Author's response to reviews

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

Authors:

Albert Bolstad (albert.bolstad@diakonsyk.no)
Ole A Andreassen (o.a.andreassen@medisin.uio.no)
Jan I Røssberg (j.i.rossberg@medisin.uio.no)
Ingrid Agartz (ingrid.agartz@medisin.uio.no)
Ingrid Melle (ingrid.melle@medisin.uio.no)
Lars Tanum (lars.tanum@diakonsyk.no)

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Author's response to reviews: see over
Dear Editor-in-Chief

In line with the reviewers' constructive criticism, we have revised the text according to the suggestions, performed new statistical analysis, included more data from the ongoing study, and rephrased the title; "Previous hospital admissions and disease severity predicts use of antipsychotic combination treatment in schizophrenia".

Response to the referee's comments (Referee 1)

Comments by Reviewer #1: (typed in bold)

We have now revised the text according to the suggestions, performed new statistical analysis and included more data from the ongoing study, and rephrased the title.

1: It would be very nice to see more sociodemographic and clinical parameters
Response: We agree and have revised table no.1 and added more sociodemographic and clinical background variables including PANSS scores. Unfortunately we have data on Age of onset and Duration of psychosis (DUP) only in 140/142 out of 329 patients (appr. 43%). These data are therefore only used in the correlation analyses.

2: Besides using the WHO defined daily doses, it would be nice to see the dosages of Antipsychotics according to CPZ.
Response: Dose comparisons between different antipsychotic drugs are not within the scope of this paper. However, we do have a manuscript in preparation on the same study population where the primary scope is inter-individual differences in dosing and corresponding plasma concentrations.

3. I would suggest to present a table with sociodemographic data and to describe the study sample and result in detail.
Response: We agree and have revised table no.1 which now describes the sociodemographic data in more detail, and table no. 2 which now describes the main clinical characteristics of the patients. Table no. 4 now describes the main results and not only the data from the logistic regression model.

4: Is psychopathological data available (e.g. PANSS)? Is data concerning non responders to monotherapy available?
Response: Yes, PANSS data is available for most patients and is now included in the description of the sample as well as in the analysis and results. Unfortunately we do not have any data on the patients' degree of response or non-response to monotherapy.

5: Is it possible to do a separate analysis comparing out- and inpatients? Is there a gender effect?
Response: From 2003 -2008, we did not possess accurate data concerning out- or inpatient status at the time of inclusion in the study. A number of patients were recruited while being hospitalized, but actually included after discharge. Due to the low accuracy on the present inpatient versus outpatient treatment status we considered analyses comparing the two groups to be of limited value and we did not include this factor in the logistic regression analysis. We did not find any gender effect related to antipsychotic combination treatment.

Discretionary Revisions: Title and abstract: Abstract is well - written, but "clinical characteristics" is too generic because only the GAF was assessed.
Response: We agree, and suggest changing the title to “Previous hospital admissions and disease severity predicts use of antipsychotic combination treatment in schizophrenia”.

Minor Essential Revisions: Methods: Sample should be described more in detail. Was it a prospective or retrospective design?
Response: We agree, and the sample is now described in more detail in Table no.1. The study design was cross-sectional with retrospective data.

Minor Essential Revisions: Results well -arranged and comprehensive. The aforementioned parameters should be included, if available. It is noteworthy that SGA are very highly subscribed, which may be led back the local health care system or to the schizophrenia symptoms (negative > positive?). The fact that no patient had haloperidol and only one flupentixol in their medication is really interesting. The low prescription rate of clozapine, which is an often used combination partner, is interesting, too (see reference no 26.) Can these results led back to "local guidelines"
Response: This is an interesting point. Our local guidelines recommend the use of a second generation antipsychotic in the long-term treatment of schizophrenia, regardless of the load of negative symptoms. Prescription of clozapine demands close follow-up of the patients including regularly analysis for early detection of possible blood dyscrasies. Due to this clozapine is mainly given as a second or third choice.
Response to the referee’s comments (Referee 2)

Comments by Reviewer #2 Sebastian Meyer (typed in bold)

We have now revised the text according to the suggestions, performed new statistical analysis and included more data from the ongoing study, and rephrased the title.

1. Results: Missing reference to table 4
Response: The missing reference to table 4 is now corrected

2. Results: The probability of two or more antipsychotics increased...
Response: This is now corrected and reads "The probability of two or more antipsychotics increased ..."

3. Table 3: correlation typing error "-197"
Response: Table 3a), showing Spearman's correlation coefficients, is now added with table 3b) showing t-test results. This is in line with reviewers comments to the statistical analyses. Typing error is eliminated.

4. Results: When remarking a significant correlation, the direction of association should also be mentioned.
Response: This is now corrected and mentioned in the text.

5. The article repeatedly states that antipsychotic combination treatment "deviates from current treatment guidelines". Does this also hold for treatment-refractory patients?
Response: It may be an assumption that treatment-refractory patients are more likely to receive antipsychotic combination treatment, but we do not have clinical data showing this. To the best of our knowledge, there are no major clinical guidelines that specifically recommend antipsychotic combination treatment for treatment-refractory patients”. This is the rationale behind our expression "antipsychotic combination treatment deviates from current treatment guidelines". In order to clarify this, we have now specified in the manuscript:

6. Assessment ICC estimation for GAF-F necessitates multiple ratings per patient. The details are not apparent from the assessment description. Please complete or provide an appropriate reference where the details on type of raters can be found. Also, if there are multiple ratings per patient, which measure has been used in the current analyses?
Response: All raters were actually investigators in the study, with a background either as medical doctor or clinical psychologist. Assessments were not performed by study nurses or trial assistants. All raters were trained in clinical interviews and assessments, scored videos and case reports, and testing for actual rating reliability was performed for diagnosis, PANSS and GAF. This information is now included in the manuscript.
7. Following the text, Table 2 shows the primary medication (Olanzapine 38.8%, etc). However, the numbers in the table do not sum up to 311, so the numbers in the table correspond to the overall medication (a patient can have multiple antipsychotics).
Response: We realize that table 2 may seem slightly confusing. Table 2 is now revised, including data from a higher number of patients in the ongoing study.

8. Table 2. 9 patients not using antipsychotics should equal 2.9 %
Response: We apologize for this incorrect number. In our revised analysis we have excluded patients not using antipsychotic medication to better focus on our main findings.

9. Table 2. Why do the last three lines not sum up to 311 patients.
Response: We realize that table 2 may seem slightly confusing. Table 2 is now revised, including new data form the ongoing study.

10. It is unclear to which absolute number of the 6.4 % for Olanzapine and the 4.2% refer. Is it out of 58 or 95 or 311?.
Response: We apologize for these incorrect numbers. These numbers are now replaced in the revised manuscript.

Among the 95 patients with combination treatment, what are the primary antipsychotic (numbers FGA and SGA)? Or how many of the 95 patients have FGA+FGA, SGA+SGA, FGA+SGA and SGA+FGA respectively.
Response: First generation antipsychotics vs. second-generation antipsychotics were not thought of as a main issue in this study. However the high proportion of SGA is due to both a national and local guideline and not necessarily representative for Europe. Our intention was not to focus too much on this but rather on the clinical characteristics related to antipsychotic combination treatment. We have now included the numbers on the different types of combination therapy in the manuscript.

11. In the logistic regression model, the number of previous hospitalisations is dichotomized into 0/1 and 2+ without reasoning. Categorization seems plausible, but the reader is left wondering about the choice of the cut point.
Response: The reason for this cut point was based on a clinical relevant distinction between patients who have been readmitted and patient who were not. It may be assumed that readmitted patients have more difficulties in functioning outside hospital. The probability to be prescribed antipsychotic combination treatment increases up to 4 previous admissions. Our data did not indicate that more than 5 previous admissions make further increase in probability of getting antipsychotic combination treatment. In table 4a we display data showing the increase in combination treatment for related to previous hospitalization and for up to the first four.

12. What about the proportion of combination treatment among patients with one previous admission?
Response: We agree that this information is important. We now present a table (Table 4 a) showing the increase in likelihood for combination treatment from none to five admissions,
including one previous admission. The proportion of combination treatment among patients with one previous admission was 22.8%.

13. What is the informative value of the odds ratio with respect to 2-5 or 2-40 previous admissions in the last paragraph?
Response: We apologize for this confusing information. We intended to show that a high number of previous admissions that is above 5 previous admissions did further not increase the likelihood for receiving combination treatment. This has now been clarified in the text.

Discussion:

14. "enabled us to detect important associations for subgroups of patients": Which subgroups with respect to the GAF are meant here?
Response: We agree that the term subgroup is not appropriate in this context. Our point is that a rather wide spectrum in GAF scores among the patients enables us to detect important relationships between GAF and other clinical and pharmacological variables, in contrast to studies including mainly patients with a low GAF scores, such as inpatients. We have now revised the text to clarify this issue.

Major Compulsory Revision

15. Statistical Analysis:
There is no information on the model selection strategy. (backward/forward stepwise, Wald/LQ tests or information criterion).
Response: We used a stepwise backward conditional regression model. Wald is now in the table. (Table 5). We have now provided information on the model selection strategy in the manuscript.

The selected regression model is missing some measurement of goodness-of-fit, e.g. the AUC or Nagelkerke’s R2
Response: In our reanalysis Nagelkerkes R Square was 0.146 in the last step. This information is now provided in the manuscript.

The correlation analysis using Spearman’s correlation coefficient with dichotomous variables are not appropriate or at least non-standard. Group comparisons concerning gender and combination therapy using Wilcoxon or t-test - also providing groupwise means (sd) or medians (IQR) - would be much more adequate; especially as the combination therapy indicator is the man variable in the analyses
Response: We agree, and in the revised manuscript we have used Pearson Chi-square Tests.

16. Results: The "nominal increase" of antipsychotic combinations from two to five previous admissions should be documented by numbers:
Response: We agree. This is now documented in table 4 a)
We appreciate that the topic was found within the interest field of your journal and appreciate the opportunity to resubmit a rewritten manuscript.

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Yours sincerely

Albert Bolstad, M.D

e-mail: 'albert.bolstad@diakonsyk.no'
Department of Psychiatry Research
Diakonhjemmet Hospital
P.O. Box 85 Vinderen
N-0319 Oslo, NORWAY