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: Carolyn Dewa

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The study compared one year risk of psychiatric hospitalization and treatment costs in commercially insured patients with bipolar disorder, treated with aripiprazole, ziprasidone, olanzapine, quetiapine or risperidone.

Major Compulsory Revisions

The main concern arises with the censoring of those who switched antipsychotics and those who discontinued use. Both groups may have represented people who may have more complex courses of treatment. This complex course could be associated with increased hospital use, but the censoring prevents the exploration of this possibility. Table 2 indicates that a large proportion of people who used antipsychotics discontinued use. It seems that the largest group to discontinue use were those who used aripiprazole. The authors seem to overlook this outcome, focusing instead on hospitalizations; however, the percentage of people who discontinued use was almost 10 times greater than the percentage with a psychiatric hospital admission.

Also, although adherence to medication is an important factor contributing to hospitalization, this was not adjusted for in the statistical analyses; in fact, subjects who were non-adherent were dropped from the analysis.

In addition, the authors conclude that aripiprazole is associated with lower total health care costs. Yet, this conclusion must be qualified by the fact that the authors only looked at those who had positive costs. This raises the question of what results would have been observed if all subjects had been included in the analyses. Based on their selection criteria, the sample decreased from 198,919 to 7,169 people. The analyses are based on only 3.6% of the entire sample.

Specific comments

Page 9, Paragraph 1: Why were the variables chosen for the logistic regression? Is there a rationale for them? There does not seem to be adjustment for the length of time a person had bipolar disorder.

Page 9, Paragraph 1: How were the p-values calculated in Table 1? How were groups matched (e.g., 1:1)?

Page 9, Paragraph 2: More detail is needed about the Deyo Charlson
Comorbidity.

Page 9, Paragraph 2: Why was a gamma regression chosen? How was it estimated? Did the model fit the data?

Page 9, Paragraph 2: Why were only those with healthcare costs in the follow-up period chosen? How could this have biased the results? Would a two part model help address these concerns?

Page 13, Paragraph 2: The authors indicate, “These results suggest an economic advantage for aripiprazole based on the presence of incremental clinical benefit without higher total expenditures.” The cost analysis was not of average expenditures but of average expenditures given there was some spending. It is possible for the average to be higher even if the conditional average is lower.

Page 14, Paragraph 2: The authors indicate they did not address adding or switching antipsychotics. Yet, these factors could have been important to examine. Perhaps, they could compare the results of the two analyses – one analysis with only those who used the antipsychotic all the way through versus an analysis that includes those who switched and discontinued use.

The authors assert, “Propensity score matching, however is a widely accepted method for minimizing the effects of treatment selection bias in observational data.” Instrumental variables (IV) is a widely accepted method for controlling unobserved selection bias. Future analyses using IV might seek to reduce the potential bias that remains in this analysis.

Page 15, Paragraph 1: The authors conclude, “Total healthcare costs of patients treated with aripiprazole were lower than those with quetiapine.” This is not exactly accurate; overall healthcare costs were not studied.

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

**Quality of written English:** Acceptable

**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.