

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)	The effectiveness and safety of metoclopramide in treatment of intractable hiccup: a protocol of systematic review and meta-analysis
AUTHORS	Wang, Die; Zi, Changyan; zhang, baocheng; wang, baojia; Chen, Tao; wang, long; Gao, Yongxiang

VERSION 1 – REVIEW

REVIEWER	Kearney , Alison Mary Royal Brisbane and Women's Hospital, Department of Palliative and Supportive Care
REVIEW RETURNED	16-Feb-2022

GENERAL COMMENTS	Thanks for the opportunity to review your protocol I researched this topic myself a few years ago and found a dearth of studies. A quick literature review today does not show any new work in this area. I think instead of a meta analysis you should aim to perform a RCT into this subject. I agree that there is a lack of data so a robust RCT would be greatly beneficial
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REVIEWER	Munger, Kathleen University of Rochester
REVIEW RETURNED	24-Mar-2022

GENERAL COMMENTS	<p>The effectiveness and safety of metoclopramide in treatment of intractable hiccup: Protocol of a systemic review and meta analysis.</p> <p>The authors have described a protocol for a systematic analysis of the effectiveness and safety profile of the use of metoclopramide for intractable hiccups. A prior systematic review that they reference from 2015 suggested that the use of metoclopramide was supported by small randomised, placebo-controlled trials, but that review was not able to demonstrate high quality data on which to base treatment recommendations. The proposed study will add to the literature as it will be an updated study (with 6 additional years of studies to review) with expanded scope (querying nine databases).</p> <p>Strengths and limitations, point #3 - Unless you've already done the systematic review, it would be hard to know that there's only one RCT. I think you may be trying to say that a strength of this proposed study is that it will be an updated and more</p>
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	<p>comprehensive review compared to what has been published previously.</p> <p>Strengths and limitations, point #4 - Please elaborate. For example, the many etiologies of hiccup may contribute to heterogeneity of the response to metoclopramide or heterogeneity in the populations studied?</p> <p>Introduction - aripiprazole is not a benzodiazepine - “At present, researches have confirmed that metoclopramide is effective for relieving the symptom of intractable hiccup...” If this were true you would not be needing to do this study. Would change “confirmed” to “suggested that metoclopramide can be effective”.</p> <p>Search strategy - please clarify what “from the initial database” means.</p> <p>Data extraction and management - Please clarify “randomness”, do you mean use of randomization in the study?</p> <p>The text needs further editing for grammar and typos, which currently undermine the otherwise important message of the manuscript.</p>
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REVIEWER	Filmann, Natalie Institute of Biostatistics and Mathematical Modeling, Goethe-University, Frankfurt/Main
REVIEW RETURNED	15-Jul-2022
GENERAL COMMENTS	Nice study design, no further comments.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer Dr. Alison Mary Kearney

Thanks a lot for your comment, my response is below.

Comment 1 “I think instead of a meta-analysis you should aim to perform a RCT into this subject. I agree that there is a lack of data so a robust RCT would be greatly beneficial.”

Response: We greatly thank Dr. Alison Mary Kearney for your insightful comments and suggestions. We agree that there is a lack of researches on metoclopramide in the treatment of intractable hiccup. Currently there are only three randomized controlled trials in the English literature investigating metoclopramide in treating intractable hiccup, one of which is prevention³⁻⁵. In recent years, there have been some randomized controlled trials of metoclopramide in the treatment of intractable hiccup in China. However, there are no large sample size and multicenter randomized controlled trials. It shows that people do not pay enough attention to intractable hiccup. The aim of this article we wrote is to arouse everyone's attention. At present, we cannot conduct a randomized controlled trial due to the small number of intractable hiccup patients and limited funding. Firstly, we accomplish a meta-analysis to assess the overall situation. We believe through a thorough appraisal of published studies, this systematic review could help to highlight the need for research in this field as well as provide

suggestions in study design and implementation. Secondly, if the conditions are perfect enough, we will try our best to complete relevant RCT studies in the future.

3. Stav A, Weksler N, Berman M, et al. Premedication with metoclopramide decreases the frequency of methohexital induced hiccup. *J Anesth* 1992;6(1):17-20. doi: 10.1007/s0054020060017
4. Wang T, Wang D. Metoclopramide for patients with intractable hiccups: a multicentre, randomised, controlled pilot study. *Intern Med J.* 2014 Dec;44(12a):1205-9. doi: 10.1111/imj.12542.
5. Madanagopalan N. Metoclopramide in hiccup. *Curr Med Res Opin.* 1975;3(6):371-4. doi: 10.1185/03007997509114789.

Response to Kathleen Munger

We appreciate your careful reading of our manuscript and valuable suggestions. After carefully studying your comments, we have made corresponding changes to the paper.

Comment 1 “Strengths and limitations, point #3 - Unless you’ve already done the systematic review, it would be hard to know that there’s only one RCT. I think you may be trying to say that a strength of this proposed study is that it will be an updated and more comprehensive review compared to what has been published previously.”

Response: Thank you for your positive and encouraging comments on our manuscript. We have revised the point 3 of strengths and limitations.

Comment 2 “Strengths and limitations, point #4 - Please elaborate. For example, the many etiologies of hiccup may contribute to heterogeneity of the response to metoclopramide or heterogeneity in the populations studied?”

Response: Thank you for the advice. We have revised the point 4 of strengths and limitations.

Comment 3 “aripiprazole is not a benzodiazepine”

Response: Sorry for the typo. We corrected it accordingly (line18, Page2).

Comment 4 “At present, researches have confirmed that metoclopramide is effective for relieving the symptom of intractable hiccup...” If this were true you would not be needing to do this study. Would change “confirmed” to “suggested that metoclopramide can be effective”.

Response: Many thanks for your comments and suggestion. We have revised this part. Please refer to page2, line30 for details.

Comment 5 “Search strategy - please clarify what “from the initial database” means.”

Response: Many thanks for raising this good point. Our original intention was to express from databases establishment to November 11, 2021. Confused you due to misrepresentation in English. We're sorry for the trouble. We've replaced initial with inception.

Comment 6 “Data extraction and management - Please clarify “randomness”, do you mean use of randomization in the study?”

Response: We would like to apologize for this mistake. We have removed this error.

Comment 7 “The text needs further editing for grammar and typos, which currently undermine the otherwise important message of the manuscript.”

Response: Thank you for your positive and encouraging comments on our manuscript. We would like to apologize for the weakness of our written English language. We asked English-speaking professionals to revise the manuscript in terms of grammar, typos and so on.

Response to Dr. Natalie Filmann

Thank you for your comments and support very much!

Comment: Nice study design, no further comments.

Response: We thank you for your encouragement and affirmation of this article.