Bergen Mental Health Research Center
Haukeland University Hospital
Division of psychiatry, Sandviken

Bergen, 01.09.2016

Editor
World Journal of Psychiatry

Dear Editor,

We thank the Editor and Reviewers for their constructive comments on our manuscript, and hereby resubmit the revised manuscript titled "*The influence of different second generation antipsychotics on the QTc interval: a pragmatic study.*" for publication in the World Journal of Psychiatry (ID 03529071).

The Reviewer and Editor comments will be addressed point by point in the following, and changes in the manuscript will be indicated by red lettering.

Reviewer # 1 (Reviewer's code: 01205020)

Abstract: "AIM: To to investigate whether differential influence on the QTc interval exists among four second generation antipsychotics (SGAs) in." Please correct "To to..". in "what"?

The sentence has been corrected in the revised manuscript according to the suggestion by the Reviewer (Page 3).

Discussion: Abbreviation (TdP) should be defined on their first appearance in the text.

TdP is defined on the first appearance in the revised manuscript (Page 5).

Discussion: "as as accounted for in a previous publication.." Please correct "as as..".

The repetition is deleted in the revised manuscript (Page 15).

Reviewer # 2 (Reviewer's code: 00504286)

(1)The data in this work were collected from the patients of Psychiastric Department. Although inability to use oral antipsychotics was declared in the manuscript, it is hard to exclude the possibility that patients took minor tranquilizers or anti-histamines. Those drugs may somehow mask any QTc prolongation caused by SGAs.

We thank the reviewer for pointing out this important issue.
We have added analyses regarding concomitant medication in the revised Results section (page12), and have added a notion on this in the Discussion (Page 16).

(2)About 73 % of patient population was males in this study. Elevation of plasma beta-estradiol level may prolong QTc intervals. The proportion of male individuals tends to be higher and may cause negative results. Also, the patients' age, heart rate and electrolytes (e.g., serum potassium level) should be included in the manuscript. Heart rate may necessarily know if the patients have taken drugs with anticholinergic effect.

We agree with the Reviewer that the gender distribution may have led to lower mean QTc values. However, as the male/ female ratio was evenly distributed among the drug groups, this should not have biased the results. A comment on this is added to the Discussion (page 16). Unfortunately we do not have heart rate recordings in the study, but all QTc assessments were heart-rate corrected thus adjusting the QT interval for different heart rates. Analyses of electrolytes have been added to the Results section (Page 12).

(3)Is it possible to check plasma prolactin level during oral treatment of antipsychotic agents?

Analyses of plasma prolactin have been added to the revised Results section (Page 12 and 13). There were higher prolactin levels at baseline and the first point of follow-up

in the risperidone group, but not thereafter. A comment is added in the revised Discussion (Page 16).

(4)Perhaps notably, "acute" or short-term treatment of SGAs may not have adequate plasma level to block the rapid component of delayed rectifier K+ current inherently in heart cells. Pharmacokinetic estimations for these SGAs should be evaluated carefully.

A comment on this is added in the revised manuscript (Page 14).

Comments from the Editor:

Postal codes have been added in the revised manuscript

Grant forms: The grants mentioned are part of much more comprehensive funding. We suggest that the information about specific grants is taken out of the manuscript since it might confuse the reader.

Signed PDF files: These have been attached

Biostatistics: An external biostatistician, Tore Wentzel-Larsen, has been consulted for review of the statistics. The statistics have been revised according to his suggestions. Figure 2 has been replaced with a new figure to account for slopes with different intercepts. Importantly, the additional analyses did not change any of the main results or conclusions.

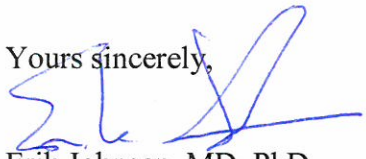
Audio Core Tip: This is provided along with the revised manuscript

The references have been revised according to the request of the Editor. For some of the older references only the PMID was available and the DOI missing.

A decomposable figure has been added in the revised manuscript.

Cross checks have been done. The highest similarity score was for a previous paper from our own group. There are only so many different ways to describe the design and methods of the main project, leading to similarities in the Methods section in different studies from the main project.

Yours sincerely,



Erik Johnsen, MD, PhD

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