PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

A retrospective cohort study of long-acting injectable (LAI) antipsychotic initiation in the inpatient setting: impact of LAI characteristics on transition and continuation of care among patients with schizophrenia in the United States

Authors

Patel, Rashmi; Liman, Christian; Oyesanya, Mayowa; Ker, Sheryl; Jayaraman, Aishwarya; Franzenburg, Kelli R.; Hansen, Rolf T.; Philbin, Mike J.; Thompson, Stephen

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Jakobsen, Michelle Iris**
Affiliation	**Psychiatric Services Region Zealand East**
Date	**11-Nov-2024**
COI	**None**

The authors have conducted a classic retrospective data analysis, and they have reported thoroughly on their results and applied methods. The authors have disclaimed the limitations of their study and they have discussed the issues that come to mind when reading the results; that the increased risk of treatment discontinuation and rehospitalization for patients co-prescribed LAI and OA might be due to a difference in the underlying illness severity with an increased risk of relapse amongst severely ill patients and a need for higher AP doses to reach an adequate response or, due to an increased risk of adverse side effects with the LAI-OA combination due to higher plasma concentrations of AP - and thereby and increased risk of treatment discontinuation. It could also be a combination of the two and the authors should add this option as well. Overall, it is a good manuscript.

However, I do have some comments that I feel could improve the reporting of the study:

1) To strengthen the discussion and conclusion sections the authors should more thoroughly discuss the reported clinical practice of AP polypharmacy and high dose prescribing beyond the LAI initiation phase as opposed to guideline recommend practice. This practice is not

supported by guidelines, at least until clozapine has been trialed, and, as these findings underline, it does not seem to benefit the patients.

2) Patients who discontinued treatment but were re-hospitalized and then re-commenced within the allowed two injection periods would not be counted as discontinued – would they? This could potentially underestimate the fraction of patients who discontinued treatment and hence influence the difference between discontinuations in the LAI+OA group vs the LAI alone group. Furthermore, it seems that most patients had less than 12 months post-discharge data and were excluded from analysis? It would have been interesting to know how many patients who discontinued treatment within these first months and the distribution in terms of LAI+OA and LAI alone prescriptions. Leaving out so many patients could potentially bias the analysis. Why not include patients with 3 months post discharge data as in the transition of care analyses? These issues should be addressed.

3) In the results section, table 2, the authors have provided the mean, SD and median for the same variable. Why? It is not wrong per se, but since the only symmetric variable is "CGI-S at admission", it would be more appropriate to leave out the means and SDs and provide the median and IQR, and perhaps the full range, for all variables instead. The authors could mention the mean and SD of CGI-scores in the text, at p. 16, where they comment on the CGI-S scores for patients prescribed LAI alone and patients co-prescribed an OA at discharge.

4) There are no figure legends/numbers on the figures…?

5) Abbreviations should be explained the first time they are used. SG AP is used in the abstract and two times in the main text before the explanation on p.12. FG AP is used once prior to the explanation on pa 15.

Reviewer	**2**
Name	**Gadelha, Ary**
Affiliation	**Universidade Federal de São Paulo**
Date	**15-Nov-2024**
COI	**None**

This study investigates long-acting injectable (LAI) antipsychotic prescribing patterns and their associations with transition and continuation of care as well as healthcare resource utilization (HCRU) in a retrospective cohort of patients with schizophrenia in the United States. Data were retrieved from electronic health records of 1,197 patients who initiated an LAI in inpatient settings. Three primary outcome measures were analyzed: transition-of-care, continuation-of-care, and HCRU endpoints.

The results focus on the association between LAI and oral antipsychotics (OA). The conclusion highlights poorer outcomes for the combination of LAI and OA.

The large sample size and real-world nature of the data are strengths of the current work. However, I believe certain aspects require attention to improve the interpretation and generalizability of the results:

Abstract

• The primary outcomes are clearly stated before the results. However, the results section does not clearly address them, focusing instead on co-prescription with oral antipsychotics. I suggest revising this part to focus on the results and discussion of the primary outcomes.

Introduction

• The authors do not reference some relevant "mirror studies" that could provide context for understanding the role of LAIs and transition/continuation of care.

• At the last sentence of this section, please clarify whether the outcomes mentioned are primary or secondary.

Methods

• Please specify the period during which data were collected.

Results

• A figure summarizing the sample characteristics and outcomes could help readers better understand the data.

• The relatively low proportion of patients using LAIs should be explicitly highlighted.

• Continuation of Care: A larger proportion of patients co-prescribed OA alongside LAI demonstrated improvements in CGI-S. Did you analyze whether this finding holds when controlling for dose equivalents?

• For the OA+LAI versus LAI-alone groups, did you examine differences in clinical variables such as severity or comorbidity? These could clarify potential confounding factors.

• The primary outcomes seem overly assessed through the perspective of LAI+OA co-prescription. I suggest analyzing the primary outcomes in more detail and highlighting their results. Consider evaluating potential confounders like clinical variables, dose equivalents, and relative potency.

• Regarding LAIs with less frequent administration, did you explore potential confounding factors? If the sample size allows, comparisons within the same LAI group based on administration frequency could be insightful.

Discussion and Conclusion

• What is the main result? Is it the poorer outcomes of OA+LAI co-prescription, or the better outcomes associated with LAIs with less frequent administration? I suggest revising this section to clearly highlight the central findings. It seems that the take-home messages are misaligned throughout the text, from the abstract to the conclusion.

VERSION 1 - AUTHOR RESPONSE

Reviewer 1 comments to the author

The authors have conducted a classic retrospective data analysis, and they have reported thoroughly on their results and applied methods. The authors have disclaimed the limitations of their study and they have discussed the issues that come to mind when reading the results; that the increased risk of treatment discontinuation and rehospitalization for patients co-prescribed LAI and OA might be due to a difference in the underlying illness severity with an increased risk of relapse amongst severely ill patients and a need for higher AP doses to reach an adequate response or, due to an increased risk of adverse side effects with the LAI-OA combination due to higher plasma concentrations of AP - and thereby and increased risk of treatment discontinuation. It could also be a combination of the two and the authors should add this option as well. Overall, it is a good manuscript.

> Author response: Thank you for the feedback. We are glad that you found the results presented here informative. In addition, we have included the following text in the Conclusion to mention the possibility that treatment discontinuation and risk of rehospitalisation could be due to underlying illness severity and risk of adverse events:
>
> > This warrants further exploration to distinguish illness severity from other causes of rehospitalisation (eg, increased side effect burden which could negatively impact treatment adherence and subsequently increase risk of relapse). **Increased risk of rehospitalisation and treatment discontinuation could also be due to a combination of underlying illness severity and subsequent risk of relapse together with increased risk of adverse events (due to higher antipsychotic plasma concentrations).**

However, I do have some comments that I feel could improve the reporting of the study:

1) To strengthen the discussion and conclusion sections the authors should more thoroughly discuss the reported clinical practice of AP polypharmacy and high dose prescribing beyond the LAI initiation phase as opposed to guideline recommend practice. This practice is not supported by guidelines, at least until clozapine has been trialed, and, as these findings underline, it does not seem to benefit the patients.

> Author response: The following text has been added to the first paragraph of the Discussion:
>
> > However, outside of this LAI initiation period, there is limited evidence that co-prescription of an OA with an LAI has increased benefit compared with LAI monotherapy, and the combination of OA and LAI could lead to increased side effect burden and subsequent issues with poor adherence and risk for relapse.[1, 41] **The reported prevalence of AP co-prescription in hospitalised patients ranges from 20% to 66%, and this practice appears to occur primarily with patients with schizophrenia.[42-44] A recent systematic review highlighted the prevalence of AP polypharmacy in mental health disorders (of which 52% were schizophrenia spectrum disorders), which**

has increased significantly from 1970–2023 and was higher among inpatients than outpatients (31% vs 20%, respectively). The review also showed that AP polypharmacy was associated with increased risk of relapse, hospitalisation, worse global functioning and higher risk of adverse events compared to AP monotherapy.[45]

2) Patients who discontinued treatment but were re-hospitalized and then re-commenced within the allowed two injection periods would not be counted as discontinued – would they? This could potentially underestimate the fraction of patients who discontinued treatment and hence influence the difference between discontinuations in the LAI+OA group vs the LAI alone group.

Author response: The reviewer is correct that this situation would not have been considered a complete discontinuation, as a short gap in treatment, as would be observed in this case, could have been due to a number of causes, including nonadherence. We have included the following text in the Limitations section of the Discussion:

> Other limitations of the study are that the classification of the treatment paths was estimated at a population level based on external expert inputs, and therefore, it is difficult to determine the treating clinician's true intention with their prescribing decisions for a specific patient**. Additionally, patients would not be considered to have discontinued LAI if they received doses within the dosing window, regardless of rehospitalisation. This could potentially underestimate the proportion of patients who discontinued treatment and influence the differences in discontinuations between the LAI+OA and LAI-alone group.**

Furthermore, it seems that most patients had less than 12 months post-discharge data and were excluded from analysis? It would have been interesting to know how many patients who discontinued treatment within these first months and the distribution in terms of LAI+OA and LAI alone prescriptions. Leaving out so many patients could potentially bias the analysis. Why not include patients with 3 months post discharge data as in the transition of care analyses? These issues should be addressed.

Author response: The 12-month period post discharge was necessary as it allowed us to establish whether patients completely discontinued treatment or were on treatment at a different healthcare provider or insurer, which is unfortunately not captured in the database. This also enabled us to maintain a sufficient sample size while not biasing our cohort towards patients with very short follow-up (i.e., 3 months). Appropriate adjustments were made to account for follow-up length in analyses of healthcare resource utilisation outcomes.

3) In the results section, table 2, the authors have provided the mean, SD and median for the same variable. Why? It is not wrong per se, but since the only symmetric variable is "CGI-S at admission", it would be more appropriate to leave out the means and SDs and provide the median and IQR, and perhaps the full range, for all variables instead. The authors could mention the mean and SD of CGI-scores in the text, at p. 16, where they comment on the CGI-S scores for patients prescribed LAI alone and patients co-prescribed an OA at discharge.

Author response: For the variables in table 2, we have included the median and IQR in the table, and mentioned the means and SD of the CGI scores in the text of the Results section:

> Of the 1197 total patients, 887 (74%) patients had CGI-S data **(mean score [SD] of 5 [1.0])**, of whom 33.7% were severely ill (CGI-S score 6–7), 61.0% moderately ill (CGI-S score 4–5) and 5.3% mildly ill (CGI-S score 1–3) (**table 2**).

4) There are no figure legends/numbers on the figures…?

Author response: During submission of the manuscript, figure numbers and captions are usually removed and placed separately in the body of the manuscript. Please see at the bottom of the revised manuscript after the references.

5) Abbreviations should be explained the first time they are used. SG AP is used in the abstract and two times in the main text before the explanation on p.12. FG AP is used once prior to the explanation on pa 15.

Author response: Thank you for noticing the discrepancies in the abbreviations. They have been checked and are now spelled out at first use.

Reviewer 2 comments to the author

This study investigates long-acting injectable (LAI) antipsychotic prescribing patterns and their associations with transition and continuation of care as well as healthcare resource utilization (HCRU) in a retrospective cohort of patients with schizophrenia in the United States. Data were retrieved from electronic health records of 1,197 patients who initiated an LAI in inpatient settings. Three primary outcome measures were analyzed: transition-of-care, continuation-of-care, and HCRU endpoints.

The results focus on the association between LAI and oral antipsychotics (OA). The conclusion highlights poorer outcomes for the combination of LAI and OA.

The large sample size and real-world nature of the data are strengths of the current work. However, I believe certain aspects require attention to improve the interpretation and generalizability of the results:

Abstract

• The primary outcomes are clearly stated before the results. However, the results section does not clearly address them, focusing instead on co-prescription with oral antipsychotics. I suggest revising this part to focus on the results and discussion of the primary outcomes.

Author response: The Results section of the abstract has been updated as follows:

> **Of 339 patients with ≥3 months pre- and post-index data, median time to rehospitalisation was 135 days. Patients discharged taking an LAI alone had lower frequency of rehospitalisation (IRR=0.62 [95% CI, 0.46–0.84]), lower risk of longer hospital stays (IRR=0.60 [95% CI, 0.43–0.84]), lower risk of becoming rehospitalised (HR=0.49 [0.35–0.69]), and lower risk of outpatient visits (IRR=0.50 [95% CI, 0.36–0.70]) versus patients co-prescribed an oral antipsychotic (LAI+OA). Patients**

discharged taking an LAI dosed once every 1–2 months or once every 2 weeks had lower frequency of rehospitalisation (IRR=0.85 [95% CI, 0.64–1.14]), lower risk of longer hospital stays (IRR=0.90 [95% CI, 0.70–1.15]) and lower risk of becoming rehospitalised versus an LAI dosed once every 2 weeks; risk of becoming rehospitalised was no different (HR=1.00 [95% CI, 0.76–1.32]) and risk of outpatient visits was greater (IRR=1.25 [95% CI, 0.96–1.63]). During hospitalisation, 73.4% of patients were co-prescribed an oral antipsychotic (OA), most frequently risperidone, with their index LAI. ~~Among the 44.6% of patients co-prescribed an OA at discharge, 74.1% were rehospitalised within 12 months versus 68.5% prescribed an LAI alone.~~

In addition, the following text have been added to the main Results of the manuscript:

Median number of outpatient visits increased from pre-admission to post discharge among patients discharged with an LAI dosed once every 1–2 months (haloperidol, fluphenazine, paliperidone palmitate, aripiprazole and aripiprazole lauroxil) from 0 (interquartile range [IQR], 0–13) to 1 (0–32; p<0.01), whereas there was no increase among patients discharged with an LAI dosed once every 2 weeks (risperidone; 0 [0–7.75] to 0 [0–8]; P=0.08); however, the difference between post-discharge values was not significant (P=0.10). **Patients discharged taking an LAI dosed once every 1–2 months or once every 2 weeks had lower frequency of rehospitalisation (IRR=0.85 [95% CI, 0.64–1.14]), lower risk of longer hospital stays (IRR=0.90 [95% CI, 0.70–1.15]) and lower risk of becoming rehospitalised versus an LAI dosed more often; risk of becoming rehospitalised was no different (HR=1.00 [95% CI, 0.76–1.32]) and risk of outpatient visits was greater (IRR=1.25 [95% CI, 0.96–1.63]).**

Introduction

• The authors do not reference some relevant "mirror studies" that could provide context for understanding the role of LAIs and transition/continuation of care.

Author response: References of additional real-world claims database studies have been included in the Introduction with additional text added before the last paragraph:

Other studies investigating claims databases have also shown that in patients with early diagnosed schizophrenia, LAI use was very low (approximately 4%), and although initiation of LAIs were successfully completed, OAs were generally the first-line therapy.[33] Factors that were predictive of LAI implementation included unsuccessful OA implementation and more monthly schizophrenia-related hospitalisation and emergency room visits.[34] Healthcare resource utilisation (HCRU) and costs were considerably higher for patients who initiated LAIs later in their disease course, with primary costs being emergency department visits and other outpatient visits.[35]

• At the last sentence of this section, please clarify whether the outcomes mentioned are primary or secondary.

Author response: We have revised the final sentence of the Introduction as follows:

This study expands on previous work by investigating healthcare resource utilisation in relation to **primary outcomes consisting of adherence and discontinuation rates**

for LAIs post hospital discharge and secondary outcomes consisting of LAI dosing frequency **and** characterising patterns of OA supplementation. ~~and determining rates of adherence and discontinuation for LAIs post hospital discharge.~~

Methods

• Please specify the period during which data were collected.

Author response: The data collection period of NeuroBlu has been included in the Methods:

This was a retrospective cohort study of adults aged ≥18 years with a schizophrenia diagnosis who initiated LAI treatment during a psychiatric inpatient admission/hospitalisation as recorded in the NeuroBlu Database Version 21R2, a database of EHRs containing data from US mental healthcare providers operating an EHR called MindLinc **with data collected between 1999 and 2020**.

Results

• A figure summarizing the sample characteristics and outcomes could help readers better understand the data.

Author response: We have removed table 2 and table 4 and included figures 3, 4, and 6 to highlight some of the outcomes from those tables. We have also expanded table 3 (now table 2) to include the clinical characteristics of patients together with their demographics. References to figures and tables in the main text have also been updated.

• The relatively low proportion of patients using LAIs should be explicitly highlighted.

Author response: The proportion of patients in the database who used LAIs has been highlighted in the first sentence of the Results:

Among 538,565 patients included in the NeuroBlu Database, **only 2450 patients with schizophrenia diagnosis were prescribed an LAI and** 1197 met the **study** inclusion criteria; 339 patients had ≥3 months of pre-admission and post-discharge data and were included in the transition-of-care and HCRU analyses, 449 patients had ≥12 months of post-index data and were included in continuation-of-care analyses (table 1).

• Continuation of Care: A larger proportion of patients co-prescribed OA alongside LAI demonstrated improvements in CGI-S. Did you analyze whether this finding holds when controlling for dose equivalents?

Author response: This specific relationship was not analysed in this study. We have included additional text in the limitations of the Discussion section to emphasize that confounding variables for certain observed relationships were not examined.

In addition, due to the descriptive nature of this work and limitations of the real-world dataset, there was no adjustment for confounders among certain observed relationships. For example, we did not control for the confounding influence of illness severity when comparing outcomes between patients who were prescribed LAIs versus OA+LAI, or for

the influence of dosing frequency and strength on CGI-S improvement in the context of LAI co-prescription. Also, about 75% of the data in NeuroBlu are from at least a decade ago, and the LAI landscape has changed substantially since that time.

• For the OA+LAI versus LAI-alone groups, did you examine differences in clinical variables such as severity or comorbidity? These could clarify potential confounding factors.

Author response: Treatment severity at discharge (based on CGI-S) was compared between OA+LAI and LAI-alone groups as mentioned in the Continuation of Care section of the Results. However, differences in other clinical variables such as comorbidity were not examined in such detail but were controlled for in the regression analysis.

• The primary outcomes seem overly assessed through the perspective of LAI+OA co-prescription. I suggest analyzing the primary outcomes in more detail and highlighting their results. Consider evaluating potential confounders like clinical variables, dose equivalents, and relative potency.

Author response: As the aim of this study was to investigate LAI prescribing patterns in the US, the results were analysed in the context of LAI+OA co-prescription (considering that this was a very common practice in clinical settings). Additionally, we were also interested in the effect that LAI dosing frequency might have on transition and continuation of care of patients with schizophrenia in the context of the primary outcomes. Due to the limitation of real-world datasets, it is difficult to account for some of these variables; however, we do acknowledge that these are important analyses that can be considered for future studies.

• Regarding LAIs with less frequent administration, did you explore potential confounding factors? If the sample size allows, comparisons within the same LAI group based on administration frequency could be insightful.

Author response: We agree with the reviewer that this is an important research question, and it would be useful to investigate in a future study. However, the current study was not designed to conduct direct comparisons on clinical outcomes between products with different dosing frequencies and would require a matched study design. We do, however, note the difference in discontinuation rates between LAIs with shorter versus longer dosing intervals.

• What is the main result? Is it the poorer outcomes of OA+LAI co-prescription, or the better outcomes associated with LAIs with less frequent administration? I suggest revising this section to clearly highlight the central findings. It seems that the take-home messages are misaligned throughout the text, from the abstract to the conclusion.

Author response: We have adjusted the abstract and conclusions to better align the main result with that of the Discussion. In the abstract conclusions, the text was changed as follows:

~~The availability of a longer-duration (≥1 month) LAI could facilitate continuation of care for patients being transitioned from an OA or from an LAI with more frequent~~

~~administration. Importantly,~~ **P~~p~~**atients prescribed a combination of LAI and OA at discharge had a higher ~~likelihood~~ **risk** of rehospitalisation compared to those prescribed LAI alone. Additionally, **the study findings suggest that patients are more likely to be prescribed** oral risperidone**,** ~~was~~ the most frequently used second-generation OA, which may support an easier transition to an LAI of the same molecule.

For the main conclusions, the following changes were made to the text:

> This real-world evidence study demonstrated ~~that LAIs with less frequent administration, particularly those administered once monthly or less frequently, were associated with reduced discontinuation rates. An important observation is~~ that patients prescribed a combination of LAI and OA at discharge had a higher risk of rehospitalisation compared to those prescribed LAI alone.

As well as:

> This warrants further exploration to distinguish illness severity from other causes of rehospitalisation (eg, increased side effect burden which could negatively impact treatment adherence and subsequently increase risk of relapse). Increased risk of rehospitalisation and treatment discontinuation could also be due to a combination of underlying illness severity and subsequent risk of relapse together with increased risk of adverse events (due to higher antipsychotic plasma concentrations). **LAIs with less frequent administration, particularly those administered once monthly or less frequently, were associated with reduced discontinuation rates.**

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Jakobsen, Michelle Iris**
Affiliation	**Psychiatric Services Region Zealand East**
Date	**26-Feb-2025**
COI	

The authors have answered the review comments well and revised the manuscript accordingly.