

Biological Psychiatry fax number: ~~203-764-4324~~

Manuscript number 5380, Incidence and Rate of Treatment-emergent Potential Impaired Glucose Tolerance (IGT) and potential Diabetes with Olanzapine Compared to Other Antipsychotic Agents and Placebo by Charles M. Beasley, Jr., Kenneth Kwong, Paul H. Berg, Cindy C Taylor, Jamie Dananberg and Alan Breier

Referee # 1

REVIEWER'S COMMENTS FOR AUTHOR(S):

The authors present the results of a comparison of non-fasting glucose measures among patients treated with olanzapine, placebo, and comparator antipsychotics from the Lilly clinical trial database. This is a welcome and important study since concerns have been raised regarding the propensity of olanzapine and other atypical antipsychotics (except ziprasidone) to cause glucose intolerance. The authors also examined risk factors for glucose intolerance including age, body wgt, and increase in adiposity during treatment.

The Introduction is scholarly and complete. Importantly, it provides an often forgotten historical perspective that abnormalities in glucose metabolism have been ascribed to typical antipsychotics and to psychoses. The importance of this study thus rests with its ability to compare the incidence and rate of treatment-emergent IGT or diabetes during treatment with various atypical antipsychotics versus typicals and placebo.

My only concern regarding the methods of the study, and thus with interpretation of their results, is whether the data were biased toward short-term studies of insufficient duration to detect the effect the authors were examining. This is especially relevant to the estimates obtained for patients receiving placebo. It would be very helpful to know how many of the 6374 patients in the database were actually in treatment trials beyond 8 weeks.

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Referee # 2

REVIEWER'S COMMENTS FOR AUTHOR(S):

The authors present a highly curious dataset. Since their own work has shown that olanzapine is associated with a clinically and statistically pertinent increase in weight compared to both haloperidol and placebo, they seem to be suggesting that olanzapine exerts a sizeable antidiabetic power. It is estimated by the American Diabetic Association that a one pound increase in adipose tissue is associated with a fourper cent increase in the risk of diabetes. Given that olanzapine induces significant weight changes and the authors believe and report that it does not increase the risk of diabetes, olanzapine appears to be in the enviable position of eliminating the known risk of glucose intolerance associated with weight gain.

Ref # 4

Comments for authors

The authors address one of the critical questions in the pharmacotherapy of schizophrenia: do newer agents – in this case olanzapine – lead to impaired glucose tolerance and a greater risk of the development of diabetes. The approach is the measurement of random blood glucose concentrations in a large number of different studies. These include trials that include olanzapine, haloperidol, risperidone, and clozapine.

1. The authors do not adequately emphasize how crude their method is for finding an effect. Random glucose values represent an insensitive method for assessing glucose tolerance.
2. Most of the values were probably drawn during the first three months of each trial. It would be helpful to know the number of samples in each condition that were collected during the later stages of the trials. For example, the number of specimens that were drawn for each drug condition during months 6-12.
3. Many of the early studies of olanzapine were biased toward low doses of the drug. Since there is a consensus that most patients require 10 mg or more of olanzapine, it would be helpful to know if there is a dosage effect on glucose tolerance.
4. This study is important since there is relatively little controlled data in this area. At the same time, it is a study with a good deal of commercial interest, and a study that was designed and the data was analyzed by olanzapine's manufacturer. For this reason, it would be important to have an independent analysis of the findings. If there is a Type II error in these findings, this could lead clinicians to underestimate a serious drug risk.

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