Reviewer's report

Title: Paliperidone ER and oral risperidone in patients with schizophrenia: a comparative database analysis

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Reviewer: Stefan Weinmann

Reviewer's report:

This publication is a post-hoc statistical analysis of a selection of published and unpublished short-term randomized placebo-controlled studies with paliperidone or risperidone using a propensity score matching design. The aim was to indirectly compare the efficacy of paliperidone ER and risperidone as there are no head-to-head trials. A variety of covariates was taken into a logistic regression model for propensity score matching of selected patients of the studies. With this pooled analysis the authors found that the change in PANSS scores was greater for paliperidone ER compared to risperidone 2-4 mg, but comparable between paliperidone ER and risperidone 4-6 mg. Paliperidone was superior to risperidone 2-4 mg in placebo-controlled completion rates. The authors conclude that paliperidone ER may more efficacious than risperidone 2-4 mg. The study was funded by the manufacturer of paliperidone (and risperidone).

Major Compulsory Revisions:

Propensity score matching is a second-best choice when randomization is not possible, however, it does not “approximate” (as written in the abstract) a randomized controlled trial. I would NOT call it a “head-to-head” comparison (as written on page 4 last para), it is rather more an indirect comparison.

The methodology chosen by the authors has severe limitations.
A look into the Methods section shows that the selection procedure of studies is not fully transparent, but selective and not state-of the art any more. The authors did not perform a systematic literature search in order to identify all relevant studies with paliperidone. They included only 3 studies with risperidone. One wonders about the selection criteria of these studies.

An evaluation based on this kind of study selection has severe limitation and a high risk of bias. The difference between the 2 sets of studies (time when they were performed and previous treatment) indicates that these studies may not be comparable and suited for propensity score analysis further limiting this indirect comparison.

In the absence of baseline data of the whole study populations, the selective inclusion of only some individuals from the single studies (of course for matching reasons) is not fully transparent.

Propensity score matching appears technically correct, but cannot really judged
in the absence of data.

It is not explicitly stated why the independent variables on page 8 were chosen.

It is well known that each study context is particular and placebo-controlled studies may differ considerably from three-arm or head-to-head studies. Taken together: When true head-to-head trials are possible this would be the right way to test the hypotheses generated in this analysis.

The Discussion section needs to take more into account the critical literature on indirect comparisons. In addition, the severe limitation of (study) selection bias has to be named and discussed. Why were exactly these risperidone studies chosen? Why was no systematic review performed?

Minor Essential Revisions

Page 9: Risperidone subjects receiving 4 mg/day were included in both risperidone groups. This may be a problem as variance is reduced.

Which statistical package has been used?

Page 7 Statistical analysis: I would not call it a “direct comparison” but an indirect comparison.

Authors’ contribution: Did JPL and NS have full access to the data? Did anyone outside the sponsoring company have full access?

Level of interest: An article of limited interest

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.