Reviewer's report

Title: Relapse according to antipsychotic treatment in schizophrenic patients: a propensity-adjusted analysis

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Reviewer: Lone Baandrup

Reviewer's report:

General comments:
The study uses data from a multicenter cohort study to investigate the association of antipsychotic co-prescribing with risk of relapse in schizophrenia patients. The question posed by the authors is well defined and the choice of pragmatic effectiveness measure is considered relevant to the field because the rising frequency of antipsychotic polypharmacy is not justified by current evidence. Investigating pragmatic outcomes is an important supplement to randomized clinical trials focused on efficacy. The methods are appropriate and sufficiently described.

However, some weaknesses can be observed and should be adjusted.

Specific comments:

Abstract:
1) 3rd paragraph: The expression “antianxiety or mood stabilizer medication” is used to cover what is called “sedative drugs” in the results section and Table 1. This is confusing; the same expression should be used throughout the manuscript (minor essential revision).

2) 4th paragraph: See comments on conclusion below (minor essential revision).

Introduction:
3) 2nd paragraph: An increase in metabolic syndrome due to antipsychotic polypharmacy cannot be claimed based on reference number 9, because the association with metabolic syndrome in this publication was explained by known demographic, clinical and anthropometric risk factors, i.e. antipsychotic polypharmacy was not independently associated with higher rates of metabolic syndrome (minor essential revision).

4) The references on a negative association between risk of death and antipsychotic polypharmacy are not updated; at least two newer studies have been published in the field (se first comment for discussion section below) (minor essential revision).

Patients and methods:
5) 1st paragraph: Specifications of the patients included in the cohort are lacking: In- or outpatients? Debutants or chronics? How was the diagnosis established (interview, medical record review, using an already set diagnosis)? How was the
sample/cohort size determined – any prespecified power calculation? How was “not-relapse” defined at baseline, e.g. did the patients fulfill remission criteria at baseline? Were there no drop-outs/lost to follow up during the 2-year period? Data were collected every 6 months – does that mean 4 times in total, and which data were then used in the analyses – only baseline (as is stated for the antipsychotic medication variable)? Who collected the data every 6 months (and how) and who decided which patients fulfilled the criteria for relapse? (minor essential revisions).

6) 3rd paragraph: How was antipsychotic polypharmacy defined (on a specific cross-sectional date? Any requirements for prior duration of combination treatment? (the measured frequency of antipsychotic polypharmacy is highly dependent on how antipsychotic polypharmacy is defined, cf. Kreyenbuhl et al., Schizophr Res 2006, 84(1):90-91). Was “as-needed” (PRN) medication included? (minor essential revision).

Results:

7) 2nd paragraph: I miss information on total dose of antipsychotics in the two medication groups and number of antipsychotics in the polypharmacy group in Table 1 – this would be desirable to better describe the sample. Also, information on the most frequent combinations would be informative (not in the table but mentioned in the text) (discretionary revisions).

Discussion:

8) 1st paragraph: It is stated that the current finding (antipsychotic polypharmacy not associated to an increase of relapse) is in contrast to the generally upheld notion that there is no support for combining 2 antipsychotics. This conclusion is not supported by the results: no association merely means that the two treatment regimens seem equivalent with regard to risk of relapse - the authors did not find a protective effect of antipsychotic polypharmacy on risk of relapse. Actually, there was an increased risk of relapse with antipsychotic polypharmacy (HR 1.7), but it was not statistically significant (minor essential revision).

9) It is not accurate that “the majority of previous studies reported higher rates of mortality” – the referenced papers are methodologically flawed and two recent register-based studies (Baandrup et al., J Clin Psych 2010, 71(2):103-108; Tiihonen et al., Lancet 2009, 374(9690):620-7) with much larger sample sizes report no association of antipsychotic polypharmacy with increased risk of death (minor essential revision).

10) 3rd paragraph: It is stated that the findings suggest that the most severely ill patients were given polypharmacy – nevertheless, there was no difference between the monotherapy and polypharmacy groups on several measures of disease severity and social functioning - the discussion should be more balanced including this fact, including the fact that a 3-point difference in PANSS is probably not clinically significant although apparently statistically significant. Likewise, there is no comment on the discrepancy between more antidepressant prescriptions in the polypharmacy group and lack of difference in CDSS score – alternative explanation for increased antidepressant prescribing: more secondary negative symptoms due to higher dose in the polypharmacy group (as is usually
11) 4th paragraph: These statements ("This results can also explain...increase of relapse") seem highly hypothetical and difficult to understand – should either be deleted or rewritten/clarified (minor essential revision).

Perspectives and limitations:
The following limitations need to be addressed in the paper (minor essential revisions):

12) All combinations of antipsychotic drugs are put in the polypharmacy group. This is a strong simplification which could lead to false conclusions – antipsychotic combinations are a very heterogeneous group and the different combinations might be associated with different risks of relapse.

13) Monotherapy vs. polypharmacy at baseline – is this a good proxy for polypharmacy exposure the next two years and how might this be problematic?

Conclusion:

14) It is stated that "methodological tools such as propensity score are useful to strengthen results of observational studies" – this might be the case but it does not seem to be supported by the results in this particular study: both the logistic regression model and propensity-score analysis found that there was no effect of polypharmacy on risk of relapse, so judged from this study the results are similar (minor essential revision).

Tables:
Table 1:

15) “Drugs for side effects” and “sedative drugs” should be specified in a footnote (which drug types, e.g. benzodiazepines, are included in each group?) (minor essential revision).

Table 2:

16) The title of the table indicate the results of three different statistical models:
1) Univariate, 2) multivariate-adjusted, and 3) propensity score-stratified. However, the table only has one result per variable – it needs to be clarified if this is the univariate (unadjusted) or multivariate adjusted result? (Minor essential revision)

17) The title of the table mentions “HR and their corresponding 95% CIs”. This is misleading since the HR is only reported for polypharmacy (and therefore should not be mentioned as in plural). Cf. section of “statistical analysis”: “…used to estimate the HR and its corresponding 95% CI”. (Minor essential revision).

18) “Drugs for side effects” and “sedative drugs” should be specified in a footnote (which drug types, e.g. benzodiazepines, are included in each group) (minor essential revision).

19) Information on other variables potentially associated with risk of relapse would be desirable, including coercion, educational level, drug/alcohol abuse (discretionary revision).
Minor issues not for publication:

20) Data collection:

“The number of previous hospitalization” should be corrected to “the number of previous hospitalizations”

Same correction should be applied to Table 1 and 2.

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

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I declare that I have no competing interests