Author’s response to reviews

Title: Trends in hospital admissions due to antidepressant-related adverse drug events from 2001 to 2011 in the U.S.

Authors:

Harish Parihar (harishparihar@hotmail.com) (harishpa@pcom.edu)

Hongjun Yin (hongjunyin@yahoo.com)

Jennifer Gooch (jennifergooch@pcom.edu)

Shari Allen (sharial@pcom.edu)

Samuel John (samueljo@pcom.edu)

Jianwei Xuan (jwx02467@gmail.com)

Version: 1 Date: 24 Jun 2016

Author’s response to reviews:

Cover Letter:

Dear Editor:

We have revised the manuscript as per reviewer comments and suggestions. We have addressed each and every comment made by all reviewers. Please note point by point summary of all the revisions below:

Reviewer reports:

Reviewer #1: This is a well-written manuscript for an interesting research that is of clinical value to those practicing in mental health. Overall, I think the research methods used and the results obtain area adequate. I have provided various recommended edits mainly to improve the readability of the manuscript, please read all the sticky notes embedded throughout the attached revised article, some of which are summarized below:

Response: Thanks. I have addressed (accepted) all sticky note comments in the PDF file and revised accordingly.

Page 3: I recommend to remove the last sentence in the conclusions section of the abstract, this is best included under the overall discussion of the findings and possible future research implications.
Response: Revised as per suggestion

Page 5: The section on Identification of ArADE-caused admissions needs attention. The definition for ADEs is slightly different that the one provided in the Introduction, which needs clarification.

Response: Revised as per suggestion

Page 6: There are sections in the results that should have been included in the methods section. I have highlighted these within the attached revised manuscript and provided recommendations in the embedded sticky notes.

Response: Revised as per suggestion

Pages 8 and 9: To simplify some of the findings and reporting them in the Results section, I suggest reporting only the findings that were statistically significant and referring the readers to the tables for more information on the rest of the data that did not show significant differences in the two periods compared.

Response: Revised as per suggestion

Page 9: Under discussion. I recommend to delete the first sentence, this could be used later to explain some of the findings.

Response: Revised as per suggestion

Page 13: Under conclusion. I recommend to delete the last sentence. I think the suggestion of using pharmacist-led med rec/reviews/counseling/follow up is of value, but such a statement should not be introduced in the conclusion without first having been at least proposed and discussed somewhere else in the manuscript. I suggest to add a short paragraph in the discussion section, when talking about future research, or suggesting actions needed to address the increased burden associated with ArADEs as found in this research, and even mention other studies in which pharmacist-led programs have shown to have an impact in reducing over ADEs could be included here.

There are some inconsistencies on how detailed are the legends of the tables, I recommend that the legends for all the tables should be consistent, and use the same abbreviations and icons to explain the results summarized in the tables to avoid confusion.

Response: Revised as per suggestion

Reviewer #2: Reviewers Report

Compulsory Revisions:
Results and Discussion:

* Page 9, when reporting changes in hospital charges, the authors need to disclose in the analysis section how they adjusted for inflation during the 10-year time frame?

Response: The charges are reported in the respective year dollars.

* Please include in the discussion section that the increased incidence of ArADEs might be related to provider awareness about ADE-related conditions. A great deal of evidence has been brought forward since 2001 about the occurrence of ADEs in general. Provider awareness to more appropriately diagnose these related conditions could therefore account for the perceived "higher" incidence.

Response: Revised as per suggestion

Conclusion:

* Page 13, the final line of this section states, "One such area of great significance could be the utilization of pharmacist led medication reconciliation, medication review, counseling, and follow up." This assertion requires further description with appropriate citations, perhaps in the discussion section or included as a separate, Implications for Practice section. Since the assertion is included in the abstract, the reader is led to believe that the relationship between a pharmacist led intervention and reducing the incidence ArADE might be more saliently discussed within the manuscript.

Response: Revised as per suggestion

Discretionary Revisions:

Background: Page 3, Line 19 Consider the term mental "health" disorder in lieu of mental disorder throughout the manuscript.

Response: Revised as per suggestion

Reviewer #3: BHSR-D-15-00066

This mss. reports on a topic of interest to clinical and research communities on the risks associated with antidepressant use. The data source is HCUP national data on hospital admissions according to ICD-9 codes for antidepressant-related adverse drug events. The main outcome is trend in ArADE-related hospital admissions across 11 years and further broken down according to patient age group, gender, neighborhood median income and hospital region (urban/rural). Among the admissions, mean and median LOS data are shown by age group and mean and median hospital charges.
There are considerable strengths to the findings. However, they could be presented in a simpler fashion. There are 6 tables; perhaps, 2-4 can be combined and 1, 5 and 6 can be combined. These would show columns as study year above age groups and then the rows would be the covariates of interest (gender, neighborhood income and hospital region, for example.

Response: Thank you for the comments. I assume these were discretionary revisions, however, I tried my best to combine tables. However, it was not easy to combine the tables as for example, Table 1 provides change by Age, however, table 2 provides changes by Age and gender. It is important to view the change by overall Age (as in table 1). Then, table 2 provides distinction in terms of males and females. I assume providing separate table clarifies the information and is better in terms of width of the tables and information provided. However, if the reviewer and/or editor would like us to combine tables in order for better publishing I would be happy to try again.

Not sure why means and medians are needed for LOS and charges—medians are usually important for these typically skewed data.

Response: Our understanding is that more information is better for clarification of data for the reader. The combined information of Mean and standard deviation proposes a non-parametric or skewed data. This is further confirmed by viewing the median value. Hence, all data are provided. Also, please note that as explained in the statistical analysis section, appropriate statistical procedure (by transforming the skewed variables by taking the square root before conducting statistical tests) were performed. I would be happy to remove the mean values if the reviewer/editor so desires, however, these are required for understanding the statistical tests and overall data distribution.

Finally and most important is the rationale for both change in absolute numbers and change in rate which is not well explained and not understandable from the data on the tables. In table 1, showing the change in admissions followed by change in rate is excessive. It is sufficient to show the change in rate and easier for a clinically oriented researcher to appreciate the change. Same for tables 2-4.

Response: To clarify, rate for 2001 and 2011 is calculated based on the total number of admissions of the respective year. This is important since the base number of total (all) ADE admissions is different for the two years. So, it is better to compare the percentage change as opposed to just the change in rate because of difference in the baseline. We accept this comment that these two numbers may cause more confusion to the reader, hence we have deleted the rates and in the revised manuscript are only presenting the percentage rate change with 2001 as base.

Abstract. I would suggest removing the last sentence from the abstract. Leaving it in the text is fine but as part of the abstract it is quite a leap from these population-based data to pharmacist-led improvements in the use and quality of ATD care.

Response: Revised as per suggestions.
Problematic use of the term 'antidepressant-caused ADEs, (ArADEs)—'cause' is a big word which is better reported as antidepressant-related as the 'r' in ArADEs suggests. Many of these cases may involve polypharmacy, excessive or accidental dosage and other preventable problems—hence, prescriber/patient error problems.

Response: Revised as per suggestions.

Limitations. The simplifying of the quartile data is not discussed re whether lumping bottom half with top half dilutes the differences in the subgroups.

Response: Yes, I agree that there is such a limitation. But if we use more categories, there will not be sufficient sample size in some categories for certain analysis. Also the current categorization is fine to answer the major research