Reviewer's report

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

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Reviewer: Vicki L Ellingrod

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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.

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.

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.

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.

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.
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.

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.

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.

Declaration of competing interests:

Dr. Ellingrod has the following competing interests to declare:
Member of Eli Lilly Advisory Board
Author for Lexi-Comp
Grant support received from NARSAD and NIMH