PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of the GLP-1 receptor agonist semaglutide on metabolic disturbances in clozapine- or olanzapine-treated patients with schizophrenia: Study protocol of a placebo-controlled, randomised clinical trial (SemaPsychiatry)
AUTHORS	Sass, Marie; Danielsen, Andreas; Köhler-Forsberg, Ole; Storgaard, Heidi; Knop, Filip; Nielsen, Mette; Sjödin, Anders; Mors, Ole; Correll, CU; Ekstrøm, Claus; Vinberg, Maj; Nielsen, Jimmi; Vilsbøll, Tina; Fink-Jensen, Anders

VERSION 1 – REVIEW

REVIEWER	David Wright University of Guelph
REVIEW RETURNED	11-Oct-2022

GENERAL COMMENTS	Sass and colleagues describe a placebo-controlled, randomized clinical trial examining the effect of the GLP1 receptor agonist, semaglutide, on metabolic disturbances in clozapine or olanzapine treated patients with schizophrenia. Given the growing number of individuals being treated with antipsychotics this is an important and timely question that will be addressed. With this being said, the anticipated results would be expected given the authors previous findings demonstrating beneficial effects of concurrent liraglutide treatment in individuals with schizophrenia being prescribed antipsychotics. Within this framework the authors are encouraged to highlight the novel aspects of the proposed trial in comparison to the aforementioned liraglutide study. Other points to consider are as follows: 1. Pg 7,line 12 the authors mention that despite the presence of metabolic complications that antipsychotic treatment is associated with reductions in mortality. Is this related to decreases in suicide? For the naïve reader this should be discussed in a bit more detail. 2. In Box 3 (page 15) it would seem that standard blood sampling will be used for the determination of HbA1c. However, in Table 1 this will only be done in week 8 and 16. As change from baseline HbA1c is the primary outcome its not clear how this would be calculated. Related to this point it would be informative to have additional readouts of glucose homeostasis throughout the investigation at multiple time points as it may allow for a greater temporal sensitivity in teasing out weight loss dependent vs. independent effects. 3. Would it be possible to measure serum semaglutide concentrations at various time points throughout the study? This could provide useful information regarding responders vs non-responders and compliance regarding self-administration of the drug.

REVIEWER	Usama Bin Zubair Mater Misericoiade University Hospital
REVIEW RETURNED	02-Nov-2022

GENERAL COMMENTS	very important study especially for clinicians who prefer second generation antipsychotics

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. David Wright, University of Guelph
Comments to the Author:
Sass and colleagues describe a placebo-controlled, randomized clinical trial examining the effect of the GLP1 receptor agonist, semaglutide, on metabolic disturbances in clozapine or olanzapine treated patients with schizophrenia. Given the growing number of individuals being treated with antipsychotics this is an important and timely question that will be addressed.With this being said, the anticipated results would be expected given the authors previous findings demonstrating beneficial effects of concurrent liraglutide treatment in individuals with schizophrenia being prescribed antipsychotics. Within this framework the authors are encouraged to highlight the novel aspects of the proposed trial in comparison to the aforementioned liraglutide study:

Thank you for your observation. You are completely right. The novel aspects of the study have now been highlighted in the introduction of the paper. We hope that you will find this adequate.

Other points to consider are as follows:

1. Pg 7,line 12 the authors mention that despite the presence of metabolic complications that antipsychotic treatment is associated with reductions in mortality. Is this related to decreases in suicide? For the naïve reader this should be discussed in a bit more detail.

Author response: Thank you. This is a good point. We have now added some more information.

2. In Box 3 (page 15) it would seem that standard blood sampling will be used for the determination of HbA1c. However, in Table 1 this will only be done in week 8 and 16. As change from baseline HbA1c is the primary outcome its not clear how this would be calculated. Related to this point it would be informative to have additional readouts of glucose homeostasis throughout the investigation at multiple time points as it may allow for a greater temporal sensitivity in teasing out weight loss dependent vs. independent effects.

Author response: Standard blood sampling appeared by mistake under fasting blood samples at Day 0 and week 26. This has been revised in table 1 and Box 3. Thank you for the important correction.

3. Would it be possible to measure serum semaglutide concentrations at various time points throughout the study? This could provide useful information regarding responders vs non-responders and compliance regarding self-administration of the drug.

Author response: Following our protocol, serum semaglutide will be measured on Day 0 and week 26 (as part of the fasting blood samples). We apologize for the missing information. The analysis has now been added to box 3. Due to the set-up of the blood sampling procedures in our study and the assay of serum semaglutide it will unfortunately not be possible to measure serum semaglutide concentrations at various time points.

Reviewer: 2
Usama Bin Zubair, Mater Misericoiade University Hospital Comments to the Author:
very important study especially for clinicians who prefer second generation antipsychotics

Author response: Thank you so much for revising the manuscript and for the positive comment.

VERSION 2 – REVIEW

REVIEWER	David Wright University of Guelph
REVIEW RETURNED	14-Dec-2022

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.