Reviewer’s report

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

Version: 1 Date: 16 Dec 2018

Reviewer: C Lee

Reviewer's report:

BPSY-D-18-00596R1
Reviewer's comments:

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
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.

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.
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.

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.

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.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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