Author's response to reviews

Title: Impact of atypical long-acting injectable versus oral antipsychotics on rehospitalization rates and emergency room visits among relapsed schizophrenia patients: A retrospective database analysis

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Author's response to reviews: see over
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Dear BMC Psychiatry Editorial Team:

I am pleased to re-submit the enclosed manuscript, “Impact of atypical long-acting injectable versus oral antipsychotics on rehospitalization rates and emergency room visits among relapsed schizophrenia patients: A retrospective database analysis” for consideration as a publication in \textit{BMC Psychiatry}.

Please find, appended to this letter, our responses to the reviewers’ comments that were transmitted to us on April 3\textsuperscript{rd}, 2012. We have reviewed the comments raised by the two reviewers and have provided a point-by-point response to each of the reviewers’ concerns, detailing exactly how we addressed each point and the associated page number for the amendment in the revised manuscript. Modifications made to the originally submitted manuscript are highlighted using the track-change feature of MS Word.

On behalf of my co-authors, we thank you for the opportunity to contribute to \textit{BMC Psychiatry}. I look forward to hearing the final editorial decision in the near future.

If there are any other materials you require in considering this submission or if you have any other questions, please feel free to contact me at 617-425-8131 or via email at mduh@analysisgroup.com.

Thank you for your consideration.

Sincerely,

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Responses to Reviewers’ Comments from BMC Psychiatry

Reviewer # 1

Summary

This manuscript examines differences in outcomes for patients diagnosed with schizophrenia treated with an oral antipsychotic (AP) to those treated with a long-acting injectable therapy (LAT). Results indicate that, in relapsed schizophrenia patients, atypical LATs were associated with lower reshospitalization and ER visit rates, compared to oral APs.

MAJOR COMPULSORY REVISIONS

1. Introduction – Importance of topic
   While the introduction does a good job of laying out the costs of schizophrenia and alternative treatment regimens for schizophrenia, it does not clearly lay out the rationale for the project. Specifically, while the paper tells us what it is going to do (compare LATs to oral APs), it does not tell us why such a research question is important. The last paragraph of the introduction should not only tell us what they are going to do, but why we should care about what they are going to do.

Response:

We thank the reviewer for this comment. One of the novelties of this paper is its matched-cohort study design, as most of the previous studies used a pre-post study design. In addition, the current analysis evaluates the risk of recurrence of hospitalizations, whereas previous studies mostly analyzed the rate of rehospitalization. The last paragraph of the introduction has been amended to reflect these elements (page 6, paragraph 2).

Methods

2. Methods – Rationale for examining rehospitalizations
   The authors examine as primary outcomes (a) rehospitalizations, and (b) ER visits. However, no rationale is discussed for focusing on subsequent hospitalizations (e.g., rehospitalizations) and any ER visit (e.g., not subsequent ER visits). I presume that the focus on rehospitalization was used to identify a more severely ill patient population – but this criteria is never explained.

Response:

We thank the reviewer for this comment. It has been clarified in the study design section that the rationale for requiring a prior schizophrenia-related hospitalization was to identify a schizophrenia-relapsed population (page 7, paragraph 2). However, it is not clear whether imposing this criteria resulted in a more severely ill population, as about 80% of the population was discharged at home.

3. Methods – Identifying schizophrenia-related hospitalizations
The authors identify a schizophrenia-related hospitalization as any hospitalization with an accompanying diagnosis of schizophrenia. However, as Table 1 illustrates, patients may have had an admitting or primary diagnosis such as diseases of the circulatory system or diseases of the respiratory system, and still be categorized as having a schizophrenia-related hospitalization. I would suggest that, at a minimum, the authors restrict the criteria for hospitalizations to those with (i) a primary or admitting diagnosis of schizophrenia, (ii) a primary or admitting diagnosis of other mental disorders and an accompanying diagnosis of schizophrenia, or (iii) a primary or admitting diagnosis of injury and poisoning and an accompanying diagnosis of schizophrenia.

Response:

We thank the reviewer for this comment and suggesting this algorithm to identify schizophrenia-related hospitalizations. We have modified our inclusion criteria following the reviewer’s suggestion and have updated the results throughout the manuscript (Study design: page 7, paragraph 2; Results: throughout the manuscript). Updated results yield similar findings.

4. Methods – Rehospitalizations and ER visits
In addition to examining rehospitalizations and ER visits separately, the analysis also examines a composite endpoint of rehospitalization or ER visits. Again, no rationale is given for the creation of such an endpoint.

Response:

We thank the reviewer for this comment. These two endpoints, frequency of hospitalizations and of ER visits, are avoidable events representing relapses that could not be managed through outpatient services. This has been clarified in the Study End Points section (page 7, paragraph 3). However, as hospitalizations and ER visits are two different events in nature, we have removed this composite endpoint from the presentation and chose to present results for these two events separately.

5. Results – Inconsistency with methods
It is not entirely clear in the manuscript why the study design discussion focuses on schizophrenia related hospitalizations and rehospitalizations while the study end points discussion focuses on all-cause and mental disorder-related hospitalizations.

Response:

We thank the reviewer for this comment. The rationale for reporting mental disorder-related and all-cause related ER visits and re-hospitalizations was to capture healthcare utilization of this schizophrenia population that may not have been coded specifically with a diagnosis of schizophrenia, potentially because of inconsistencies or errors. In addition, as schizophrenia is associated with higher incidence of comorbid conditions, such as diabetes, hypertension, obesity, it was found of interest to look at a larger set of healthcare resource utilization than just specific schizophrenia-related resource utilization.
However, we fully agree that the subset of hospitalizations/ER visits directly related to schizophrenia is also of interest. Therefore, we have added results for schizophrenia-related events to the manuscript. Specific adjustments have been made to the methods (page 8, paragraph 1; page 9, paragraph 3) and results (page 10, paragraph 2; page 11, paragraph 3) sections.

6. Methods – Propensity score matching

While propensity score matching is a well-understood and appropriate methodology for the research question of interest, the authors do not address any of the limitations of this methodology. For example, it has been argued that matched subjects are more likely to have similar outcomes than are randomly selected subjects and that such a lack of independence should be accounted for when estimating the variance of the treatment effect. As such, McNemar tests and paired t-tests may be more appropriate than traditional t statistics and chi-square statistics. The authors make this adjustment without discussing the rationale.

Response:

We thank the reviewer for this comment. We have adjusted the text in the Statistical Analysis section to mention that the choice of the statistical tests for the matched cohorts was made to adjust for the non-independence of the matched cohorts (page 9, paragraph 2).

In addition, when using matching with replacement, untreated subjects are allowed to be included in more than one matched set. In this case, the variance estimation must account for the fact that the same subject may be in multiple matched sets. The authors fail to consider the effect of such an adjustment.

Response:

We thank the reviewer for this comment. In the matching approach that has been used, random selection of control patients was made without replacement. Control patients could be selected only once. The text in the Matching Algorithm section has been revised to clarify this aspect of the methodology (page 8, paragraph 2).

Finally, the authors fail to discuss the rationale for using the 2.5 percentiles of the propensity score distribution for matching as well as how using such a stratification on the propensity scores affects estimates of the variance of the estimated treatment effect.

Response:

We thank the reviewer for this comment. The choice of the 2.5 percentiles was made as the smallest caliper to ensure a proper balance of baseline characteristics between the matched cohorts in maximizing the number of patients selected in the match. The purpose of keeping as many LAT patients as possible is to make sure the matched population is similar to the general LAT population before matching. In addition, maximizing the sample size will have
the effect of diminishing the variance in estimates. The following sentence has been added in the “Matching Algorithm” section: “These criteria were chosen to achieve both clinical and statistical balance between cohorts without losing a significant proportion of the atypical LAT group.” (page 8, paragraph 2)

7. Discussion – Link to previous literature

The authors spend one brief paragraph of the discussion section linking the results of their research to previous research which has compared oral APs to LATs. They state that their study generally corroborates other research (citing 14 such studies) although most of these studies were pre-post study designs. Similarities and differences between this study and other studies should be more clearly identified and discussed in the discussion section. Such a discussion may help as well with comment #1 – e.g., explaining the importance of this research.

Response:

We appreciate the reviewer’s comment of expanding this paragraph of the Discussion section to discuss in greater details results from the published literature and how they compare with the current study. This paragraph has been revised as follows:

“This study corroborates the findings from other studies that have found a beneficial effect of atypical LATs in terms of rehospitalizations [9,20,22,30,33-42]. Some of these studies used a pre-post study design, where each patient acted as his or her own control, and found that LATs were associated with a decrease in hospitalizations ranging from 34% to 89% [20,22,30,33-39]. The current analysis based on a matched cohort design found that LATs were associated with a 19% reduction in the risk of recurrence of hospitalizations when compared to matched oral AP patients. The slightly smaller effect found in the current analysis may be explained in part by the study design, where the comparison was made on relapsed oral AP patients, which are likely an healthier population than the subset of patients switching to LATs (and hence are expected to have fewer rehospitalizations). Focusing on the relapsed population (patients already experiencing a second schizophrenia-related hospitalization) and the matching approach have helped to address this bias, but it is possible that unobservable characteristics were still different between cohorts, therefore explaining the smaller effect found here. However, the general consistency of the results throughout different methods, study designs, and study populations suggests that atypical LATs may be more effective than oral APs in avoiding patient relapse.” (page 13, paragraph 2)

These elements were also included in the Introduction section to provide a stronger rationale for the objective of this study. (page 6, paragraph 2)

**MINOR ESSENTIAL REVISIONS**

1. Study Design - Aps should be APs on top of page 7

Response:
We thank the reviewer for this comment; this typo has been fixed. (page 7, paragraph 2)

DISCRETIONARY REVISIONS

1. The lead paragraph uses the word schizophrenia 6 times – it seems overly repetitive. Perhaps synonyms can be used in some of these cases.

Response:

We thank the reviewer for this comment. We have revised this paragraph and reduced the number of times the word schizophrenia is used. (page 5, paragraph 1)
Reviewer # 2

I think the data are important and should be published. I believe the methods are ok.

MAJOR COMPULSORY REVISIONS

1. But I think the authors should highlight in the results that there was no difference between the two groups in number of days as inpatients and also mention this in the discussion. This should also be included in the abstract. The number of days as inpatients is usually a more important factor than number of rehospitalisations in costs of healthcare

Response:

We thank the reviewer for this comment. We realized that the number of days in hospital was reported only for a maximum of 6 months following the index hospitalization. We calculated the number of days in hospital for the entire observation period of approximately 30 months for both cohorts, and found a statistical difference between cohorts for all-cause and mental disorder-related events (LAT vs. Oral AP; all-cause: 13.46 vs. 15.69, p=0.0081; mental disorder-related: 13.44 vs. 15.62, p=0.0093, schizophrenia-related: 12.79 vs. 14.28, p=0.0893). These overall numbers were added to Table 2; for readability of the Table, we removed the stratification by 1 month, 3 months, and 6 months.

Results on the number of days in hospital have been added in the abstract (page 3, paragraph 3) as well as in the results section (page 11, paragraph 1).

MINOR ESSENTIAL REVISIONS

Discussion

2. The two groups might differ with more difficult to treat patients in the LAT group: Even if the authors have tried to match the oral AT patients with the LAT group, the patients receiving LAT might be more difficult to treat than the oral AT group. The reason for choosing LAT instead of oral AT might for some patients be problems with non-adherence to medication in combination with very disturbing symptoms.

Response:

We agree with that patients receiving atypical LAT instead of oral AP may be more difficult to treat, with poorer adherence to medication and/or with more severe symptoms. As you mention, the matching algorithm attempted to address this issue, along with the choice of identifying a relapsed population. This rationale for choosing these statistical methods has been clarified in the Discussion section (page 12, paragraph 2).
In addition, we acknowledge in the Limitations that patients were matched based only on information available during hospitalizations occurring at the same hospital as no information on services received outside the hospital or on pharmacy utilization was available, which may have limited our ability to fully adjust for differences in baseline severity of the disease (page 14, paragraph 1).

3. **Even if the differences between the groups for several items are significant, the differences are mostly between 80 and 95% and no difference in days as inpatients. If this is a clinical important difference when choosing medication for a patient should be discussed.**

Response:

We thank the reviewer for this comment. As hospitalizations account for up to two-thirds of total healthcare costs in the US in this population, a 19% decrease in the risk of recurrence of rehospitalization found in this study may be associated with substantial cost savings in relapsed patients with schizophrenia. Further studies analyzing costs of hospitalizations between patients using atypical LATs and matched oral AP patients are warranted. These elements have been added to the Discussion section of the paper. (page 13, paragraph 2)

4. **The lack of difference in number of days as inpatients which usually is the most important factor in health care costs should also be mentioned in the discussion.**

Response:

The difference in mean number of days in hospital calculated over the entire observation period was statistically significant. Please see response to Comment #1 above.

5. **In my copy of Table 2, the markers of the confidence intervals are not correct.**

Response:

We thank the reviewer for this comment. To report the variance of the data, Table 2 shows the standard deviations (SDs) of variables rather than confidence intervals. SDs are typically reported using the plus/minus sign ("±") after the mean.

6. **The authors state that an approval from an ethics committee is not needed, I am not sure if that is correct and ask the editor to look into the question.**

Response:

As this was an analysis of claims data, IRB approval was not required. Per Title 45 of CFR, Part 46.101(b)(4) (www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.101), the administrative claims data analysis of our study is exempt from the IRB review for two reasons: (1) it's a retrospective analysis of existing data (hence no patient intervention or interaction), (2) no patient-identifiable information is included in the claims dataset.