Reviewer’s report

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

Version: 0 Date: 19 Sep 2018

Reviewer: C Lee

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This is a systematic review and meta-analysis to evaluate whether use of antipsychotics is associated with increased risk of stroke and myocardial infarction. The search was based on major electronic databases from database inception through May 28, 2017 and concerned observational studies.

Ten studies on MI and 19 studies on stroke were considered eligible. Significant increase in risk of stroke was associated with second generation antipsychotics (SGAs) among cohort studies [pooled HR 1.71, 95% CI 1.16 to 2.53; Figure 2b]. Use of any antipsychotics in patients was not associated with MI risk. The authors conclude that the available evidence suggests that the use of any antipsychotics significantly increased the risk of stroke, but risk of MI remains unclear.

Comments
1. This paper/study confused drug categories between antidepressant and antipsychotics. They authors used confounders in confounding adjustment from the included studies as drug exposure and received incorrect the estimate in their meta-analysis. The conclusion therefore was misleading.

Chen (2008) and Correll (2015) indeed investigated antidepressants use and risk of cerebrovascular accidents (CVA). The authors misunderstood the concept of confounding adjustment. They used confounding effects on the risk of CVEs from the use of other medications that are known or proposed to affect risk of CVEs such as risperidone as SGA use vs no use in their meta-analysis. In fact, Chen's Table2 was Hazard Ratios for the Risk of CVEs Associated with the Use of Antidepressants. Correll's study used SGA use and antidepressant use as covariate in the model, which cannot use in this study. The similar mistake was found when the meta-analysis included Lan et al, 2015 (stroke with lithium exposure in bipolar disorder). The results and conclusions, therefore, are misleading.

2. The authors did not explain the reasons why Douglas et al., 2008 was included in Table 1, but eventually was excluded in meta-analysis.

3. The authors kept mentioning and quoting 'general' population. I don't see any necessity for it. It is unnecessary to use 'general' population (e.g. a cohort identified from primary care/medical insurance records) again. SIGN 50 checklist was used as the tool of quality assessment. Although 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. Besides, NOS evaluates whether exposed and non- exposed cohort represent the general
population or the average in the community. Using NOS, the study does not need to make any redundant quote of "general population." Not using a tool of quality assessment properly may include unnecessary bias.

4. The study included conference abstracts. Although it is true that both published and unpublished results are available, mitigating concerns of publication bias, the study did not mention how many conference abstracts were used and the results of quality assessment.

5. Among included studies reported antipsychotics and MI risk, the most recent year of publication is 2015, but did not show more evidence as compared with two previous studies of meta-analysis (Yu et al., 2016, and Huang et al., 2017; J Psychopharmacol. 2017 Dec;31(12):1544-1555). So what is really new?

6. In discussion, the authors mentioned "more detailed and comprehensive search strategy." However, it may be resulted from misunderstanding confounding adjustment, comparison group, antidepressants and antipsychotics, and misusing a tool of quality assessment. The authors further criticized the previous meta-analysis (Hsu et al., 2017) "appeared to have pooled studies irrespective of study population, study design and type of effect estimate," and "pooling together different study designs and different effect estimates is methodologically inappropriate and can result in misleading findings." Nevertheless, the previous meta-analysis conducted subgroup analyses of the elderly population, dementia population, population-based studies, and case-control studies. I am afraid that I cannot agree with what the authors criticized in the discussion. The authors may need to scrutinize the previous meta-analysis again.

7. In 2016, Yu et al. published a meta-analysis of antipsychotics and risk of MI. I do not see much discussion. The authors mentioned "this previous review identified the same studies and included subgroup analyses, they combined results from different study designs or study populations and often pooled different effect estimates, which affects reliability and interpretability of pooled results." However, the authors did not explain why they included different studies seeing that the two meta-analysis indeed have the same period of included studies. I did not find this simple sentence was not persuasive. The authors did not quoted "Huang et al., 2017; J Psychopharmacol. 2017 Dec;31(12):1544-1555." Huang et al., 2017 found that antipsychotics was associated with an increased risk of MI (pooled OR, 1.55; 95% CI, 1.33-1.79 compared with non-use) based on 10 observational studies. Zivkovic et al. presented inconsistent results, and failed to show any evidence that this study is more robust than the previous two.

8. Abstract
The authors succinctly summarized data sources in the abstract, but they did not include years searched, which should be addressed in the abstract.
Abstract, "In particular, their effect on risk of stroke and myocardial infarction (MI) remains unclear." I don't think there is any doubt that antipsychotic agents increase the risk of stroke, so that it is misleading to say "remains unclear."

In conclusion, the authors included studies that did not fit their inclusion criteria. They misunderstood confounder, confounding adjustment and risk effects of confounders in population-based studies. The study incorrectly included antidepressant agents in the meta-analysis. The study did not use an appropriate tool of quality assessment. Hence, the results and conclusion are misleading. Unfortunately, revisiting the protocol and reviewing all potential relevant studies may not correct the mistakes, since there are not enough new observational studies to add more evidence currently.
**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?**
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