PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Antidepressant use and interpersonal violence perpetration: a protocol for a systematic review and meta-analysis
AUTHORS	Keen, Claire; Foulds, James A; Willoughby, Melissa; Newton-Howes, Giles; Knight, Josh; Fazel, Seena; Borschmann, Rohan; Kinner, Stuart; Young, Jesse

VERSION 1 – REVIEW

REVIEWER	Yongliang Jia University of Macau Macau SAR, China
REVIEW RETURNED	14-Sep-2020

GENERAL COMMENTS	It's better to make sure how to select a random-effects model or a fixed-effect model in This protocol "If there are sufficient studies that report measures of effect in a form which can be meta-analysed, random or fixed effects meta-analysis will be performed, depending on heterogeneity."

REVIEWER	Luís Monteiro Center for Health Technology and Services Research, Faculty of Medicine, University of Porto, Porto, Portugal
REVIEW RETURNED	21-Sep-2020

GENERAL COMMENTS	Interesting topic. The limitations were identified. Will they find RCTs addressing this issues?

REVIEWER	Bradley N Gaynes University of North Carolina School of Medicine
REVIEW RETURNED	02-Dec-2020

GENERAL COMMENTS	I appreciated the chance to review this protocol of a systematic review. The topic is important, the methods detailed and relevant, and the strategy relatively well-described. My suggestions below are meant to help improve their presentation of the protocol. 1. The authors discuss an approach that addresses data from high quality papers, but a few points need better clarification. First, what is the rationale to include any low quality/high risk of bias papers? Why not exclude those. Second, more justification is needed for defining high quality papers as being in the upper 30% of included. I can accept these are "higher" quality papers, but if most paper are of low quality, a lot of poor quality data will be involved. Why is upper 30% acceptable, and why not use some kind of ROB quality assessment thresholds? 2. How will the authors account for other potential confounders, such as medication dose or psychiatric diagnosis?

	3. Can the authors provide greater rationale for why violence against others, rather than violence against self, is the preferred focus? Either would be okay, but why did they decide to focus on one vs. the other. Also, at the least, I would add "violence against others" to title to cue the reader in immediately. 4. The protocol paper could benefit from a table (maybe in a PICOTS format) that very clearly presented the eligibility criteria). 5. While the objectives are quite clear, the paper could also benefit from a clarification of specific questions (key questions?) that the paper plans to address. 6. Specific dates for the literature search need to be included. 7. On page 13 of 18, lines 6 and 7 (discussing the MOOSE recommendations), something is missing before "will not be used" and needs to be corrected.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Yongliang JiaUniversity of Macau
Macau SAR, China
Please state any competing interests or state ‘None declared’:
None declared

Comments to the Author
It's better to make sure how to select a random-effects model or a fixed-effect model in This protocol "If there are sufficient studies that report measures of effect in a form which can be meta-analysed, random or fixed effects meta-analysis will be performed, depending on heterogeneity."

As the decision to perform a random or fixed effects meta-analysis is based on the likelihood of heterogeneity between the included studies, we wanted to leave this decision open until the included studies had been evaluated. However, given the diversity of study designs, treatment types, and participants included in this review, it is highly likely that we will use a random effects model. We have revised this section on page 12, paragraph 3 accordingly to state: “If there are sufficient studies that report measures of effect in a form which can be meta-analysed, a random effects meta-analysis will be used to estimate a pooled effect size. A random effects model is appropriate as it accounts for unexplained heterogeneity due to the diversity in study designs, treatment types, and study populations which will be included in this review.(1)”

Reviewer: 2
Luís Monteiro
Center for Health Technology and Services Research, Faculty of Medicine, University of Porto, Porto, Portugal
Please state any competing interests or state ‘None declared’:
None declared

Comments to the Author
Interesting topic. The limitations were identified. Will they find RCTs addressing this issues?

Thank you for this positive assessment. Based on an initial search during the development of our search strategy we expect there to be some RCTs, but for most included research to be observational studies.

Reviewer: 3
Bradley N GaynesUniversity of North Carolina School of Medicine
Please state any competing interests or state ‘None declared’:
None declared

Comments to the Author
I appreciated the chance to review this protocol of a systematic review. The topic is important, the methods detailed and relevant, and the strategy relatively well-described. My suggestions below are meant to help improve their presentation of the protocol.

1. The authors discuss an approach that addresses data from high quality papers, but a few points need better clarification. First, what is the rationale to include any low quality/high risk of bias papers? Why not exclude those. Second, more justification is needed for defining high quality papers as being in the upper 30% of included. I can accept these are "higher" quality papers, but if most paper are of low quality, a lot of poor quality data will be involved. Why is upper 30% acceptable, and why not use some kind of ROB quality assessment thresholds?

We are including all papers as this is an under-researched area and there is unlikely to be much existing research. As such, one of the aims of this review is to examine the current extent and quality of the literature. We agree with the reviewer that selection of a cut point for ‘high quality’ papers is somewhat arbitrary. There is not clear evidence with respect to where any cut point should be, particularly as the MASTERs scale is a newly developed scale which is designed to assess relative risk of bias, rather than absolute risk of bias or study quality. However, a comparison between lower and higher quality papers may still provide some information on the impact of study quality on effect size estimates. As such, we have revised this section to state that we will conduct a sensitivity analysis which includes only “higher-quality papers”. We will acknowledge and discuss the potential implications of including all available studies and its implications for the interpretation of our findings in the full review manuscript.

2. How will the authors account for other potential confounders, such as medication dose or psychiatric diagnosis?

As noted on page 12 (paragraph 4), we plan to conduct subgroup analyses where we separate by medication, study designs (as some designs may be better able to adjust for different types of confounding) and psychiatric diagnosis. Where possible, we will use measures from the existing studies that adjust for medication dose or psychiatric diagnosis. However, confounding is still likely to be an unavoidable limitation in many of the included studies. We will acknowledge this limitation in the review manuscript and articulate its implications for interpretation of our findings.

3. Can the authors provide greater rationale for why violence against others, rather than violence against self, is the preferred focus? Either would be okay, but why did they decide to focus on one vs. the other. Also, at the least, I would add "violence against others" to title to cue the reader in immediately.

We chose to focus on violence against others as violence against self has been the focus of multiple previous systematic reviews on the association between antidepressants and violence (2-4). Violence against others is a serious public health concern, and while there are some individual research projects investigating the association between antidepressants and violence against others, this association has not been investigated to the same extent as the association between antidepressants and violence against self.

We have revised to title to read: “antidepressant use and interpersonal violence perpetration: a protocol for a systematic review and meta-analysis” and have added a sentence to the introduction (page 4, paragraph 5) explaining the lack of previous systematic reviews focusing on violence against others.

4. The protocol paper could benefit from a table (maybe in a PICOTS format) that very clearly presented the eligibility criteria).

We have added a Table summarising the inclusion and exclusion criteria (Table 1, page 5).

5. While the objectives are quite clear, the paper could also benefit from a clarification of specific questions (key questions?) that the paper plans to address.

We have added a sentence before the study aims explaining the key study questions. It states: “This study seeks to examine the following key questions: to what extent has the association between antidepressant use and violence against others been investigated? What is the quality of research examining this association, and what is the nature of the association (if present) between antidepressant use and violence against others? Therefore, in this study we will…..”

6. Specific dates for the literature search need to be included.

We have added the dates of the literature search to the “search strategy” section of the methods. “The initial search was performed on the 19th March 2020, and an update will be conducted on the 1st March 2021.”

7. On page 13 of 18, lines 6 and 7 (discussing the MOOSE recommendations), something is missing before "will not be used" and needs to be corrected.

We have fixed this sentence, it now reads “As recommended by… MOOSE study groups, summary quality scores will not be used to weight analyses…