

## Note to Reviewer

Reference is made to your May 1, 2000 letter in which the Division requested that Eli Lilly and Company investigate the possibility of collaborating with organizations having large pools of patients treated with atypical antipsychotics to examine evidence of hyperglycemia or new-onset diabetes mellitus temporally associated with olanzapine. As described in our July 31, 2000 response under Section 8. Ongoing Studies, we have conducted two epidemiological studies in order to determine the incidence of diabetes from two large external databases.

The first retrospective cohort study was conducted utilizing data from the Advance PCS database to estimate the risk of developing diabetes during treatment with antipsychotic exposure relative to the general PCS patient population in the United States. Only subjects who were prescribed antipsychotics as monotherapy were included in the study. The incidence of diabetes was determined using prescription claims for antidiabetic agents in the general patient population cohort (N=5,816,473), and the following antipsychotic cohorts: conventional antipsychotics combined (N=19,782), haloperidol (N=8,476), thioridazine (N=3,133), atypical antipsychotics combined (N=38,969), olanzapine (N=13,863), risperidone (N=20,633), quetiapine (N=4,196) and clozapine (N=277). Proportional hazards regression was used to adjust for difference in age and gender in the estimation of risk for developing diabetes. Hazard ratios (HRs) of diabetes of antipsychotic cohorts were determined relative to the general PCS patient population and between selected antipsychotic cohorts.

The HRs of diabetes during treatment with conventional and atypical antipsychotic cohorts were 3.5 (95% CI: 3.1-3.9) and 3.1 (CI: 2.9-3.4), respectively. The HRs and 95% confidence intervals of individual antipsychotics were quetiapine (1.7; 1.2-2.4), olanzapine (3.0; 2.6-3.5), haloperidol (3.1; 2.6-3.7), clozapine (3.3; 1.4-8.0), risperidone (3.4; 3.1-3.8) and thioridazine (4.2; 3.2-5.5). When selected antipsychotic cohorts were compared to each other, there was no significant increase in risk of diabetes in the conventional vs. the atypical cohorts (HR=0.966; CI: 0.8-1.1; p=0.6). Upon comparison of single atypical antipsychotic cohorts and the haloperidol cohort, a statistically significant increase in risk in diabetes was observed during treatment with risperidone (HR=1.2; CI: 1.0-1.5; p=0.04), but not during treatment with olanzapine (HR=1.09; CI: 0.9-1.4; p=0.5). On comparison of the olanzapine cohort relative to the risperidone cohort, no statistically significant difference in risk in diabetes was observed during treatment (HR=0.9; CI: 0.8-1.1; p=0.23). A positive dose relationship for the risk of diabetes was observed in the atypical antipsychotic cohorts. This dose relationship was not observed in the atypical antipsychotic cohorts, with the possible exception of quetiapine.

It is also important to note the limitations of this study: 1) the PCS database did not contain any disease diagnostic information; 2) due to the nature of the database, only incident cases of diabetes that resulted in intervention with anti-diabetes medications were included; 3) all indications for antipsychotic prescriptions were included, regardless

of psychiatric illness spectrum or severity. Further, the selection of a given antipsychotic reflects clinical choices rather than randomized assignment. Potentially, certain patient attributes that influence treatment selection might also affect likelihood of developing diabetes. While pharmacoepidemiological studies can control for some important factors (e.g., age), others cannot be addressed with available data (e.g., severity of illness): 1) the average duration of antipsychotic treatment was not long, ranging from 68 days to 137 days; 2) the database did not contain information on body mass index thus it was not possible to adjust for difference in this risk factor of diabetes between cohorts; 3) the average daily doses of antipsychotic cohorts were low; 4) this study could be confounded by observation bias as patients in the antipsychotic cohorts might receive more frequent medical attention than the general patient population in the PCS database, and therefore be more likely to be screened for and diagnosed with diabetes; 5) finally, the majority of subjects whose prescription claims are covered by Advance PCS are either employed or are close family members of employed individuals. This would tend to exclude more severely ill patients who are more functionally debilitated and unable to work from the analysis. The full report of this study is provided as Attachment 1.

The second retrospective cohort study was conducted utilizing data from the General Practice Research Database (GPRD) to determine the hazard ratio of diabetes in patients prescribed antipsychotics compared with the general adult population in the United Kingdom. GPRD is a longitudinal database containing information on gender, age, weight, height, diagnoses, prescriptions, hospitalizations and doctor visits on 8 million residents in the United Kingdom enrolled by selected general practitioners. The study population was comprised of adults who were registered in standard general practices and were prescribed an antipsychotic. Any patient who had a diagnosis of type 1 or type 2 diabetes mellitus or who was prescribed any hypoglycemic agent(s) indicated for the treatment of diabetes was considered as having diabetes. A conventional antipsychotic cohort (N=44,046), an atypical antipsychotic cohort (N=2,527), and a general patient population cohort (N=269,049) derived from the GPRD database was studied. The Cox proportional hazard regression model was used to determine the hazard ratio (HR) of diabetes development between these cohorts. The covariates included in the model were age, sex, and the presence or absence of obesity.

The most commonly prescribed agents were thioridazine (44%) and fluopenthixol (22%) among conventional antipsychotics, and risperidone (71%) and olanzapine (21%) among atypical antipsychotics. Less than 120 patients received monotherapy of clozapine, quetiapine or amisulpride. As compared to the general population cohort in the UK, patients exposed to either class of antipsychotics had a higher risk of developing diabetes [HR=3.3; (CI: 1.7-6.5) for the atypical antipsychotic cohort; and HR=1.3; (CI: 1.003-1.8) for the conventional antipsychotic cohort]. As compared to the conventional antipsychotic cohort, the atypical antipsychotic cohort has a higher risk of developing diabetes (HR=2.6; 95% CI: 1.3-5.3). Though the study suggests a higher risk of developing diabetes during treatment with atypical antipsychotics relative to the conventional antipsychotics, the comparison was limited by the predominance of patients who received risperidone in the atypical antipsychotic cohort (71%). The sample sizes of thioridazine and risperidone cohorts were sufficiently large to discern a statistically

significant increase in the risk of diabetes relative to the general patient population cohort in UK. Though the sample size of other monotherapy cohorts were not adequately powered to discern a significant treatment effect, the 95% confidence interval of their hazard ratios provide an estimation of diabetes risk temporally associated with these agents.

This study has the following limitations. First, the number of patients who received atypical antipsychotics was relatively small. Thus, the small number of new cases of diabetes and the number of patients who took antipsychotics other than risperidone were too small for accurate determination of the risks of diabetes associated with those drugs. Second, unlike the conventional cohort that was comprised of antipsychotic naive patients, the atypical cohort consisted mainly of patients who had prior exposure to conventional antipsychotics. If both classes of antipsychotics induced diabetes by the same mechanism, the selection of subjects for the atypical antipsychotic cohort may have enriched this cohort with subjects with relative resistance to developing diabetes, since patients who had developed diabetes while taking conventional antipsychotics were excluded. Third, paucity of information on the family history of diabetes in this database precluded a meaningful inclusion of this variable in our Cox regression model. Fourth, the diagnosis of diabetes in this retrospective study was ascertained by a physician's diagnosis or by a recorded use of a glucose-lowering drug in the database. Without the primary clinical data, an unqualified diagnosis of diabetes is uncertain. However, it is reasonable to assume that a patient diagnosed with diabetes or is receiving a glucose-lowering drug has a high likelihood of having diabetes. The full report of this study is provided as Attachment 2.

In addition to these epidemiological studies, we are also providing a manuscript submitted to the American Journal of Psychiatry describing additional analyses from our clinical trial database (Attachment 3). In our July 31, 2000 response, we provided analyses from our clinical trial database under Section 6 (New Clinical Trial Analyses). The present analyses represent an elaboration of our previous analyses of the incidence and rates of treatment-emergent potential impaired glucose tolerance (IGT) and potential diabetes with olanzapine (N=4574) compared with haloperidol (N=888), risperidone (N=267), clozapine (N=200), and placebo (N=445). The objective of the first set of analyses was to define the relative risk of developing sustained, possibly clinically significant hyperglycemia according to categorical definitions of hyperglycemia based on random blood glucose thresholds of 160 and 200 mg/dl. For this purpose, patterns of random glucose elevations (e.g., persistent, uncertain, transient, probable error) found to be recurrent in the database were identified and operationalized. Clinical trials of schizophrenia, bipolar disorder, Parkinson's disease, and dementia were included. Patients were excluded if they had known hyperglycemia/diabetes or baseline random glucose >140 mg/dl.

In contrast, the enclosed clinical trial database analyses sought to investigate glycemic changes during treatment with olanzapine (overall N of integrated database=2251) relative to antipsychotic treatment comparators (haloperidol [N=792], risperidone [N=151], clozapine [N=85]) and placebo (N=114) by conducting an analysis of group

mean change in random blood glucose concentrations (maximum likelihood-based repeated measures ANOVA). Because the clinical relevance of mean group changes may sometimes be difficult to interpret, categorical analyses were also performed. To address the known variability of random glucose measurements, multiple random glucose thresholds (126, 140, 160, or 200 mg/dl) were used in these categorical analyses to evaluate the relative hazards of experiencing a diabetic event associated with mean random blood glucose concentrations at or above the predetermined thresholds (Cox proportional hazards regression). The present analyses only included clinical trials of schizophrenia-spectrum disorders, in order to achieve a greater diagnostic homogeneity in the study population. In contrast to the original analyses, all patients entered in the trials were included, with the only exception being those who had known diabetes or were taking antidiabetic medications at baseline.

The results of the enclosed clinical trial database analyses show that elevations in mean random blood glucose concentrations during treatment with olanzapine were relatively small in magnitude across all databases. The mean random glucose concentrations (mg/dl) observed during olanzapine treatment were significantly greater than those observed during treatment with placebo (0.77 vs. -1.28;  $F=8.68$ ,  $df=1$ ,  $p=0.004$ ) or haloperidol (4.56 vs. 0.22;  $F=20.47$ ,  $df=1$ ,  $p<.001$ ), significantly less than those observed during clozapine treatment (3.17 vs. 13.22;  $F=16.48$ ,  $df=1$ ,  $p<.001$ ), and not significantly different from those observed during risperidone treatment (4.51 vs. 2.58;  $F=3.5$ ,  $df=1$ ,  $p=0.06$ ). Consistent with the original categorical analyses, the new categorical analyses did not identify any significant differences between olanzapine vs. placebo, haloperidol or risperidone for any threshold. Compared with clozapine-treated patients, olanzapine-treated patients were one-third less likely to have random glucose elevations at or above the 126 and 140 mg/dl thresholds. In summary, although significantly different from haloperidol and placebo, glucose elevations during treatment with olanzapine were relatively small in magnitude across all comparisons. In addition, there were no significant categorical differences between olanzapine and haloperidol, placebo, or risperidone.

It is important to note that there are several limitations to the present analyses. These include the use of random blood glucose concentrations, the possible effect of increased appetite and resulting increase in meal frequency on the timing of random glucose draws relative to food intake, the relatively short duration of the trials (olanzapine vs. haloperidol: 52 weeks; olanzapine vs. risperidone: 28 weeks; olanzapine vs. clozapine: 18 weeks), a potentially more medically healthy clinical trial patient population, the limited statistical power for some of the categorical analyses, especially with respect to the ability to detect differences in the likelihood of crossing higher glucose thresholds (e.g. 200 mg/dl) because of the relative infrequency of events at higher thresholds, and the potential impact of baseline risk factors, which may have been inherent to the underlying psychiatric illness or the high prevalence of diabetes in the general population.

As previously described in our July 31, 2000 response under Section 8. Ongoing Studies, we submitted the protocol for Study F1D-MC-HGIM (Effect of Antipsychotic Therapy on Glycemic Control: A Comparison of Olanzapine, Risperidone and Placebo in Healthy

Subjects) to IND 28, 705 on January 17, 2000. Study HGIM has recently completed and we are in the process of analyzing the data. When available, we will provide you the clinical study report.

In summary, the results of two pharmacoepidemiological studies indicate an increased incidence and risk of diabetes in patients treated with either typical or atypical antipsychotics compared to reference populations. It remains unclear whether the observed increases may be due to factors intrinsic or extrinsic to the psychiatric disorder(s) treated with these classes of drugs. While the integrated clinical trial analysis showed modest mean elevations in random glucose during treatment with olanzapine, categorical analyses did not indicate an increased risk of clinically significant random glucose elevations during treatment with olanzapine in comparison to placebo, haloperidol or risperidone. In the same analyses, the risk of potentially clinically important random glucose elevations was markedly lower during treatment with olanzapine in comparison to clozapine.

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