Reviewer's report

Title: Choice of observational study design impacts on measurement of antipsychotic risks in the elderly: a systematic review

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Reviewer: Gianluca Trifiro

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I read with interest this systematic review, which is aimed at exploring the effect of using different study design on the evaluation of the risks in association with the use of antipsychotics in elderly patients. The research topic is highly relevant. As follows, some major and minor criticisms:

Major compulsory revisions

1. Paragraphs summarizing the evidence concerning different adverse events of antipsychotics should be much more detailed. The authors should report information on dose and duration effect as well as on effect modifiers for each antipsychotic-adverse drug event association, as documented in RCT and observational studies. The exact outcome definition and the clinical setting for each reported observational study should be always indicated. Likewise, in the discussion the summarized evidence concerning different risks should be more deeply commented.

2. Besides study design, a lot of other factors may play a role in the observed differences among observational studies investigating similar associations. Differences in underlying population, drug prescribing pattern, clinical setting (i.e. primary vs. secondary care), outcome definition (i.e. hospitalized event versus event as documented in general practice), confounders being taken into account may all account for the differences in the estimated risk of different adverse events. Authors should acknowledge and comment this issue in the discussion.

3. With respect to atypical and typical antipsychotics, authors tend to consider a class effect for risks of different adverse events. However, substantial differences exists among the receptor binding as well the safety profile of individual compounds belonging to atypical antipsychotics (i.e. risperidone vs. quetiapine and clozapine) or typical antipsychotics (i.e. phenothiazines vs. butyrophenones vs. benzamidases), as documented in some studies (see Trifirò et al, 2010). Whenever available, authors should report in the results the differential risk for adverse events as documented in some studies concerning both stroke and pneumonia. Moreover, the issue of class effect for the risk of pneumonia, stroke and death with typical and atypical antipsychotics should be commented in the discussion.

4. As regard the paragraph “Observational Evidence: Studies that compared atypical and conventional antipsychotic treatment”, authors indicate: “Only one study could be located comparing the risk of pneumonia between the classes”.

That's not correct. Trifirò et al reported that: “When current use of typical antipsychotic drugs was considered the reference group, current use of atypical antipsychotic drugs showed no statistically significant difference (P > 0.20) in the risk for pneumonia (OR, 1.48 [CI, 0.84 to 2.60]). When current use of atypical antipsychotic drugs and phenothiazines, which have comparably high H1-receptor affinity, was combined, the risk for pneumonia was higher than that with current use of butyrophenones (OR, 1.86 [CI, 1.09 to 3.17])”. Accordingly, this section should be corrected and these findings should be commented in the discussion. All the studies should be carefully revised in order to avoid missing relevant information.

5. In the discussion, authors state: “Case-control studies often employ techniques to minimise possible bias, such as matching or numerical adjustment for potential confounders, however, studies of this type may still be subject to unmeasured confounding”. It seems that the other study designs do not suffer from the same epidemiologic issues, while this is not absolutely true. Even applying new techniques to deal with confounding in cohort designs, such as multi-dimensional propensity score matching, yet the issue of unmeasured confounder remains. Missing information about severity of diseases and other covariates which are not commonly registered or are selectively registered in healthcare databases (i.e. smoking, alcohol consumption) may influence negatively the results also when using cohort approach. Authors should strongly revise the comments concerning the superiority of cohort designs compared to case control design as this systematic review does not clearly support this evidence. To adequately compare the performance of different study designs, the same data sources, study population, outcome and exposure definition, and covariate selection should have been considered and subsequently the risk estimates should have been compared. To compare studies which differ, not only in term of study design, but also for all other relevant methodological aspects may lead to draw wrong conclusions. Authors should strongly revise the discussion based on this consideration.

Minor essential revisions

1. In the methods (page 5), authors should better indicate that they included in the review only the studies concerning elderly patients with dementia, as reported in the search domain

2. Stroke was used as MESH term for searching the studies concerning all the cerebrovascular disorder. Was this enough? Comment on it.

3. In the methods, authors should indicate who and how many researchers retrieved and assessed the publications to be included in the final review. Were there multiple assessors who independently revised the publications? If yes, what happened in case of disagreement?

4. Authors indicate that RCT in general are high quality study (methods, page 6). The scientific literature is full of RCTs of low quality. A properly conducted observational study may be more reliable of a poor quality RCT. Authors should comment on it in the discussion

5. Authors should indicate a reference supporting clearly the statement
“observational cohort studies were considered of higher quality than case-control designs” (methods, pag 6). This sentence is strongly debatable and authors should convince the reader about it.

6. Authors state: “Study designs such as the self-controlled case-series or instrumental variable analysis are not formally recognised in the hierarchy of evidence, however, we have considered these studies as they attempt to account for the common problem of unmeasured confounding in observational studies.” Authors should reconsider this sentence as self controlled case series may address only the unmeasured confounders which do not vary along time.

7. In the heading of each paragraph, authors should report “meta-analysis and RCT evidence” for consistency with the categorization of the evidence

8. General practitioners note should be replaced all over the manuscript with General practitioners’ medical records

9. Pag 12, replace odds with risk

10. In the discussion (pag 15), authors indicate: “The potential for antipsychotics to be associated with pneumonia was highlighted in a Cochrane Review [1] which found significantly increased risks of upper respiratory tract infections with risperidone”. Upper respiratory tract infections are not related with pneumonia and this sentence should be removed.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests