Author's response to reviews

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

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Author's response to reviews: see over
To the Editor,

Please find enclosed the revised manuscript entitled “Choice of observational study design impacts on measurement of antipsychotic risks in the elderly: a systematic review” for consideration for publication in BMC Medical Research Methodology.

We thank our reviewers for their thoughtful and detailed review of our manuscript. We have addressed each comment through track changes in the document and point-by-point below. We have substantially changed our discussion and limitations sections to address the reviewers concerns. We believe that we have provided a novel review of how the use of observational study designs and techniques to adjust for confounding can impact on study results.

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Yours sincerely

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Reviewer's report
Title: Choice of observational study design impacts on measurement of antipsychotic risks in the elderly: a systematic review
Version: 1 Date: 29 July 2011
Reviewer: Gianluca Trifiro

Reviewer's report:
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 aim of this systematic review was to explore the effects of study design and methods used to control for confounding on results of observational studies. Several detailed systematic reviews have explored the adverse effects of antipsychotics by dose and duration of effect and effect modifiers (in particular Trifiro and Sacchetti). We have referenced these studies in our introduction and commented on our simplification to class effects as per comment 3 below.

We have included additional text and references in the introduction as follows:

“Previous reviews of observational studies of antipsychotics have focused on the clinical safety of conventional and atypical antipsychotics, [10-13]. The aim of this review was to synthesise the current evidence from observational studies, regarding the serious adverse events of antipsychotics in elderly patients and [SM1] to determine the impact of the observational study design utilised and the technique employed to control for confounding on study results.”

The exact outcome definition and the clinical setting for each reported observational study should be always indicated.

We have amended our Tables to include a more detailed description of outcome definition and the clinical setting

Likewise, in the discussion the summarized evidence concerning different risks should be more deeply commented.
We have amended our discussion section substantially to address this issue.
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.

We have included the following statement in the last paragraph of the discussion

“Besides study design, many other factors may have contributed to the differences observed among observational studies. These include differences in populations studied, in terms of drug utilization patterns and health care settings, differences in the definition of outcome and variations in the number and type of confounders that may have been included in the analysis. We have attempted to limit the impact of these effects by considering the effects of antipsychotics in the elderly only and by limiting our events to serious adverse events potentially requiring hospitalization. In the case of cerebrovascular events we considered cerebrovascular events separately to hospitalizations for stroke as these were the two events most often considered in observational studies.”

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. benzamides), 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.

We have included the following statement in the last paragraph of the discussion

The aim of this review was to explore the effects of study design on the results of observational studies of antipsychotics. To do this we simplified our comparisons to with-in class comparisons and we have not considered differences according to individual products, dose or effect modifiers. The majority of published studies have only provided comparisons between the classes, however, where available we have presented the results by individual products and doses.

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 \((P \geq 0.20)\) 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.

We have amended the results as follows, and Table 4 has been updated to include these results

Two studies were located comparing the risk of pneumonia between the classes. Both studies found no difference in the risk of pneumonia between the classes. (Table 4).

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.

We have substantially changed our discussion to address this issue. In particular we have deleted or amended sentences that suggest the superiority of cohort studies and we have added that the SCCS still may suffer bias due to time varying unmeasured confounding.

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

We included double-blind randomised controlled trials (RCTs), meta-analyses and published observational studies that evaluated adverse events of either typical or atypical antipsychotic medications in elderly populations

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

We used Stroke as our search term which is a MESH heading that includes, Cerebral Stroke; Cerebrovascular Accident; Cerebrovascular Accident, Acute; Cerebrovascular Apoplexy; Cerebrovascular Stroke; CVA (Cerebrovascular Accident); Stroke, Acute; Vascular Accident, Brain. The MESH term cerebrovascular disorder would have included carotoid artery diseases, dementia and so on. Our manual search of bibliographies identified other studies using a broader MESH definition.

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?

We have included a sentence in the methods as follows:

“Author 1 (NP) was responsible for the retrieval and review of studies to be included in the final review. Author 2 (ER) provided independent assessment of studies when required. [Tminor3].”

4. Authors indicate that RCT in general are high quality study (methods, pag 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

“RCT evidence is generally considered of higher quality than observational studies,[18] however, there are many examples where RCTs on the same clinical topic have produced conflicting results [59]. High quality observational studies, whether cohort or case-control designs, have consistently found similar results to RCTs [59] [Tminor4]”

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.
We have excluded this sentenced and have now based our assessment of quality on the measures employed to reduce confounding rather than pre-specifying based on study design.

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.

This design attempts to limit the effects of major unmeasured confounders as the within-person study design controls implicitly for confounders that do not vary over time, however, the self controlled case-series design may still be affected by confounders that vary by time.

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

This change has been made throughout the Results section

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

This change has been made throughout the manuscript

9. Pag 12, replace odds with risk

This sentence has been revised as follows:

“Two case-control studies found a significantly increased risk of pneumonia with typical antipsychotics”

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.

We have amended this sentence as follows:

“Meta-analyses [19, 57] of randomized controlled trials found that one of the major causes of death associated with atypical antipsychotics was pneumonia.”

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
Reviewer's report

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

Version: 1 Date: 26 August 2011
Reviewer: Emilio Sacchetti

Reviewer's report:

- Major Compulsory Revisions

1. The techniques of instrumental variable analysis and self controlled case series should be described with more details, since they are not probably familiar with conventional readers.

We have included the following text and references to explain the instrumental variable and Self controlled case-series design in the methods section [page 6]

“We included observational studies that employed either a case-control design, a cohort design or a self-controlled case-series design [S1]. Studies that also used an instrumental variable analysis in addition to the standard cohort analysis were also included. The use of instrumental variables has been suggested as a possible alternative to conventional analyses when there is concern about the effect of unmeasured confounding. [14 15] Instrumental variable (IV) analysis attempts to mimic the process of randomisation in an RCT by exploiting the existence of another variable (the instrument) which can be measured in the available data, which is highly correlated with the probability of exposure but unrelated to the outcome of interest except through its association with treatment.[16] The instrument is similar to random arm assignment in that it should distribute both measured and unmeasured patient characteristics evenly between exposure groups resulting in an estimate less affected by confounding. The self-controlled case-series design compares the risk of adverse events in periods of exposure compared to non-exposure within the same person. This design attempts to limit the effects of major unmeasured confounders as the within-person study design controls implicitly for confounders that do not vary over time.[17]”

2. Authors miss the historical perspective that saw RCTs coming years before observational studies, so that it is rather nonsense pretending that RCTs should confirm something that came years after (like at page 13, end, when noting that RCTs have produced no evidence to confirm ...) or thinking of RCTs as something that could compare classes of antipsychotics.

We thank the reviewer for highlighting this. The reason we included RCT and meta-analysis data was purely for comparison purposes and our use of the word “confirm” was incorrect. We have amended this sentence as follows

“No RCT evidence comparing the risks between the classes was available to compare these analyses”
And in the limitations section

“Where possible we compared available meta-analyses and randomised controlled trial evidence with the results of observational studies. Experimental evidence was typically generated prior to when many of the observational studies were performed and may have included different patient populations. [Smajor 2] RCT evidence is generally considered of higher quality than observational studies,18 however, there are many examples where RCTs on the same clinical topic have produced conflicting results [59]. High quality observational studies, whether cohort or case-control designs, have consistently found similar results to RCTs. [59] [Tminor4]”

3. The choice of “limiting” data analysis to only four outcomes and excluding other like diabetes is justified by the very personal opinion that the four outcomes selected can be “consistently defined” (why not diabetes?).

We have included these outcomes primarily because we believe that their occurrence would generally manifest as a hospitalisation event. We have not included diabetes as many of the studies have used metabolic abnormalities as outcomes, which may include weight gain or effects on glucose levels, total cholesterol etc. These outcomes are not readily available in administrative claims database and therefore have not been included. We have addressed our reasons for including the specified outcomes in the methods section as follows:

“We only included outcomes that could be consistently defined to limit heterogeneity across studies. The endpoints for this study, cerebrovascular events, hip fracture and pneumonia, were chosen because we believed that patients were likely to present to hospital for these conditions, and therefore were outcomes that would most likely be available in observational studies using administrative claims databases. The application of methods such as the self controlled case-series and instrumental variable analyses have evolved mainly to address unmeasured confounding due to the lack of clinical information in claims databases. Antipsychotics have also been associated with other adverse events such as deep vein thrombosis, diabetes onset and heat stroke which were not included in this review.”

Additionally, some studies suggest that diabetes effects with antipsychotics tend to be attenuated in the elderly. (Trifiro et al Pharmacological Research 2008)

4. The discussion is a replication of the results section, and should be expanded.

We have revised the discussion section considerable, by expanding our summary of results and limitations of our study.

- Minor Essential Revisions
“elderly patients to determine”
Elderly patients and to determine

We have changed this sentence as suggested

“relative increased risk”
Better: increased relative risk. This is repeated some times in the following text.

We have revised as suggested

“antispsychotics”

We have made this change

“significantly increased 50-80% increased odds”
??
We have changed this sentence to read:

“Two case-control studies found significantly increased risk of pneumonia with typical antipsychotics…”

“risk differ between studies”
The preceding verb was the past tense “showed”

The sentence has been revised as follows:

“Collectively, observational evidence showed that typical antipsychotics are associated with a greater risk of death than the atypical antipsychotics, however, the estimates of absolute risk differed between studies.”

“traditional” is used for “conventional”. The meaning is clear, but this is not the language currently used in psychiatry.

Traditional in this sentence refers to the statistical design rather that the class of antipsychotic. I have amended as follows:

“These discrepancies suggest that unmeasured confounding may have contributed to an underestimate of risk in the cohort studies.”
Authors should decide if dots are to be placed after or before the citations.

Thank you, I have standardized the placement of dots before citations.

- Discretionary Revisions
  None

Level of interest: An article whose findings are important to those with closely related research interests

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 have received funding for research, advisory board memberships and/or sponsored lectures from Abbott Laboratories, AstraZeneca Pharmaceuticals, Boheringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, GSK, InnovaFarma, Lundbeck, Pfizer Inc., Sanofi-Aventis, Wyeth.