

To: CN=Alan Breier/OU=AM/O=LLY@Lilly; CN=Patrizia Cavazzoni/OU=AM/O=LLY@Lilly;
jbuse@med.unc.edu; CN=Nitai Mukhopadhyay/OU=AM/O=LLY@Lilly
Date: 01/24/2003 02:52:13 PM
From: CN=Christopher Carlson/OU=AM/O=LLY
Subject: DECISION on Diabetes Care DC02-1269

All,

Sorry to be the bearer of bad news but....

----- Forwarded by Christopher Carlson/AM/LLY on 01/24/2003 02:42 PM -----

diabetescare@diabet
es.org To: carlson_christopher@lilly.com
01/24/2003 02:16 PM cc: editorialoffice@diabetes.org
Subject: DECISION on Diabetes Care DC02-1269

Dear Dr. Christopher Carlson:

Re: Retrospective Analysis of Risk Factors in Patients with
Treatment-Emergent Diabetes during Clinical Trials of
Antipsychotic Medications

Thank you for submitting your manuscript as titled above. It has
been examined by reviewers and by the Editorial Committee. I am
sorry to inform you that after careful consideration, we were
unable to assign it sufficient priority to allow publication in
Diabetes Care.

In addition to essential features (hypothesis testing, suitable
controls, appropriate statistical methods, clear reporting of
results, and conclusions supported by the results), papers are
also evaluated on their uniqueness, timeliness, and importance.

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As you may know, because of limited editorial space we cannot accept the majority of manuscripts submitted. Copies of the reviewer remarks are included with this letter for your consideration.

We appreciate receiving your manuscript and having the opportunity to consider it. I do hope that the points raised will assist you in the eventual disposition of this manuscript and in your further search in this area. Although I know you will be disappointed by our decision in this case, I hope you will continue to send us your contributions.

Sincerely,

Mayer B. Davidson, MD
Editor, Diabetes Care

Comments to Author:

Reviewer A Comments:

In the research design and methods: I would be interested to know how many studies and subjects were including in the medication crossover where only the initial period of monotherapy was used- what was considered baseline (and what drugs were the coming off of?)

The baseline glucose values (pre-randomization): is this the mean per patient or was the highest value taken? How many subjects, per drug group, had baseline random glucose >7.8 mmol/l?

Please provide data on the number of samples taken post-randomization and per drug category.

Also, need more demographic data on subjects such as race/ethnicity, gender.

While the 27 subjects with baseline single random glucose values > 11.1 mmol/L are not excluded from the analysis, a final glucose

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> 11.1 is considered diagnostic of treatment-emergent diabetes. Why is this? Please provide a breakdown of which drugs these 27 patients were randomized to and their outcomes. Also, I wonder what the impact of removing the endpoint glucose > 11.1 would have on the analysis. Please be consistent.

A better justification (and references) is needed for the UGT category where it is stated that a postprandial glucose level rarely exceeds 7.8 mmol/L. In this retrospective report, there is no information on the time course of blood test in relation to meals - which likely varied a great deal based on inpatient and outpatient status as well as individual study sites.

Additionally, (page 6) the authors cite a paper by Rolka et al, to justify using a cut-off of 7.8 (140), then why not use the 120mg/dl cut-off which was more sensitive than the 140mg/dl and only slightly less specific? There were also differences based on gender in this study.

No mention of other risk factors for DM such as FH (not obtained?) and lipid abnormalities (likely obtained).

Please provide the N's in the analysis related to weight - 20% of patients. BMI could not be calculated and assumed to be of normal weight? This assumption may influence results related to the impact of weight gain.

Because haloperidol is not thought to be associated with increased rates/reports of diabetes, I would compare olanzapine to haloperidol alone (as a separate analysis) and not lump risperidone in the group.

Concerning the risk factor assessment, I would compare the 3 categories (TED, UGT, NGT) for olanzapine patients to see if the differences in risk factors also hold up for subjects treated with this drug...

Results section: of the 94 TED, age >35 is cited as a risk where in the methods section, age >45 is used...

Need data on the observation time difference between TED patients and NGT patients. Is it possible that if the time course were equal, more patients would have crossed over to UGT or TED? The time course on change in glucose values and average number of measurements per drug group would be useful.

The limitations outlined are accurate. However, the authors still overstate the data by making the statement that "...olanzapine did not have a significantly greater risk of TED with non-olanzapine cohort..." Again, these are nonfasting, random glucose values in a study not intended to screen for diabetes.

Reviewer C Comments:

- 1) This retrospective study of random glucose levels does not contribute meaningfully to the literature on this topic.
- 2) Registration studies usually do FASTING baseline lab work. Why are they not presented?
- 3) The study by Glick et al (presented at ADA) of olanzapine ziprasidone show significant hyperglycemia and hyperinsulinemia with olanzapine in a 6-week prospective study. That stands in contrast to this retrospective study.
- 4) The authors misrepresent at least two studies (references 23 and 25) where contrary to their assertion, olanzapine was indeed associated with higher diabetes rates than risperidone.