Author's response to reviews

Title: Predictors and Correlates for Weight Changes in Patients Co-Treated with Olanzapine and Weight Mitigating Agents; a Post-Hoc Analysis

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Author's response to reviews: see over
Dear Dr. Norton:

On behalf of all the authors, thank you very much for the opportunity to resubmit our manuscript, “Predictors and Correlates for Weight Changes in Patients Treated with Olanzapine and Weight Mitigating Agents; a Post-Hoc Analysis”, to BMC Psychiatry.

We appreciate the helpful suggestions of the reviewers and believe that we have responded completely to all questions and comments. Please find detailed responses listed below and modifications highlighted in the manuscript.

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Sincerely,

Virginia Stauffer, PharmD
Eli Lilly and Company

Reviewer #1:

Major Compulsory Revision
1. First, it remains unclear why the authors only included patients with a BMS #25 kg/m². They state in the discussion that people with a lower BMI are more likely to gain weight. Thus, there is a risk of Bias when only including patients with a higher BMI. Second, if the major question is whether a weight changes during antipsychotic treatment can be predicted it seems more appropriate to me to include patients who only received the antipsychotic and not a weight mitigating agent. These may have an influence on the time dependent variables such as decrease in appetite, craving for carbohydrates or hunger. Again, this is a potential source of bias.

Response: We included patients with a BMI greater than or equal to 25 kg/m², not only patients with BMI = 25 kg/m². While patients with a lower BMI are more likely to gain weight during treatment with olanzapine, this phenomenon was not the focus of our analyses. We expanded the list of cited publications that examined weight changes during treatment with olanzapine to provide more complete information:


We agree with the reviewer that focusing on patients with a BMI $\geq 25$ kg/m$^2$ might potentially bias the analysis. Nevertheless, limiting populations using selection criteria is a commonly accepted process in clinical trials, wherein results are considered valid for the sub-population within which the study was performed. We feel that it was necessary to exclude patients with a BMI $< 25$ kg/m$^2$ to homogenize the study population, as our primary focus was on predictors for weight change after addition of weight-mitigating agents to olanzapine treatment in overweight subjects. To state this objective more clearly, we changed the manuscript title:

“Predictors and Correlates for Weight Changes in Patients Co-Treated with Olanzapine and Weight Mitigating Agents; a Post-Hoc Analysis”

And expanded the following passage in the introduction (p. 6):

“This study focuses on pharmacological interventions and their ability to prevent weight gain or to induce weight loss when combined with olanzapine treatment. The aim is neither to extract predictors for weight change during olanzapine monotherapy nor to compare different weight mitigating agents, but to evaluate patients’ characteristics and changes in their eating behaviors during treatment with olanzapine and weight mitigating agents in overweight patients. These predictors may be useful in identifying subgroups of patients who may be susceptible to the effect of weight mitigating agents during olanzapine treatment.”

2. I understand why the authors did not perform a subgroup analysis of patients with schizophrenia and bipolar disorder, they could, however, include “diagnosis” to the regression model. This could give an idea, whether patients with schizophrenia and bipolar disorder may differ in reasons for weight change.

Response: We agree with the reviewer and included “diagnosis” in the regression model. Note, however, that since 1 of the 3 studies analyzed did not include bipolar subjects, the "disease" was partially confounded with the "study" effect that was used as a stratification factor in our Cox regressions. Investigating possible differences across disease type (bipolar vs. schizophrenia) in reasons for weight change as suggested by the reviewer, would require including "covariate-by-diagnosis" interactions in the Cox model in addition to "diagnosis" which, like the subgroup analyses, would not be feasible given our "stratified by study" models. However, to the section detailing that "disease" (equivalent to “diagnosis” variable) was included in the model as a single covariate, we added in parenthesis for clarification (p. 11):
“To examine associations between measures of craving, eating factors, and eating behaviors and subsequent or concurrent weight loss or weight gain, a proportional hazards Cox regression with study-specific baseline hazard functions and time-varying covariates was employed, with disease (psychiatric diagnosis) as one of the baseline covariates in the model.”

In the discussion they should more clearly point out that the analysis was only done in patients who were treated with olanzapine. Maybe reasons for weight change differ when using another antipsychotic.

**Response:** We added explanations in the discussion of the results that the analyses were only done in patients who were treated with olanzapine (p. 14):

“Five variables were identified as predictors for weight loss in patients treated with olanzapine and weight mitigating agents,...” and

“Interestingly, all significant predictors for weight gain in patients treated with olanzapine and weight mitigating agents...”.

3. In the introduction they spend a whole page on describing the CATIE results. This can only be of interest in this context if drop-out rates in the olanzapine arm are mainly due to weight gain. Otherwise this passage can be omitted.

**Response:** We shortened the passage in question (p. 4) to read as follows:

“Recently, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study evaluated the overall treatment effectiveness of olanzapine, perphenazine, quetiapine, risperidone, and ziprasidone. In this study, patients treated with olanzapine showed the greatest treatment effectiveness as determined by measuring the length of time patients remained on their prescribed medication. Patients treated with olanzapine remained on their medication statistically significantly longer compared to patients treated with quetiapine or risperidone, but not compared to patients treated with perphenazine or ziprasidone. [6] However, olanzapine-treated patients gained significantly more weight than patients in the other treatment groups (p<.001), and significantly more patients treated with olanzapine reported potentially clinically significant weight gain ≥7% increase from baseline weight (p<.001) and discontinued treatment due to weight gain or changes in metabolic parameters (p<.001). [6]”