Reviewer's report

Title: One year risk of psychiatric hospitalization and associated treatment costs in bipolar disorder treated with atypical antipsychotics: a retrospective claims database analysis

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Reviewer: Angus Thompson

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This retrospective cohort study of insurance claim records of bipolar patients who had been administered atypical antipsychotic medication investigated one-year risk of hospitalization and treatment costs as a function of the type of atypical antipsychotic that was administered. The strengths of the study include a relatively large sample size, a potentially high file completion rate that was fuelled by its payment-related contingency (although that may produce other problems), and some sophisticated methods designed to lessen bias due to the lack of random assignment and variation among “extraneous” variables.

The paper should be published, although there are three points that should be attended to. I fear, though, that the conclusions made in the paper may prove to be untenable, particularly if significance levels prove to be wanting. Whatever the case, the authors have important data that presumably reflect the real world and it is useful to describe the findings that they have.

Major Compulsory Issues to be Addressed:

1. There are two concerns about the key statistical significance values reported in Table 3 (i.e. for “Comparator vs. Aripiprazole”).
   i. There are four paired-comparisons reported – each involving aripiprazole. Ordinarily, the p-level is adjusted to compensate for this form of multiple comparison. Thus, some of the marginal findings (i.e. for Olanzipine and Quetiapine) may not prove to be statistically significant.
   ii. Most journals prefer significance levels to be set at $p<.01$. Table 3 levels are set for 95% confidence intervals. Again, it is likely that some of the comparisons judged to be statistically significant will not prove to be so.

In sum, considering these two points, it may be that none of the comparisons will prove to be statistically significant. At best one might be marginally so.

2. The propensity score-matching on mood stabilizers for Aripiprazole vs. Ziprasidone produced a higher percentage on all six of these mood stabilizers for Ziprasidone (Table 1). This may not look like much, but a simple binary (higher vs. lower) analysis results in a $p$ level of about 0.03. Suggest either reselecting the sample, or explaining why my concern will not affect the results (note from the point just above that Ziprasidone showed the highest significance level).
3. The propensity-score matching exercise involved 59% of the 776 aripiprazole patient pool in the comparison with ziprasidone. The figures for the other three antipsychotics, however, were 95% or better. This means that the comparisons of aripiprazole with the other medications are based on two unequal samples (one for ziprasidone and one for the other three). Does this matter? It would be useful to allay the readers’ possible concerns about what this might mean.

Discretionary Issues:

1. In spite of the attempts to control selection bias, studies on treatment seeking have shown us that adjustment for supposedly important covariates does not guarantee its (bias) removal. The authors should be commended for their approach to this issue and for mentioning the limitation. However, given the attention they have paid to the details it is surprising that they have not provided the readers with some conjectures about means for further improvement.

2. Why were only “positive healthcare costs” included in the economic analysis? Other forms of indirect costs are often illuminating. Please clarify this omission. If other costs could not be estimated, please say so and acknowledge what might be lost.

3. Would it have been useful/possible to assign medication costs to either psychiatric and medical treatment as was done for inpatient and outpatient Rx?

4. Why was aripiprazole selected as the reference antipsychotic? Was it selected on the same basis in the previous study on the same antipsychotics?

5. A strength of the Cox proportional hazards analysis is that it makes allowance for drop-outs. But the ability to produce a number is one thing, the interpretation of what it means in light of the huge number censured here, is another. What does it mean to attribute an outcome to, for example, aripiprazole, when 88.3% of the sample discontinued its use (including those that switched to another antipsychotic) before the end of follow-up? At best, the comparisons pertain to the drug prescribed at time of the beginning of the study period – but many things occurred after that. Aripiprazole showed the highest rate of discontinuance – perhaps that accounts for the apparent benefit.

6. It appears that psychiatric, medical, and pharmacy costs do not follow the same pattern across the atypical antipsychotic medications. If this is systematic, then there is something to be learned by examining the relationships further. The authors may wish to comment on this.

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

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

I declare that I have no competing interests