Author's response to reviews

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

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**Author's response to reviews:**

The BioMed Central Editorial Team

MS: 1748644102448898.

Title; "Previous hospital admissions and disease severity predicts the use of antipsychotic combination treatment in patients with schizophrenia".

Oslo, 1st July 2011.

Dear Editor-in-Chief

We appreciate that the topic was found within the interest field of your journal and appreciate the opportunity to resubmit a rewritten manuscript.

In line with the reviewers' constructive criticism, we have performed new statistical analysis and revised the text according to the suggestions.

Response to the referee's comments (Referee 1)

Comments by Reviewer #1: (typed in bold)

The Authors present the revised version of their initially submitted manuscript and they have addressed adequately all questions of the reviewers.

Major Compulsory Revisions: N/A

Minor Essential Revisions: According to the answer to question 5 of reviewer 2 "to the best of our knowledge, there are no major clinical guidelines that specifically recommend antipsychotic combination treatment for treatment-refractory patients", I just want to refer to the international treatment guidelines for long term treatment in schizophrenia (Falkai et al (20006), The
world Journal of Biological Psychiatry, 2006, 7 (1): 5-40). In this guidelines) and
the references quoted in this guidelines. Maybe the authors wish to add this to
their manuscript. Furthermore, Wolff-Menzler and colleagues published recently a
review about the combination Therapy in the Treatment of Schizophrenia (2010,
Pharmacopsychiatry) addressing this question and reviewing the literature.

In this case their conclusion ("which deviates from current treatment guidelines")
should be eased a bit.

Response: Both Faikai (2006) and Wolff-Menzler (2010) are now included. We
have eased our conclusion according to Revivers comment.

Discretionary Revisions: N/A

General remarks: This is an interesting article. The lacking information of age
and DUP is a major disadvantage of this work. However, the authors can answer
their initial questions and provide some interesting information on the field of
schizophrenia research and clinical practice.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I have been invited to scientific congresses by Astra Zeneca, Lundbeck and
Janssen Cilag but this is not related to this report. Therefore, I declare that I have
no competing interests.

Response to the referee's comments (Referee 2)
Comments by Reviewer #2 Sebastian Meyer (typed in bold)

Discretionary Revisions

1. Results: Typo: "antispsychotic"

Response: Now corrected to antipsychotic

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 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.

Response: We agree, and have now commented the low prescription of FGA
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).

Response: We agree have now removed the term "conditional" in the results section as well.

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.

Response: We have indentified one patient using both Quietiapine and Olanzapine, wrongly labelled in the analysis as using only one antipsychotic agent. This case is now relabelled and we have repeated the relevant analysis. Pearson Chi-square test statistic is now checked and we have corrected values. The commented value is corrected to 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.

Response: Two previous admissions mean at least one readmissions. According to the current dichotomization it should be “Patients with no or only one admission in their history”.

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

Response: Caption in Table 4 a) " Number of previous hospital admissions. Comparing group of patients with only one antipsychotic vs. group of patients with 2 or more antipsychotics."

Table 4 b) is now omitted.

7. Table 4 b) could be omitted as it does not provide additional information.

Response: We agree. Table 4 b) is now omitted

8. Table 4a: Typo: Shouldn't the number of patients with two or more antipsychotics be 101 instead of 91.

Response: Number of patients with two or more antipsychotics is now corrected to 101.

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.

Response: We have explored the data but unfortunately we can still not establish whether DUP was random or not. We are not sure that this missing date is random. Due to our retrospective collection of data, this parameter is difficult to verify. Patients' inaccurate memory, limited insight and maybe interpretations form the patients as well as the raters and investigators in the study. Not only is a large amount of data missing. The data we have on DUP have may be biased. The non-significant result from Mann-Whitney test should not be emphasised too much. For further research we will recommend to explore on DUP as a possible interesting parameter.

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

Response: Number of patients included in the PANSS subscales is now 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 hospitalisation" (i.e. readmissions), which was not implemented in the analyses.

Response: In a number of the patients first admittance to hospital was not necessarily due to problems with ongoing treatment, but due to a more acute or dramatic onset of symptoms of schizophrenia. Choosing a cut-off between one and two admissions therefore reflects to a greater extend patients with poor compliance or lack of response to ongoing treatment. Two previous admissions mean at least one readmission.

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 authors should report comparisons between the group of patients with monotherapy and those with two or more antipsychotics - also providing groupwise mean (sd). Group comparisons with respect to DUP and number of hospitalisations should be evaluated using Mann-Whitney-Wilcoxon rank sum tests (due to their skewed distribution). For other patient characteristics one could also use Mann-Whitney-Wilcoxon tests or otherwise Welch's t-test. There is no "table 3 b) showing t-tests results" (as indicated in the authors' response) in the current version of the manuscript.
Response: Between-group comparisons are now performed using independent sample t-test and Mann-Whitney test. Table 3 a) in showing group wise means, and Table 3 b) displaying t-tests results, comparing patients with only antipsychotic agent and patients with one ore more antipsychotic agent. Mann-Whitney test-results are reported.

13. Results: There is no sense in incorporating both the PANSS total score and a PANSS subscale in the same regression model - both form 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 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 futher. 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.

Response: We agree there is not appropriate to compare PANSS total and PANSS subscales in the same regression model. In our log. regression analysis we have now entered the three subscales, PANSS positive, PANSS negative and PANSS general score, as well as GAF-symptom, GAF-function general, and previous admissions (Nagelkerke 0.135 in the last step). Replacing the there PANSS subscales, with PANSS-total in regression analysis did not keep PANSS-total in the last step (Nagelkerke R Square 0.112 in the last step.)

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

Quality of written English: Need some language corrections before being published.

Response: We have now improved our written English.

Yours sincerely

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