Reviewer’s report

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

Version: 2 Date: 28 Feb 2019

Reviewer: C Lee

Reviewer's report:

Reviewer's comments:

1. It is a misconception that the term "selection bias" is sometimes referred to lack of generalizability of measures of frequency or effect. That is indeed not the meaning of "selection bias." When you select specific indications or populations, you may not have selection bias. Selection bias means that the selection of control or case cause the distortion of exposure-outcome relationship. In the case of selection bias, conditioning on "Selection," a "collider," makes the casual path open. The selection bias lack of conditional exchangeability because the collider Selection was conditioned on common effects. Theoretically, it is possible selection on common effect, but we don't obtain selection bias when the analysis is restricted to a single level of the common effect. Please refer to Hernán MA, Robins JM (2019). Causal Inference. Boca Raton: Chapman & Hall/CRC, forthcoming.

2. Page 6 Line 28 Zivkovic et al wrote "We anticipated that confounding by indication could be a limitation of many studies and so we did include studies which attempted to address this by comparing people taking APs versus those on other medications for mental illness (but not taking APs)." Confounding by indication means a spurious association between the treatment and the outcome caused by physicians' judgment on patients' indication. The authors may explain this concept here. (You may use Hernán MA, Robins JM (2019). Causal Inference. Boca Raton: Chapman & Hall/CRC, forthcoming as your reference.) Line 30-33 Zivkovic et al wrote "We excluded studies: that compared AP drug use with active comparators, since we were interested in comparing AP drug use versus no AP drug use only." You made your study design really clear before (Line 28). I would suggest you delete "since we were interested in comparing AP drug use versus no AP drug use only."

3. Page 12 Line 50-58, Zivkovic et al wrote "This review identified 10 studies and is therefore less comprehensive than our review, which includes almost double that number. In particular we identified far more cohort studies (8 versus the two identified in Hsu et al). This may reflect our more detailed and comprehensive search strategy…"

Since you are experts in epi study design, you may have noticed that Hsu et al have a different study design. They used nonuse of any antipsychotic to serve as a reference group/comparison. They therefore have a smaller number of included studies than Zivkovic et al. You need to mention their
eligibility criteria are different from yours. It is not true that you conducted more detailed comprehensive search. Please delete "This may reflect our more detailed and comprehensive search strategy, which we applied to the PsycInfo database as well as Medline and EMBASE." accordingly, and write something about different study designs/eligibility criteria. Zivkovic et al mentioned "PsycInfo database" in the method part, it is unnecessary to have duplicated information in the discussion part.

4. Page 13 Line 35-42
"In contrast, Hsu et al appeared to have pooled studies irrespective of study population, study design and type of effect estimate. Pooling together different study designs and different effect estimates is methodologically inappropriate and can result in misleading findings."

Again, as No.3, you and previous meta-analysis used different study designs. Hsu et al used non-users of AP as the comparison. This is exact what Zivkovic et al tried to make the difference.

OR is a good approximation to the HR or RR when we have rare events. You can theoretically combine them especially for rare events. Please refer to "Approximation of Risk Ratios by Odds Ratios When Outcomes Are Rare" in JAMA pediatrics (Cummings, P., 2009. The relative merits of risk ratios and odds ratios).

You may not use such strong tone to criticize the previous meta-analysis--methodologically inappropriate and can result in misleading findings may not suite here.

5. It appears that Zivkovic et al. did not include the following study: Liu HC, Yang SY, Liao YT, Chen CC, Kuo CJ. Antipsychotic medications and risk of acute coronary syndrome in schizophrenia: a nested case-control study. PloS one. 2016 Sep 22;11(9):e0163533. Please include this one and conduct a meta-analysis again. If not, please mention the reasons in method and result part.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

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

No

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

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