

22 January 2004

Richard Kahn, PhD
Chief Medical and Scientific Officer
American Diabetes Association
1701 N. Beauregard St.
Alexandria, VA 22311

RE: Consensus Development Conference on
Antipsychotic Drugs and Obesity and Diabetes

Dear Dr. Kahn,

Eli Lilly and Company commends the American Diabetes Association for its initiative in addressing issues concerning metabolic adverse events in patients using atypical antipsychotics. As the sponsor that initially brought these issues to the attention of the ADA, Lilly appreciated the opportunity to partner with ADA, APA, AACE, NAASO, and other sponsors in presenting data at the Consensus Development Conference.

We have reviewed the Consensus Statement forwarded to us by the ADA and commend the working group for bringing focus to the critical issue of increased rates of diabetes in patients with serious mental illness. However, we have significant concerns regarding the conclusion that there are differential rates of treatment-emergent diabetes among second-generation antipsychotics (SGAs). We disagree with the following conclusion as stated on page 600:

“Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia. Risperidone and quetiapine appear to have intermediate effects. Aripiprazole and ziprasidone are associated with little or no significant weight gain and no diabetes or dyslipidemia, although they have not been used as extensively as the other agents” (pg. 600).

Specifically, we do not believe that currently available data support differential diabetes rates among SGAs, based on the following:

- 1) In a recent study of over 38,000 Veterans Administration patients, Sernyak and colleagues (2002) found that quetiapine was associated with increased diabetes risk; among younger age groups, risperidone was also associated with increased diabetes risk compared to first-generation antipsychotics (FGAs). In a second large VA study, Cunningham and colleagues (2003) found similarly increased risk for diabetes among patients treated with olanzapine, quetiapine, or risperidone compared with FGAs, notwithstanding the fact that the smaller quetiapine cohort did not achieve statistical significance. The Cunningham study is particularly important because it was considered by the FDA to derive class-labeling changes for all SGAs.
- 2) The authors' statement that "the data consistently show an increased risk for diabetes in patients treated with clozapine or olanzapine compared with patients not receiving treatment with FGAs or with other SGAs" (pg. 598) is not supported by the data and is misleading. The data are inconclusive with respect to such comparisons. The most informative and scientifically rigorous way of evaluating relative risk of diabetes across SGAs in epidemiological studies is to directly compare cohorts of patients treated with SGAs. Only a minority of epidemiological studies have conducted direct comparisons among the SGAs; out of these, several studies demonstrated comparable and overlapping confidence intervals among the SGAs. An important study not cited in the Consensus Statement analyzed a database of over 50,000 patients taking either FGAs or SGAs, and found that risperidone, but not olanzapine, had significantly higher risk of diabetes compared with haloperidol (Buse et al. 2003), which further challenges the assertion contained in the Consensus Statement.

Similarly, we disagree with the information regarding the relative risk of diabetes across SGAs as presented in Table 2 (pg. 597) of the Consensus Statement. Not only do we disagree with the conclusions as presented in the table, but find that the visual representation is potentially misleading in its use of the symbol "0" to reflect "discrepant results." More typically, discrepant findings are represented with "+/-" or "?."

- 3) Although the Consensus Statement recognizes the limited data available for aripiprazole and ziprasidone, it nonetheless concludes that these compounds have “not shown an increased risk for diabetes” (pg. 598). In fact, in large clinical trials by Lilly, Pfizer, and Bristol-Myers Squibb, no significant differences in treatment-emergent hyperglycemia/diabetes were observed between patients treated with olanzapine vs. aripiprazole, nor between patients treated with olanzapine vs. ziprasidone. In Bristol-Myers Squibb’s 6-month registration trial for aripiprazole, rates of treatment-emergent hyperglycemia/diabetes or glucose-related adverse events were similar between olanzapine and aripiprazole (Abilify NDA 21-436, FDA WWW). In two prospective, double-blind clinical trials, one Pfizer-sponsored (Glick et al. 2001) and one Lilly-sponsored (Kane et al. 2003), glucose levels in patients treated with ziprasidone were shown to be similar to those observed in olanzapine-treated patients.
- 4) In addition to the Buse study cited above, the findings of three additional important studies were provided and presented to the panel, but were not included in the Consensus Statement. One study analyzed a clinical trial database of over 5,000 patients with schizophrenia and found that pretreatment glucose levels and total number of diabetes risk factors (eg, age, non-Caucasian ethnicity, pretreatment BMI) are significant predictors of subsequent treatment-emergent diabetes (Cavazzoni et al. British J Psychiatry, in press). Contrary to the Consensus Statement’s conclusions, these analyses demonstrated that treatment-emergent weight gain and/or antipsychotic treatment assignment did not predict treatment-emergent diabetes.

The other two omitted studies included clamp assessments. As indicated in the Consensus Statement, clamp studies are important components for evaluation of diabetes and SGAs. In a prospective, randomized, placebo-controlled study using a hyperglycemic clamp, no impairment of insulin secretion was observed with either olanzapine or risperidone treatment (Sowell et al. 2002). In a similar study using a hyperinsulinemic-euglycemic clamp, no impairment of insulin sensitivity was observed with either olanzapine or risperidone treatment (Sowell et al. 2003).

- 5) The conclusion of differential diabetes rates among SGAs is inconsistent with the class-labeling approach adopted by the FDA. On the basis of extensive review of data over a number of years, the FDA concluded, “epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics” (FDA Class Labeling Letter, received by Lilly on 15 September 2003). In this class-labeling letter, the FDA directed all sponsors of SGAs to implement class labeling with regard to hyperglycemia/diabetes. In addition, contrary to the suggestion in the Consensus Statement, the FDA labeling recognizes that patients with diabetes and patients with risk factors for diabetes may be started on any SGA with appropriate clinical monitoring.

In conclusion, while we agree with many facets of the Consensus Statement, we disagree that the currently available literature supports the conclusion of differential rates of diabetes among SGAs. This assertion may have detrimental clinical implications leading to inappropriate discontinuations of certain SGAs and lack of appropriate monitoring of metabolic effects during treatment with others.

Lilly shares the ultimate objectives of the Consensus Panel in evaluating the data related to diabetes, serious mental illness, and SGAs; conducting further research; and providing guidance to clinicians on this important topic. However, we would like to have an opportunity to discuss the concerns outlined above, prior to publication of the Consensus Statement, to ensure that these objectives are met.

Sincerely,

Alan Breier, MD
Chief Medical Officer and Vice President, Medical
Eli Lilly and Company

cc: Nathaniel Clark, MD, Vice President, Clinical Affairs, ADA
Darrel A. Regier, MD, MPH, Director, Office of Research, APA
Philip Levy, MD, President, American College of Endocrinology, AACE

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