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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Reviewer: Jean-Daniel Carrier

Reviewer's report:

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

1.1. 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).

1.2. 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.
1.3. 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.

1.4. Research objective

Line 130 onward, the authors suggest they subscribe, for this study, to the "fundamental objective of REACH-OUT", 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.

2. Methods

2.1. 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?)
2.2. 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)

3. Results

3.1. 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.

3.2. 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.
3.3. 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.

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.

4.1. 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.

4.2. 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.

4.3. 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.
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:


Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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