Author's response to reviews

**Title:** Acute Weight Gain, Gender, and Therapeutic Response to Antipsychotics in the Treatment of Patients with Schizophrenia

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**Version:** 3 **Date:** 24 November 2004

**Author’s response to reviews:** see over
To the BioMed Central Editorial Team:

Thank you for considering the publication of our manuscript “Acute Weight Gain, Gender, and Therapeutic Response to Antipsychotics in the Treatment of Patients with Schizophrenia” (Manuscript ID 384733023437996). We have carefully addressed each of the reviewers’ helpful comments and followed all their requests for major compulsory revisions and their suggestions for minor essential revisions (please see below). We opted to not make one “discretionary revision” because we felt that this manuscript is not well suited for presenting specific speculative explanations to the observed phenomenon. We did, however, present several broadly stated potential explanations of the findings.

We wish to thank you for carefully choosing fair and balanced experts to review our paper. Each reviewer was well versed in the research topic and both made excellent suggestions that we believe have greatly improved the quality of the revised manuscript. We sincerely hope you will accept this manuscript for publication in BMC Psychiatry.

Best regards,

Haya Ascher-Svanum

Response to BMC Psychiatry reviewer: Douglas Noordsey

Major compulsory Revisions:

1. Address the possibility that weight change is a proxy for treatment adherence, which could explain the relationships found. Treatment adherence is not mentioned in this manuscript. Was it measured?

   Response: Indeed, the possibility that weight gain and improvement occur together because improvements occur mostly in those patients who are adherent needs to be addressed. In the current study, medication adherence was measured by pill count of “daily blister medication cards” at each weekly visit. Patients who missed medication intake for 5 consecutive days were discontinued from the study. Although pill count is not the optimal way to assess medication adherence, the protocol-driven study discontinuation of nonadherent patients suggests that the observed association between weight gain and better outcome was not likely to be an artifact of differential medication adherence. Meltzer and colleagues [16] investigated this possibility in a rigorous manner upon finding a significant association between clozapine-emergent weight gain and improved psychopathology. In their study, non-adherent patients were expected to have lower or absent plasma clozapine levels, but there was no relationship between plasma clozapine levels and weight gain or clinical response. Meltzer and colleagues also monitored adherence closely during weekly visits to determine white blood count and found no evidence of intermittent or poor adherence in their study patients. This important information was added to the Methods section (pg 8) and the Discussion (pg 22).

2. Address the possibility that acute associations between weight gain and functional outcomes may change over time as greater weight gain accrues. This may explain disparity between shorter term, prospective studies and longer-term studies
discussed on pages 16-18. This is acknowledged as a limitation of the study on pg 19, but needs to be included in the earlier discussion as well. Why was the acute treatment period chose, and not longer-term data?

**Response:** There is clearly a need to explain why we chose the 6-week acute treatment period, and discuss in more details the possibility that the observed associations between weight gain and functional improvements may change over time as patients accrue more weight. Per your helpful suggestion, we added information to the Methods section (pg 7) and the Discussion section (pg 20-21), where we elaborated on the reasons for using data from the acute phase. First and foremost, this was a 6-week randomized double blind clinical trial with a 46-week “responder maintenance period“, in which only patients who responded to the acute 6-week treatment per predetermined response criteria were eligible to continue. Consequently, the study design did not permit a longer-term analysis on the link between weight gain and improvement because only patients who improved during the first 6-weeks phase were followed-up for a longer time period. Second, the 6-week period represents a relevant time frame used in clinical practice to determine treatment outcome and decide on treatment discontinuation. For many clinicians the initial 6-weeks of antipsychotic therapy is a minimal time period in which to critically evaluate how patients are responding to a new course of therapy (Basson et al, 2001). Next, the rate of weight gain previously reported on clozapine was greatest in the first 6 weeks and slowed thereafter. Meltzer et al (2002) reported the increase between 6 weeks and 6 months to be equivalent in magnitude between baseline and 6 weeks. This observation further enhanced the relevance of studying this phenomenon during the first 6-weeks of treatment. And lastly, the short duration of the current study is comparable to most previous studies of antipsychotic-emergent weight gain and clinical improvement, thus enabling more direct comparisons between the present and the previous findings.

It is important, however, to note that the association between weight gain and functional outcomes may change over time as patients accrue greater weight gain. Although weight gain appears to be greatest and most rapid during the first 12 weeks for olanzapine with a trend toward a plateau after approximately 39 weeks of treatment, [50] longer-term studies will be needed to determine the validity of the current findings as patients accrue more weight. This may be, however, difficult to study. Patient attrition from studies is not random, with those experiencing poor treatment efficacy or poor tolerability being more likely to discontinue the study, leaving a relatively homogeneous group of study completers who are also treatment responders. Such reduction in the variability of treatment outcomes may diminish the likelihood of finding this phenomenon in long term randomized double blind studies. Further, if this phenomenon were to be investigated in long-term naturalistic observational studies, one would likely face another problem, namely the prevalent use of polypharmacy [51], and the dynamic nature of treatment
for schizophrenia, [52] with frequent changes in antipsychotic regimens and in concomitant psychotropic medications. Such complexity may increase the difficult in identifying which treatment at what time was associated with which weight gain and treatment outcome (manuscript pg 21).

3. The authors do not address the impact of multiple comparisons on the meaning of their statistical findings. They do not specify what p values were chosen to indicate statistically significant differences, and how.

Response: A paragraph has been added to the statistical analysis section (pg 10) indicating that we have chosen an alpha value of .05 to specify statistically significant differences and identifying the multiple comparison procedure we chose to employ for the primary analyses. The primary analysis consists of the 4 sets of regression assessing the correlation between change in clinical symptoms and change in weight. We applied the Hochberg alpha correction procedure [37] for these four analyses resulting in all four hypotheses remaining statistically significant. We have chosen not to complete alpha correction for the other significance tests because they are presented as supporting information for this primary analysis (i.e., differences in baseline characteristics, differences in outcomes by treatment or medication, or alternative assessments of this same finding using different methodology to be more comparable to previous literature).

Minor Essential Revisions:

1. Revised as suggested: The p-values in Table 1 refer to differences between women vs. men. This information was added as a footnote to Table 1.
2. Aripiprazole was added, as suggested (pg 4).
3. Revised as suggested. Now reads (pg 11) “Further, 17.6% of the haloperidol treatment group and 41.4% of the olanzapine-treated patients gained at least 3% of their baseline body weight.”
4. Revised as suggested: added to pages 10-11: “At baseline, the weight and BMI of the haloperidol-treated women and men, were significantly greater than the weight and BMI of olanzapine-treated women and men (Table 2). Further, men in either medication group weighed significantly more than women at baseline, on the average, and their mean baseline BMI was significantly lower than that of women.”
5. Revised as suggested to “…every one-kilogram increase in weight at 6-weeks was associated with approximately…” (pg 14).
6. Pg 14 last PP, 1st sentence is confusing. Be more specific. That sentence now reads (pg 15) “Although weight gain was identified as a prognostic marker of therapeutic response for both treatment groups, it was unclear if this marker is stronger for the olanzapine than the haloperidol treatment group because the
olanzapine-treated patients had greater weight gain and greater therapeutic improvements compared to the haloperidol treatment group. To address this question, we calculated the…”

7. Results from Table 3 are presented in page 15, and the sentence “with a stronger link observed in the olanzapine than the haloperidol treatment group” was replaced with “This link impacted olanzapine-treated patients more than those treated with haloperidol because improved clinical and functional outcomes were more pronounced for the olanzapine-treated patients, who were also more likely to experience weight gain than patients treated with haloperidol.” (pg 15).

8. Revised to “were numerically larger than those found in…” Page 17.

9. Greater specificity on what footnotes mean in Table 2. Revised to indicate that there was a statistically significant (p < .05) difference between groups at endpoint after controlling for baseline scores.

**Discretionary Revisions:**

1. Suggested discussing causality of the findings (page 18) by stating the speculative possible relationships between fatty acids that comprise neurona membranes, symptoms, and lipid metabolism.

**Response:** Considering the speculative nature of the relationships between fatty acids, symptoms, and lipid metabolism, we opted to discuss potential causes of the present findings only in general terms. We mentioned the numerous factors that may impact patients’ weight gain during treatment, which include environmental, behavioral, neurochemical, genetic, and clinical factors [17], and added (pg 20-21, per another reviewer’s suggestion) that the association between weight gain and therapeutic improvement may reflect for some patients the restoration of weight lost during an acute episode because patients tend to lose weight during an acute psychotic episode and were previously found to restore their original body weight upon recovery [47].

Thank you again for your helpful suggestions that helped to greatly improve the quality of this manuscript.
Response to BMC Psychiatry reviewer: Johannes Hebebrand

Major Compulsory Revisions.

1. The study (only) shows that this is true after 6 weeks of treatment. Thus, both in Results and Conclusions of the abstract, the time period should again be made very clear.

   **Response:** As suggested, we added the 6-week time frame to the Results and the Conclusions of the abstract. (pg 2,3).

2. Several related comments that warrant separate responses:
   a. How were the patients randomized? …Why is the ratio for the two medication groups for males not 2:1.

   **Response:** Participants were randomly assigned in 2:1 ratio (2 olanzapine subjects for each haloperidol subject). Although randomization was not stratified by gender or any other patient characteristic, the ratio of males to females was similar for the two treatment groups. The ratio was 1.86:1 for the olanzapine treatment group (N=1337), which included 870 men and 467 women, and 1.83:1 for the haloperidol treatment group (N=659), which comprised of 426 men and 233 women. We added this information to the Methods section, top of pg 7.

   b. The potential bias introduced by prior medication, because if HAL-treated patients were previously treated with atypical antipsychotics, patients might have lost weight under HAL merely because they had previously gained weight on an atypical.

   **Response:** This is an important consideration that was not discussed in the manuscript. We added information (pg 7) to clarify that the type of antipsychotic medication used prior to enrollment was not assessed in the current study, but the likelihood of previous treatment with an atypical antipsychotic drug was very low, because the study was initiated in 1994 when only clozapine was available in some of the sites. Further, randomization worked for patient and illness characteristics [32], and there is no reason to expect that the randomization did not work for other characteristics such as type of prior antipsychotic medication.

   Please also note that we have reported in the introduction that the association between weight gain and therapeutic response was observed with first-generation antipsychotics many years before the introduction of atypical antipsychotics, suggesting that this phenomenon is not an artifact of weight loss following weight gain on an atypical antipsychotic such as clozapine or olanzapine. To help highlight this issue, we revised the introduction (pg 4) to read “This expanding body of evidence augments studies on first-generation antipsychotics predating the introduction of atypical antipsychotics by about 30 years, also suggesting a link between weight gain and improved therapeutic response [20-22].”
More patients treated for the first time with neuroleptic medication may render a comparison between HAL and OLZ difficult.

**Response:** This is an important point that needs to be addressed. It appears that only a small number of study participants were first episode patients (83/1996 or 4.2%). Of the 83 first episode patients, 59 were randomized to olanzapine and 24 to haloperidol. This indicates a ratio of 2.46:1, which is only slightly higher than the 2:1 ratio in which patients were randomized to olanzapine or haloperidol in this study. The relatively small sample size of the first episode patients, along with the 2.46:1 randomization ratio suggest that our findings are not likely to be an artifact of differential rates of first episode patients in the two treatment groups. We added information about first episode patients to the Methods section, Subjects and Study Design (pg 7).

3. The authors themselves address the importance of whether weight gain occurs in a lean versus an already obese individual. Maybe the data actually imply that lean patients (who potentially gain more weight under neuroleptic medication) have a better outcome at six weeks than those with overweight? This issue should be addressed by correlating BMI upon entry into the study with outcome measures.

**Response:** This is a very important point that needed further discussion, because prior research has shown that one of the most robust factors predicting acute treatment-related weight gain in patients with schizophrenia is low baseline BMI \[27,28,15,16,49\]. This observation does not conflict, however, with the present findings. In the main regression analyses that demonstrated the association between clinical outcomes and weight change, we included baseline weight as covariate, indicating that the finding is independent of baseline weight (and therefore BMI). To augment this original information, we followed your suggestion and correlated the change in BPRS core symptoms and changes in weight while controlling for time in the study separately for individuals who were underweight (BMI < 20), average weight (20 ≤ BMI < 25), overweight (25 ≤ BMI < 30), or obese (BMI ≥ 30). We found the correlation to be similar in magnitude (-.17 for underweight, -.11 for average weight, and -.13 for overweight) and statistically significant for all groups except the obese group (-.01). Further investigation revealed that the obese group had the least severe baseline symptoms, the least amount of weight gain, and the least amount of symptom reduction. A paragraph has been added to the results section conveying this important additional information (pg 15).

4. Inform the reader that weight gain at 6-weeks under OLZ is small compared to weight gain accrued by the time weight gain plateaus for OLZ-treated patients.

**Response:** This is an important issue that we neglected to address in the manuscript, but revised per your helpful suggestion to state in the discussion (pg 22), “It is noteworthy that this study assessed treatment-emergent weight
gain at 6-weeks, although patients continue to accrue weight beyond the acute treatment phase. For olanzapine-treated patients, the mean weight gain observed at 6-weeks (2.0 kg) was about a third of 6.26 kg mean weight gain found at 39 weeks, when weight gain tends to plateau on olanzapine [50]. Similarly, the haloperidol-treated patients had a 0.3 kg mean weight gain at 6 weeks, which was less than half of 0.69 kg mean weight gain observed for these patients after 39 weeks of treatment. This observation highlights the need to study the association between weight gain and treatment outcomes in longer-term studies. The choice of 6-weeks was not only driven by the design of the study, in which treatment responders in the acute phase were followed up in the 46-week maintenance period of the study, but also by the clinical relevance of the acute treatment phase. Clinicians often use the first 6-weeks of treatment to assess the tolerability and effectiveness of a new antipsychotic regimen and to decide whether to continue or discontinue that course of therapy [15]. Further, the study of the first 6 weeks of treatment enabled comparisons of the current findings with other studies, which were typically of short-term duration.”

5. Some weight gain may reflect return to original body weight. The issues of restorative weight gain.

Response: It is indeed likely that the association between weight gain and therapeutic improvement reflects for some patients the restoration of weight lost during an acute episode. This possible etiology has been added to the discussion (pg 21) to read, “There are numerous factors that may impact patients’ weight gain during treatment, including environmental, behavioral, neurochemical, genetic, and clinical factors [17]. It is especially notable that the association between weight gain and therapeutic improvement may reflect for some patients the restoration of weight loss during an acute episode because patients tend to lose weight during an acute psychotic episode and were previously found to restore their original body weight upon recovery [47].”

6. The correlations are low, explaining a small proportion of the variance in outcome.

Response: Although the correlations are relatively low, we feel it is important to evaluate the findings beyond the magnitude of the correlation coefficients. To that end we revised the discussion (pg 23) to read, “Another study limitation is the correlational nature of the analyses, which precludes cause-effect relationship and allows for the possibility that the observed associations might be due to an unobserved variable or set of variables. Further, the relatively low correlations suggest that the association explains only a small proportion of the variance in treatment outcomes. Response to antipsychotic medications is a complex phenomenon that is associated by numerous relatively independent components [16] and weight gain is only one of them. Nonetheless, this link was demonstrated when using other statistical approaches, including contrasting of weight gains between responders and
patients who did not respond, by identifying the degree of improvement associated with every 1-kg gained at 6 weeks, and by calculating the conditional probability of therapeutic response given various amounts of weight gain. These findings are important as they suggest that acute weight gain is a valuable prognostic marker in the treatment of schizophrenia.”

Thank you again for your valuable suggestions that have greatly helped improve the quality of our manuscript. We are especially grateful for your kind general comments that helped us realize the need to follow special precautions because this study was conducted at Lilly, and our scientific findings, despite being consistent with previous independent research, may be trivialized as a marketing tool. Much appreciated.