Author's response to reviews

Title: Patterns of Initiation of Second Generation Antipsychotics for Bipolar Disorder: A Month-by-Month Analysis of Provider Behavior

Authors:

Christopher J Miller (christopher.miller8@va.gov)
Mingfei Li (mli@bentley.edu)
Robert B Penfold (penfold.r@ghc.org)
Austin F Lee (fong@bu.edu)
Eric G Smith (eric.smith5@va.gov)
David N Osser (david.osser@va.gov)
Laura Bajor (laura.bajor@va.gov)
Mark S Bauer (mark.bauer@va.gov)

Version: 3 Date: 3 November 2014

Author's response to reviews: see over
Response to Reviewer Critiques

We thank the reviewers for their thoughtful comments and edits to our manuscript, and were pleased to see that they were enthusiastic about the paper’s quality, relevance, and impact. We think that incorporating the edits outlined below strengthens the paper significantly, and we hope that these changes will satisfactorily address all of the reviewer comments.

Reviewer 1

1) “The manuscript is concerned with a very important question, namely what variables influence clinical decision making regarding prescription of SGA. It uses data from the well-known large VA database. However, I have several concerns: Overall the fact that some of the SGA are recommended by up-to-date international guidelines as one of the first choice options in mania and bipolar depression is not really mentioned but could explain that the prescription frequency raised within the last years.”

We have added text and two references to recent treatment guideline reviews in the introduction (page 3, first paragraph of the background section). This new material indicates as requested that treatment guidelines suggest SGAs as frontline treatments for some patients with bipolar disorder. We have added similar material early in the discussion (page 11, first paragraph of the discussion), acknowledging that these more recent guidelines may in part be driving our findings.

2) “The abstract does not really report the primary outcomes in a balanced way. The study was interested in variables influence clinical decision making regarding prescription of SGA. However, the results on demographic and clinical variables with significant influence are not mentioned in the abstract (e.g., psychotic features, anti-manic prescriptions). In the abstract, the focus is on the doubling of prescription frequency, even so in the main text it is mentioned that also cases of bipolar disorder raised significantly and that overall there is even a slight decrease in the annual prescription odds. And in the abstract there is mentioned that prescriptions were widened to less complex cases, a fact that I could hardly find validly shown in the results section. The regional differences found were not as large in figures than one could suggest from the highlighting in the abstract.”

We thank the reviewer for bringing these important issues to our attention, and have addressed them as follows:

§ Regarding the mismatch between the abstract and the results/discussion: as suggested, we have rewritten the abstract to present a more balanced report of our findings. This has involved tempering our presentation of increases in SGA use as well as geographic differences. In parallel, we have reduced our emphasis on geographic differences in the discussion (now covered without its own heading on page 13, right before the limitations). Furthermore, we have rearranged the results section of the abstract to
emphasize the modest size of the associations between comorbidities and overall SGA initiation.

§ Regarding the spread of SGA initiation to less severe populations, we have added clarification in the Results (page 10, section entitled “The Role of Clinical Complexity in SGA Initiation Rates over Time”) to make more tentative our interpretations in the discussion (page 12, section entitled “SGA Initiation Spreading to Less Clinically Complex Cases”).

3) “There are errors in the description of the years and numbers included etc.: in the abstract fiscal years 2003-2010 are mentioned, in the title and one figure (2) only 2004-2010 are mentioned. The number of patients without prior SGA use is 133,510 in the abstract and 113,510 in the text.”

Thank you for pointing out these inconsistencies. Regarding the discrepancies in fiscal years, our overall data collection spanned FY2003-2010. Our primary analyses required a 6-month washout period to label any patient as an SGA initiator, however, meaning that it was not possible to qualify as an SGA initiator until halfway through FY2003 (6 months into our data collection). Thus, we had originally included the FY2004 in the title and the note for Figure 2 (page 16) in acknowledgment of the fact that our primary analyses did not span all of FY2003. In order to reduce confusion, we have removed the “2004-2010” from the title of the manuscript. We will retain the 2004-2010 time frame for Figure 2, however, and hope that the note to be included beneath Figure 2 will make the reasoning behind the 2004-2010 time frame clear.

Regarding our total sample size, we thank the reviewer for catching our mistake: while a total of 113,510 patients received an SGA prescription during the study period (many of whom received these drugs for issues other than bipolar disorder), our primary analytic sample—consisting of patients eligible for our definition of “SGA initiation” for their bipolar disorder whether they ended up receiving an SGA or not—was 126,556. We have clarified these numbers throughout the document, including the abstract, methods (middle of page 4), and results (top of page 8 and top of page 9).

Reviewer 2

4) “In the methods section, clinical course variables, I found intriguing how the authors chose 10% to classify somebody as bipolar I. Even if sensitivity analysis showed that 30% was no different from 10% I still consider that a low cutoff. I would have liked to see a cutoff of at least 50%, that way one could at least say that most times than not (>50%) patients were classified as bipolar I.”

The reviewer raises an important point, and in our a priori analysis development discussions we wrestled with how to differentiate bipolar I versus bipolar II/NOS. We originally conducted a sensitivity analysis comparing 10% to 30% cut-off and at the reviewer’s suggestion have now extended the cutoff to >50% bipolar type I diagnoses to qualify. We found the following:

§ 57,654 patients met our original bipolar I cutoff (>10% of diagnoses)
§ 53,986 patients met the suggested bipolar I cutoff (>50% of diagnoses)
Thus, only 6% of patients originally labeled as bipolar type I would be reclassified as bipolar type II/NOS based on this more stringent cutoff.

We have therefore retained the 10% cutoff as in our original analyses, but have noted that we varied our sensitivity analysis from 10-50% revealing little change in proportions of bipolar I versus II/NOS (page 6, section entitled “Clinical Course Variables”).

5) “I would have liked to see more data (demographics, education, academic interests) from the “practitioners at risk” and their role in the outcome measures. Perhaps, the type of practitioner could have been entered as a variable in the regression model (psychiatrists vs. advanced nurse practitioners vs. general practitioners, etc).”

We agree that provider-level variables would be of interest to many readers (including ourselves!). We are in the beginning stages of merging patient and provider data analyses, and felt that the current report would be substantive even without the latter. However, we have added this to the limitations section, suggesting this as a future direction (page 14, just before the conclusions).

6) In the “Other factors related to SGA initiation” (Discussion section), the phrase “future studies including race-by-time interactions may be warranted” is not clear. It would be better to say that future studies should consider including race by time interaction terms in their statistical analysis.

We have clarified the wording of this sentence as requested (bottom of page 12).

Reviewer 3

7) “One limitation of the study is the lack of comparison with lithium (as reference treatment) that could provide better insight of differences in factors associated with SGA. It is not clear if all treatments for bipolar disorder are more prescribe or not. It is not clear if patients who benefit of SGA would be benefited in the past of lithium, other mood stabilizers or antidepressant. Detailed about this limitation could be added in discussion.”

This is an excellent point, and we have added it to the limitations (page 14, just before the conclusions).