Author’s response to reviews

Title: Antipsychotic drug use and risk of stroke and myocardial infarction: a systematic review and meta-analysis

Authors:

Sanja Zivkovic (szivkovic@rogers.com)
Chan Hee Koh (s1205416@sms.ed.ac.uk)
Nandita Kaza (s1202668@sms.ed.ac.uk)
Caroline Jackson (caroline.jackson@ed.ac.uk)

Version: 2 Date: 21 Jan 2019

Author’s response to reviews:

Authors’ comments to the editor:

Thank you for the opportunity to resubmit our article. Firstly, there appeared to be no comments from reviewer 1, so we assume that they were happy with our revised manuscript. Secondly, we have responded to the second reviewer’s comments, but would like to flag that he/she does not appear to have read our first rebuttal, since we addressed all of the comments about inclusion of specific studies in some detail in our response to the first round of comments, to which the reviewer has not responded. It appears that the reviewer has overlooked our thorough rebuttal. We have drawn the reviewer’s attention to this, asking them to read our first rebuttal in addition to our more condensed response to the same questions in this round of reviews. We also request that if the reviewer remains unhappy with our responses that the editor reviews this to provide a third opinion. We have serious concerns about the reviewer’s understanding of epidemiological concepts and review methodology and believe that the remaining changes he/she recommends are not valid and could themselves introduce bias to our review.

Zivkovic et al made a lot of changes in introduction, method, and discussion.
The manuscript now is clearly written and easy to follow.
Thank you for your efforts.

Comments

Authors’ overall response to queries about the flagged studies:

We would like to draw the reviewer’s attention to our rebuttal following the first review of this article, in which we describe in some detail our reasons for including these studies. We have also addressed each query briefly below, but please refer to our first rebuttal for more detailed and thorough
explanations. Perhaps the reviewer overlooked our previous responses?

1. Chen (2008) conducted a population-based, nested case-control study including only patients with depression (a diagnosis of depression, indicated by ICD-9 codes 300.4, 296.2x, 296.3x, or 311 in the method part and figure 1). The indications of antipsychotics do not all contain "depression." US FDA only recommended "Treatment resistant depression" for Olanzapine. However, antipsychotic agents' indications normally include Bipolar disorder, and the ICD-9 codes are 296.0x, 296.40, 296.4x, 296.5x, and 296.6 x, 296.7 x, 296.80, 296.89 and 301.13. Other included studies in Zivkovic et al's meta-analysis did not focus on the patients with depression. Using this data in your pooled meta-analysis causes even more bias. Zivkovic et al's would have confounding by indication, which occurs when the clinical indication for selecting a particular treatment affects the outcome. Please rule out this study and conducted your meta-analysis again.

Authors’ response:
• We did not set out to exclude any indications for AP use, therefore excluding this study solely because they are a population of patients with depression would introduce selection bias
• Although we outline schizophrenia, bipolar and dementia as indications for APs, this list is not exhaustive
  In addition, we include studies with ‘general’ populations of AP use which presumably contains patients with dementia and AP use
• Furthermore we do stratify results by indication in our meta-analyses which should help to account for any confounding by indication in our results

Lan et al, 2015 (stroke with lithium exposure in bipolar disorder) compared lithium users and non-users including antipsychotic agents. Lithium is not one of antipsychotic agents, so that has been excluded from other eligible studies in Zivkovic et al's meta-analysis. PS-matched cohort to explore the relationship between lithium exposure and the occurrence of stroke, adjusted for age, gender, comorbidities, use of antipsychotic agents, and use of mood stabilizers. Antipsychotic use was one of confounders and covariates.

This study therefore was not eligible to Zivkovic et al's study design. Failing to recognize the related bias caused false conclusions and was potentially misleading. Please rule out this study and conducted your meta-analysis again.

Authors’ response:
• Please note we used results reported from the unmatched cohort (not the PS matched cohort) – therefore the sample included patients with bipolar disorder (both with and without lithium exposure)
  Therefore the HR reported on typical and atypical AP use (Table 2) indicate the risk of stroke among bipolar patients and AP use, not lithium exposure and AP use
• Exclusion of this study is not appropriate based on our study selection criteria

Correll's study used nonusers of SGA use and nonusers of antidepressant agents as the definition of comparison cohort which is different from what Zivkovic et al's revision mentioned "comparing AP drug use versus those on other medications for mental illness. Please rule out this study and conducted your meta-analysis again.

Alternatively, Zivkovic et al may consider to run subgroup analyses of different comparison (no use of
AP, use of Antidepressants, use of lithium separately. Zivkovic et al needs to conduct subgroup analyses of different populations or indications.

Author’s response:
• Correll et al compared AP users (SGA) to antidepressant users
  o comparing patients with psychiatric disorders to patients with depression to account for confounding due to severe mental illness
  o there is no basis for excluding this study from our inclusion/exclusion criteria and its exclusion would not introduce bias in our results
  o please note stratified meta-analysis by indication has already been conducted and is presented in our results

2.
Although Scottish Intercollegiate Guidelines Network (SIGN) checklist may be developed for the critical appraisal of observational studies, SIGN 50 checklist is used mainly for guideline development. For observational studies, here Newcastle-Ottawa scale (NOS) is more appropriate. Researchers were encourage the use of NOS scale in the field of psychiatry.


Inter-rater reliability is poor for the SIGN, but moderate to good for the NOS.
SIGN contains 6 The poor reliability is likely because response options for each item, and choosing between response options potentially were more subjective on the part of the raters. Therefore, SIGN has shown the poor reliability.
Not using a tool of quality assessment properly may include unnecessary bias.
Please revise your quality assessment.

Authors’ response:
• Although each researcher may have a preference for specific scales/methods used to assess risk of bias in studies, there are no current guidelines for best practice when appraising non-randomised studies. Indeed, numerous articles have concluded that there is no gold standard for quality assessment of non-randomised studies including the most recently published article on this subject, which we

• Furthermore, the PRISMA checklist and guidelines recommend risk of bias is assessed and discussed (Items 12, 15 and 19 on the checklist) in each systematic literature review; however, PRISMA does not specify a preferred scale/method

• In addition, we do not believe that the choice of quality assessment tool will have introduced bias, since we did not include or exclude studies on the basis of the quality assessment. Perhaps the reviewer could explicitly explain exactly how they think we could have introduced bias (i.e. systematic error) through our choice of quality assessment tool? Quality assessment of non-randomised studies is challenging for various reasons, not least of which, poor/incomplete reporting of methods in articles. Thus, we performed quality assessment purely as a vehicle for assessing and discussing potential methodological issues across identified studies. We have addressed the potential for these biases within individual studies in some depth in our article.

• Given the SIGN tool is comprehensive and covers the same domains of bias/confounding as NOS we do not believe it is appropriate to re-assess all included articles with the NOS.

3. Further to previous question 6, assuming the OR is a good approximation to the HR or RR in included studies, you can theoretically combine them especially for rare events.

Authors’ response:
We would like to point out to the reviewer that HRs and RRs are not good approximations for each other, even when events are rare. HRs take into account time, whereas RRs do not – the interpretation of each of these measures is therefore a bit different. It is not considered good practice to combined RRs or ORs with HRs even when events are rare. We generally did not combine ORs with RRs because of differing study design and believe that it is methodologically inappropriate and potentially misleading to pool together effect estimates from different study designs (e.g. case control and cohort studies).