Author's response to reviews

Title: The potential role of appetite in predicting weight changes during treatment with olanzapine

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Author's response to reviews: see over
June 25, 2010

Melissa Norton, MD
Editor-in-Chief, *BMC Psychiatry*

Dear Dr. Norton:

On behalf of all the authors, thank you very much for the opportunity to resubmit our manuscript, “The potential role of appetite in predicting weight changes during treatment with olanzapine” to *BMC Psychiatry*.

We appreciate the helpful suggestion of the reviewers and believe that we have responded completely. Please find a detailed response listed below and modifications highlighted in the manuscript.

Please address correspondence to Michael Case using the contact information listed below.

Sincerely,

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**Editorial request:**

Ethical issues within the manuscript? - Data were used from adult patients for whom both appetite and weight data were available from 4 prospective, 12- to 24-week clinical trials. The authors should simply state that this secondary analysis is consistent with the original ethics approval for these trials.

**Response:** We added the following statement to the Methods section (page 6):

“…and the analyses presented here are consistent with the original ethics approvals.”

**Reviewer 1:**

**Major Compulsory revisions**

1. The title of the paper doesn’t convey the findings of the paper. i.e., “change of appetite is not a predictor of weight gain”

**Response:** We changed the title to “The potential role of appetite in predicting weight changes during treatment with olanzapine”

2. Authors try to present too much of data, which is understandable in the light of the fact that they are taking data from 4 trials, but this makes the paper difficult to read because of different scales used in different trials.

**Response:** We added a table (Table 1) summarizing the study designs of all 4 studies to aid the readers understanding.

3. The authors have not taken the baseline psychopathology including insight and changes in the same over the time while reporting the changes in the various appetite assessment questionnaires. It is quite possible that these variables would affect the rating on appetite assessment questionnaires.

**Response:** We added a disclosure of the lack of adjustment for baseline psychopathology to the study limitations in the Discussion section (page 14):

“Also, the analyses were not adjusted for baseline psychopathology in the different patient groups and for dose of olanzapine.”
4. The authors have also not reported the relationship of appetite assessment questionnaires and weight changes with the dose of the medication used.

Response: We added a disclosure of the lack of adjustment for dose of olanzapine to the study limitations in the Discussion section (page 14):

“All analyses were not adjusted for baseline psychopathology in the different patient groups and for dose of olanzapine.”

5. Although the authors have tried to study the relationship between weight changes and appetite assessment questionnaires, much of the data presented in the Introduction section appears redundant, as it is not related to the current paper.

Response: We shortened the “Background” section.

6. Similarly in the discussion section the authors don’t discuss their findings in proper perspective and present new results.

Response: We shortened the “Discussion” section.

Reviewer 2:

1) This is an important study, on an unresolved issue.
2) The manuscript is well written.
3) Figures are a little difficult to read. They might be made easier.

Response: We increased the font size in the figures to enhance readability.

4) There are critical references and studies that are missing: a) Kroeze WK et al. Neuropsychopharmacol. 2003, 28:519-526; b) The study of Kinon et al. J Clin Psychopharmacol. 2005, 25:255-258, showing the same results that the authors found here.

Response: We added the suggested references:

“Kroeze et al. demonstrated that affinity to the histamine H1 receptor predicts weight gain associated with typical and atypical antipsychotics.” (page 4, Background)

“Our observation that early weight changes correlate strongly with long-term weight changes is in agreement with earlier findings.” (page 12, Discussion)
5) In the Discussion, the authors refer to studies in rats suggesting an interaction between hyperphagia and sedation. Hence, they look for support in these studies for a non-hyperphagia mechanism in the effects of olanzapine. However, early studies with sulpiride found that there are not weight gain without hyperphagia in female rats (Baptista T, et al. Prog Neuropsychopharmacol & Biol Psychiat. 1998, 22;187-198. This study might be quoted.

Response: We added the suggested reference (page 12, Discussion):

“However, earlier studies with sulpiride showed that there is no weight gain in female rats in the absence of hyperphagia.”

6) While limitations are well acknowledged, it should be insisted that the appetite scales have not been validated. Are you sure they differentiate well from "no change to increased appetite" to "no change to decreased appetite" particularly in severely disturbed patients?

Response: We added the absence of a validation of the scales to the limitations section (page 14, Discussion):

“Additionally, the use of different appetite assessment scales limits comparisons across studies and most of the appetite scales used here have not been validated.”

Reviewer 3:

GENERAL COMMENT:
Case and colleagues examine potential associations between change in appetite and weight changes during treatment with olanzapine, using data from 2 double-blind studies, an open label study and an observational trial. They report an inconsistent association between change in appetite and weight changes. The topic is interesting and the conclusion that ‘early score changes on appetite assessment scales are not a useful predictor for long-term weight changes’ plausible. However, there are several limitations to this manuscript:

1. The studies included markedly differ in terms of methodology, (double blind, open label...), appetite assessment scales, baseline demographics, dietary counseling and sample size. Accordingly, the authors could not pool the data but just describe them separately.

Response: The authors agree with the reviewer that these were the reasons for not pooling the studies.
2. Just one study used validated scales.

**Response:** We added the absence of a validation of the scales to the limitations section (page 14, Discussion):

“Additionally, the use of different appetite assessment scales limits comparisons across studies and most of the appetite scales used here have not been validated.”

3. It appears somewhat questionable to include a study in which “at enrolment patients had been taking 5–20 mg SOT daily between # 4 and # 52 weeks and experienced weight gain # 5 kg or a change of # 1 kg/m2 BMI.”

**Response:** We included this study due to the fact that the described baseline characteristics are similar to values observed in clinical practice. We recognize the limitation of study design heterogeneity in our “Discussion” section (“Our analyses were limited by the differences in study design across the 4 studies…”, page 13) and we chose not to pool the data for this same reason. However, the authors feel that comparisons between weight and appetite in this cohort are nevertheless valuable.

4. The fact that only one study reported an increase but three a decrease of appetite is surprising. Indeed, there is evidence that appetite is increased with olanzapine what, for example, our group showed in a RCT [Kluge et al. Clozapine and olanzapine are associated with food craving and binge eating: results from a randomized double-blind study. J Clin Psychopharmacology 2007, 27(6):662-6].

**Response:** We added the suggested reference (page 5, Background):

“Treatment with both clozapine and olanzapine have been temporally associated with food craving and binge eating.”

5. Unfortunately, the ms. cannot answer the interesting question how appetite and weight are related in olanzapine-induced weight gain.

**Response:** We agree, our data do not allow us to draw conclusions as to how appetite and weight are related during treatment with olanzapine.
SPECIFIC COMMENTS

Introduction
The introduction too broadly discusses potential reasons for weight gain related to the rather modest findings. Instead, it should be focused on appetite and abnormal eating behavior such as food craving and binge eating under treatment with olanzapine. (Interesting and strong associations between food craving and (some aspects) of binge eating with weight gain are displayed in Table 2 but neither mentioned in the introduction nor discussion section.) (Major Compulsory Revision).

Response: We shortened the introduction and added the following statement to the discussion to present associations between binge eating and weight gain within our data (page 13, Discussion):

“Additionally, score increases of several EBA and EAS items that might indicate binge eating showed strong correlations with weight gain.”

Please include the (sparse) relevant literature [e.g. see above; Theisen FM et al. The Spectrum of binge eating symptomatology in patients treated with clozapine and olanzapine. J Neural Transm. 2003, 110(1):111-21.] (Minor Compulsory Revision)

Response: We added the suggested references (page 5, Background):

“Treatment with both clozapine and olanzapine have been temporally associated with food craving and binge eating [12,13].”

Methods
Study design
The studies included need to be described in much more detail. This is particularly necessary as two of them are not fully published. (Minor Compulsory Revision)

Response: We added a table (Table 1) summarizing the study designs of all 4 studies.

Please put the reference just after the described study. (Minor Compulsory Revision)

Response: We put the references directly after the described studies.

Discussion
Please include the limitations listed above that are not already mentioned. (Minor Compulsory Revision)

Response: We added the limitations that were pointed out by the reviewer (see above).
Figures
Please consider to reduce the number of figures if possible. (Discretionary Revision)

Response: We deleted Figures 3a, 3b, 4a, 4b, 4c, and 4d as they did not illustrate statistically significant results.