Author's response to reviews

Title: Early evaluation of patient risk for substantial weight gain during Olanzapine treatment for schizophrenia, schizophreniform, or schizoaffective disorder

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Author's response to reviews: see over


Reviewer's report
Title: Early identification of patients at risk for substantial weight gain during Olanzapine treatment for schizophrenia, schizophreniform, or schizoaffective Disorder

Version: 1 Date: 25 March 2008

Reviewer: Douglas Noordsy

Reviewer's report:
This report describes a post-hoc analysis of 2 Lilly datasets involving patients with schizophrenia randomly assigned to olanzapine treatment to evaluate early predictors of substantial weight gain at 26-34 weeks. This report is clear and well written. It presents the hypotheses, methods, results, limitations and conclusions in a methodical, precise and balanced way. I lack the expertise to fully evaluate the statistical methodology, but it appears sound.

- Major Compulsory Revisions
  NONE

- Minor Essential Revisions
  1. RESULTS, 2nd paragraph, second sentence should read: “…was a gain of 5.2 kg at Week 28 (Figure 1B).”
  Thanks for catching that. This change has been made.

- Discretionary Revisions
  2. METHODS, Variables, page 6 and DISCUSSION, Limitations, page 17 refer to the fact that the available data for evaluating long-term weight gain (26-34 weeks) are within the 21 to 39 week range when weight gain has been reported to plateau in previous studies. You might point out that data that exceeded the 21-39 week range would be more valuable than data that fall within that range, as they would give greater confidence that the period of primary weight gain had passed.
  We have added a statement to this effect to the limitations section of the manuscript.

  3. METHODS, Statistical Methodology, last paragraph, page 9: It is not clear from the explanation provided why an evaluation of missing values for weight at week 30 would generate 100 different datasets in order to account for uncertainty in missing values. This section attempts to prepare the reader for RESULTS, Evaluating potential impact of dropouts on the results, where the notion of multiple datasets is not mentioned. The last paragraph of this section on page 14 describes the results of this analysis, in which the correlation between weight change at 3 weeks (measured) and weight change at 30 weeks (imputed) is reported to be higher than in the primary analysis. Although the purpose and importance of this analysis is clear, it is not clear how calculation of correlation of
imputed data to the data it was extrapolated from is valid. I would anticipate many readers coming from a clinical perspective will struggle with this concept. The manuscript also describes this imputed data in terms that make it sound like real data, which is confusing. We have rewritten the section in the methods and in the results to clarify this.

**What next?:** Accept after minor essential revisions

**Level of interest:** An article of outstanding merit and interest in its field

**Thank you.**

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Reviewer's report**

**Title:** Early identification of patients at risk for substantial weight gain during Olanzapine treatment for schizophrenia, schizophreniform, or schizoaffective Disorder

**Version:** 1 **Date:** 31 March 2008

**Reviewer:** Vicki L Ellingrod

**Reviewer's report:**

The authors present an interesting investigation on the relationship between using early weight gain (or lack of weight gain) to predict sustained weight gain (or lack of weight gain) with olanzapine use at 30 weeks. This study utilized two samples of convenience where subjects were randomized to either olanzapine or haloperidol for up to 30 weeks. Weight was measured every week for up to four weeks and then at endpoint (28 or 30 weeks). Overall the authors report that 88% of subjects who gained less than 2kg, did not go on to gain substantial weight (<10 kg) by 30 weeks.

Overall this is an interesting article that benefits from data already collected and aims to address a very important clinical question. The authors point out that use of a simple measurement such as weight obtained weekly would greatly enhance the clinicians’ ability to predict those at greatest risk for substantial weight gain with olanzapine treatment. However, there are a few issues associated with this manuscript that the authors may consider revising.

**Major Compulsory Revisions**

1. Within the abstract it states that 88% of subjects who gain less than 2kg by week 3 will gain less than 10kg after 26-34 weeks. This statistic comes from the negative predictive value (NPV) outcome of this study. The tone of the rest of the manuscript seems to focus on those subjects who gain >4.5 kg and the ability to
predict substantial weight gain at 30 weeks. Given that the positive predictive value (PVV) of this measurement is very low (37.5%) perhaps the focus of the rest of the manuscript should be on the NPV figures and not the PVV figures. This also holds true for the conclusion, especially since data related to bipolar disorder is included here and the summary of results from this investigation are not. Perhaps the title should also be changed to correctly reflect the NPV and not the PPV.

We have changed the title as requested. Reference to the published bipolar data (reference 15) has been removed from the conclusion and placed earlier in the discussion section. Also, it is apparent from this reviewer’s comments that our analysis to estimate the effect of selection bias in the population was confusing, we have tried to clarify this.

2. It would be helpful for the authors to include some data on how many subjects did not gain > 2kg at week three and thus were not at risk for substantial weight gain later. From Figure 1, it may be roughly estimated that 70% of subjects in the two treatment trials gained > 4kg. If this is true then really a small minority of subjects would meet the NPV criteria for risk.

The information on how many patients did not gain >2 kg at week three is included in table 2, however this is a very busy table and we understand why that was not apparently to the reader. We have added additional text explaining the table and specifically mentioning the 2.0 kg data.

3. Additional details regarding the number of subjects who dropped out the treatment trials due to weight gain should be included to give the reader a better understanding of subjects included in this study.

Less than 1% of patients dropped out of these studies due to weight gain. This information has been added to the manuscript.

4. It is interesting that the authors did not report any of this data related to BMI. Since BMI is given as a baseline predictive variable, the authors had access to the necessary information to calculate these values. Although use of a simple weight gain measure may be practical in the clinic, any potential relationships with BMI changes may help to underscore the importance of monitoring metabolic and weight changes with antipsychotic use. Given that a 5kg increase in weight may indicate different overall cardiovascular risks depending on body composition (i.e. height and BMI), it would be interesting to have this data available.

We have added an additional table with BMI analyses, and some discussion of these results.

Minor Essential Revisions
1. Inclusion of previous studies that used early weight gain to predict substantial weight gain later on should be part of this discussion section so that the reader can gain a better understanding of the literature evolving on this topic.

We have expanded on this in the discussion section.
2. Also, inclusion of recommendations regarding the NPV should be included in the discussion, especially since it appears that the number of subjects that would meet the <2kg weight gain criteria seems to be extremely low.

We have clarified in the discussion that 39.6% of patients gained more 2 kg or more at 3 weeks (60.4% did not). We had added a paragraph better explaining how to interpret the results in the tables, including the NPVs.

Discretionary Revisions
1. Perhaps the most exciting part of this manuscript is the data concerning the negative relationship between weight change and PANSS score. It is too bad this data was not highlighted more within this manuscript. Although this is not the focus of this manuscript, we have added a brief discussion of this point to our discussion.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.