Author's response to reviews

Title: Healthcare utilization and costs in patients with schizophrenia or bipolar disorder receiving second-generation antipsychotics at hospital discharge: a retrospective cohort study

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Author's response to reviews: see over
Dear Dr. Alam:

My colleagues and I wish to thank you for your interest in our manuscript (MS: 2285582695223602 "Healthcare Utilization and Costs in Hospitalized Patients with Schizophrenia or Bipolar Disorder Receiving Second-Generation Antipsychotics: A Retrospective Cohort Study") for consideration for publication in *BMC Psychiatry*. We have revised the manuscript, based on the comments that received, as follows:

**Reviewer 1 (Carolyn Dewa)**

1. The authors point out that the small sample is one of the limitations of the study. It would be helpful if more information was provided regarding the inclusion criteria. For example, why was attention focused on people who received oral ziprasidone, aripiprazole or quetiapine? Why were people with evidence of epilepsy dropped? What data are not captured through carve outs?

   *We focused attention on patients who received ziprasidone, aripiprazole, or quetiapine because these three agents are not currently available generically in the US, and we have added explanatory text to the Background section of our manuscript to clarify this point. Patients with epilepsy were excluded from the study, since antiepileptics are also used as mood stabilizers (i.e., we would not be able to ascertain why patients received an antiepileptic—that is, for the treatment of epilepsy or schizophrenia/bipolar disorder). For patients enrolled in insurance plans with mental health “carve-outs”, information on services related to the treatment of mental disorders would be incomplete. We have added text to the Methods section of our manuscript to more fully explain why we excluded patients with epilepsy, as well as those enrolled in insurance plans with mental health carve-outs.*

2. It would helpful if the authors provided a rationale for why they included an analysis of switching.

   *As suggested, we revised our Methods section to explain why we included an analysis of switching.*
3. On page 4, paragraph 1, the authors assert, “It has been hypothesized that the improved tolerability of SGAs in comparison with older agents may result in ... and lower costs of care.” However, there is no comparison made with SGAs and older agents. What is the rationale for the cost figure?

We agree with the reviewer, and have deleted this sentence from our Background section.

Reviewer 2 (Haya Ascher-Svanum)

1. Title page: The current title is inaccurate. The manuscript actually reports healthcare utilization and costs in patients with schizophrenia or bipolar disorder following hospital discharge on quetiapine, aripiprazole or ziprasidone: A retrospective cohort study. Please revise.

We modified the title of our manuscript, as requested.

2. Abstract: The background section needs to also indicate that these are patients are assessed following hospital discharge (not “hospitalized” patients) on quetiapine, aripiprazole or ziprasidone.

We modified the Background section of the Abstract, as requested.

3. Background section: This section needs to provide a clear and well supported rational for the study’s focus on only 3 atypicals (quetiapine, aripiprazole or ziprasidone). Why exclude risperidone and olanzapine?

As noted in our response to Comment #1 from Reviewer #1, we focused attention on the three second-generation antipsychotics that are not currently available generically in the US (i.e., quetiapine, aripiprazole, ziprasidone), and we have added text to the Background section to explain why this was the case.

4. The authors appear to misinterpret (page 3) the results of the CATIE (reference 9), stating that results “support the similar efficacy” of first and second generation antipsychotics. The CATIE study actually concluded differently (page 1209): “The majority of patients in each group discontinued their assigned treatment owing to inefficacy or intolerable side effects or for other reasons. Olanzapine was the most effective in terms of the rates of discontinuation, and the efficacy of the conventional antipsychotic agent perphenazine appeared similar to that of quetiapine, risperidone, and ziprasidone. Olanzapine was associated with greater weight gain and increases in measures of glucose and lipid metabolism.” The CATIE paper also stated (page 1218): “Within this limited range of effectiveness, the olanzapine group had the lowest rate of discontinuation, which might lead one to consider olanzapine the most effective of the medications studied. Its apparent superior efficacy is also indicated by the greater reduction in psychopathology, longer duration of successful treatment, and lower rate of hospitalizations for an exacerbation of schizophrenia. The results for the other second-generation antipsychotic agents and the representative conventional drug, perphenazine, were similar in most respects.”
We modified the text in the Background section to note that: (a) risperidone, quetiapine, and ziprasidone had similar “overall effectiveness” (as measured by discontinuation rate at 18 months) to first-generation agents; (b) olanzapine had a significantly lower discontinuation rate in comparison with other second-generation agents; and (c) the discontinuation rate for olanzapine, while superior to those of other second-generation agents, is still high.

5. Please note that 2 recent meta analyses have shown the atypicals are not all alike on efficacy when compared to first generation antipsychotics (Leucht S, Corves C, Arbter D, et al. Lancet. 2009;373:31-41) and also when compared head to head (Leucht S, Komossa K, Rummel-Kluge C, et al. Am J Psychiatry. 2009;166:152-163). Please revise the background section or delete this segment altogether, considering it is not clear how the statements about CATIE results are related to the current analysis/manuscript.

Given the substantial modifications we have made to the Introduction in response to other comments received from both reviewers, we believe that this point is now moot, and we therefore have taken no further action.

6. Please revise the last sentence (bottom of page 3) which states the CATIE results …“suggest that patients with schizophrenia discontinue therapy at a high rate regardless of the agent received, due to lack of efficacy and/or intolerable side effects.” Although CATIE indeed found a high rate of discontinuation for any cause, the time to all-cause medication discontinuation (the study’s primary outcome measure) ranged widely from 9.2 months (olanzapine) to 3.5 months (ziprasidone). Longer time on the medication is a clinically meaningful outcome, as it was repeatedly found – in CATIE and other studies - to be linked to better clinical and functional outcomes (Davis SM, Stroup TS, Koch GG, et al. Stat Biopharm Res. 2011;3(2):253-265; Liu-Seifert H, Osuntokun OO, Feldman PD. Compr Psychiatry. 2011 Feb 8 [Epub ahead of print]; Liu-Seifert H, Adams DH, Kinon BJ. BMC Med. 2005;3:21; Dunayevich E, Ascher-Svanum H, Zhao F. J Clin Psychiatry. 2007;68(8):1163-1171).

We have deleted this sentence from the manuscript.

7. Methods. This information needs to be incorporated in the Background, if you opt to keep the CATIE in it.

We are unsure of the intent underlying this comment. As noted in our responses to Comments #4 - #6, we have made substantial modifications to the Background section of our manuscript. No further action has been taken on this comment.

8. Study sample: It appears the analysis included patients who “received oral ziprasidone, aripiprazole or quetiapine on their day of hospital discharge or the immediately preceding one.” Please clarify if these patients were only receiving the specified antipsychotic drug - monotherapy. If patients were not on antipsychotic monotherapy, then please report in the Results section - for each medication group and by diagnosis (schizophrenia, bipolar) - the proportion of patients who were also treated with olanzapine or risperidone at the time of discharge or the prior day.
We have added the number of patients who received olanzapine or risperidone during the “qualifying” admission to the Results section of our manuscript, as requested; we also have added the number of patients who received other antipsychotics (e.g., haloperidol, mesoridazine, trifluoperazine) during their qualifying admission.

9. The authors report (page 6) that levels of healthcare utilization and cost during the 6 months pre-admission were examined. Please add this pertinent information to Table 2.

Table 2 currently reports all pre-admission measures of healthcare utilization and cost that we examined (i.e., antipsychotics, other psychotropic medications, total healthcare costs). We have revised the Methods section to explicitly state which variables were examined during the pre-admission period.

10. Please clarify if the adherence parameters (MPR, CMGs) were calculated on a uniform follow-up period for all patients (e.g., 6 months post discharge).

MPRs and CMGs were calculated using a uniform follow-up period for all patients (i.e., 183 days [6 months]); we have clarified this point in the Methods section of our manuscript, as requested.

11. The authors are using a unique database that links health insurance claims and hospital admission records, but the current report could have been based on any other claims database in the US - due to the focus on resource use and costs in the 6 months post discharge. Please provide unique information, including as the cost of patients’ index hospitalization by diagnosis, the mean hospitalized duration by diagnosis, and the duration of treatment with the studied antipsychotics prior to hospital discharge.

We respectfully disagree with the Reviewer’s comment. Specifically, while the outcomes of interest could have been examined in various US healthcare claims databases, the method by which we selected the study sample (i.e., receipt of oral ziprasidone, aripiprazole, or quetiapine on the day of hospital discharge or the immediately preceding one) could only be undertaken using a database that provided information on medications received on an outpatient basis as well as in hospital. Our study therefore could not have been undertaken with a traditional healthcare claims database. As noted in our response to Comment #8 from Reviewer #2, we have added information on the extent to which patients received other antipsychotic medications during their “qualifying” index admissions; we also have added to the Results section information on the cost of the index admission (mean [SD] cost = $6512 [$7666] for patients in the schizophrenia cohort; $6663 [$8900] for patients in the bipolar cohort) and duration of therapy with the three antipsychotics of interest during this admission (7.8 [6.0] days and 4.6 [4.3] days, respectively)

12. Minor Essential revisions: The authors claim (page 4) that “the relationship between treatment tolerability and persistency has not been well documented in the literature” citing Cramer et al 2008. However, Cramer et al did not state it. Please provide a supporting reference.
Upon review, the sentence was incorrect; tolerability has a well-established relationship with persistency. We apologize for the error, and we have modified our manuscript accordingly.

Editorial Requests

1. Ethics- Please confirm if ethical approval was obtained for this study. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/en/30publications/10policies/b3/index.html), and any experimental research on animals must follow internationally recognized guidelines. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

Our research involved retrospective analyses of an electronic healthcare claims database in which all patient-identifying information had been either encrypted or removed. Since the database was fully de-identified and our research was entirely retrospective, ethical approval was neither required nor sought.

We thank you again for your interest in our manuscript. Please feel free to contact me if you have any additional questions or concerns. My colleagues and I look forward to hearing from you soon.

Sincerely,

Ariel Berger, M.P.H.