

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Acupuncture related adverse events – systematic review and meta-analyses of prospective clinical studies
AUTHORS	Bäumler, Petra; Zhang, Wenye; Stübinger, Theresa; Irnich, Dominik

VERSION 1 – REVIEW

REVIEWER	Yoon, Sang-Hoon Chung-Yeon Medical Institute, R&D
REVIEW RETURNED	15-Dec-2020

GENERAL COMMENTS	<p>1. This is a good study on AEs of acupuncture treatment.</p> <p>2. However, it seems that Causality Assessment should be analyzed again according to the standardized framework below.</p> <p>World Health Organization, (WHO)-Uppsala Monitoring Centre, The Use of the WHO-UMC System for Standardized Case Causality Assessment, (2012) http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf .</p> <p>3. The incidence of pain or bleeding will differ because the criteria for reporting minor AEs are different depending on the study included. As the author pointed out, it seems that the reporting standards for acupuncture AE should be established. Please add the acupuncture AE reporting criteria of the included research in a table or supplement format.</p>
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REVIEWER	Xu, Shifen Shanghai University of Traditional Chinese Medicine, Acupuncture
REVIEW RETURNED	08-Jan-2021

GENERAL COMMENTS	The authors have overviewed the risks for acupuncture related AE, this proposal fulfills all of the requirements outlined in the PRISMA-P
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REVIEWER	Hung, Yu-Chiang Kaohsiung Chang Gung Memorial Hospital , Chinese medicine
REVIEW RETURNED	09-Apr-2021

GENERAL COMMENTS	The authors overview on risks for acupuncture related adverse events. This is an interesting and important issue. The methods and the results of the meta-analysis should follow the guideline of Meta-analysis Of Observational Studies in Epidemiology (MOOSE).
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REVIEWER	JANG, SOOBIN Korea Institute of Oriental Medicine
REVIEW RETURNED	14-Apr-2021

GENERAL COMMENTS	<p>I think that this review is worth to be reported. I have several comments below.</p> <ol style="list-style-type: none"> 1. The inclusion criteria of study design should be described in more detail. Cohort is not clinical trial therefore the title should be changed. 2. What is "Weidenhammer 2008 ther" ? Please describe what it means. 3. In table 1 - I suggest to change 'n needles' to 'n acupoints' . 4. In table 1 - Please change Medical background of Park 2009 and 2010 to 'Korean medicine doctor' which is official English term in South Korea. 5. This review only searched English databases and this could be a limitation because many studies on acupuncture have been reported in Chinese databases such as CNKI. Please add this as limitation part.
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REVIEWER	Han, Dongwoon Hanyang University, global health and development
REVIEW RETURNED	14-May-2021

GENERAL COMMENTS	<p>This paper presents the results of a systematic review & meta-analyses of prospective clinical trials related to acupuncture related adverse events. The research is weakened by several issues including incomplete description of method, results and discussion. Details relating to these and other issues are presented below.</p> <p>General comments The authors need to revise the method section in detail, to avoid negative effects on the quality and validity of systematic reviews and meta-analysis.</p> <p>Page 11 line 4: Search strategy The authors also need to indicate which MeSH terms were used.</p> <p>Page 11 line 31: "Meta-analysis of 11 studies including 845,637 patients...." : It is not clear why only those 11 studies were included in the meta-analysis. if there was an additional inclusion criteria set for the meta-analysis, the authors need to clearly explain in the methods section.</p> <p>Page 10 line 2: "Meta-analysis combining eight studies....": Again, it is not clear why only those 8 studies were included in the meta-analysis.</p> <p>Page 12 line 31: "Meta-analysis combining eight studies including 1,211,791....": Again, it is not clear why only those 8 studies were included in the meta-analysis.</p> <p>Page 15 line 1: "Risk of bias assessment"</p>
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	<p>This should be in the beginning of the result section.</p> <p>the authors need to clearly summarize the result of risk of bias assessment (how many studies were scored having a high/low risk; therefore, how many studies were excluded/included in the final analysis) at the end of the subsection.</p> <p>(end)</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Sang-Hoon Yoon, Chung-Yeon Medical Institute, Chung-Yeon Korean Medicine Hospital

Comments to the Author:

1. This is a good study on AEs of acupuncture treatment.

->Thank you for the recognition.

2. However, it seems that Causality Assessment should be analyzed again according to the standardized framework below.

World Health Organization, (WHO)-Uppsala Monitoring Centre, The Use of the WHO-UMC System for Standardized Case Causality Assessment, (2012)

"http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOCausality_assessment.pdf".

->This is an important hint, as indeed categories of the causality assessment of SAE attempted in our manuscript follows the standard categories of the WHO-UMC system. We have added this information to the method section. However, this causality assessment tool is designed for case reports of AE that are directly observed. Thus, it is not applicable for reviews summarizing published SAE cases.

Therefore, as we explain in the method section at the end of page 5, categories of SAE causality were reduced to possibly or unlikely related to acupuncture, or unclassifiable, as experts performing the causality assessment could only refer to the limited information provided in the articles included in this review.

3. The incidence of pain or bleeding will differ because the criteria for reporting minor AEs are different depending on the study included. As the author pointed out, it seems that the reporting standards for acupuncture AE should be established. Please add the acupuncture AE reporting criteria of the included research in a table or supplement format.

->In preparation of our manuscript, we had collected the definitions of AE and severity ratings applied in the included publications. We are happy to provide this compilation as an additional supplementary table (online supplementary appendix S4).

Reviewer: 2

Dr. Shifen Xu, Shanghai University of Traditional Chinese Medicine

Comments to the Author:
The authors have overviewed the risks for acupuncture related AE, this proposal fulfills all of the requirements outlined in the PRISMA-P.

->Thank you for the recognition.

Reviewer: 3

Dr. Yu-Chiang Hung, Kaohsiung Chang Gung Memorial Hospital

Comments to the Author:
The authors overview on risks for acupuncture related adverse events. This is an interesting and important issue. The methods and the results of the meta-analysis should follow the guideline of Meta-analysis Of Observational Studies in Epidemiology (MOOSE).

-> We have revised the method and result section also in accordance with the remarks of reviewer 5 and have added the MOOSE checklist to online supplementary appendix S2.

Reviewer: 4

Dr. SOOBIN JANG, Korea Institute of Oriental Medicine Comments to the Author:

I think that this review is worth to be reported.

I have several comments below.

1. The inclusion criteria of study design should be described in more detail. Cohort is not clinical trial therefore the title should be changed.

-> Thank you for this important remark. We changed the title to "...clinical studies" and define the inclusion criteria of study design more clearly.

2. What is "Weidenhammer 2008 ther"? Please describe what it means.

-> The abbreviation "ther." means in this case the therapists' reports of AE. Weidenhammer and colleagues describe AE reported by patients and therapists separately. This is now clearly explained in the legends of figure 2 and figure 3 where this abbreviation was used.

3. In table 1 - I suggest to change 'n needles' to 'n acupoints'.

-> In this case we would prefer the wording "n needles" as we indeed refer to the number of needles applied. Acupuncture points can either be treated unilaterally with one needle or bilaterally with two needles.

4. In table 1 - Please change Medical background of Park 2009 and 2010 to 'Korean medicine doctor' which is official English term in South Korea.

-> Thank you for providing us with the correct term, we have amended table 1 accordingly.

5. This review only searched English databases and this could be a limitation because many studies on acupuncture have been reported in Chinese databases such as CNKI. Please add this as limitation part.

-> We have added this to the limitation part.

Reviewer: 5

Dr. Dongwoon Han, Hanyang University

Comments to the Author:

This paper presents the results of a systematic review & meta-analyses of prospective clinical trials related to acupuncture related adverse events. The research is weakened by several issues including incomplete description of method, results and discussion. Details relating to these and other issues are presented below.

General comments

The authors need to revise the method section in detail, to avoid negative effects on the quality and validity of systematic reviews and meta-analysis.

Page 11 line 4: Search strategy

The authors also need to indicate which MeSH terms were used.

-> Both "acupuncture" and "adverse effects" are MeSH terms themselves. This is now clearly stated in the search strategy. Pubmed automatically translates search terms to MeSH terms (Automatic Term Mapping) in the course of the Medline search.

Page 11 line 31: "Meta-analysis of 11 studies including 845,637 patients...." :

It is not clear why only those 11 studies were included in the meta-analysis. if there was an additional inclusion criteria set for the meta-analysis, the authors need to clearly explain in the methods section.

Page 10 line 2: "Meta-analysis combining eight studies....":

Again, it is not clear why only those 8 studies were included in the meta-analysis.

Page 12 line 31: "Meta-analysis combining eight studies including 1,211,791....":

Again, it is not clear why only those 8 studies were included in the meta-analysis.

-> Meta-analyses were performed for the overall risks for an AE, for SAE, for AE requiring treatment and the risks for the different types of AE given as the number of patients with AE per total number of patients undergoing an acupuncture series or as the number of treatments with AE per total number of treatments performed. No further criteria for inclusion in the respective meta-analyses were applied. This is now clearly stated in the method part in the chapter "Data analysis". To further clarify this issue, we have amended the respective sections in the result part; e.g. "Data of eleven studies assessing the overall AE risk as patients with AE among the total number of patients undergoing an acupuncture series..."

Page 15 line 1: "Risk of bias assessment"

This should be in the beginning of the result section.

-> We have moved the paragraph on risk of bias assessment to the beginning of the result section. It now appears after the study characteristics.

the authors need to clearly summarize the result of risk of bias assessment (how many studies were scored having a high/low risk; therefore, how many studies were excluded/included in the final analysis) at the end of the subsection.

-> All articles were rated as having an overall unclear risk of bias. This is now clearly stated at the end of the ROB-chapter.

We hope that we were able to improve our manuscript to the reviewers' discretion and are looking forward to your response.

VERSION 2 – REVIEW

REVIEWER	JANG, SOOBIN Korea Institute of Oriental Medicine
REVIEW RETURNED	11-Jun-2021

GENERAL COMMENTS	I think that this paper was properly revised and is qualified to be published. It will help for many researchers who want to know the adverse events of acupuncture.
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REVIEWER	Han, Dongwoon Hanyang University, global health and development
REVIEW RETURNED	02-Jun-2021

GENERAL COMMENTS	<p>Thank you for addressing the comments. The draft is improved but there are several points that needs to be addressed as stated below.</p> <p>Overall: 1. the manuscript should be carefully reviewed to eliminate grammatical errors.</p> <p>Abstract lines 29: "Out of 7679 screened articles 22 reporting.." : I am not sure what this means</p> <p>Introduction: <input type="checkbox"/> overall: the authors should carefully review the text to eliminate any grammatical errors-- especially the missing commas.</p>
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	<p>Methods:</p> <p>Data Analysis: Page 7: line 34 -38: “Meta-analyses.....performed.”: this should be explained more clearly Line 54: “Patient and public involvement” : This section should be listed in PRISMA.</p> <p>Results: Line 29: “(WZ and PB, TS and PB, or LM and PB)”.: Who is LM?</p> <p>Overall: <input type="checkbox"/> paragraphs/sentences should be broken down to improve readability of the text. Study characteristics The results should be presented in following order: - study selection - risk of bias assessment - study characteristics - ... (end)</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 4

Dr. SOOBIN JANG, Korea Institute of Oriental Medicine Comments to the Author:

I think that this paper was properly revised and is qualified to be published. It will help for many researchers who want to know the adverse events of acupuncture.

We thank you for your positive appraisal.

We hope that we were able to improve our manuscript to the reviewers' discretion and are looking forward to your response.

Reviewer: 5

Dr. Dongwoon Han, Hanyang University

Comments to the Author:

Thank you for addressing the comments. The draft is improved but there are several points that needs to be addressed as stated below.

Overall:

1: the manuscript should be carefully reviewed to eliminate grammatical errors.

We have had a native speaker check of our manuscript and have corrected grammatical errors including commas.

Abstract

Lines 29: “Out of 7679 screened articles 22 reporting...”: I am not sure what this means.

The respective sentence has been rephrased.

Introduction:

overall: the authors should carefully review the text to eliminate any grammatical errors – especially the missing commas.

As stated above we corrected grammatical errors including commas.

Methods:

Data Analysis:

Page 7: line 34 – 38: “Meta-analyses.....performed”: this should be explained more

clearly.

The respective sentence was divided in two sentences that are now clearly phrased.

Line 54: "Patient and public involvement": This section should be listed in PRISMA.

We are sorry, but it appears unclear to us, how the PRISMA checklist could be amended. The respective chapter can be found on page 6 which is appropriately cited in the PRISMA checklist.

Results:

Line 29: "(WZ and PB, TS and PB, or LM and PB)": Who is LM?

LM stands for Luise Möhring, who assisted the article screening. We now introduce the abbreviation of her name when mentioning her contribution in the acknowledgements.

Overall:

Paragraphs/sentences should be broken down to improve readability of the text.

We have revised the manuscript and have shortened/divided long sentences.

Study characteristics

The results should be presented in the following order:

- Study selection
- risk of bias assessment
- study characteristics
- ...

According to your previous comment we have moved the risk of bias assessment from the end to the beginning of the results section. However, also after reviewing other systematic reviews in BMJopen, we believe that it is correct and common to first provide the study flow-chart, describe characteristics of the included trials and then describe the results of the risk of bias assessment. Thus, we would favor keeping the order of the chapters of the result part as it is.

VERSION 3 – REVIEW

REVIEWER	Han, Dongwoon Hanyang University, global health and development
REVIEW RETURNED	25-Jul-2021

GENERAL COMMENTS	<p>Thank you for addressing my comments. The second draft was properly revised. Besides the few extra comments below, I have no further comments to add.</p> <ul style="list-style-type: none">- As a final DRAFT, the authors should carefully review the text to eliminate any grammatical errors-- especially the missing commas.- Page 4: line 51: Revise the sentence: Therefore, this review aimed to ---- Page 7: line 40-41: "as before said Weidenhammer....acupuncture.(52)": Instead of the authors' name, start the sentence with the number of articles (similar to the other sentences in this paragraph) to make the sentence structures more coherent.- Page 9: line 45-46" "for all studies.....of bias.": This sounds very misleading and may potentially make the reader question the quality of this review. If the overall risk of bias is unclear for all studies, why should they be included in the final analysis?
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