Author's response to reviews

Title: Healthcare utilization and costs in patients with schizophrenia or bipolar disorder receiving aripiprazole, quetiapine, or ziprasidone at hospital discharge: A retrospective cohort study

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Author's response to reviews: see over
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Emily Crow, Ph.D.
Editor
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Dear Dr. Crow:

My colleagues and I wish to thank you for your continued 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"). We have revised our manuscript based on the additional comments that we received, as follows:

**Reviewer 1 (Carolyn Dewa)**

1. The authors have attempted to address most of the comments. However, it would be useful if they could elaborate further on why they chose to the three SGAs (sic). They indicate “We focused attention on these three SGAs as none of them are currently available as generic products (quetiapine and ziprasidone were included in the CATIE).” Specifically, what are the implications for these facts? How do the results of this study contribute to the existing literature? Isn’t lack of adherence to medication an established problem?

   We chose what we believed to be a relatively homogenous group of SGAs, and that are distinguished from the other two SGAs—risperidone and olanzapine—by their relatively favorable adverse event profiles. Specifically, olanzapine is associated with a much higher incidence of weight gain, and risperidone has a higher incidence of extrapyramidal symptoms (EPS) (Treatment Guidelines from *The Medical Letter* 2006). Olanzapine also was reported to be superior in efficacy to other SGAs in the CATIE trial. Despite the relatively benign adverse effect profiles of the SGAs we chose to study (i.e., quetiapine, aripiprazole, ziprasidone), our results suggest that adherence is not substantially better with these agents than with other SGAs (e.g., rates of discontinuation in the Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE] study ranged from 64% [olanzapine] to 82% [quetiapine] [Swartz 2008]). Although there have been a number of studies that have examined adherence with SGAs, few studies (cited in the Discussion section) have examined adherence among patients post-discharge, during which adherence would seem to be of particular importance.

The authors have added a more detailed description of their sample. In addition, for clarity, the authors could add a diagram that shows the number of cases that were dropped for each of their exclusion criteria.

As requested, we have added a diagram to our manuscript.

2. In the Discussion section, the authors talk about adherence. However, they do not spend much time discussing their cost results. Instead, they refer to utilization of services. A bit more of the relationship between these two outcomes would be interesting.

Prior research in both schizophrenia and bipolar disorder has established an inverse correlation between levels of adherence with antipsychotic medications and risk of relapse and healthcare costs, respectively (Ascher-Svanum 2010, Joyce 2005, Eaddy 2005a, Eaddy 2005b, Gilmer 2004, Hong 2011, Hassan 2009, Marcus 2008, Sun 2007, Becker 2007, Knapp 2004, Thieda 2003, Li 2002). Unfortunately, the small numbers of patients in our study sample (linkage between the two databases used in our study was possible for only 43 patients with schizophrenia and 84 patients with bipolar disorder) coupled with the relatively short duration of follow-up (6 months) precluded a formal analysis of the relationship between adherence and healthcare costs. No further action has been taken on this comment.


1. The title of the manuscript 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. The authors indicated they have “modified the title of our manuscript, as requested.” However, the title reads as before.

   We apologize for the misunderstanding. We modified our original title, adding the phrase, “a retrospective cohort study”. As requested, we have further modified the title to reflect the fact we focused attention exclusively on aripiprazole, quetiapine, and ziprasidone.

2. The Background section now provides a rational (sic) for the study’s focus on only 3 atypicals (quetiapine, aripiprazole or ziprasidone). Please add a study limitation indicating that although the current analysis focused on the three second generation antipsychotics not currently available generically in the US (i.e., quetiapine, aripiprazole, ziprasidone), two other frequently used second generation antipsychotics were excluded (i.e., olanzapine, risperidone) although they were branded (not generic) during the 8-year study period (Jan 1, 2001 – Sept 30, 2008).

   We have added the requested limitation to our Discussion section.

3. The discussion section indicates that patients are “sometimes discharged from hospital with a small supply (e.g., 3 days) of medication to insure continual use of needed treatment until they can fill prescriptions for such therapies at outpatient (i.e., retail) pharmacies.” Please clarify, using JCAHO Standards, the recommended number of days supply of medication for psychiatric patients at the time of psychiatric hospital discharge. It is very likely higher than 3 days. This is an important point that should be elaborated in the manuscript. Please clarify if the Medstat Marketscan® Hospital Drug Data captures the “supply” medications type and their duration at the time of discharge. If not, this should be noted as a study limitation, as compliance calculations may not be accurate due to lack of information about the days supply at the time of discharge. If this is captured, please add this information to the Methods section and to the Discussion (as a study strength).

   We are unaware of any JCAHO (current name “The Joint Commission” [TJC]) standards concerning the amount of antipsychotic medication that patients should be given at hospital discharge. (There are, however, TJC standards with respect to the number of antipsychotic medications patients should receive at discharge, as well as the maximum number of days that should elapse before documentation of discharge medications is transmitted to the next level of care provider [5 days]) (The Joint Commission 2012). We cited 3 therapy-days as an example, but patients may receive more. Unfortunately, the database does not provide information on medications patients are given at
hospital discharge. We thought this was implicit in our Discussion, but we have now made it explicit. Our Discussion already states that "our reliance on therapy-days as noted on paid claims from retail pharmacies may understate the amount of medication actually taken."


4. It appears that 26% of schizophrenia patients (11 of 43) were rehospitalized at least once for schizophrenia during the 6 month follow-up. Please clarify if the compliance measures incorporated data on antipsychotic medication these patients received during their rehospitalizations. If not – why not (as the Medstat Marketscan® Hospital Drug Data captures medication use during hospitalizations). If not – please add this as a study limitation. If yes – identify this as study strength.

The compliance measures we used included information on all antipsychotic medication received during follow-up (i.e., time out of hospital plus time in hospital due to readmission[s]). We have added text to both the Methods and Discussion sections to clarify this point and note it as a study strength.

Editorial Requests

1. Thank you for addressing our concerns about ethical approval in your cover letter. We ask that you please insert this statement into the Methods section of the manuscript.

   We have inserted this statement into the Methods section of our manuscript, as requested.

2. Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

   We have reviewed the manuscript and made the appropriate revisions.

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.