Reviewer’s report

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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Reviewer: Marueen Lage

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REVIEW
Impact of Atypical Long-Acting Injectable Versus Oral Antipsychotics on Rehospitalization Rates and Emergency Room Visits Among Relapsed Schizophrenia Patients: A Retrospective Database Analysis

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 rehospitalization 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.

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.

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.

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.

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.

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, McNemer 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.

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.

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.

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.

MINOR ESSENTIAL REVISIONS:
1. Study Design
Aps should be APs on top of page 7

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.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I have received consulting fees from firms that manufacture both oral APs and LATs in the previous 5 years.