Reviewer's report

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

Version: 1 Date: 9 September 2004

Reviewer: johannes hebebrand

Reviewer's report:

General
Ascher-Svanum et al. have conducted an excellent study based on a very large sample size. The paper is well written. The study clearly represents a major advancement in this important research field. However, the reviewer is critical of the rather one-sided interpretation of the data. Because the authors stem from the Lilly Research Laboratories and because the results of the study can be used for marketing purposes, special precautions are warranted to ensure that readers do not uncritically equate weight gain with a better outcome.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The study (only) shows that this is true after six weeks of treatment. Thus, both in Results and Conclusions of the abstract, the time period should again be made very clear (currently only addressed in methods in parentheses).
2. How were the patients randomized? This is of critical importance, because haloperidol is frequently given as first medication. Thus, I would expect that many patients in the olanzapine group had already been pre-treated with haloperidol, whereas it is uncertain what medications the haloperidol patients had received prior to entry into the study (e.g. if they had received atypical neuroleptics, patients might have lost weight under haloperidol merely because they had previously gained weight on an atypical). Furthermore, why is the ratio for the two medication groups for males not 2:1 (n = 870 versus n = 426)? Clearly, differences in prior medication potentially introduce a bias. Thus, if e.g. the haloperidol group included more patients treated for the first time with neuroleptic medication, this might render a comparison with the olanzapine group difficult. I would expect that previously neuroleptic free patients treated with olanzapine would gain more weight than those pre-treated with haloperidol. In sum, the authors should provide detailed information on the type of previous neuroleptic medication and the total amount of time the patients had been taking neuroleptic medication prior to entry into the study (present data for each medication group separately). If such data are not available, these aspects need to be discussed at length.
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.
4. In the discussion the authors should mention the range of average weight gain under olanzapine upon reaching a weight plateau. This is important to document that this amount is not readily comparable to the in comparison small weight gain achieved after 6 weeks.
5. The authors need to discuss that some of the patients who were potentially psychotic upon initiation of treatment with haloperidol or olanzapine might have lost weight during their acute psychosis (this is reported to occur in the literature). In this scenario, weight gain would merely be secondary to the effectiveness of the medication; the weight gain would thus reflect the return to the original weight prior to onset of an acute episode.
6. The correlations between weight gain and the different weight outcomes are low. For simple-minded readers it should be explained that weight gain only explains a small proportion of the outcome.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

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Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

none