Author’s response to reviews

Title: The Research and Evaluation of Antipsychotic Treatment in Community Behavioral Health Organizations, Outcomes (REACH-OUT) Study: Real-World Clinical Practice in Schizophrenia

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Ursula Franziska Bailer, MD
BMC Psychiatry

Dear Dr. Bailer,

My co-authors and I would like to thank the reviewers for their comments on our manuscript, “The Research and Evaluation of Antipsychotic Treatment in Community Behavioral Health Organizations, Outcomes (REACH-OUT) Study: Real-World Clinical Practice in Schizophrenia,” which was recently submitted to BMC Psychiatry.

We have revised the manuscript based on the reviewers’ recommendations and have provided a detailed description of the modifications on the following pages. Please note that all page numbers refer to the changes-visible version of the manuscript.
We hope that you approve of this revised manuscript and we look forward to your response. Thank you for your time and attention.

Best regards,

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Reviewer 1

The manuscript "The Research and Evaluation of Antipsychotic Treatment in Community Behavioral Health Organizations, Outcomes (REACH-OUT) Study: Real-World Clinical Practice in Schizophrenia" deals with the important issue of evaluating health care resource utilization in patients with mental illness treated at outpatients facilities, such as community behavioral health organizations (CBHOs) across the United States. The main objective of the study was to provide a holistic picture of schizophrenia treatment practices in the community setting to health care providers, researchers, policy makers, and other stakeholders.

The data of the study suggest differences in the patient characteristics, treatment patterns, and clinical and economic outcomes among patients with schizophrenia treated with long-acting injectable antipsychotics or oral antipsychotics.
The manuscript is well written, the data presented are interesting and important. The study could contribute to establish treatment patterns that might reduce relapse rates and improve treatment outcome in patients with schizophrenia and bipolar disorder.

The strength of the study is the number of the patients included and that the patients were followed up prospectively for 12 month.

There are two major shortcomings in this manuscript:

1. No information is given about how the diagnosis was assessed. Were the patients diagnosed by DSM-IV, DSM-IV-TR, SCID, MINI, ICD-10?

Authors’ response: We thank the reviewer for this comment. Diagnosis was determined using the DSM-IV Axis I codes 2.95.1x, 2x, 3x, 6x, and 9x for schizophrenia and Axis I codes 296.0x, 4x, 5x, 6x, and 7 for bipolar disorder. We have revised the Methods section accordingly (page 7).

2. The article compares the group of patients that received oral antipsychotics with the group receiving depot medication. This comparison is highly interesting, but it seems that the decision to allocate a patient is depending from the actual availability of a substance as depot formulation. If a physician decides for a therapy with risperidone there is a clear choice between oral risperidone and risperidone LAI. If a physician decides for a therapy with clozapine there is no alternative to the oral application. In addition to the analysis that has already been performed, we suggest to analyze the data using the following groups:

   a. oral antipsychotic (only oral availability of this substance, e.g. clozapine) vs.

   b. oral antipsychotic (the substance is available as depot, e.g. oral risperidone) vs.

   c. depot antipsychotic.
Authors’ response: We thank the reviewer for this interesting suggestion. The objective of the study was to describe baseline characteristics of patients, not report outcomes. Therefore, the protocol was not designed to address this question, and the data were not collected in a manner that would allow us to conduct this analysis. Additionally, we do not have information on why physicians selected a particular antipsychotic medication (ie, was the choice based on availability or other factors?). We only recorded what medication a patient was receiving at the time of enrollment and whether they were new users or continuous users of that medication.

Reviewer 2

This study is motivated by an important observation: long-acting injectable antipsychotics (LAI APTs) are underused for schizophrenia in the US compared to other countries. Importantly, when asked, many patients do prefer monthly injections to day-to-day medication self-management - but they might not be asked, depending on prescribers' pre-conceived notions about these preferences. This article investigates the patient characteristics associated with the use of either oral or injectable antipsychotics for schizophrenia in actual clinical practice in the US, and delves into some relevant outcomes associated with these treatments.

1. Background
   a. Presentation of bipolar disorder:

   While I understand that the REACH-OUT study includes bipolar disorder (BD) patients, data presented in this article concerns schizophrenia patients exclusively. Therefore, the presentation of bipolar I disorder (lines 75 to 78) is a source of confusion for the reader. I suggest removing any mentions of BD from the Background section (and removing any references exclusively focused on BD).

Authors’ response: We thank the reviewer for this comment. Bipolar disorder has been removed from the second paragraph of the Background section (page 4) and references 3 and 5 have been deleted (page 23).
b. LAI APT literature:

The authors clearly introduce the potential benefits of LAI APTs in improving treatment adherence. The point is well made by line 97. The additional sentences, starting with "For example" (lines 97 through 106), tend to raise skepticism as to how the individual articles presented were identified and chosen by the authors, especially given their focus on paliperidone. I suggest cutting these two sentences from the article, or at least removing any data on effect sizes from these other studies as they can be confusing for many readers without additional information.

Authors’ response: We thank the reviewer for this comment. The sentences in question have been removed (page 5) as requested.

c. Observational studies:

Throughout this article, the authors, in my humble opinion, undersell the importance of observational studies for clinical practice. Indeed, their utility goes well beyond the representativeness of the patients included in such studies (see Ligthelm et al. 2007, for example). I will expand later in my comments on the Discussion.

Authors’ response: We thank the reviewer for this comment. A statement about the importance of observational studies has been added to the Discussion (page 17).

d. Research objective

Line 130 onward, the authors suggest they subscribe, for this study, to the "fundamental objective of REACHOUT", which is "to provide health care providers, researchers, policy makers, and other stakeholders a holistic picture of schizophrenia treatment practices in community setting". In my opinion, there seems to be an additional motivation specific to this article submitted for publication, which can be made out from the information the authors chose to present throughout the rest of the Background section. My impression is that the discrepancy in prescription rates of LAI APTs between other countries and the US is a central motivation for
this article. By including both patient characteristics and patient outcomes associated with LAI APT use in this study, the authors offer arguments which could be used to promote the targeting of some subpopulations of patients to increase LAI APT prescription. This is an extremely relevant objective from a public mental health perspective, and it would be worth stating this objective explicitly if the authors agree that it was a motivation for this study. Additionally, the authors could offer a greater impression of transparency if they elaborated on the specific objectives of this study, which I consider very important given their financial relationship with Janssen.

Authors’ response: We thank the reviewer for this comment. The objective of this study is correct as stated in the manuscript: to describe real-world usage of oral and LAI APT medications in CBHOs in the United States. Our objective was not to identify subpopulations of patients who could benefit from LAI APT use for the purpose of increasing LAI APT prescriptions. We have revised the text (page 6) to clarify the objectives of the REACH-OUT study.

2. Methods

a. Study population

In the REACH-OUT study, participants could be recruited "within 8 weeks of initiation or switch to RLAI or other APTs, or after >24 weeks of continuous RLAI treatment with no gaps between injections of more than 30 days" (line 157). However, "Patients with schizophrenia were eligible to enter the study at any time after initiation of PP LAI" (line 158). Please explain, if it applies: A. The rationale behind having different inclusion criteria for paliperidone palmitate; B. In the Discussion section, the possible impact of such differences on the patient profiles and outcomes reported; C. Both in the Methods and Discussion sections, if and how this was taken into account in data analysis, especially in group assignment as a new or continuous user; D. If the authors consider this a caveat of the REACH-OUT study, and elaborate on this limitation in the discussion section; E. I might also be missing something in the distinction between the REACH-OUT inclusion criteria and data specifically included in the reported analyses, in which case please make this distinction more obvious (for example, is Figure 1 only the REACH-OUT study or does it also show which data was included in this article's analyses?)

Authors’ response: We thank the reviewer for these comments. PP LAI was launched in the United States in July 2009, and REACH-OUT was conducted between August 2010 and
November 2013. Given the low utilization of LAI at the time of enrollment, the study team expanded the enrollment for PP LAI by including patients who initiated PP LAI in the 8 weeks prior to or on the day of enrollment and by including those who were on continuous PP LAI for any time period prior to enrollment. The Methods have been revised (page 8) and the Discussion has been modified (pages 18-19) to address this point. Figure 1 depicts the REACH-OUT study design; paragraph 1 of the Results section (page 11) describes which patients were included in this analysis: “This article describes the characteristics and outcomes of patients with schizophrenia at enrollment and at the 12-month follow-up visit.”

b. Data analysis

This article includes a "Statistical Methods" subsection, but there are some wider data analysis issues to consider. Lines 161 through 165 explain how patients were divided according to their new or continuous user status. Yet data on oral APT users don't seem to be analysed by subgroup. Moreover, no distinction is made according to the specific APT treatment received orally, which doesn't allow the reader to have any idea about the oral APT molecules used in this cohort. The number of oral APT users might be insufficient to analyse the impact of specific treatment options, but information as to the makeup of oral APT treatments in this cohort should be expanded for the reader's benefit. (For data on the real-world association between specific antipsychotics and relevant outcomes, see for example Vanasse et al. 2016)

Authors’ response: We thank the reviewer for this comment. The types of oral APTs used by patients were not collected. By definition, all patients who were using oral APTs were new users. The Study Population section has been modified (page 8) to clarify the study population definitions.

3. Results

a. Table 1

The inclusion of bipolar disorder patients in this table doesn't seem relevant to this study, as per comment 1.1. I would suggest removing that part of the table. Mentioning BD in the first paragraph of the Results section, to situate this study within REACH-OUT, is enough in my opinion.
Authors’ response: We thank the reviewer for this suggestion. Bipolar patient data have been removed from Table 1 but retained in the Patient Disposition section (pages 10-11).

b. Other tables

Table 2: Authors compare LAI APT Total, New Users and Continuous Users each with the lot of oral ATP users. From my understanding of the results presented, it would make sense to compare: A. Total LAI vs Total oral; B. New LAI vs New Oral; C. Continuous LAI vs Continuous Oral; D. New LAI vs Continuous LAI; or E. New oral vs Continuous Oral. These are the comparisons where group membership is mutually exclusive and only one independent variable is known to differ. Using only the data included in Table 2, the authors could show the numbers and percentages similarly, but only statistically compare New vs Continuous LAI users, and Total LAI vs Oral APT. Table 2 is also quite long. Since all the relevant information is included, p-values can be calculated by the reader and don't need to be spelled-out exactly, a symbol could be used instead to make the table easier to read (e.g. * if p < 0.05, ** if p < 0.001).

Table 3: See Table 2, the same problem arises of comparison between hardly comparable groups.

Table 4: I have no issue with this table, nor with the additional tables, which don't report statistical comparison between groups.

Authors’ response: We thank the reviewer for this comment. Please see our response to point 2b above. All patients in the oral APT group were considered new users per protocol. Only patients in the LAI APT group were classified as new users and continuous users. All treatment arms were compared to oral APT; no new user versus continuous user comparisons were done. We have revised the Discussion (page 18) to clarify this issue.

c. Comparison between groups

The same issue is present in the results reported as text. The comparison between Total oral ATP users and diverse subgroups of LAI ATP users seems hard to justify, conceptually. To give an example, I explained in comment 1.4 that I'm under the impression that the authors were interested in characteristics associated with underprescription of LAI ATP. The most relevant comparison to answer that question would be between new oral ATP and new LAI ATP users, which would allow to compare two groups representing patients with a relatively new ATP, which could be either oral or LAI depending on hypothesized caused x or y. The independent
variables associated with belonging to one group or the other could then be considered conceptually related to prescription patterns in real-life situations. If it is not possible to isolate new oral ATP users, then only comparing Total oral vs Total LAI, and New LAI vs Continuous LAI would also allow a deeper interpretation of the results of this study.

Authors’ response: Please see our response to point 3b above. All patients receiving oral APT were new users. New user and continuous user groups were established in the LAI APT group to enhance enrollment of patients using LAI APT, given the low use of LAI APTs in the US market.

4. Discussion. A lot of information is presented in the Results section of this article, which makes a solid Discussion essential for the understanding of more time-pressed readers.

a. Recruitment vs data

In the first paragraph of the Discussion section, lines 358 to 367, the authors draw a general picture of the differences between LAI and oral APT users in this study. They write (line 360) "At enrollment, approximately two-thirds of patients were receiving LAI APT and approximately one-third were receiving oral APT." Superficially, this sentence sounds as if two-thirds of patients in the larger schizophrenia population are receiving LAI APT, while this fraction is a consequence of the design of the REACH-OUT study. It would seem more accurate to say that twice as much patients with LAI APT were recruited compared to oral APT patients.

Authors’ response: We thank the reviewer for this comment. The statement in question has been revised (page 17) to clarify that the proportion of patients in REACH-OUT receiving oral APT and LAI APT was influenced by study design.

b. New vs continuous LAI APT users
Line 363, the authors write that "New and continuous users of LAI APT had similar characteristics in general." This conclusion doesn't seem obvious to me, as these two groups were compared to Total oral users instead of to each other.

Authors’ response: We thank the reviewer for this comment. The sentence in question has been removed (page 17).

c. Scope of the discussion

Apart from this first paragraph, the Discussion section is relatively short and conservative, limited in scope. In my opinion, the authors could afford to be less so if they changed data analysis design, especially the way they selected the groups to compare statistically.

Authors’ response: We thank the reviewer for this comment and suggestion. However, additional data analyses are beyond the scope of this manuscript.

d. In this article, the authors decided to look simultaneously at various issues in community patients treated for schizophrenia: LAI vs oral antipsychotic use, new vs continuous LAI use, patient characteristics, service utilization, and patient-reported outcomes. The stated objective is quite wide. In my opinion, this article would benefit if the authors considered the stated objective as an over-arching aim, which could be divided into narrower, more focused objectives which would be directly linked with methodological decisions. I would expect the threads of such objectives, identifiable throughout the article, to help flesh out a discussion that is currently very sober. References: Ligthelm, R.J. et al., 2007. Commentary: Importance of Observational Studies in Clinical Practice. Clinical Therapeutics, 29(Theme Issue), pp.1284-1292. Vanasse, A. et al., 2016. Comparative effectiveness and safety of antipsychotic drugs in schizophrenia treatment: a real-world observational study. Acta Psychiatr Scand, 134(5), pp.374-384.

Authors’ response: We thank the reviewer for suggesting the Ligthelm et al and Vanasse et al articles, which have been added to the references (page 29). A statement about the importance of observational studies has been added (page 17).