Reviewer’s report

Title: Previous hospital admissions and disease severity predicts use of antipsychotic combination treatment in schizophrenia

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Reviewer: Sebastian Meyer

Reviewer’s report:

The authors have well improved their manuscript since the first review. They also provide more information on their study sample which is even slightly bigger now. However, there remain some points which need clarification and improvement.

Discretionary Revisions

1. Results: Typo: “antispsycotic”

2. Introduction: If I have properly understood, it is stated that some studies indicate a higher rate of FGA compared to guidelines. It might be worth remarking in the discussion that in the authors’ own study, only 7.3% had prescribed an FGA as primary medication “due to both a national and local guideline and not necessarily representative for Europe” (from authors’ response). However, the differentiation between FGA and SGA is not in the authors’ focus.

3. Statistical Analysis: If a _conditional_ logistic regression model has been fitted to the data, then it has to be mentioned on which strata the conditioning is based. However, there is no need for conditional logistic regression in this analysis, and apparently this is just a misunderstanding as it seems that a logistic regression model has been used, i.e. as usual without conditioning. In this case the term “conditional” should be removed (also in the results section).

4. Results: Please check the value 10.067 of Pearson’s chi-square test statistic for the association of two or more previous admissions with antipsychotic combination treatment. With the numbers provided in Table 4a (or 4b) this should be 9.086.

5. Results: “Patients with no readmissions in their history” should be “Patients with no or only one readmission in their history” according to the current dichotomization.

6. Table 4 a) and b): These tables are missing captions.

7. Table 4b) could be omitted as it does not provide additional information. The respective numbers can be derived from Table 4a).

8. Table 4a: Typo: Shouldn’t the number of patients with two or more antipsychotics be 101 instead of 91?
Minor Essential Revisions

9. Table 1: Regarding the huge amount of missing data on age of onset and DUP, is the patient subgroup with known values specific to the kind of treatment or is this random missingness? It would be nice if this could be clarified.

10. In Table 3, the PANSS subscales seem to be unavailable for some patients. This should be indicated in Table 1 as well.

11. Discussion: Concerning the reasoning behind the choice of the cut-off value 2 for the dichotomization of the number of previous hospital admissions, the authors emphasize the “clinical relevant distinction between patients who were readmitted and those who were not”. However, this argument rather supports the dichotomization “zero previous hospitalisations” versus “one or more previous hospitalisations” (i.e. readmission), which was not implemented in the analyses.

Major Compulsory Revisions

12. Statistical Analysis / Results: As already mentioned in the original review, correlation analyses using Spearman’s correlation coefficient with dichotomous variables (like the indicator “antipsychotic combination treatment”) is not appropriate. In Table 3 the authors should report comparisons between the group of patients with monotherapy and those with two or more antipsychotics - also providing the groupwise mean (sd). Group comparisons with respect to DUP and the number of hospitalisations should be evaluated using Mann-Whitney-Wilcoxon rank-sum tests (due to their skewed distribution). For the other patient characteristics one could also use Mann-Whitney-Wilcoxon tests or otherwise Welch’s t-test. There is no “table 3b) showing t-test results” (as indicated in the authors’ response) in the current version of the manuscript.

13. Results: There is no sense in incorporating both the PANSS total score and a PANSS subscale in the same regression model - both from a statistical point of view (high correlation, ambiguous covariate effects) as well as regarding interpretability. Currently, the proper effect of PANSS general actually is the sum of the coefficients of PANSS general and PANSS total, and the parameter estimate of PANSS total is linked to the sum of PANSS positive and PANSS negative. This might also be the reason for OR(PANSS general) < 1, which the authors do not discuss further. Please include either the PANSS subscales or the PANSS total in the selection procedure. If necessary, the authors could then compare the final model based on the subscales with the model containing PANSS total only with respect to the goodness-of-fit.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published
Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests.