

Response: Thank you for your suggestions. Modifications have been made in the discussion part. (Page 8 line 188-190)

Reviewer 3 (Deshire Alpizar Rodriguez):

Comment 14: Major comments

The study has some aspects to improve:

- Authors could limit their conclusions to knee OA
- PEMF effect on pain of hand OA of one clinical trial should not be reported as results in the meta-analysis. This finding on hand OA could be only part of the introduction or discussion.

Response: Thank you for your professional suggestions. Because the number of clinical trial focusing on hand or cervical OA is limited, the hand and cervical OA findings may not be robust enough to inform practice. We have made some modifications of our conclusions. In the other hand, because OA is a multi-joint disease. We considered that it is also meaningful to include all joints that have been studied in previous trials.

Comment 15: Minor comments

- 1) Introduction: page 5, line 70, please define PES.

Response: Thanks for your suggestion, PES is the abbreviation of pulsed electrical stimulation. we have made some modification in manuscript. (Page 4 line 67-68)

2) Methods: Please specify in page 6, line 105, that adverse events were your safety outcome.

Response: Modification as followed: Adverse events were considered as the safety outcome. (Page 5 line 104-105)

Reviewer 4 (Crystal Lynn Keeler):

Comment 16: p5 lines108/109/110 slight wording change . . ".to calculate the change degree" from what to what? More specificity here would be good, from time zero to end of treatment sequence? . . ."the higher score one" not sure what one means, and this sentence should be reworded for better clarity.

Response: Thank you for your great suggestions. (1) We have specified it in the methods section. (Page 5 line 110-111)

(2) Since various scales used to evaluate pain in different trials, the priority of scale selection is crucial for this meta-analysis. According to the suggested hierarchy of continuous pain-related outcomes used in the meta-analyses, [1] the outcome data that expressed in higher ranking scale was extracted if multiple pain scale measured simultaneously. (Modifications have been made in the methods part. Page 5 line 107-109)

References:

1. Jüni P, Reichenbach S, Dieppe P. Osteoarthritis: rational approach to treating the individual. *Best Practice & Research Clinical Rheumatology* 2006;20(4):721-40.

Comment 17: Pain relief section, p.7 I am interested why the authors chose only to do analysis between sham groups and treatment groups, if in any of these studies they pulled there was a control of no treatment at all (not even sham). It probably would have been too complicated to report additional detail, the study has clean tables with just sham vs. PEMF. However, within acupuncture and other types of energy medicine, the sham groups have a great deal of treatment effect because they are not purely sham. Can the authors respond on their thoughts on how inert PEMF sham seems to be? Are there any functional MRIs of the brain during sham PEMF vs PEMF like there are in acupuncture? This comment should not affect publication, but would be helpful answered.

Response: We chose the sham treatment group as a control group rather than a blank group because of the following reasons. Firstly, it is difficult to achieve double-blind in a blank control group, which may reduce the quality of the study. Secondly, if a blank control group is selected, the influence caused by the placebo effect cannot be ruled out. For the above two reasons, we chose the sham-controlled group.

Comment 18: p.7 line 140/151 probably wording "when exposure" should be changed to "with exposure" for better English clarity.

Response: Done accordingly. (Page 7 line 151, 153, 165)

Comment 19: p.8 line 172 "et al" should be edited/removed/clarified and "there was no" should be changed to conditional "there were no"

Response: Modification as followed: Three trials reported the adverse events of each treatment group, which mainly included increased knee pain, hip pain, spine pain, vomiting, warming sensation, increased blood pressure, numbness of feet, paraesthesia of foot and cardiomyopathy, and there were no AE related drop outs in each trial. (Page 8 line 172-175)

Comment 20: p8 Adverse events section: Was there any difference in protocol between the 7 studies that had no AE and the 3 studies that had AE? Also, how many AE? The numbers are usually quite low in AE categories of work of this nature.

Response: The details of the treatment intervention were inconsistent in different studies, but most of the details have not much different. Three studies reported AE in their results. They reported 8 AE in 71 participants, 6 AE in 75 participants and 18 AE in 83 participants respectively in these 3 studies. All of 3 studies had no balance treatment in PEMF and sham group. All of participants in 3 studies were knee OA patients. The exposure time of the study which reported 18 AE were 2 hours per session, and treatment rate were 5 times/week. But there is no evidence that exposure time over 2 hours per session will cause some adverse events to the patients.

Comment 21: Discussion: I disagree with their blanket statement of "This study provided a comprehensive assessment on the efficacy and safety of the PEMF therapy in patients with knee, hand and cervical OA. Given that only one study examined OA, the analysis is not comprehensive on OA. Adding the term comprehensive assessment "of the scientific literature" might help smooth out the overgeneralization.

Response: We have made some modifications according to your great suggestions. (Page 8 line 180)

Comment 22: p. 8 line 190 there is an extra citation number in the middle of the sentence that should be removed.

Response: Done accordingly. (Page 9 line 196)

Comment 23: p. 9 line 198 The discussion of the OA cases is a little strong in generalization and a little weak in possibility of factors affecting. Minor alteration can solve this. as a suggestion. . .The poor efficacy of the treatment for cervical OA may be due to the anatomical factors of cervical spine. .

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or the limited number of studies available,
the methods used in that particular study,
or the sample size used in that study

Response: Done accordingly. (Page 19 line 202-212)

Comment 24: p.9 line 205 grammar, "compression that can lead to"

Response: Done accordingly. (Page 9 line 211)

Comment 25: p.9 line 218 Why was the reliability limited? reliability is a statistical word. Do they instead just mean that the conclusions were limited due to small sample size? The authors should be careful not to use a statistical meaning here if none is intended. If they actually mean reliability, in what way was the reliability of those studies limited? The reliability coefficients, etc.

Response: Thank you so much for your professional comments. We have made some modifications. (Page 10 line 225)

Comment 26: p.9 Conclusion is concise and understandable, covers the gist of the article. However, given that people will often read just the abstract and conclusion, it might be worth noting in the conclusion that not enough sample size was available for OA.

Response: Thanks for your great suggestion. Modifications have been made in conclusion of abstract and main body. (Page 2 line 40-41 and page 10 line 236-238)

Comment 27: In the tables, the numbers look well-reported. However, I am curious if the authors performed a subgroup analysis on the number of treatments. No such report was available in the article, the authors reported a different type of subgroup analysis. Many of the articles had 3 or 6 weeks of sessions, for 15-18 sessions. However, others had 84 sessions in six weeks or 30 sessions. Was there a subgroup comparison done between high rate of treatment and low rate of treatment? Did the number of treatments make a difference like the length of time made a difference? I know they

ran overall heterogeneity, but I did not see the information on analysis of the number of treatments in the data.

Response: Thank you for your great suggestions. Some studies showed that short-time treatment may be more effective than long-time, [1] so we put more attention to it. Regarding the rate of treatment, we must to say it is really important to clinical practice as you suggested. However, significant heterogeneity exists among trials included in this study, for example, 30 sessions were completed within 6 weeks in one trial and 84 sessions were completed within the same duration in another trial, 15 sessions were completed within 3 weeks in one trial and 30 sessions were completed within 4 weeks in another trial. Therefore, the significance of its implication may be attenuated, so we did not do a subgroup analysis in the present study.

References:

1. Parate D, Franco-Obregon A, Frohlich J, et al. Enhancement of mesenchymal stem cell chondrogenesis with short-term low intensity pulsed electromagnetic fields. *Sci Rep* 2017;7(1):9421.

Special thanks to the Editors and Reviewers for their good and professional comments.

VERSION 2 – REVIEW

REVIEWER	Gianluca Bagnato University of Messina Italy
REVIEW RETURNED	25-Jul-2018

GENERAL COMMENTS	The authors addressed appropriately all the comments raised during the first review round.
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REVIEWER	Fred RT Nelson Henry Ford Hospital, Detroit, MI, USA
REVIEW RETURNED	30-Jul-2018

GENERAL COMMENTS	Thanks for you revision and recognition of the wide range of signals used in this study.
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