

# Update to Olanzapine and Glucose Homeostasis

**[Prepared for FDA]**

**Eli Lilly and Company  
(20 June 2003)**

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Olanzapine (LY170053)  
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Update to Olanzapine and Glucose Homeostasis  
20 June 2003 (Internal 24 June 2003)

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## 1. Introduction

In October 2002, Lilly provided the Division with an update on the topic of diabetes and antipsychotics (refer to Lilly briefing document "Olanzapine and Glucose Homeostasis," submitted to FDA on 2 October 2002). That document presented new Lilly data on olanzapine and glucose homeostasis, and reviewed the relevant body of literature.

The conclusions on the basis of the data submitted in that document were that patients with serious mental illness appear to be at increased risk for diabetes compared to the general population, and that the cumulative data did not support a consistent or clinically significant increased risk for glycemic abnormalities in patients taking olanzapine compared with other antipsychotic medications.

Since Lilly's October 2002 update to the Division, researchers and clinicians have been focusing increased attention on the topic of serious mental illness and diabetes, and on treatment with antipsychotic medications and diabetes. This attention has resulted in a marked expansion of the available body of literature, which present studies that vary in study design, sample size, methods, and specific comparisons. These recent studies are reviewed in this document (source documents are listed in the reference section of this document, and hard copies are available upon request).

The scope of this review encompasses three main areas: 1) prevalence of diabetes in patients with serious mental illness, including schizophrenia and bipolar disorder; 2) risk of diabetes in patients treated with atypicals compared to conventional or other atypical antipsychotics; and 3) new Lilly data.

This recent literature lends additional support to the evidence that serious mental illness (including schizophrenia and bipolar disorder) is associated with a greater risk for diabetes compared to risk in the general population. At the same time, the cumulative data do not currently allow a determination whether treatment with antipsychotic medication contributes to the increased risk of diabetes observed in the seriously mentally ill. Nor does the current evidence allow for conclusions regarding an increased risk of diabetes between patients treated with atypical antipsychotics and patients treated with conventional antipsychotics.

Finally, the current body of literature does not support specific conclusions regarding differences in likelihood of diabetes between patients treated with specific atypical antipsychotic medications. Studies comparing the risk of diabetes among patients treated with atypical antipsychotics are consistent, however, in demonstrating the impact of risk factors for diabetes that are well established in the general population.

## 2. Risk of Diabetes in Serious Mental Illness

### 2.1. Risk of Diabetes in Serious Mental Illness Prior to Antipsychotic Use

Reports suggesting an association between diabetes and psychotic disorders began to appear long before the introduction of pharmacological agents for the treatment of schizophrenia and bipolar disorder (Lorenz 1922; Braceland et al. 1945; Freeman 1946; Langfeldt 1952). This area of the literature presents some challenges in interpretation, given the use of dated or non-standardized diagnostic criteria in pre-antipsychotic era patient cohorts.

The following section summarizes two studies by Bellnier et al, which lend additional support to the existing reports indicating that disturbances of glucose regulation in patients diagnosed with serious mental illness were substantially more prevalent than the general population prior to the introduction of antipsychotic medications.

**Bellnier TJ, Patil K, Ortega T, et al. The Prevalence of Metabolic Disturbances in Schizophrenic and Bipolar I Patients Prior to Antipsychotic Use. Presented at 156th American Psychiatric Association Annual Meeting; May 17-22, 2003; San Francisco, California.**

The goal of this study was to evaluate the prevalence of risk factors for metabolic syndrome in psychiatric patients prior to the introduction of antipsychotic drug therapies.

This retrospective report was based on review of 1000 randomly selected charts of patients admitted to a state psychiatric hospital between the years 1940-1950. Records were independently reviewed by 2 psychiatrists using pertinent physical exam information and available laboratory results to identify patients who appeared retrospectively to meet DSM-IV diagnostic criteria for schizophrenia or bipolar I disorder. The prevalence of diabetes, hypertension, and weight status were determined and compared to the expected rates from "national norms" of the general population reflective of the time period (Harris et al. 1998).

Over half the sample was female; the average age of patients was  $37 \pm 13$  years. The majority of patients had a diagnosis of schizophrenia (n=429). Diabetes was identified based on documented clinical diagnosis or the presence of glycosuria. From 592 patient charts, the rate of diabetes was approximately 21%, compared with the literature-based rate of diabetes of 2% for the general population in the same era. Twenty-nine percent of the sample was determined to have hypertension, compared with 16.5% estimated for the general population; 28% of patients were overweight, compared with an expected rate of 22% in the general population.

This retrospective study was limited by reliance on a surrogate measure of diabetes (ie, glycosuria), lack of specification on criteria used to diagnose hypertension and obesity, the lack of a matched control group who did not have the diagnosis of schizophrenia or bipolar I disorder, on comparison of hospitalized patients with an ambulatory control population order, and the need to estimate general population norms from extant literature.

While there are inherent limitations in applying current diagnostic principles and questions to patient charts from an earlier era, this approach potentially offers useful historical perspective. Nonetheless, the findings of this chart review suggest that widespread metabolic disturbances in patients diagnosed with either schizophrenia or bipolar I disorder were substantially more prevalent than in the general population prior to the use of antipsychotic medications.

**Bellnier TJ, Decatur A, Patil K, et al. The Prevalence of Metabolic Disturbances in State Hospital Patients Prior to the Use of Antipsychotics and After the Widespread Use of Atypical Antipsychotics. Presented at the 6<sup>th</sup> Annual College of Psychiatric and Neurologic Pharmacists Meeting, May 1-4, 2003, Charleston, SC.**

The goal of this retrospective chart review was to analyze the prevalence of metabolic disturbances among psychiatric patients prior to and after the widespread introduction of antipsychotic medications. This study was performed by the same research group as the study described above; it involves further analyses of the charts reviewed in the aforementioned study, and comparison to a contemporary cohort.

The sample for this chart review consisted of two groups: the first group consisted of 1000 randomly selected patients admitted to a psychiatric hospital between the years of 1940-1950 (pre-antipsychotic); and group 2 (post-antipsychotic), which included the entire adult population admitted during 1999-2002 who were receiving an atypical antipsychotic. Both groups were determined to meet DSM-IV criteria for schizophrenia or bipolar I disorder based on two independent psychiatrist reviews of patient records. In the pre-antipsychotic and post-antipsychotic groups, a total of 569 and 688 patients, respectively, met diagnostic criteria for schizophrenia or bipolar I disorder. Subjects were matched for age, sex, ethnicity, and diagnosis. Markers available for review included diabetes (based on presence of glycosuria), hypertension (blood pressure >140/90), and overweight/obesity (BMI  $\geq$  25). (Criteria on markers were not included in the poster, and were obtained via personal communication with the primary author.) Diabetes, hypertension, and obesity rates were compared to the expected rates from "national norms" and to a matched-pairs analysis.

The majority of patients in both groups had a diagnosis of schizophrenia and were female. The average age was  $37 \pm 13$  years in the pre-antipsychotic group, and  $38 \pm 12$  years in post-antipsychotic group. There was a statistically significantly greater prevalence of diabetes in the pre-antipsychotic group compared to the general population of the same era (20.9% versus 2%,  $p < .00001$ ). In addition, the rates of hypertension and overweight were significantly higher in the pre-antipsychotic psychiatric patients compared to the general population. Rates of diabetes, hypertension, and overweight were also higher in the post-antipsychotic group compared with a contemporary survey of the general population. Finally, in comparing pre- and post-antipsychotic psychiatric patients, the pre-antipsychotic group had significantly higher rates of diabetes (20.9% versus 10.4%,  $p < .00001$ ) and hypertension (29.1% versus 15.6%,  $p < .00001$ ), whereas the post-antipsychotic group had significantly higher rates of overweight (28.2% versus 68.6%,  $p < .00001$ ). Metabolic disturbances for each group were significantly greater than the corresponding general population for diabetes, hypertension, and overweight. An increase in overweight and decrease in hypertension from pre-antipsychotic and post-antipsychotic groups reflect similar trends in the general population. The reduction in the prevalence of diabetes from the pre-antipsychotic group to the post-antipsychotic group was not seen in the respective control groups.

In this study, there appeared to be an association between having a diagnosis of schizophrenia or bipolar I disorder and increased prevalence of metabolic abnormalities, independent of antipsychotic drug use.

This retrospective study was limited by reliance the use of surrogate markers for some components of metabolic syndrome (eg, glycosuria as a surrogate for insulin resistance, BMI  $\geq 25$  as a marker for central obesity); the lack of information of other components of metabolic syndrome, such as lipid profile; and on comparison of hospitalized patients with ambulatory control populations.

Nonetheless, this study is consistent with several other studies in the literature (Regenold 2002; Ryan 2003) showing that patients with either schizophrenia or bipolar I disorder have an increased prevalence of type 2 diabetes and/or related metabolic disturbances, which is independent of psychotropic drug use.

### **Discussion and Conclusions: Risk of Diabetes in Serious Mental Illness Prior to Antipsychotic Use**

Reports suggesting an association between diabetes and serious mental illness began to appear long before the introduction of pharmacological agents for the treatment of schizophrenia and bipolar disorder (Lorenz 1922; Braceland et al. 1945; Freeman 1946; Langfeldt 1952). New data in studies such as ones described in this section suggest that the prevalence of metabolic disturbances may have been greater in patients with serious mental illness than in the general population prior to advent of antipsychotics in clinical practice. The authors hypothesize that the reduction in frequency of metabolic abnormalities observed in the period following the introduction of antipsychotics may be a result of improved control of the psychiatric condition, leading to overall improvement of medical health and improved compliance with medical treatment, in conjunction with improved standards of medical care for psychiatric patients. These studies lend additional support to existing reports of glucose dysregulation in association with severe psychiatric disorders.

## 2.2. Risk of Diabetes in Schizophrenia or Bipolar Disorder

Since Lilly's last update to the Division (October 2002), additional evidence has emerged to support the view that the prevalence of diabetes and diabetes-related events is greater among patients with serious mental illness, including those with schizophrenia and bipolar disorder. Prevalence of diabetes-related events in these patients may be as much as several times the prevalence observed in the general population. The reasons for these observations remain unclear, largely because there have been few studies comparing antipsychotic-naïve patients with the general population. The following section presents a number of reports investigating the prevalence of diabetes and diabetes-related events in patients with serious mental illness.

**Ryan MCM, Collins P, Thakore JH. 2003. Impaired Fasting Glucose Tolerance in First Episode, Drug-Naïve Patients with Schizophrenia. Am J Psychiatry 160:284-289.**

In a recent study, Ryan and colleagues evaluated fasting blood glucose levels in first-episode, antipsychotic-naïve, schizophrenic patients. Particular attention should be focused on this report, given that it represents one of rare studies comparing antipsychotic-naïve patients with schizophrenia to healthy controls. The study of antipsychotic-naïve patients with severe mental illness is can be a particularly informative approach to evaluate the risk load of diabetes in severely mentally ill patients compared with the general population.

Patients included in this cross-sectional study (n=26) had first-episode schizophrenia diagnosed by DSM-IV criteria, had no comorbid psychiatric or physical disorders, and were antipsychotic drug-naïve. In a case-control design, patients were matched with controls for age, sex, race, diet, smoking, physical activity, and anthropometric measurements (including BMI and waist circumference).

Compared with the healthy subjects, the patients with schizophrenia had significantly higher fasting plasma levels of glucose (mean=88.2 mg/dL, SD=5.4, for the healthy subjects versus mean=95.8 mg/dL, SD=16.9, for the patients), insulin (mean=7.7  $\mu$ u/mL, SD=3.7, versus mean= 9.8  $\mu$ u/mL, SD=3.9), and cortisol (mean= 303.2 nmol/liter, SD=10.5, versus mean= 499.4 nmol/liter, SD=161.4) and were more insulin resistant, as measured with homeostasis model assessment (mean=1.7, SD=0.7, for the healthy subjects versus mean=2.3, SD=1.0, for the patients). The frequency of impaired fasting glucose tolerance (defined as glucose >110 mg/dL and <126 mg/dL) was 15.4% (n=4) in the patient group compared to 0% in the control group.



Limitations of this study include its cross-sectional design and the relatively small sample size. Also, the study design did not allow for differentiation of potential intrinsic effects of schizophrenia on metabolic parameters from the potential stress-mediated effect of the acute psychotic state.

In summary, drug-naïve patients with schizophrenia had higher fasting levels of glucose, insulin, and cortisol, and were more insulin-resistant than the control group. These findings are consistent with other reports indicating that schizophrenia is associated with an increased prevalence of metabolic abnormalities, including glucose dysregulation, which are independent of treatment with antipsychotic medications. This study is particularly relevant to the discussion, given that it represents one of the rare studies comparing antipsychotic-naïve patients with schizophrenia to healthy controls.

**Shiloah E, Witz S, Abramovitch Y, Cohen O, Buchs A, Ramot Y, Weiss M, Unger A, Rapaport MJ. 2003. Effect of Acute Psychotic Stress in Nondiabetic Subjects on Beta Cell Function and Insulin Sensitivity. Diabetes Care 26(5):1462-1467.**

The purpose of this recent study was to determine the effects of acute psychotic stress on glucose homeostasis in nondiabetic subjects.  $\beta$ -cell function and insulin sensitivity were determined using the homeostasis model assessment (HOMA) in 39 nondiabetic subjects with an acute psychotic stress reaction admitted to an inpatient psychiatric ward. A clinical global impressions (CGI) score was used to evaluate the level of psychological stress experienced by each patient. Stress CGI and HOMA were recorded on admission, 2 weeks after admission, prior to discharge, and 6 months post-discharge. During hospitalization, patients were treated for their psychosis with either a phenothiazine or thioxanthene antipsychotic agent. Patients were excluded from participation if they had 1) presence of any endocrine or concomitant acute disease or 2) current use of an atypical antipsychotic or any medication known to effect insulin secretion or cause hyperglycemia, 3) Fasting blood glucose (FBG) >126 mg/dL or a HbA<sub>1C</sub> > 6.4%.  $\beta$ -cell function and insulin sensitivity were assessed by HOMA at the same timepoints. BMI was recorded for each patient. Statistical analysis included ANOVA with repeated measures and Pearson's correlations.

Prior to admission, 33/39 (85%) of the patients had chronic psychiatric disorders; however, all patients were reported to be "well-controlled" prior to admission. The mean CGI score upon admission was  $5.3 \pm 0.8$  and gradually improved during hospitalization to a mean of  $1.6 \pm 0.7$  prior to discharge ( $p < 0.001$ ). Mean fasting glucose levels were normal at baseline ( $93.7 \pm 12.0$  mg/dL) and did not change significantly throughout the study period. Fasting insulin levels also did not change significantly during the study; however, significant changes in the HOMA indices of  $\beta$ -cell function and insulin sensitivity were noted. Mean  $\beta$ -cell function was lowest upon admission and increased significantly throughout the study ( $p < 0.003$ ). In contrast, mean insulin sensitivity was highest upon admission and decreased significantly after discharge ( $p < 0.001$ ).

In a subgroup analysis, patients with the highest CGI scores ( $\geq 6$ ) upon admission had significantly elevated fasting glucose and insulin levels when compared to those patients with lower CGI scores. There was a positive correlation between CGI and fasting insulin and glucose levels upon admission ( $p = 0.021$  and  $p = 0.003$ , respectively). There was an inverse correlation between admission CGI score and insulin sensitivity, but no differences were seen in  $\beta$ -cell function between the low- and high-CGI subgroups. In contrast to statistically significant correlations between admission CGI and fasting insulin, glucose, and insulin sensitivity, these measures were not significantly correlated with BMI, age, or sex.

This study indicates that acute psychotic stress may have adverse effects on glucose metabolism in nondiabetic psychiatric patients. The authors suggest that as psychotic stress increases in acutely ill patients, there is a directly related increase in blood glucose and insulin, and that increasing acute psychotic stress may temporarily suppress  $\beta$ -cell function and decrease insulin sensitivity.

Limitations of this study include lack of measurement of change in weight or BMI, and exclusion of patients with baseline metabolic abnormalities as noted above (ie, potentially eliminating subjects with the most pronounced adverse metabolic impact or stress). The remaining cohort of patients were without any baseline endocrine disorder or concomitant acute disease, yet had several risk factors for diabetes (eg, elevated BMI, positive family history for diabetes, and chronic psychiatric illness). The report lacks an adequate explanation for the longitudinal decline in insulin sensitivity concomitant with psychiatric improvement, but is consistent with the body of literature demonstrating that a variety of physiological and mental stresses can impact glucose metabolism.

In summary, this study suggests that acute stress may adversely affect glucose regulation in patients with severe mental illness in states of acute psychotic stress.

**Arranz B, Rosel P, Ramírez N, et al. Insulin resistance and Increased Leptin Concentrations in Antipsychotic-Free and Not in Naïve First-Episode Schizophrenic Patients. Manuscript under review by American Journal of Psychiatry, June 2003.**

Arranz and colleagues compared glucose metabolism parameters in two patient groups: noncompliant unmedicated patients with schizophrenia (antipsychotic-free) and first-episode antipsychotic-naïve patients with schizophrenia, as well as a healthy control group, in order to examine the potential relationships of previous antipsychotic treatment with glucose metabolism and of diagnoses of schizophrenia and diabetes.

Patients were included in this non-randomized comparative clinical trial if they had a diagnosis of schizophrenia and did not have: a comorbid DSM-IV diagnosis of substance abuse or dependence; a physical illness; or treatment that could influence glucose homeostasis. Patients with schizophrenia in the antipsychotic-free group (n=50, mean age  $35.4 \pm 1.2$  years) were considered treatment non-compliant and were included in the study after hospitalization due to exacerbation of psychotic symptoms. The mean duration since most recent antipsychotic drug therapy was  $17.8 \pm 2.8$  months. Thirty-six percent of the patients in this group had a family history of Type 2 diabetes. The naïve-naïve group included 50 patients with a first psychotic episode (mean age  $25.2 \pm 0.6$ ) in which the diagnosis of schizophrenia was confirmed after 6 months according to the DSM-IV criteria and who had never received an antipsychotic, antidepressant, or mood stabilizer. Thirty-five percent of the patients in this group had a family history of Type 2 diabetes. The control group included 50 subjects (mean age  $29.8 \pm 0.7$ ) that did not have a psychiatric diagnosis and were not receiving psychotropic agents. Ten percent of the control group had a family history of Type 2 diabetes.

A single blood sample under fasting conditions was used to determine serum glucose, plasma leptin, plasma insulin, and C-peptide concentrations. Insulin resistance was calculated through the homeostatic model assessment (HOMA). The primary analyses were to compare the demographic and biochemical parameters between both the patient groups and the control group. Factorial ANOVA tests with the diagnosis (naïve, free, and control groups) as the independent variable, and the biochemical parameters, HOMA, age, and BMI as dependent variables were used. Bonferroni tests were used for post hoc comparisons between groups. The General Linear Model (univariate) procedure was used to perform analysis of covariance (ANCOVA) so as to control for the effect of age, BMI, familiar history of Type 2 diabetes and sex (covariates) on the dependent variable, being the diagnosis (naïve, free and control groups) the fixed-effect factor.

Comparisons between both sexes were performed through the Student's t test unpaired, two-tailed. Comparisons between dichotomic variables were assessed through the chi-square test. Pearson's correlation coefficients were determined to assess the relationship between quantitative variables. The overall significance level was set at  $p=0.05$ .

Results of this study indicated antipsychotic-free patients were significantly older than both the antipsychotic-naïve patients and the control group. They also had significantly higher BMI ( $24 \pm 0.9 \text{ kg/m}^2$  versus  $22 \pm 0.3 \text{ kg/m}^2$ ;  $F=6.4$ ;  $p=0.002$ ). Sex distribution was not significantly different between the studied groups. Leptin levels were significantly higher in women than men, both among patients and controls. Glucose concentrations were not significantly different between antipsychotic-free and antipsychotic-naïve patients and the control group. There was significant effect of the patient's age, sex, family history of diabetes, or BMI upon this biochemical variable. However, antipsychotic-free patients showed significantly increased insulin and peptide-C concentrations in comparison to the antipsychotic-naïve patients, as well as the control group after using age, BMI, family history of diabetes, and sex as covariates, with the main effect being the diagnoses.

Antipsychotic-free patients also showed a significantly higher degree of insulin resistance, as measured with the HOMA index ( $2.79 \pm 0.3$ ), in comparison to the antipsychotic-naïve ( $1.82 \pm 0.07$ ) and the control group ( $2.01 \pm 1.8$ ;  $F=3.4$ ;  $p=0.003$ ), with a lack of significant effect of any of the covariates tested. With regard to leptin, the significantly increased concentrations noted in the schizophrenic-free patients ( $11.4 \pm 1.9$  versus  $4.7 \pm 0.5$  and  $7.2 \pm 0.4 \text{ ng/mL}$  in the naïve patients and control subjects, respectively) in the corrected model were attributed largely to the effect of BMI and sex, with the effect of the diagnosis being smaller. Age and family history of diabetes had no significant effect upon any of the tested variables.

This is the first study comparing glucose metabolism and weight-related hormones between patients with schizophrenia who had been antipsychotic-free for several months and first-episode never-medicated patients. These findings demonstrated no significant difference in fasting glucose concentrations between the three groups studied. The findings in this study differ from the recent finding of Ryan et al, which showed that first-episode, antipsychotic-naïve patients had higher levels of plasma glucose, insulin, and cortisol than a healthy control group.

With respect to limitations, it is important to note that the antipsychotic-free group in this study was on average 10 years older and had been diagnosed with schizophrenia on average 10 years earlier than their schizophrenic antipsychotic-naïve counterparts, and had a significantly higher BMI. Therefore, it cannot be ruled out that the duration of schizophrenia, patient age, and previous antipsychotic treatment are factors that contribute to glucose metabolism and weight-related hormones, compared to antipsychotic-naïve patients with schizophrenia and healthy controls.

In summary, these results suggest that further study is needed regarding potential effects of antipsychotic treatment on glucose metabolism parameters and weight-related hormones such as leptin and the extent of preexisting impairment of glucose metabolism in antipsychotic-naïve, first-episode schizophrenic patients.

**Lamberti JS, Crilly JF, Olson D, Maharaj K, Costea GO, Bushey M, Dietz MB. 2003. Prevalence of Diabetes Among Outpatients Receiving Antipsychotic Drugs. IX International Congress on Schizophrenia Research, March 29-April 2, 2003, Colorado Springs, CO. Schizophrenia Research 60 (suppl 1):360.**

The purpose of this study was to examine the point prevalence of type 2 diabetes among adult outpatients with schizophrenia and schizoaffective disorder receiving antipsychotic medication. A retrospective chart review was conducted on 436 outpatients receiving antipsychotic drug monotherapy for at least 3 months at the University of Rochester Department of Psychiatry. Patients were allowed concomitant psychotropic medications. Patients were primarily on atypical antipsychotic therapies (clozapine n=141, olanzapine n= 104, risperidone n=86, quetiapine n=57), however a small number of patients taking haloperidol decanoate (n=19) or fluphenazine decanoate (n=29) were included for comparison purposes. A diagnosis of diabetes was established through the presence of documentation in the patient's medical record.

Seventeen percent of the patients had a documented family history of diabetes. Overall prevalence of diabetes mellitus was 14.2%. The prevalence of diabetes in each of the atypical antipsychotic drug cohorts was similar: clozapine n=22/141 (15.6%), olanzapine n= 15/104 (14.4%), risperidone n=13/86 (15.1%), and quetiapine n=9/57 (15.8%). Significant effects of age, family history of diabetes, and gender were observed.

This study further suggests that known diabetes risk factors (age, family history, ethnicity) likely play a role in predicting those psychiatric patients at risk for the development of type 2 diabetes.

A limitation of this study is that it did not assess relative risk of diabetes in patients treated with different antipsychotic medications.

In summary, the authors do not rule out a potential contribution from psychotropic medication, and suggest that duration of antipsychotic drug exposure may also be a significant risk factor for developing diabetes. Although this study did not attempt to quantify the relative risk of diabetes associated with different antipsychotic medications, there were no qualitative differences among patients taking different atypical agents. Results of this study are also consistent with previous studies showing a high prevalence of diabetes in patients with serious mental illness.

**Regenold WT, Thapar RK, Marano C, Gavirneni S, Kondapavuluru PV. 2002. Increased Prevalence of Type 2 Diabetes Mellitus among Psychiatric Inpatients with Bipolar I Affective and Schizoaffective Disorders Independent of Psychotropic Drug Use. Journal of Affective Disorders 70:19-26.**

This study examined the prevalence of diabetes among hospitalized psychiatric patients. The medical records of 243 inpatients, aged 50 to 74 years, with diagnoses of major depression, bipolar I disorder, schizoaffective disorder, schizophrenia, and dementia were reviewed. Psychiatric and type 2 diabetes mellitus diagnoses, medications, body mass index (BMI), age, gender, and race were recorded. Diabetes rates were compared to age-, race-, and gender-matched rates in the US general population.

Rates of type 2 diabetes mellitus were: schizoaffective (50%) > bipolar I (26%) > major depression (18%) = dementia (18%) > schizophrenia (13%) ( $p < 0.006$ ). Diabetic patients had a higher mean BMI ( $p = .01$ ), but not a significantly higher use of psychotropic medications previously reported to be associated with new-onset type 2 diabetes (eg, phenothiazines, clozapine, olanzapine). Logistic regression revealed that psychiatric diagnosis and BMI were the only significant and independent predictors of diabetes diagnosis. Compared to "national norms," diabetes rates were significantly elevated only in bipolar I affective and schizoaffective patients.

The authors concluded that their findings suggest an intrinsic relationship between abnormal glucose metabolism and bipolar I and schizoaffective disorder, which is independent of body mass or psychotropic medications. The results of this study are consistent with previous reports of increased rates of diabetes in patients suffering from bipolar disorder. Lilliker (1980) reported a 3-fold higher rate of diabetes in 203 hospitalized, manic-depressive patients compared with other psychiatric inpatients and to the general US population. Cassidy et al (1999) also found increased rates of diabetes in 354 hospitalized, manic-depressive patients compared with the expected general US population rate weighted for age, gender, and race. Unlike other studies, Regenold et al did not observe higher rates of diabetes in patients with schizophrenia. The reasons for this finding are unclear.

In summary, these reports support the view that serious mental illness, including bipolar disorder and schizoaffective disorder (though less so for schizophrenia in this study), is associated with an increased risk of diabetes, which may be independent of treatment with psychotropic medication.

## Discussion and Conclusions – Risk of Diabetes in Schizophrenia or Bipolar Disorder

The study by Shiloah and colleagues indicates that acute psychotic stress has adverse effects on glucose control in psychiatric non-diabetic patients. These findings are consistent with those of Ryan et al (2003) in a population of first-episode schizophrenics, where patients in an acutely psychotic state had increased levels of impaired glucose tolerance, higher fasting blood glucose, and greater insulin resistance. While the study by Arranz and colleagues did not replicate these findings, this may be explained by differences in disease chronicity or severity across samples. Finally, results of the study by Lamberti et al (2003) are consistent in showing that diabetes risk factor load at baseline is a major predictor for glucose dysregulation in patients treated with antipsychotics, irrespective of treatment assignment.



### **2.3. Prevalence of the Metabolic Syndrome among Patients with Schizophrenia**

In previous briefing documents (eg, 2 October 2002 document on Olanzapine and Glucose Homeostasis), Lilly has submitted data that supports the view that patients with severe mental illness have a higher prevalence of diabetes. This view has been documented in a number of studies, some of which predate the introduction of atypical antipsychotics. Furthermore, there are reports of an association between diabetes and mental illness that predate the introduction of conventional antipsychotics by several decades. The factors underlying this link are uncertain. However, it is well known that insulin resistance is of primary importance in the etiology of type 2 diabetes in the general population. In addition to increased diabetes risk, individuals with insulin resistance frequently display a constellation of clinical or laboratory findings that have collectively been referred to as the "metabolic syndrome" (also "syndrome X" or the "insulin resistance syndrome"). Manifestations of this syndrome include hypertension, dyslipidemia, cardiovascular disease, and type 2 diabetes, among others.

Recent studies have demonstrated that insulin resistance and metabolic syndrome are more common among individuals with schizophrenia. Although these studies do not directly address the risk of diabetes during exposure to antipsychotic medications, they support the hypothesis that this population carries a higher burden of diabetes risk. Furthermore, these studies suggest that the pathophysiological changes of insulin resistance may possibly be inherent to these patient groups, independent of drug treatment.

The following section summarizes recent studies that have investigated the prevalence of the metabolic syndrome among patients with schizophrenia.

**Heiskanen T, Niskanen L, Lyytikainen, R, Saarinen P, and Hintikka J. 2003. Metabolic Syndrome in Patients With Schizophrenia. J Clin Psychiatry 64(5):575-579.**

This recently published study examined the prevalence of the metabolic syndrome among Finnish patients with schizophrenia. Anthropometric and laboratory evaluations were performed on 35 outpatients with long-term schizophrenia or schizoaffective disorder (time since diagnosis 3 to 40 years). The frequency of patients with metabolic syndrome was determined using criteria defined by the National Cholesterol Education Program (3 or more of the following: fasting blood glucose  $\geq 5.6$  mmol/L; serum triglycerides  $\geq 1.7$  mmol/L; serum HDL cholesterol  $< 1.0$  mmol/L in men or  $< 1.2$  mmol/L in women; blood pressure  $\geq 135/85$  mm Hg or on antihypertensive medication; and waist girth  $> 100$  cm or  $> 88$  cm for men or women, respectively). Differences in the percentage of patients meeting diagnostic criteria were compared by the chi-square test; continuous variables were compared by the Student's t test or Mann-Whitney U test.

The frequency of the metabolic syndrome was 37% in the study group (47% of men and 25% of women,  $p=0.17$ ). There were no statistically significant differences in the percentage of patients with the metabolic syndrome comparing patients treated with clozapine (7 of 21), olanzapine (3 of 7), or a group taking conventional agents (3 of 7;  $p=0.72$ ). There was a significant inverse correlation between the diagnosis of metabolic syndrome and dose of antipsychotic medication (expressed as chlorpromazine equivalents). With the exception of diastolic blood pressure, there were significant differences in the mean values for all of the individual metabolic syndrome parameters comparing patients that did, or did not, meet diagnostic criteria. Significant between-group differences were also shown for BMI ( $p<.004$ ) and hemoglobin A1c ( $p=.002$ ), and there was a trend for higher fasting insulin levels among those with the metabolic syndrome ( $p=.06$ ).

This small study is limited by the lack of a control group. The authors conclude that the frequency of the metabolic syndrome is 2- to 4-fold higher among patients with schizophrenia than in the general population, based on previous studies in the same geographic area. With respect to comparisons between drugs, this study may lack statistical power to detect small differences between treatment groups. Also, over half of the study group used clozapine and the only other atypical agent represented was olanzapine, which precludes generalizing to the larger class of atypical agents. Nonetheless, the increased rate of the metabolic syndrome in both the atypical and conventional antipsychotic cohorts, and the lack of observed significant differences between the cohorts, are consistent with studies by Littrell and Kato presented in this briefing document. Furthermore, since the component criteria of the metabolic syndrome are independent risk factors for the development of diabetes, this study supports the view that patients with schizophrenia represent a population with an increased risk of diabetes.

**Littrell K, Petty R, Hilligoss N, Kirshner C, Johnson C, Ortega T, Tsou-Hung L, Moore D, Ballard A, Clough R, Selby C. 2003. Insulin Resistance and Syndrome X Among Schizophrenia Patients. Poster presented at American Psychiatry Association, San Francisco, May 2003.**

The primary objective of this epidemiological study was to assess the prevalence of insulin resistance and Syndrome X (ie, the metabolic syndrome) among individuals with schizophrenia. A total of 98 outpatients from the United States and 27 inpatients from Taiwan were evaluated using fasting laboratory testing and clinical assessment. Approximate mean age and duration of illness were 42 years and 18 years, respectively. The metabolic syndrome was diagnosed based on National Cholesterol Education Program (NCEP) guidelines (Laaksonen et al. 2002), whereas insulin resistance was identified using the Homeostasis Model Assessment, which utilizes concomitant fasting glucose and insulin levels. This study reports the point prevalence of these conditions among patients taking a variety of antipsychotic drugs. No statistical analysis is reported.

Among outpatients in the study, 51% met criteria for the metabolic syndrome, but 70% had insulin resistance. The prevalence among Taiwanese inpatients was 40-50% lower than among US patients. Rates among patients taking different antipsychotics were variable, but without obvious qualitative differences. The prevalence of these syndromes as a function of drug used was not reported for inpatients. Eight patients with previously unrecognized diabetes were identified in this study.

Limitations of this study include (as with the study by Heiskanen [2003]), the lack of a non-psychiatric control group. The authors' conclusion that insulin resistance and Syndrome X is more common among patients with schizophrenia than in the general population is supported by comparison to the prevalence of the metabolic syndrome for adults in the US, recently reported to be 23% (Park 2003). No normal reference group is described for the Taiwanese cohort. This study is also limited by the lack of any statistical comparison between drug treatment groups. However, as with the Heiskanen study, the results support the notion of a higher burden of diabetes risk among patients with schizophrenia regardless of current antipsychotic use.

**Kato M, Gonzalez-Blanco M, Hall L, Grant M, Santana O, and Currier B. 2002. The Prevalence of the Metabolic Syndrome in Patients with Schizophrenia: A Pilot Study. Poster presented at American College of Neuropsychopharmacology, San Juan, November 2002.**

The objective of this cross-sectional study was to determine the prevalence of the metabolic syndrome among patients with schizophrenia. Thirty-six patients on stable doses of antipsychotics, including clozapine (n=11), olanzapine (n=7), risperidone (n=7), or haloperidol (n=7), were recruited from an outpatient clinic. Patients taking medications known to affect glucose or lipids were excluded. The prevalence of the metabolic syndrome was determined using NCEP diagnostic criteria (Laaksonen et al. 2002).

Sixty-one percent of subjects met criteria for the metabolic syndrome. In individual treatment groups, the prevalence of the metabolic syndrome was as follows: clozapine 91%, risperidone 57%, olanzapine 43%, and haloperidol 43%. No statistical association was found between current antipsychotic treatment and metabolic syndrome prevalence. The criteria most strongly associated with a diagnosis of metabolic syndrome were waist circumference, diastolic blood pressure, and HDL (all  $p < 0.05$ ). In linear regression analysis, the associations remained significant after controlling for age, gender, ethnicity, smoking, BMI and antipsychotic medications.

The results of this study are consistent with those from Heiskanen and Littrell (presented above) in showing a higher prevalence of the metabolic syndrome among patients with schizophrenia (61%) versus 22% in the general US population (Park 2003). The authors further support the high frequency of cardiovascular risk factors in this population. As a cross-sectional and uncontrolled study, selection and ascertainment biases are possible and could mask differences between treatment groups. Nonetheless, given the absence of qualitative differences in the proportion of patients with the metabolic syndrome during treatment with a variety of antipsychotic agents, the authors suggest that their study "challenges the current paradigm of drug relatedness to diabetes mellitus in schizophrenia patients."

### **Discussion and Conclusions – Prevalence of the Metabolic Syndrome among Patients with Schizophrenia**

Insulin resistance is a central component of the metabolic syndrome, and a major predictor of diabetes risk. The studies presented in this section suggest that insulin resistance and the metabolic syndrome are more prevalent among patients with schizophrenia than in the general population. Thus, these studies lend additional support to the view that schizophrenia may be associated with an intrinsically greater risk factor burden for diabetes, possibly due to shared genetic or environmental susceptibilities.

### **3. Risk of Diabetes in Patients Treated with Atypical Antipsychotics versus Other Atypicals and/or Conventionals**

Since Lilly's last update to the Division ("Olanzapine and Glucose Homeostasis," 2 October 2002), an increasing number of studies have examined a possible association between antipsychotic medications and diabetes. These studies vary in study design, sample size, methods, and specific comparisons. The following section presents studies that examined the risk of diabetes in patients treated with atypical antipsychotics versus risk with other atypicals and/or conventional antipsychotics.

### 3.1. Retrospective Cohort Studies

The four retrospective cohort studies presented in this section applied similar methodologies to independent databases to evaluate the risk of diabetes in patients treated with atypical versus conventional antipsychotics, and with olanzapine versus risperidone

**Lee DW, Fowler RB, Kadlubek PJ, Haberman M. 2002. No Significant Difference in Diabetes Risk During Treatment with Typical Versus Atypical Antipsychotics: Results from a Large Observational Study. Drug Benefit Trends 14(11):46-52.**

The objective of this study (for which Lilly provided financial support) was to estimate the 1-year relative risk of diabetes mellitus (DM) onset for a large cohort of treatment-naive patients after initiation of antipsychotic therapy.

Data from a US managed care organization were used to select a cohort of nondiabetic patients aged 18 to 65 years who initiated typical or atypical antipsychotic therapy between 30 September 1997 and 31 December 1999 (N=2315). Using the date of the first antipsychotic prescription as the "index date," inclusion criteria were identified as no other antipsychotic prescription within 180 days prior to the index date, continuous eligibility for 365 days prior to and after the index date, between age 18 and 65, and no diabetes medication prescription or medical claim for diabetes in the 365 days before the index date. There were 981 (42.4%) patients on typicals and 1,334 (57.6%) patients on atypicals. Among the atypical group, 513 (38.5%) initiated therapy with olanzapine and 750 (56.2%) initiated therapy with risperidone. Of the remainder, 66 patients (4.9%) were on quetiapine. Logistic regression was used to compare the odds of patients in selected antipsychotic treatment groups developing DM in the year following initiation of therapy, after controlling for age, sex, geographic region, mental health disorder, length of therapy, and hypertension/heart disease comorbidities.

No detectable differences were observed in the 1-year risk of DM onset among patients who initiated atypical antipsychotic therapy compared with those who initiated therapy with typical antipsychotics. Furthermore, no differences in the 1-year risk of DM onset were found between patients who initiated therapy with olanzapine versus any typical antipsychotic, risperidone versus any typical antipsychotic, or olanzapine versus risperidone.

Patients prescribed atypicals were more likely to be younger, female, and have a diagnosis of bipolar disorder or depression. Length of therapy in the atypical group was longer than for typicals (126.1 days versus 108.3 days;  $p < .0001$ ). The unadjusted 1-year rate of DM onset for patients in the atypical group (3.0%) was nearly identical to the rate observed in the typical group (3.16%) ( $p = .8237$ ). The unadjusted 1-year rate of DM onset between the olanzapine (2.53%) and risperidone (3.33%) treatment groups were also similar ( $p = .4142$ )

Using logistic regression models, no detectable difference in the 1-year risk of DM onset among patients who initiated atypical antipsychotic therapy compared with those who initiated therapy with typical antipsychotics (odds ratio = 1.010;  $p=.9685$ ). Additionally, no differences in the 1-year risk of DM onset were found between patients who initiated therapy with olanzapine versus any typical antipsychotic (odds ratio = 0.864;  $p=.6796$ ), risperidone versus any typical antipsychotic (odds ratio = 1.074;  $p=.8023$ ), or olanzapine versus risperidone (odds ratio = 0.786;  $p=.5109$ ).

These findings should be interpreted in the context of the limitations of the study. First, the results may not be generalizable to the US population overall because they are based on a nonrandom sample. Second, the administrative claims database, and hence, the logistic regression models, lack certain variables that are well-known risk factors for DM (eg, family history, ethnicity, and weight). The results presented in this study are biased to the extent that these missing variables are correlated with therapy choice. Also, the study did not directly control for specific antipsychotic exposure; rather, it used an intent-to-treat methodology and controlled for overall duration of the index antipsychotic therapy.

Another limitation was that the timeframe for conducting that analysis coincided with concerns about the potential risk of atypical antipsychotics. It is possible, therefore, that the results are biased because of confounding by indication – that is, patients at risk for diabetes may have been more likely to receive typical rather than atypical antipsychotics. This possibility may have been counterbalanced, however, by patients who were prescribed atypical antipsychotics having been screened more frequently for diabetes.

In summary, there were significant differences in demographics characteristics of patients treated with typical versus atypical antipsychotic in the database used for this study. Efforts were made to use statistical modeling to control for demographic variables that can impact diabetes risk. The study did not find clinically meaningful differences in the risk of diabetes between different antipsychotic treatment groups. The findings that a history of hypertension or heart disease was associated with a higher risk of diabetes are consistent with what is seen in the general population. Finally, the relatively high annual rate of diabetes (about 3%) in this survey underscores the significant risk that exists in the psychiatric population regardless of treatment choice.

**Le K, Wogen J, Boccuzzi S. (2003, manuscript under review). Use of Antipsychotic Agents and the Association of Diabetes Mellitus Diagnosis. Abstract presented at the 15th Annual Psychiatric Congress, Las Vegas, NV, October 28-31, 2002.**

In this Lilly-funded study, Le and colleagues examined the onset of diabetes mellitus (DM) in patients new to therapy with atypical antipsychotics versus typical antipsychotics, and olanzapine versus risperidone. In this retrospective cohort study using medical claims data from approximately 4 million total patients, the authors focused on patients age 18 to 65 receiving a single antipsychotic agent. Rather than selecting based on diagnosis, the investigators examined all users of each medication, and corrected for diagnosis as a potential risk factor for diabetes. The resulting cohort consisted of 4,234 patients receiving antipsychotics. Diabetes onset was defined as having one or more fill for an agent used to treat diabetes, or more than one medical service visit for diabetes based on ICD-9 codes. Using logistic regression, the analyses adjusted for age; sex; length of therapy; and presence of major depressive disorder, schizophrenia, bipolar disorder, or other psychiatric diagnosis.

The mean age for the study cohort was 41 years; females comprised 59% of the study population. Eighty-two percent of patients initiated therapy with atypicals compared to 18% with conventionals. Olanzapine (40%) and risperidone (41%) were the most prescribed atypicals. After adjusting for significant clinical and demographic variables (eg, age, gender, length of therapy, depression, schizophrenia, bipolar disease, and other psychotic disorders), the odds of a subsequent reported diabetes mellitus diagnosis was 0.762 for patients on atypicals versus conventionals (95% CI=0.355-1.638; p=.4863). Similarly, the odds were 0.676 for olanzapine-treated patients versus typicals (95% CI=0.272-1.679; p=.3990), and 0.642 for risperidone patients versus conventionals (95% CI=0.251-1.641; p=.3549). There was no difference between olanzapine and risperidone in the rate of new-onset diabetes; the adjusted odds ratio was 1.141 for olanzapine versus risperidone (95% CI=0.437-2.981; p=.7872).

The study's strengths included its reliance on a large cohort in managed care data, and the use of statistical risk adjustment for psychiatric illness, age, gender, and length of therapy. The focus on a monotherapy population reduced the likelihood of attributing differences in DM risk to factors associated with polypharmacy. Limitations included the absence of public payer patients, which make up a large portion of the seriously and persistently mentally ill. Lack of information on ethnicity precluded adjustment for this known risk for DM. Finally, as with all retrospective non-randomized studies, it cannot be ruled out that patient selection bias may have impacted on drug assignment and attribution of risk of DM to individual drug cohorts.

In summary, the results of this study are consistent with other lines of evidence showing no clinically meaningful differences in the risk of diabetes among patients treated with antipsychotic therapies.



**Barner JC, Worchel J, Yang M. (2003, manuscript under review). The Incidence of New-Onset Diabetes and Use of Antipsychotics. Abstract submitted for presentation at Institute for Psychiatric Services (IPS), American College of Clinical Pharmacy (ACCP) meetings, November 2003.**

In this Lilly-funded study, Barner and colleagues evaluated the incidence of new-onset diabetes among patients who were treated with atypical and typical antipsychotic agents, to determine whether the incidence of new-onset diabetes differed in patients treated with atypical versus typical agents, or versus different atypical antipsychotic agents, and to determine what baseline and clinical factors (eg, antipsychotic agent, body mass index, diabetes-related risk factors, or demographics) are associated with new-onset diabetes.

The authors accessed clinical parameters in the Central Texas Veterans Health Care System (CTVHCS), which were included as covariates in the analyses of incidence of diabetes mellitus. This retrospective cohort study used VA medical records and claims from 30 September 1995 to 1 November 2002, and studied adult VA patients who had not received a prescription for an atypical or typical antipsychotic agent 6 months prior to the dispensing of an atypical or antipsychotic agent, had no previous use of diabetic medication or diagnosis of diabetes for 1 year prior to a prescription for a typical or atypical antipsychotic, and were continuously enrolled for 12 months prior to and following the date of an atypical or typical antipsychotic agent. There were no psychiatric diagnosis requirements for inclusion. New-onset diabetes mellitus was defined as any of: a visit with an ICD-9 diagnosis of 250.xx; any diabetes medication; or blood glucose level greater than 200. Potential predictors for diabetes mellitus onset included type of antipsychotic agent, body mass index change, previous hyperlipidemia, change in hypertension status, persistence, type of mental health comorbidity, age, gender, and ethnicity.

Logistic regression was used to evaluate the risk of new-onset diabetes based on treatment cohort, adjusting for clinical and patient-related variables. Because of frequent polypharmacy in clinical practice, the authors analyzed data both in single-use cohorts using multivariate methods; and under an intent-to-treat, unadjusted analysis separating the data into three groups (atypicals, typicals, and polypharmacy).

A total of 6735 patients were identified as taking antipsychotics in the CTVHCS database. Of those, 3916 met the study inclusion criteria. Approximately 42 % of patients met the exclusion criteria, with the majority (29.7%) being excluded because of previous antipsychotic use.

The incidence of new-onset diabetes using various criteria to define diabetes in the entire sample of 3916 patients was: (i) any criteria (n=275; 7.0%); (ii) blood glucose (n=146; 3.7%); (iii) ICD-9 (n=125; 3.2%); and (iv) antidiabetic medication (n=82; 2.1%).

The incidence of new-onset diabetes in patients treated with atypical, typical, or both atypical and typical agents was: (i) atypical (n=116/1772; 6.6%); (ii) typical (n=73/1023; 7.1%); and (iii) both atypical and typical (n=86/1121; 7.7%) [chi-square=1.3593, p=0.5068].

The incidence of new-onset diabetes in the atypical antipsychotic cohort (n=1915) was: (i) risperidone (n=51/705; 7.2%); (ii) quetiapine (n=15/216; 6.9%); and (iii) olanzapine (59/994; 5.9%) [chi-square=1.2091, p=0.5463].

The results of the logistic regression analysis of risk of diabetes in patients treated with atypical antipsychotics (n=1587) are presented below. The analysis also evaluated the contribution of age, ethnicity, BMI, hypertension, and dyslipidemia to the risk of diabetes:

	<b>Odds Ratio</b>	<b>95%CI</b>	<b>p-value</b>
Olanzapine	0.976	0.594-1.605	0.8394
Quetiapine	1.149	0.531-2.485	0.6293
Risperidone	0.926	0.544-1.579	0.6328
Age	1.213	1.016-1.447	0.0324*
Nonwhite	1.761	1.174-2.640	0.0062*
Female	0.718	0.277-1.857	0.4940
BMI	1.032	0.477-1.581	0.6439
Hypertension	0.759	0.415-1.388	0.3713
Previous dyslipidemia	1.606	1.064-2.425	0.0242*

\* p<0.05

The results of this study showed that the incidence of new-onset diabetes was not significantly different between typicals and atypicals, or among atypicals. Furthermore, the authors observed that several well-established diabetes risk factors (age, non-Caucasian ethnicity, and previous dyslipidemia) were significant predictors of risk of new-onset diabetes, but treatment cohort was not.

This study's primary strength is that it included data that are not normally available in claim databases (eg, ethnicity, history of dyslipidemia). The study replicated the observation of comparable DM rates in both the unadjusted intent-to-treat analysis for patients using multiple drugs, and the multivariate single-drug cohort analysis. However, one notable limitation was the lack of formal a priori evaluation of statistical power to detect differences in the risk of DM between antipsychotic treatment cohorts. Finally, as with all retrospective non-randomized studies, it cannot be ruled out that patient selection bias may have impacted on drug assignment and attribution of risk of DM to individual drug cohorts.

In summary, the results of this study are consistent with other lines of evidence showing no clinically meaningful differences in the risk of diabetes among patients treated with antipsychotic therapies.

**Ollendorf DA, Joyce AT, Rucker, M. (2003, manuscript under review). Rate of New-Onset Diabetes Among Patients Treated with Atypical or Conventional Antipsychotic Medications for Schizophrenia. This poster was presented at the 54<sup>th</sup> Institute for Psychiatric Services, Chicago, IL, October 2002.**

In this Lilly-funded study, Ollendorf et al also examined the rates of new-onset diabetes mellitus (DM) among patients receiving antipsychotic medications, focusing specifically on patients being treated for schizophrenia. The authors performed a retrospective cohort study of the claims data for patients with one or more medical claims with a listed diagnosis of schizophrenia, as well as one or more pharmacy claims for an antipsychotic medication between 30 September 1996 and 30 June 2001.

All patients were required to have a minimum of 3 months of follow-up; follow-up was allowed to vary, as techniques to account for right-censored data were employed in primary data analyses.

New-onset diabetes mellitus (DM) was defined as one or more prescription claims for DM medication, or two or more claims showing a DM diagnosis on or after the date of initial antipsychotic use. The analysis accounted for age, gender, health plan type, geographic region, calendar year of drug initiation, number of DM screening tests, number of laboratory tests overall, other psychiatric diagnoses recorded in the pretreatment or follow-up periods, and other medical diagnoses known to be risk factors or concomitant conditions with DM (hypertension, cardiovascular disease, obesity, and impaired glucose tolerance).

The total duration of therapy and number of prescriptions for the index medication were also examined. Cox proportional hazards models were employed to estimate DM rates where follow-up lengths varied. In the subgroup of patients with 12 months of continuous enrollment subsequent to the index date, logistic regression techniques were used to examine DM rates with risk adjustment.

New-onset DM was observed in 45 patients. Atypical antipsychotic use was temporally associated with an increased risk of DM at 1 year following initiation of therapy relative to conventional antipsychotics. There were no significant differences with regard to the risk of new-onset diabetes among patients treated with different atypical antipsychotics.

A total of 2,443 patients with schizophrenia were analyzed (n=1,826 and 617 for atypicals and conventional users, respectively). The mean duration of follow-up was 435 days, and was significantly longer among patients in the conventional group (485.0 days versus 418.8 days for atypicals,  $p < .0001$ ). Of the 45 cases of new-onset DM during follow-up for patients receiving atypical antipsychotics, 23/937 (2.45%), 16/690 (2.32%), 2/35 (5.71%), and 4/164 (2.44%) were among olanzapine, risperidone, clozapine, and quetiapine users, respectively. These differences were not statistically significant ( $p = .9363$ ).

In Cox proportional hazards models, atypical antipsychotic use imparted a moderately increased risk of DM relative to conventional antipsychotics (HR=1.17, 95% CI=1.06-1.30; p=.0063). When atypical medication cohorts were compared, there were no significant differences with respect to the risk of new-onset DM (HR=1.049, 95% CI=0.930-1.168, p=.4308; HR=1.170, 95% CI=0.967-1.372, p=.1291; HR=1.467, 95% CI=0.967-1.968, p=.1332) for olanzapine versus risperidone, quetiapine, and clozapine respectively.

This study's strengths included use of a large cohort of managed care patients, as well as risk adjustment for medical and psychiatric comorbidities and other DM risk factors. Two separate analytical methods confirmed comparable rates of DM among atypicals, although the Cox proportional hazards analysis showed moderately increased DM risk for patients treated with any atypicals when compared to patients treated with conventionals. Limitations included the absence of public payer patients, which make up a large portion of the seriously and persistently mentally ill. Additionally, as with all retrospective observational studies, effects of selection may be confounded with effect of drug. Finally, as with all retrospective non-randomized studies, it cannot be ruled out that patient selection bias may have impacted on drug assignment and attribution of risk of DM to individual drug cohorts.

In summary, the results of this study support other lines of evidence indicating no clinically meaningful differences in the risk of DM among atypical antipsychotic therapies. Consistent with the findings of Sernyak et al (2002), this study found that treatment with atypical antipsychotics was associated with an increase in risk of DM compared to treatment with conventional antipsychotics.

### **Discussion and Conclusions – Retrospective Cohort Studies**

These four cohort studies, which applied similar methodologies to distinct databases, independently support other lines of evidence showing no clinically meaningful differences in the risk of diabetes between conventional and atypical antipsychotics (Buse et al 2003; Gianfrancesco et al. 2003), or among atypical antipsychotics (Sernyak et al. 2002).

### 3.2. Glucose Dysregulation in Patients with Serious Mental Illness

**Lambert BL, Chou C, Chang K, Carson W, Tafesse E. 2003. Antipsychotic Use and New-Onset Type II Diabetes Among Schizophrenics. IX International Congress on Schizophrenia Research, March 29-April 2, 2003, Colorado Springs, CO. Schizophrenia Research 60(Suppl 1):359.**

A poster by Lambert and colleagues showed the findings of a case-control study of new-onset Type 2 diabetes (DM) using data from California Medicaid (Medi-Cal).

Cases were identified as diabetes using claims data (by ICD-9 250) among patients with schizophrenia (by ICD-9 295) who were 18 years or older, and on only one antipsychotic medication during the 12 weeks prior to their DM diagnosis. Controls were patients with schizophrenia without DM, matched for gender and age ( $\pm 5$  years). Conditional logistic regression assessed risk in patients treated with one of four different atypicals, controlling for race and exposure to other medications associated with increase DM risk. A total of 3220 cases were matched with 8791 controls. In the 12-week observation period, the authors found an increased risk of diabetes in patients treated with olanzapine or clozapine compared to conventional antipsychotics, but not for risperidone and quetiapine compared to conventionals. No significant differences in diabetes risk were reported in comparison of patients treated with clozapine, risperidone, or quetiapine. African-American or unknown race were also significant risk factors for DM, as were exposure to alpha blockers, thiazide diuretics, corticosteroids, or phenytoin.

This study presents with a number of limitations. The cases and controls were statistically different with respect to 5 out of 10 characteristics (eg, ethnicity) known to be factors associated with DM. The poster did not address disparities in these case-mix factors within or between the four antipsychotics under study, so the differences observed could be due simply to selection bias in this observation study. As with all claims-based observational studies, one cannot exclude that the observed findings may have been impacted by drug-selection biases (eg, more psychiatrically severely ill patients potentially at increased risk of DM being treated with clozapine).

In summary, the methodological limitations of this study do not allow for meaningful conclusions regarding potential differences in risk of diabetes between patients treated with olanzapine and patients treated with conventional antipsychotics, or with other atypical antipsychotics.

**Dunlop BW, Sternberg M, Phillips LS, Anderson J, Duncan EJ. 2003. Disturbed Glucose Metabolism among Patients Taking Olanzapine and Typical Antipsychotics. Biol Psychiatry 53:46S.**

The purpose of this study was to compare the risk of diabetes in patients treated with olanzapine versus patients treated with older typical antipsychotics with respect to a potential association with increased risk of diabetes. A retrospective cohort analysis was performed on 484 patients receiving outpatient prescriptions for either olanzapine (n=312) or one of four typical antipsychotics (n=172) at the Atlanta Veterans Affairs Medical Center (VAMC) from 1 October 1996 through 31 December 2000. The four typical antipsychotics were haloperidol, fluphenazine, chlorpromazine, and perphenazine. Random plasma glucose values collected over the 4-year period were classified as to whether they had been drawn before, during, or after exposure to an antipsychotic. Primary outcome measures were the development of a random plasma glucose  $\geq 160$  mg/dL or  $\geq 200$  mg/dL while on an antipsychotic.

A significant difference was observed in the percentage of antipsychotic-treated patients developing a random plasma glucose  $\geq 160$  mg/dL (olanzapine 12.5% versus typical antipsychotics 5.2%,  $p < .01$ , adjusted odds ratio = 3.6) and  $\geq 200$  mg/dL (olanzapine 5.4% versus typical antipsychotics 1.7%,  $p = .02$ , adjusted odds ratio = 5.1). For patients younger than 60 years of age, 10.5% of those taking olanzapine developed a random plasma glucose  $\geq 160$  mg/dL compared to 0% of those taking typical antipsychotics ( $p = .0003$ ). The authors concluded that among individuals without a plasma glucose value  $\geq 160$  mg/dL at baseline, treatment with olanzapine was associated with an increased risk of elevation in plasma glucose compared to treatment with typical antipsychotics.

The prevalence of diabetes observed in the olanzapine group (12.5%) is consistent with the prevalence of diabetes reported by Dixon and colleagues (2000) in a landmark study conducted in a large US healthcare database cohort from 1991 onward. This study found that the prevalence of diabetes among patients with schizophrenia was approximately 12%, over twice the prevalence reported in the US general population.

This study by Dunlop and colleagues has several limitations and draws questionable conclusions. The authors limited their analyses to a comparison of olanzapine with typical antipsychotics, based on a priori assumption that olanzapine is associated with a greater degree of diabetes compared to other atypicals. It cannot be excluded that selection bias may have had an impact on the observed rates of diabetes reported in this study, as clinicians may have been more likely to check weight and glucose in patients treated with olanzapine, given the a priori assumption of the study. Finally, the study did not control for differences in BMI, ethnicity, or concomitant medications.

In summary, the methodological limitations of this study do not allow for meaningful conclusions regarding potential differences in risk of diabetes between patients treated with olanzapine and patients treated with conventional antipsychotics.

**Smith RC, Lindenmayer JP, Bark N, Warner-Cohen J, Vaidhyanatha S, Hopkins M. 2003. A Prospective Cross-Sectional Study of Glucose and Lipid Metabolism with Atypical and Conventional Antipsychotics. Poster presented at the 43<sup>rd</sup> Annual NCDEU Meeting, Boca Raton FL, May 27-30, 2003.**

This cross-sectional study examined measures of fasting glucose and lipid metabolism in 204 patients with schizophrenia enrolled in several prospective randomized trials. Patients had received at least 1 month of treatment with either conventional antipsychotics (n=52), olanzapine (n=53), risperidone (n=50), or clozapine (n=49), and were not concurrently treated with antidiabetic drugs. Fasting laboratory parameters were collected on 2 separate days for most patients, and then averaged. Oral glucose tolerance tests (OGTT) were conducted in those patients showing borderline fasting glucose abnormalities ( $\geq 110$  mg/dL) and in selected patients with normal fasting glucose levels ( $< 110$  mg/mL). Treatment groups were matched for age, sex, and BMI. There were significantly fewer Caucasians in the risperidone cohort.

Using ANOVA, the study found no significant differences in mean values for any of the following variables among the four drug groups: glucose, insulin, insulin sensitivity (by HOMA-IR), fructosamine, HDL, LDL, or chol/HDL ratio. Risperidone users had significantly higher mean HbA<sub>1c</sub> and C-peptide levels compared to olanzapine and clozapine, respectively. The clozapine group had significantly higher mean total cholesterol than risperidone and conventional groups, and both clozapine- and olanzapine-treated patients had higher triglycerides than risperidone and conventional antipsychotic users. Mean fasting leptin levels were significantly higher in the risperidone cohort than in the olanzapine group. Using Tukey's honest statistical difference (HSD) test to control for multiple variables, the differences in all of these parameters were no longer significant. Three risperidone patients had a fasting blood glucose  $\geq 126$  mg/dL during the study, however none of the other drug groups had patients with fasting blood glucose levels  $\geq 126$  mg/mL. Oral glucose tolerance tests (OGTT) were performed in patients with fasting glucose  $\geq 110$  mg/dL and indicated abnormal results in 5 of 6 risperidone patients, 2 of 3 clozapine patients, 0 of 3 olanzapine patients, and 2 of 5 typical antipsychotic patients. ANOVA indicated 1-hr OGTT results in risperidone and clozapine patients were significantly higher in comparison to olanzapine patients ( $p < .02$ ).

This study was limited by its cross-sectional nature, although patients were recruited from randomized, prospective clinical trials. The demographics of the drug cohorts were comparable, with the exception of the risperidone group, where difference in ethnic composition may account for some of the observed-group abnormalities. Acknowledging the limitations of the study, the authors concluded that there were not "strong and consistent differences in glucose-lipid metabolism among the four treatment groups."

In summary, the results of this study do not show clinically meaningful differences in glucose regulation parameters among patients treated with antipsychotic drugs.

**Koller EA, Doraiswamy PM, Cross JT, Schneider BS. 2003. Quetiapine-Associated Diabetes Mellitus. Poster presented at 156<sup>th</sup> Annual Meeting of the American Psychiatric Association, San Francisco CA, May 17-22, 2003.**

This study was a continuation of previous work published by Dr. Koller examining case reports of hyperglycemia, type 2 diabetes, and diabetic ketoacidosis. An epidemiologic survey of spontaneously reported adverse events in quetiapine-treated patients was conducted using reports from the Food and Drug Administration (FDA) MedWatch surveillance program between January 1997 and August 2002, and published cases. The authors identified 46 reports of quetiapine-associated hyperglycemia and nine additional reports of acidosis that occurred in the absence of hyperglycemia. Of the reports of quetiapine-associated hyperglycemia, 34 patients had newly diagnosed hyperglycemia, 8 had exacerbation of preexisting disease, and 4 could not be classified. The mean age was  $35.3 \pm 16.2$  years (range 5 to 76). New-onset patients ( $31.2 \pm 14.8$  years) tended to be younger than those with preexisting diabetes ( $43.5 \pm 16.4$  years;  $p=.08$ ). The overall male:female ratio was 1:9. Most cases appeared within 6 months of quetiapine initiation. The severity of cases ranged from mild glucose intolerance to diabetic ketoacidosis or hyperosmolar coma. There were 21 cases of ketoacidosis or ketosis with 11 patient deaths reported.

This report is comparable to methodologies reported by Koller and colleagues in previous systematic reviews of clozapine (Koller et al. 2001), olanzapine (Koller and Doraiswamy 2002), and risperidone (Koller et al. 2003).

Numerous limitations exist when examining spontaneous adverse event databases such as the FDA MedWatch dataset. Given the difficulties in determining patients' exposures on the basis of prescription data, the reporting rates of new-onset type 2 diabetes can only be approximated. Further, reporting rates cannot be used to infer actual incidence of events. Detection and reporting biases are prevalent in these databases and numerous gaps in information exist in the reported cases, thereby precluding any attempt to establish a causal relationship.

In summary, the types of cases reported in temporal association with treatment with quetiapine were qualitatively very similar to those previously reported by Koller and colleagues (Koller et al. 2001; Koller and Doraiswamy 2002; Koller et al. 2003) in patients treated with clozapine, olanzapine, or risperidone. Due to the limitations of spontaneous postmarketing adverse event databases, analyses of these types of databases cannot be used to make meaningful conclusions regarding causality or actual incidence of events.



**Joseph RC, Danforth N, Goren GS, Kardos M, Wyshak G, Steingard R, Rosenquist K, Ko J, Ghaemi N. 2002. Diabetes and lipid profile risks with neuroleptics: 2-5 Year Outcomes. Poster presented at Academy of Psychosomatic Medicine Meeting, Tucson AZ, November 21-24, 2002.**

The focus of this small study was to determine whether any of the antipsychotic medications tested were associated with elevations of HbA<sub>1C</sub> in the absence of abnormal glucose measurements, and to assess the risk of diabetes and abnormal lipid profiles in patients receiving long-term treatment with antipsychotics.

This was a cross-sectional, naturalistic study conducted in 65 patients (32% bipolar spectrum and 68% schizophrenic spectrum) treated with antipsychotics for  $\geq 3$  months. HbA<sub>1C</sub>, fasting blood sugar (FBS), cholesterol, triglycerides, HDL, and LDL levels were assessed for each patient.

Overall duration of treatment averaged 3.5 years, and was significantly shorter with risperidone (n=12, 2.0 years) and olanzapine (n=15, 1.8 years) compared with clozapine (n=28, 3.7 years) or conventional antipsychotics (n=10, 8.2 years) ( $p < .001$ ). Gender, diagnosis, ethnicity, and medical illness did not significantly differ between groups. Analysis of variance was significant for HbA<sub>1C</sub> levels and duration of treatment ( $p = .04$  and  $p < .001$ , respectively). Individual t-tests suggested statistically significant elevations of HbA<sub>1C</sub> levels during treatment with clozapine compared to olanzapine ( $p = .004$ ). Elevated HbA<sub>1C</sub> levels during treatment with clozapine were significant after Bonferroni multiple comparison correction. There were no differences in FBS, total cholesterol, HDL, LDL, triglycerides levels, BMI, or age among the drug cohorts. A family history of diabetes did not show an association with elevated HbA<sub>1C</sub> levels. The authors concluded that 3- to 5-year treatment with clozapine was associated with higher HbA<sub>1C</sub> levels, while 2-year treatment with risperidone and olanzapine was associated with minimal changes in glucose parameters and lipid profiles.

This study presents with several limitations that should be noted. The sample size in each treatment group was very small. Given the absence of randomization to treatment modality, the possibility of treatment selection bias cannot be excluded. The patients were not known to have diabetes, however no fasting blood glucose data or glucose tolerance information was presented; therefore, some of these patients may have been diabetic or glucose intolerant but undiagnosed, which could have influenced the interpretation of the results. Finally, HbA<sub>1C</sub> is not recognized as a criterion for diagnosing diabetes (ADA 2002).

In summary, the methodological limitations of this study do not allow for meaningful conclusions regarding potential differences in parameters of glucose regulation between patients treated with olanzapine and patients treated with conventional antipsychotics, or with other atypical antipsychotics.

**Lindenmayer JP, Czobor P, Volvka J, Citrome L, Sheitman B, McEvoy JP, Cooper TB, Chakos M, Lieberman JA. 2003. Changes in Glucose and Cholesterol Levels in Patients with Schizophrenia Treated with Typical and Atypical Antipsychotics. Am J Psychiatry 160:290-296.**

This paper is a secondary analysis of laboratory data from a prospective, randomized, double-blind study designed to compare the efficacy of the antipsychotics studied over a 14-week time frame. This paper assessed the effects of clozapine, olanzapine, risperidone, and haloperidol on glucose and cholesterol levels in this population of hospitalized patients with schizophrenia or schizoaffective disorder.

One hundred fifty-seven patients with schizophrenia or schizoaffective disorder who were inpatients at four hospitals were originally included in the study. The 14-week trial consisted of an 8-week fixed-dose period and a 6-week variable-dose period. Planned assessments included fasting glucose and cholesterol, which were collected at baseline and at the end of the 8-week period and the following 6-week period.

Blood samples at baseline and at least at one point after random assignment to drug during the treatment trial were available in 108 of 157 patients. Seven of these patients had diabetes; their glucose levels were >125 mg/dL at baseline. Therefore, the statistical analyses was based upon data from 101 patients. During the initial 8-week period, there was an overall significant increase in mean glucose levels for all patients, with significant increases in glucose levels observed in patients given clozapine (n=27) and haloperidol (n=25). The olanzapine group showed a significant increase of glucose levels at the end of the 6-week variable-dose period (n=22). Fourteen of the 101 patients developed abnormal glucose levels (>125 mg/dL) during the trial (6 with clozapine, 4 with olanzapine, 3 with risperidone, and 1 with haloperidol). Cholesterol levels increased by the end of the 8-week fixed-dose period for patients given clozapine (n=27) and those given olanzapine (n=26); cholesterol levels were also increased at the end of the 6-week variable-dose period for patients given olanzapine (n=22).

This trial was characterized by relatively high dropout rates over 14 weeks, especially within the clozapine and risperidone groups (39% in the clozapine group, 36% in the risperidone group, 20% in the haloperidol group, and only 15% in the olanzapine group). This high dropout rate may have limited the ability to observe significant between-group changes if, in fact, the patients who dropped out had substantial changes in glucose or cholesterol levels, which the authors noted as a limitation in interpreting study results. The authors commented that the results from the first 8-week time period were the more robust findings, especially given the fixed- versus flexible-dosing design between the two study periods.

Patients treated with olanzapine showed the largest amount of weight gain over 14 weeks (7.3 kg in patients treated with olanzapine versus 4.8 kg in patients treated with clozapine and 2.4 kg in patients treated with risperidone). ANCOVA, however, indicated no main effect or treatment interaction for the relationship between glucose change and weight gain at endpoint. A significant effect between weight change and cholesterol was observed in the four groups combined, as well as in the clozapine and olanzapine groups. In the small subset of patients with preexisting diabetes (n=7), antipsychotic treatment did not appear to worsen glucose regulation.

The authors concluded that clozapine, olanzapine, and haloperidol were associated with an increase of plasma glucose levels, and clozapine and olanzapine were associated with an increase in cholesterol levels.

Strengths of this study include the well-controlled prospective nature of the design. With respect to limitations, the sample sizes of each drug cohort were relatively small, and the 14-week observation period may not have been sufficient for definitive evaluation of any potential drug differences.

In summary, this study reported a greater elevation of glucose and cholesterol levels during treatment with clozapine and olanzapine. However, these results must be interpreted in the context of several methodological limitations, including small sample size and relatively high dropout rates.

**Kurt E, Oral E, and Verimli A. 2002. Comparison of the Effects of Classical and Novel Antipsychotic Drugs on the Insulin and Glucose Metabolisms of Patients with Schizophrenia and Other Psychotic Disorders. Bull Clin Psychopharmacol 12:57-63.**

The objective of this naturalistic, prospective study was to evaluate changes in insulin and glucose metabolism in patients treated with typical versus atypical antipsychotics. Seventy-five patients with diagnoses of schizophrenia or delirium were evaluated after a minimum of 1 week off of antipsychotics, and then again after 2 months of treatment with haloperidol or various atypical agents. Plasma insulin and glucose levels were determined using a standard 2-hour oral glucose tolerance test (OGTT) after a 75 g glucose load. Patients were not randomized, but were treated according to physician preference. Groups taking typical or atypical antipsychotics were not significantly different with respect to age, gender, concomitant medications, or psychiatric diagnosis.

A significant decrease in fasting glucose was observed after 2 months of treatment among patients taking haloperidol (n=26), but no significant change was seen in the atypical group (n=49). Fasting insulin, 2-hour postload glucose, and insulin sensitivity, as determined by HOMA-IR (Littrell 2003), did not change significantly in either group. However, there was a trend for a baseline-to-endpoint increase in 2-hour glucose in the atypical antipsychotic group (95.8 to 107.9 mg/dL; p=.06) and a between-group comparison in endpoint 2-hour glucose was statistically significant (p=.014). Among patients taking individual atypical antipsychotics (n=8 to 12 for all drugs), only the clozapine group demonstrated significant increases in fasting glucose (88.5 mg/dL to 93.5 mg/dL), and only quetiapine treatment was associated with a significant increase in the 2-hour glucose (73.5 mg/dL to 95.8 mg/dL) when compared to pretreatment levels. Olanzapine, risperidone, and sulpiride groups did not have significant changes in either parameter, and none of the individual atypical antipsychotics were associated with significant changes in fasting insulin or HOMA-IR.

The strengths of this study include the prospective design and the use of standardized measures of glucose tolerance. Limitations include the lack of randomization to treatment and the omission of important demographic information including body weight (or BMI), ethnicity and family history, all of which can impact glucose metabolism. Although the study showed a significant difference in endpoint 2-hour glucose between conventional and atypical antipsychotic users, this was due in part, to the decrease in glucose in patients taking typical agents. Finally, some statistically significant changes were seen in fasting or post-load glucose in patients treated with clozapine or quetiapine, the clinical relevance of these changes is unclear, since the study did not include categorical analyses or evaluation of potential outliers.

In summary, this study did not show consistent or clinically significant changes in glucose metabolism after 2 months of treatment with conventional or atypical antipsychotics. No significant changes were seen in the olanzapine group for any of the outcome measures.

## **Discussion and Conclusions – Glucose Dysregulation in Patients with Serious Mental Illness**

The cumulative data available to date do not allow for conclusions regarding the possibility that treatment with antipsychotic medication contributes to the increased risk of diabetes observed in the seriously mentally ill. Nor does the current evidence allow for conclusions regarding increased risk of diabetes between patients treated with atypical antipsychotics versus patients treated with conventional antipsychotics.

Finally, the current body of literature does not support specific conclusions regarding differences in likelihood of diabetes between patients treated with specific atypical antipsychotic medications. Studies comparing the risk of diabetes among patients treated with atypical antipsychotics are consistent, however, in demonstrating the impact of risk factors for diabetes that are well established in the general population

### 3.3. Randomized, Prospective Studies Comparing Olanzapine and Ziprasidone

**Glick ID, Romano SJ, Simpson G, Horne RL, Weiden P, Piggott T, Bari M. 2001. Insulin Resistance in Olanzapine and Ziprasidone Treated Patients: Results of a Double-Blind Controlled 6-Week Trial. Poster presented at the following meetings: ACNP annual meeting, San Juan PR, December 2000 (interim analysis); APA annual meeting, New Orleans LA, May 2001; and Institute of Psychiatric Services, Orlando FL, October 2001.**

The objective of this study was to evaluate changes in weight, lipids, and metabolic parameters associated with insulin resistance (IR) in patients with schizophrenia treated with ziprasidone (ZIP) and olanzapine (OLZ). In a double-blind trial, 269 acute inpatients were randomized to ZIP or OLZ for 6 weeks. Fasting insulin, glucose, total cholesterol, and triglycerides were measured prerandomization and at last visit. An IR index (HOMA-IR =  $[\text{Ins} \times \text{Glu}] / 22.5$ ) was calculated.

No significant difference was observed in fasting glucose. From baseline, patients treated with OLZ had weight gain of 7.2 lb ( $p < .001$ ) and increases in fasting insulin of 36% ( $p < .001$ ) and in HOMA-IR (log) of 11% ( $p < .001$ ). Total cholesterol and triglycerides increased 9% and 20%, respectively, in patients treated with OLZ (both  $p < .001$ ). In contrast, treatment with ZIP did not significantly alter any of these parameters, and all but glucose and HOMA IR were statistically separable (ZIP versus OLZ  $p < .05$ ).

The median weight gain was significantly greater in patients assigned to OLZ compared to ZIP (7.2 lbs versus 1.2 lbs). In olanzapine-treated patients, there was a statistically significant increase in median total cholesterol (OLZ 16 mg/dL; ZIP 0 mg/dL), triglycerides (OLZ 28 mg/dL; ZIP -3 mg/dL), and LDL (OLZ 10 mg/dL; ZIP -3 mg/dL). These changes were significant versus baseline and also versus ZIP patients over the 6 weeks.

The authors conclude that these changes in metabolic parameters were suggestive of worsening of insulin resistance in patients taking olanzapine. However, this study presented with a number of limitations. The authors used the HOMA-IR as a marker of insulin resistance (fasting insulin X fasting glucose/22.5). Although the HOMA-IR increased numerically for olanzapine-treated patients, it was non-significant compared with ZIP after adjustment for baseline values. Outcome measures included weight, measures of insulin resistance (fasting insulin, plasma glucose), lipid profile (triglycerides, total cholesterol, LDL, and HDL), blood pressure, uric acid, and c-peptide. All results were reported as median values (as opposed to mean values), thus, potentially limiting the impact of outliers on the outcome measures.

**Simpson and colleagues (2002)** reported on the 6-month continuation of the 6-week study reported by Glick in the preceding summary. This 6-month, blinded continuation study followed hospitalized patients who had completed the 6-week randomized trial with satisfactory clinical response (CGI-I  $\leq 2$  or  $\geq 20\%$  reduction in symptom severity by PANSS Total), and were discharged on olanzapine 5 mg to 15 mg QD (n=71) or ziprasidone 40 mg to 80 mg BID (n=62). Primary efficacy measures were BPRS and CGI-S; secondary variables included PANSS Total, and Positive and Negative Subscale scores. Tolerability assessments included fasting lipids, insulin, glucose, and weight. Results indicated that ziprasidone- and olanzapine-treated patients demonstrated comparable changes in BPRS, CGI-S, and PANSS Total and Subscale scores from baseline of 6-week study to endpoint of 6-month continuation, with no significant difference between groups.

Olanzapine-treated patients exhibited: (i) significant mean increases versus ziprasidone in endpoint weight ( $p < .01$ ); (ii) significant median increases versus baseline in LDL-C ( $p < .05$ ) [olanzapine versus ziprasidone = not significant]; and (iii) significant median increases versus baseline in insulin ( $p < .01$ ) [olanzapine versus ziprasidone = not significant].

The 6-month study reports the median fasting glucose increased by +5.0 mg/dL for olanzapine and +2.0 mg/dL for ziprasidone. The between-group difference is reported as non-significant.

#### **Analyses of Fasting Glucose Levels in Study HGHJ: Olanzapine versus Ziprasidone in the Treatment of Schizophrenia**

Lilly-sponsored clinical trial F1D-MC-HGHJ evaluated the efficacy and safety of olanzapine compared with ziprasidone. Methods and results of this study are presented with other Lilly studies in Section 4.4 of this document.

## Discussion and Conclusion – Studies Comparing Olanzapine and Ziprasidone

This section, along with new Lilly data described in Section 4.4 (Analyses of Fasting Glucose in Study HGHJ) presents the fasting glucose results from two independent multicenter, randomized, double-blind, parallel-control clinical trials (sponsored by Pfizer and Lilly, respectively). These trials were consistent in showing no clinically meaningful differences in fasting glucose measurements between patients treated with olanzapine or ziprasidone for up to 28 weeks. No substantial differences were observed in the most clinically relevant analysis where the frequencies of treatment-emergent fasting glucose  $>126$  mg/dL were compared after exclusion of patients with evidence of glucose dysregulation at baseline.



### 3.4. Glucose Control in Diabetic Patients Treated with Antipsychotics

While the literature is fairly limited in the arena of potential effects of antipsychotic therapy on glucose regulation in diabetic patients suffering from severe mental illness, a number of reports have become available since Lilly's previous submission ("Olanzapine and Glucose Homeostasis," 2 October 2002). This section summarizes these studies.

**Wilson D, Hammond CC, Buckley PF, Petty F. 2001. Atypical Antipsychotics & Hyperglycemia: An Analysis Of 11,994 Persons Treated In Ohio DMH Hospitals, 1994-2001. Poster presented at the ACNP annual meeting, Waikoloa, HI, December 2001.**

Clinical reports associate atypical antipsychotic (AAP) treatment with a syndrome of hyperglycemia, new-onset diabetes mellitus, and diabetic ketoacidosis (DKA). However, systematic analyses of large-scale databases are too few and insufficient to reliably and validly define clinical risks, optimal monitoring, or best practices. Moreover, inferences derived from naturalistic settings and/or free of perceived corporate considerations are even less common. Hence, this naturalistic study, in a 'benchmark' public mental health system and independent of commercial support, was undertaken to better define syndromes of AAP-associated hyperglycemia.

Computer archive records of all patients in ODMH facilities from 1 January 1994 to 31 July 2001 were reviewed on a 'rolling incidence' basis. Registers of patients treated with any AAP or hypoglycemic agent were collated from pharmacy orders and then cross-tabulated with lists of patients documented as diabetic via clinical laboratory assay. A 2% subsample of clinical charts was hand-reviewed to further validate research methods and findings.

Analysis of this sample is on-going toward the further elucidation of other associated findings including: (1) features of hyperglycemia and diabetes associated with AAP treatment, (2) relative risk vis a vis specific compounds and a variety of demographic descriptors, (3) possible insights into etiopathogenesis including differential risks for DKA or type I versus type 2 new-onset diabetes, and (4) evolving patterns of AAP prescriptions. In the period under study, 11,994 unique patients were identified as having been treated with an atypical antipsychotic. Of these, 861 (7.2%) were also treated with hypoglycemic agents.

Diagnosis and treatment of diabetes followed prescription of an AAP in 719 (6.0%) persons, as documented by abnormal fasting glucose levels or treatment with hypoglycemic medication after treatment with AAPs. 'Critically High' findings (FBS >300) were recorded in 91 (0.77%) persons.

Similar degrees of worsening in glyceic control was observed in all treatment groups, including patients treated with clozapine, quetiapine, risperidone, olanzapine, or ziprasidone. Interpretation of these results is made difficult by the absence of a control group of diabetic patients not treated with antipsychotics, and by lack of reference to the progression of glucose dysregulation over time observed within the context of the natural course of diabetes in the general population.

**Dixon L, Lehman A, Donner T, Kreyenbuhl J, Bellack A, Delahanty J, Wohlheiter K, Postrado L. 2003. A Comparison of Patients with Type 2 Diabetes and Schizophrenia, Major Affective Disorder and No Mental Illness. IX International Congress on Schizophrenia Research, March 29-April 2, 2003, Colorado Springs, CO. Schizophrenia Research 60 (suppl 1):334.**

In this study, the authors attempted to examine the effects of atypical antipsychotics on glucose metabolism and the course of diabetes in schizophrenia. They compared three groups of 100 patients diagnosed with type 2 diabetes and either (1) schizophrenia (SZ), (2) major depression or bipolar disorder (MAD), or (3) no mental illness (NMI). A total of 100 SZ and MAD patients were systematically recruited from mental health centers in the Baltimore area.

All eligible patients were identified and consecutively invited to participate. The NMI group was recruited from two primary care clinics in the neighboring area and was matched to the SZ group on gender, race, and educational level. Subjects were evaluated for hemoglobin (Hb)A<sub>1C</sub>, weight, diabetes-related health behaviors and knowledge, mental and medical service utilization, quality of diabetes care, neuropsychological and social functioning, psychiatric symptoms, and quality of life.

The NMI group had significantly higher HbA<sub>1C</sub> levels than both the mentally ill groups, controlling for demographic factors, smoking rates, BMI, and other indicators of diabetes severity. The SZ group was slightly but significantly younger and had a younger age of onset of diabetes. The groups had similar prescription rates of oral hypoglycemic agents and insulin, diabetes inpatient and outpatient visit rates, quality of diabetes care, and rates of comorbid medical conditions.

Type of antipsychotic medication prescribed was not associated with changes in HbA<sub>1C</sub> or age of onset. The SZ group had higher smoking rates. The groups were similar on adherence to medication, exercise, diet, and glucose testing. However, all were significantly worse than published norms on these measures. The SZ group had lower rates of diabetes knowledge, poorer neuropsychological functioning, poorer performance on role-play tasks, and higher symptom levels. It cannot be excluded that patients with SZ may have been diagnosed with diabetes earlier than their NMI counterparts as a result of their more frequent contacts with health-care practitioners.

In summary, this study showed that the type of antipsychotic medication was not associated with changes in glucose regulation (measured by HbA<sub>1C</sub>) or in age of onset. The study did not differentiate which antipsychotic medications were being used.

**Kreynbuhl J, Dixon L, Dickerson F, Goldberg R, Delahanty J. 2003. Antipsychotic Medications and Diabetes Outcomes in the Serious Mentally Ill. IX International Congress on Schizophrenia Research, March 29-April 2, 2003, Colorado Springs, CO. Schizophrenia Research 60(suppl 1):337-338.**

In this study, the authors attempted to examine glucose metabolism and the course of diabetes in patients with schizophrenia treated with atypical antipsychotics (clozapine, olanzapine, and quetiapine).

Individuals with type 2 diabetes and schizophrenia (n=100) or a major mood disorder (n=100) were recruited from outpatient mental health centers in urban and suburban settings in Baltimore, MD. These patients underwent an interview assessment, medical record review, and measurement of glycosylated hemoglobin (HbA<sub>1C</sub>) in a cross-sectional study design.

Among those prescribed antipsychotic medications (n=131), 58% received clozapine, olanzapine, or quetiapine. Of this subgroup, 28% were concurrently prescribed an antipsychotic medication thought not to be associated with hyperglycemia. Both groups of patients were similar in terms of age, gender, race, education, marital status, and duration of diabetes. Similar proportions of patients in each group received oral hypoglycemic agents (93% versus 87%) or insulin (22% versus 16%) (p>.05). A larger proportion of patients prescribed clozapine, olanzapine, or quetiapine (91%) underwent HbA<sub>1C</sub> measurement in the previous year, compared with those prescribed other antipsychotic medications (76%) (p<.05). Mean HbA<sub>1C</sub> exceeded the ADA therapeutic target of 7% (7.8% versus 7.4%) and mean fasting blood glucose (170 mg/dL versus 163 mg/dL) exceeded the normal range in both groups (p>.05). The authors concluded that individuals with serious mental illness and type 2 diabetes prescribed clozapine, olanzapine, or quetiapine versus other antipsychotic medications exhibit similarly poor metabolic control, as well as additional risk factors for adverse diabetes outcomes.

The study had several limitations, including lack of randomization to antipsychotic therapy and a cross-sectional design. In addition, no apparent consideration was given to possible recent changes in the type of antipsychotic medication and the potential effect of the change on glucose control.

In summary, this study showed no clinically meaningful differences in diabetes control in patients with comorbid schizophrenia and diabetes across atypical antipsychotics.

**Matchett JL, Fishman NB, Radmaker SB, Casey DE. 2003. The Effect of Atypical Antipsychotic Drugs in Patients with Preexisting Diabetes. IX International Congress on Schizophrenia Research, March 29-April 2, 2003, Colorado Springs, CO. Schizophrenia Research 60(supp 1):362.**

The objective of this study was to assess a potential relationship between changes in antipsychotic medications and changes in requirement for diabetes medications in patients with type 2 diabetes mellitus (DM) who were taking conventional or atypical antipsychotic drugs. Eighty patients (olanzapine n=45, risperidone n=13, clozapine n=3, quetiapine n=2, or typicals n=17) at the Portland VA Medical Center who had DM and were taking either a typical or atypical antipsychotic medication for 12 months or more had their medications records reviewed to identify those with a clinically relevant increase (>50% increase) in medications used to treat diabetes. Comparable rates of increased antidiabetic medication requirements were observed across the various atypical antipsychotics. The authors state that patients with DM who are taking atypical antipsychotics require adjustments in DM medications more frequently and sooner compared to those taking typical antipsychotics.

This study presents with several limitations: no adjustments were made for potential differences in severity of illness between the treatment groups. In addition, the study did not examine whether any association existed between antipsychotic efficacy on cognitive improvement and self-care and patients' ability to manage their glucose control.

In summary, the observed rates of increased (>50%) use of diabetes medication in this study are not unlike those seen in historical data on progression of diabetes in obese, non-psychiatrically ill patients (Miles et al. 2002; Kelley et al. 2002).

**Yu BP, Ortiz T, Chong YS, Shaw JW, Nguyen CT, Maguire GA. 2002. Atypical Antipsychotics in Patients with Diabetes Mellitus: A Retrospective Review. Drug Benefit Trends 14(11): 42-45.**

Benjamin Yu and colleagues examined the potential effect of antipsychotic treatment on glucose regulation in patients with preexisting diabetes mellitus (DM).

Twenty-two diabetic patients were retrospectively evaluated for evidence of glucose dysregulation during treatment with antipsychotics. Investigators recorded medication use and examined fasting blood glucose levels collected during the course of DM care for patients during an episode of antipsychotic monotherapy during which blood glucose levels were recorded. Patients must have received a diagnosis of Type 1 or Type 2 diabetes before beginning treatment with olanzapine, risperidone, or quetiapine. Eleven patients received olanzapine, 9 received risperidone, and 2 received quetiapine. Blood glucose was compared from initiation to termination of study period using paired t-tests.

No significant differences in glucose regulation were observed among atypical cohorts in any pairwise comparison. Patients on all antipsychotic therapies examined in this study showed improvement in fasting blood glucose levels. Patients treated with risperidone or quetiapine required dosage changes in their antidiabetic medications during the course of study, but the authors suggested that this was likely a clinical response to higher baseline glucose levels and not necessarily related to antipsychotic drug therapy. Four of 11 patients had lower fasting blood glucose and favorable modifications in antidiabetic regimen. One olanzapine patient was able to move from injectable to oral glucose control.

Some of the limitations of this study include the relatively small sample size and the cross-sectional, retrospective evaluation of data collected in a naturalistic clinical setting.

While the limitations of this study preclude conclusions regarding a potential effect of antipsychotic therapy on glucose regulation in diabetic patients with severe mental illness, the authors suggest that in a naturalistic clinical setting, glucose may be effectively monitored and appropriately controlled in patients receiving atypical antipsychotic therapies.

## **Discussion and Conclusions – Glucose Control in Diabetic Patients Treated with Antipsychotics**

Diabetes is a disorder characterized by a chronic progressive course, where glucose regulation tends to deteriorate and the antidiabetic medication requirements tend to increase over time. A limited number of largely retrospective studies have been conducted to evaluate the potential effect of antipsychotic treatment on glucose regulation in diabetic patients with serious mental illness. In general, the available data show a tendency for glucose regulation to worsen over time, irrespective of treatment assignment, and at rates comparable to what is observed in patients assigned to placebo. Further study is needed regarding the management of diabetes in patients receiving antipsychotic therapy.

## 4. New Lilly Data

### 4.1. Analysis of Treatment-Emergent Diabetes in Bipolar Patients

This analysis is relevant to the evaluation of the risk of diabetes mellitus in patients with serious mental illness, and testing of the hypothesis that these patients (including those with schizophrenia or bipolar disorder) present with a greater baseline risk factor load compared with the general population.

See Section 2.2, "Risk of Diabetes in Schizophrenia or Bipolar Disorder," for summaries of additional relevant literature.

Lilly has recently conducted analyses of treatment-emergent diabetes and risk factors for patients with bipolar disorder who participated in 5 olanzapine monotherapy clinical trials (HGEH, HGGW, HGHD, HGHQ, and HGHL). These analyses were modeled after the analyses done for schizophrenia patients described in the 2 October 2002 Olanzapine and Glucose Homeostasis briefing document. Patients were excluded from the analysis dataset if they had preexisting diabetes, or if either their baseline condition or outcome was unknown, as demonstrated by meeting any of the following criteria: 1) absence of at least 2 baseline nonfasting glucose measurements and at least 1 postbaseline measurement, 2) two or more baseline measurements for nonfasting glucose greater than 200 mg/dL, 3) presence of preexisting conditions indicating diabetes (on the basis of MedDRA preferred terms), or 4) documented use of antidiabetic medication at baseline.

After applying these exclusion criteria, 1362 patients not known to be diabetic on the basis of diagnosis or prerandomization glucose values had postbaseline glucose values and were evaluated for treatment-emergent diabetes (TED). Patients were divided into the following categories: 1) Patients with TED, who met any one of the following criteria: two nonfasting glucose values  $\geq 200$  mg/dL at any time after baseline, final nonfasting glucose  $\geq 200$  mg/dL, had initiated any antidiabetic medication, or had a new clinical diagnosis of diabetes; 2) Patients with uncertain glucose tolerance (UGT), who had two or more random glucose values  $\geq 140$  mg/dL at any time after baseline but only one or no glucose values  $\geq 200$  mg/dL at any time after baseline prior to endpoint; or 3) patients with normal glucose tolerance (NGT), who had only one or no random glucose values  $\geq 140$  mg/dL at any time after baseline.

The majority (72.1%) of the patients received olanzapine, with 12.5% receiving haloperidol, 7.7% receiving divalproex, and 7.7% receiving placebo. In the pooled sample (all therapy assignments), postrandomization, most patients (96.0%) were categorized as having normal glucose tolerance (NGT), with 2.7% found to have uncertain glucose tolerance (UGT) and 1.3% found to have treatment-emergent diabetes (TED). The mean postrandomization observation time in the pooled sample was 107.7 days (range 2 to 466 days; median 63 days).



Table 2.1 summarizes the postrandomization glyceemic categories by treatment group.

**Table 2.1. Postrandomization Glyceemic Categories  
Bipolar TED Database**

Treatment	N	Postbaseline Glyceemic Category			Median Days of Observation (Max)
		NGT (%)	UGT (%)	TED (%)	
Olanzapine	982	932 (94.91)	34 (3.46)	16 (1.63)	69 (466)
Haloperidol	170	167 (98.24)	2 (1.18)	1 (0.59)	84 (94)
Divalproex	105	103 (98.10)	1 (0.95)	1 (0.95)	62 (406)
Placebo	105	105 (100.00)	0 (0.00)	0 (0.00)	16 (32)
Total	1362	1307	37	18	63 (466)

Abbreviations: max = maximum; N = number of patients evaluated; NGT = normal glucose tolerance;  
TED = treatment-emergent diabetes; UGT = uncertain glucose tolerance.

Source: Report TEDA02RS

The frequencies of TED and UGT noted for olanzapine-treated patients in this bipolar database were somewhat less than those observed in the schizophrenia database (TED was seen at a frequency of 1.6% in the bipolar database versus 2.3% in the schizophrenia database; figures for UGT were 3.5% versus 6.4% respectively). However, the relative difference between olanzapine patients and haloperidol patients was similar in both databases, with rates of TED and UGT being 2 to 3 times higher for olanzapine-treated patients than for haloperidol-treated patients in both databases. In the larger database of 206 placebo-treated schizophrenia patients included in the schizophrenia TED analyses, only 3 patients were identified with TED, so the fact that no placebo-treated patients were identified with TED in the bipolar database (with 105 patients) may have been due to limited sample size. Placebo-treated patients in the bipolar database also had much shorter durations of exposure than did olanzapine-treated patients.

Table 2.2 summarizes the entry characteristics of patients in the three glycemic categories within the bipolar TED database. Not surprisingly, there were statistically significant differences between patients with TED and patients with NGT with respect to baseline characteristics. For example, the TED group had statistically significantly higher mean baseline glucose levels, statistically significantly higher mean age, and statistically significantly higher mean baseline body mass index (BMI) than the NGT group. Furthermore, patients in the TED group were statistically significantly more likely than patients in the NGT group to have baseline hypertension, be non-Caucasian, and have multiple risk factors for diabetes, where risk factors were defined as age  $\geq 45$ , BMI  $\geq 25$  mg/k<sup>2</sup>, hypertension defined on the basis of diagnoses or use of antihypertensive medications, non-Caucasian, mean nonfasting baseline glucose  $\geq 140$  mg/dL (ADA 2002). Note that the clinical trials did not collect information on family history of diabetes, although this is a significant risk factor.

Entry characteristics for patients with UGT tended to fall between values for patients with TED and patients with NGT. When compared to patients with NGT, patients with UGT had statistically significantly higher baseline mean glucose, statistically significantly higher mean age, and statistically significantly higher mean baseline BMI, and were statistically significantly more likely to have baseline hypertension and have multiple risk factors for diabetes.

Irrespective of treatment assignment, all 18 of the patients found to have TED had at least one risk factor for diabetes, whereas 20.7% of patients with NGT had no risk factors.

**Table 2.2. Entry Characteristics by Glycemic Category  
Bipolar TED Database**

Characteristic	Glycemic Category			P-value	
	TED (n= 18)	UGT (n=37)	NGT (n=1307)	TED vs NGT	UGT vs NGT
BL mean NFGLU (mg/dL)	139.4 (SD 40.8)	109.2 (SD 25.1)	95.0 (SD 15.4)	<.0001	<.0001
n (%) with BL NFGLU ≥140 mg/dL	10 (55.6%)	4 (10.8%)	21 (1.6%)	<.0001	.0041
Age (years)	45.8 (SD 10.9)	43.1 (SD 12.6)	39.2 (SD 12.0)	.0194	.0491
n (%) with age ≥45	10 (55.6%)	13 (35.1%)	393 (30.1%)	.0349	.5860
BL BMI (kg/m <sup>2</sup> )	35.3 (SD 8.6)	32.3 (SD 8.0)	27.4 (SD 6.4)	<.0001	<.0001
n (%) with BL BMI ≥25 kg/m <sup>2</sup>	17 (94.4%)	32 (86.5%)	761 (58.6%)	.0012	.0005
n (%) with BL hypertension	6 (33.3%)	10 (27.0%)	176 (13.5%)	.0275	.0276
n (%) with non-Caucasian ethnicity	10 (55.6%)	8 (21.6%)	323 (24.7%)	.0053	.8467
n (%) with ≥2 risk factors <sup>2</sup>	17 (94.4%)	23 (62.2%)	478 (36.6%)	<.0001	.0028
<b>n (%) with no risk factors<sup>2</sup></b>	<b>0 (0%)</b>	4 (10.8%)	271 (20.7%)	.0337	.2121

Abbreviations: BL = baseline; BMI = body mass index; n = number; N = number of patients evaluated; NFGLU = nonfasting glucose; NGT = normal glucose tolerance; SD = standard deviation; TED = treatment-emergent diabetes; UGT = uncertain glucose tolerance; vs = versus.

<sup>1</sup> Hypertension defined based on emergence of adverse events or use of antihypertensive medications.

<sup>2</sup> Risk factors defined as: age ≥45, BMI ≥25, hypertension, non-Caucasian, baseline NFGLU ≥140 (ADA 2003). Note that BMI ≥25 was used as a risk factor in the bipolar TED database as done in the written summary and recommended by the most recent guidelines of the ADA (2003), while the schizophrenia TED database used BMI ≥27 based on older ADA guidelines.

Source: Report TEDA02RS

Limitations include the retrospective post-hoc nature of the analysis, the fact that data were from pooled clinical trials that were not intended to diagnose diabetes, the presence of baseline information for only a limited number of diabetes risk factors, the use of random glucose identify glycemc abnormalities, the uneven sample sizes and observation times between treatment groups, and the small numbers of events in individual treatment groups which limited power to detect differences.

These results demonstrate that the presence of risk factors for diabetes at baseline is associated with an increased risk of diabetes, irrespective of treatment assignment. As noted above, the results from pooled analyses of olanzapine bipolar disorder studies are similar to the findings in the schizophrenia TED database, and are consistent with the predictors of diabetes in the general population.

## 4.2. Fasting Lipids in Normoglycemic Patients with Schizophrenia

This Lilly analysis by Sowell and colleagues is relevant to the evaluation of the prevalence of the metabolic syndrome as a risk factor for diabetes mellitus among patients with schizophrenia. Refer to clinical study report F1D-MC-HGJX, submitted to IND 28,705 on 9 June 2003, serial submission #905. See Section 2.3, "Prevalence of the Metabolic Syndrome among Patients with Schizophrenia," for summaries of additional relevant literature.

The main objective of this Lilly study by was to examine differences in lipoprotein levels during stable treatment with various antipsychotics. However, relevant to the current review, parameters of glucose metabolism were also measured. This cross-sectional study included 184 patients with schizophrenia or schizoaffective disorder recruited from ongoing Lilly-sponsored clinical trials. Inclusion required at least 1 year of therapy with the current antipsychotic and  $\geq 3$  months of monotherapy. Treatment groups were matched for gender, race, BMI, and severity of psychiatric illness. Patients with a history of dyslipidemia or abnormal glucose tolerance (previous diagnosis of diabetes or fasting glucose  $\geq 110$  mg/dL) were excluded, as were patient with comorbid conditions or medications known to effect glucose or lipid metabolism. Laboratory evaluation was done after an observed overnight fast.

Patients on olanzapine (n=67), risperidone (n=65), or a group using typical antipsychotics (n=52) did not demonstrate significant differences in fasting glucose, plasma insulin, or insulin sensitivity (as determined by Homeostasis Model Assessment; HOMA-IR). The mean HOMA-IR values were 3.32 for olanzapine-treated patients, 2.72 for risperidone, and 2.91 for the typical antipsychotic group. HDL and LDL cholesterol levels, and LDL particle size also did not significantly differ between treatment groups. Apolipoprotein B, LDL particle concentrations, and fasting (log transformed, but not median) triglyceride levels were significantly higher in the olanzapine cohort compared to patients treated with risperidone, but not compared with typical antipsychotics.

Because this study was primarily designed to assess lipid parameters, patients with significant abnormalities of glucose metabolism were excluded. Nonetheless, measures relevant to glucose metabolism were included and have been correlated with diabetes risk in other studies (Bloomgarden 2002). These include fasting glucose levels, even in the normal range, as well as fasting insulin and HOMA-IR. The strengths of this study include the efforts taken to control for between-group differences in physical and historical characteristics known to impact glucose and lipid metabolism, as well the assurance of fasting status.

As a cross-sectional study, it cannot address cause-and-effect relationships. But since patients were recruited from randomized clinical trials, biases were likely minimized. Within these limitations, no significant differences in fasting glucose levels or insulin sensitivity (HOMA-IR) were seen between groups undergoing long-term, stable therapy with olanzapine, risperidone, or conventional antipsychotics. However, it should be noted that a HOMA-IR level of 1.7 has been used as a cut-off to diagnose insulin resistance (Littrell 2003). The elevated mean HOMA-IR levels in all treatment groups in this study is consistent with a high frequency of insulin resistance in patients with schizophrenia and further supports the added diabetes risk in this population.

### 4.3. Retrospective Assessment of Preexisting Diabetes Progression in Trials of Patients with Serious Mental Illness

This analysis is relevant to the analysis of potential effects of antipsychotic therapy on glucose control in diabetic patients with serious mental illness. See Section 3.2, "Glucose Control in Diabetic Patients Treated with Antipsychotics," for summaries of additional relevant literature.

The objective of this Lilly-sponsored analysis by Wang and colleagues was to explore evidence for progression of preexisting diabetes in patients with serious mental illness participating in clinical trials of olanzapine.

Eighty-eight patients with preexisting diabetes were identified from clinical trials of olanzapine in which information was available for dosages of anti-diabetic therapy and were of at least 6 weeks duration. Six studies (4 in schizophrenia and 2 in bipolar disorder) met these criteria. Progression of diabetes was defined as any of the following: increased dose of oral hypoglycemic agent or insulin, addition of either an oral hypoglycemic agent or insulin to existing regimen, or change to monotherapy with insulin at an increased dose.

The majority of the patients with preexisting diabetes were randomized to therapy with olanzapine (n=64). The remaining patients with preexisting diabetes were randomized to haloperidol (n=17), divalproex (n=4) or placebo (n=3). Numerically greater incidences of progression in anti-diabetic therapy were observed with divalproex (3/4=75%) and placebo (1/3=33.3%) than olanzapine (15/64= 23.4%) or haloperidol (2/17=11.8%). However, the incidence of progression in anti-diabetic therapy was not significantly different between olanzapine and haloperidol (p=.5) or between olanzapine and a pooled group of haloperidol plus the placebo-treated patients (p=.54), even without adjusting for differences in mean observation times among the groups (olanzapine, 275 days; haloperidol, 137 days; placebo, 183 days; divalproex, 164 days). These results are consistent with historical data documenting progression of diabetes in obese, non-psychiatrically ill patients (Miles et al. 2002; Kelley et al. 2002).

Limitations of this analysis include its retrospective nature, the small number of patients, the relatively short duration of treatment, and use of change in therapy rather than hemoglobin A1C to assess glycemic control. These limitations preclude definitive conclusions regarding differences between treatment groups in the incidence of diabetes progression.

Type 2 diabetes is a chronic disorder characterized by progressive loss of beta cell function and insulin resistance. In clinical trials comparing olanzapine to haloperidol, divalproex, or placebo over a relatively short observation period, a substantial number of patients with schizophrenia and bipolar disorders were noted to have clinically recognized progression of diabetes regardless of therapy assignment (including placebo). These results are consistent with historical data documenting progression of diabetes in obese, non-psychiatrically ill patients (Miles et al. 2002; Kelley et al. 2002).



#### 4.4. Analyses of Fasting Glucose Levels in Study HGHJ: Olanzapine versus Ziprasidone in the Treatment of Schizophrenia

Lilly-sponsored clinical trial F1D-MC-HGHJ was a multicenter, randomized, double-blind, parallel, 28-week study of patients with schizophrenia, evaluating the efficacy and safety of olanzapine compared with ziprasidone. Patients were randomly assigned to treatment with 10-20 mg/day olanzapine (n=277) or 80-160 mg/day ziprasidone (n=271). The primary efficacy measure was the PANSS total score at 28 weeks. (Note: The complete study report for study F1D-MC-HGHJ was submitted to IND 28,705 on 20 June 2003, serial submission #908. The study report contains analyses of lipid values, which are not summarized in the current document, given that the focus of this document is glucose homeostasis.)

Fasting glucose (FG) samples for these 548 patients were collected at specific visits as part of routine safety parameter evaluation. Mean change in fasting glucose (FG) from baseline to endpoint was analyzed using both observed cases (OC) at each visit, and last observation carried forward (LOCF) methods. Incidence of treatment-emergent abnormal FG ( $\geq 6.993$  mmol/L or 126 mg/dL) values at anytime during the study or at endpoint were identified for individuals with fasting glucose  $< 6.993$  mmol/L or 126 mg/dL at baseline. The incidence of abnormal FG values at anytime during the study or at endpoint was further examined for individuals without an indication of diabetes at baseline and FG  $< 6.105$  mmol/L (110 mg/dL) (corresponding to ADA criterion for impaired fasting glucose) at baseline. Tables that accompany text in this section are presented in Appendix A.

Analyses of baseline demographics showed that ziprasidone patients were significantly younger than olanzapine patients (Table A.1). No treatment-group differences were observed for gender, origin, and baseline body mass index (BMI).

No significant differences in mean change in baseline to endpoint FG were observed between the olanzapine and the ziprasidone group (LOCF analysis, mean change to endpoint: olanzapine  $0.26 \pm 1.67$  mmol/L versus ziprasidone  $0.00 \pm 1.20$  mmol/L,  $p=0.485$ ; OC analysis, mean change to endpoint: olanzapine  $0.18$  mmol/L  $\pm 1.09$  mmol/L versus ziprasidone  $-0.04 \pm 0.92$  mmol/L,  $p=0.282$ ).

The olanzapine group showed a significant within-group mean change to endpoint FG (n=150, mean change =0.18,  $p=0.045$ ) based on observed cases at Visit 15. LOCF analysis was consistent with these results. However, mean change in FG for observed cases at each visit showed no significant difference between the two treatment groups for any visit during the study.

The incidence of treatment-emergent abnormal FG ( $\geq 6.993$  SI or 126 mg/dL from normal baseline  $< 6.993$  SI or 126 mg/dL) at anytime during the study or at endpoint was not significantly different between the two groups.

These analyses were repeated excluding patients with baseline FG  $\geq 6.1050$  SI (110 mg/dL) or with known diabetes at baseline. Treatment-emergent abnormal FG incidence at anytime during study or at endpoint is not significantly different between the two groups. Patients with baseline FG  $< 6.1050$  SI (110 mg/dL), excluding known diabetics, were evenly distributed between the two therapy groups, with 51.08% in the olanzapine group and 48.92% in the ziprasidone group.

These results of this study were consistent with other olanzapine versus ziprasidone studies (described by Glick [2001] and Simpson [2002], which appear in Section 3.3 of this document) in showing no clinically meaningful differences in analyses of fasting glucose measurements between patients treated with olanzapine or ziprasidone for up to 28 weeks. Some numerical differences in mean change and categorical analyses were observed in Study HGHJ. However, no substantial differences were observed in the most clinically relevant analysis, where the frequencies of treatment-emergent fasting glucose  $> 126$  mg/dL were compared after exclusion of patients with evidence of glucose dysregulation at baseline.

## 5. Overall Summary and Conclusions

Since Lilly's last update to the Division ("Olanzapine and Glucose Homeostasis," dated 2 October 2002), an increasing number of studies have examined a possible association between serious mental illness and diabetes, and between treatment with antipsychotic medications and diabetes. These studies vary in study design, sample size, methods, and specific comparisons. This recent literature lends additional support to the evidence that serious mental illness (including schizophrenia and bipolar disorder) is associated with a greater risk for diabetes compared to risk in the general population.

At the same time, the cumulative data do not currently allow us to establish whether treatment with antipsychotic medication contributes to the increased risk of diabetes observed in the seriously mentally ill. Nor does the current evidence allow for conclusions regarding an increased risk of diabetes between patients treated with atypical antipsychotics and patients treated with conventional antipsychotics.

Finally, the current body of literature does not support specific conclusions regarding differences in likelihood of diabetes between patients treated with specific atypical antipsychotic medications. Studies comparing the risk of diabetes among patients treated with atypical antipsychotics are consistent, however, in demonstrating the impact of risk factors for diabetes that are well-established in the general population.

It is the opinion of Eli Lilly and Company that the cumulative data currently available, representing multiple lines of evidence, do not demonstrate clinically relevant or consistent differences in the risk for diabetes, or in changes in markers of glucose regulation, in patients treated with olanzapine compared with other atypical antipsychotics. Given the data demonstrating that patients with severe mental illness have a substantially increased risk of diabetes compared to the general population, it would be undesirable to encourage clinicians to narrow their vigilance to only a subset of relevant treatments.

Differential labeling would ultimately not be in the best interest of patients and caregivers, as it may selectively restrict therapeutic options for patients with severe mental disorders, or even lead to clinically unwarranted discontinuation of olanzapine in some patients, to the detriment of the overall mental and physical health of the patient. In addition, differential labeling of olanzapine may lead clinicians to switch patients who are psychiatrically stable on olanzapine to other antipsychotics, in the absence of definitive evidence that there are differences in risk of diabetes across atypical antipsychotics.

Important concepts that would be relevant to any labeling change include the epidemic increase in the prevalence of diabetes in the general population, the even greater prevalence of diabetes in patients with serious mental illness, and the lack of evidence supporting a clinically meaningful increase in the risk of diabetes in patients treated with olanzapine compared with other atypical antipsychotics.

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## Appendix A: HGHJ Data

Olanzapine (LY170053)  
Confidential

Update to Olanzapine and Glucose Homeostasis  
20 June 2003 (Internal 24 June 2003)

Zyprexa MDL 1596: Confidential-Subject to Protective Order

ZY200736127

**Table A.1. Demographic Characteristics at Baseline  
All Randomized Patients  
Study F1D-MC-HGHJ**

Variable	Olz (N=277)	ZIP (N=271)	Total (N=548)	p-Value
<b>Sex: No. (%)</b>				
No. Patients	277	271	548	
Male	180 (65.0)	172 (63.5)	352 (64.2)	.722*
Female	97 (35.0)	99 (36.5)	196 (35.8)	
<b>Origin: No. (%)</b>				
No. Patients	277	271	548	
Caucasian	115 (41.5)	124 (45.8)	239 (43.6)	
African Descent	78 (28.2)	66 (24.4)	144 (26.3)	
East/SE Asian	2 (0.7)	3 (1.1)	5 (0.9)	
Western Asian	1 (0.4)	0	1 (0.2)	
Hispanic	63 (22.7)	61 (22.5)	124 (22.6)	
Other Origin	18 (6.5)	17 (6.3)	35 (6.4)	.827*
<b>Age:yrs.</b>				
No. Patients	277	271	548	.037**
Mean	40.05	38.24	39.15	
Median	40.22	37.73	38.88	
Standard Dev.	11.59	12.14	11.89	
Minimum	19.23	18.42	18.42	
Maximum	73.40	73.19	73.40	

RMP.F1DP.JCLLIB(HJDF008)

RMP.F1DP.SASMACRO(SBASEA)

\* Frequencies are analyzed using a Fishers-Exact test.

\*\* Means are analyzed using a Type III Sum of Squares analysis of variance

(ANOVA): PROC GLM model=investigator and treatment.

XDES0001

**Table A.2. Baseline Body Mass Index (BMI)  
All Randomized Patients  
Study F1D-MC-HGHJ**

Measure	Therapy	N	Mean	Std	Median	Min	Max	P-Value
BMI	OLZ	276	26.8	6.01	26	15	51	0.798
	ZIP	270	27.1	5.91	26	17	52	

P-Value were calculated based on ANOVA model as: Model measure=therapy inv  
Inv with < 2 pat per therapy were pooled within country  
RMT.F1DSCRT3.SASPGM(BMIE01HJ) C015848

Note: Height at baseline not obtained for 2 patients.

**Table A.3.**  
**Fasting Glucose**  
**Mean Change from Baseline to Endpoint - Observed Cases**  
**All Randomized Patients, Double-Blind Phase**  
**Study F1D-MC-HGHJ**

Visit	Week	Therapy	N	Baseline		Endpoint		Change to Endpoint		P-value*2		
				Mean	Std	Mean	Std	Mean	Std		w/in P*1	Therapy Thr*Inv
3	1	1) Olz	169	5.27	1.26	5.38	1.44	0.10	0.99	.174	.684	.865
		2) ZIP	169	5.18	0.90	5.19	0.77	0.01	0.83	.937		
4	2	1) Olz	156	5.23	0.89	5.30	1.24	0.07	0.91	.336	.972	.986
		2) ZIP	154	5.31	1.26	5.27	0.83	-0.04	1.07	.656		
5	3	1) Olz	141	5.29	0.97	5.54	2.35	0.26	2.02	.134	.531	.997
		2) ZIP	133	5.23	0.86	5.25	1.21	0.02	0.83	.802		
6	4	1) Olz	133	5.28	0.96	5.61	2.68	0.32	2.37	.116	.426	1.000
		2) ZIP	122	5.24	0.85	5.13	0.68	-0.11	0.65	.064		
7	5	1) Olz	124	5.28	0.97	5.59	3.08	0.32	2.72	.199	.777	.998
		2) ZIP	103	5.15	0.72	5.14	0.70	-0.00	0.78	.990		
8	6	1) Olz	215	5.17	0.85	5.35	1.86	0.18	1.64	.107	.458	1.000
		2) ZIP	177	5.27	1.11	5.21	0.98	-0.06	0.84	.329		
9	8	1) Olz	115	5.25	0.99	5.40	1.74	0.15	1.69	.348	.789	.996
		2) ZIP	91	5.21	0.90	5.23	0.96	0.02	0.99	.819		

N - Number of patients having both baseline and endpoint.  
\*1 - Within group P-values are from t-test on mean change.  
\*2 - P-values are from Type III Sum of Squares ANOVA :  
Model = Therapy Inv Therapy\*Inv.

RMP.STASUTIL.SASPGM (MMEANVWS)  
RMP.F1DSCRT3.SASPGM (MMEANVHJ)

**Table A.3.**  
**Fasting Glucose**  
**Mean Change from Baseline to Endpoint - Observed Cases**  
**All Randomized Patients, Double-Blind Phase**  
**Study F1D-MC-HGHJ (concluded)**

Visit	Week	Therapy	N	Baseline		Endpoint		Change to Endpoint		P-value*2		
				Mean	Std	Mean	Std	Mean	Std		w/in P*1	Therapy Thr*Inv
10	10	1) O1z	90	5.21	0.97	5.35	1.52	0.14	1.52	.398	.451	.785
		2) ZIP	72	5.17	0.83	5.14	0.76	-0.03	0.94	.780		
11	13	1) O1z	179	5.15	0.84	5.40	1.90	0.24	1.89	.086	.320	1.000
		2) ZIP	139	5.24	1.13	5.36	1.67	0.12	1.18	.229		
12	16	1) O1z	36	5.34	0.94	5.86	3.11	0.52	2.98	.300	.179	.336
		2) ZIP	25	5.15	0.74	5.09	0.82	-0.06	0.89	.756		
13	20	1) O1z	154	5.19	0.88	5.40	1.49	0.21	1.45	.080	.221	.823
		2) ZIP	112	5.32	1.18	5.45	1.82	0.12	1.24	.301		
14	24	1) O1z	16	5.15	0.68	5.13	0.56	-0.02	0.64	.912	.642	.806
		2) ZIP	16	5.33	0.51	5.42	1.68	0.09	1.73	.836		
15	28	1) O1z	150	5.22	0.90	5.40	1.13	0.18	1.09	.045	.282	.932
		2) ZIP	107	5.29	1.20	5.25	1.50	-0.04	0.92	.662		

N - Number of patients having both baseline and endpoint.  
\*1 - Within group P-values are from t-test on mean change.  
\*2 - P-values are from Type III Sum of Squares ANOVA :  
Model = Therapy Inv Therapy\*Inv.

RMP.STASUTIL.SASPGM (MMEANVWS)  
RMP.F1DSCRT3.SASPGM (MMEANVHJ)

**Table A.4.** **Fasting Laboratory Analytes**  
**Mean Change from Baseline to Endpoint (LOCF)**  
**All Randomized Patients, Double-Blind Phase**  
**Study F1D-MC-HGHJ**

	N	Baseline		Change to Endpoint		P-value*1	
		Mean	(Std)	Mean	(Std)		Therapy
Weight in kg							
Olz	269	77.67	(20.53)	3.06	(6.87)	<.001	.855
ZIP	260	77.09	(18.97)	-1.12	(4.70)		
GLUCOSE, FASTING							
Olz	261	5.27	(1.15)	0.26	(1.67)	.485	.971
ZIP	244	5.31	(1.27)	-0.00	(1.20)		
GLUCOSE, NON-FASTING							
Olz	4	5.06	(0.31)	0.31	(0.43)		
ZIP	9	5.70	(1.29)	-0.60	(1.20)		
CHOLESTEROL							
Olz	250	4.99	(1.18)	0.09	(1.01)	<.001	.620
ZIP	241	4.97	(1.19)	-0.31	(0.82)		
TRIGLYCERIDES							
Olz	250	1.63	(1.25)	0.36	(1.31)	<.001	.612
ZIP	241	1.66	(1.46)	-0.23	(1.08)		
LDL CHOLESTEROL							
Olz	235	3.01	(0.97)	0.04	(0.82)	.005	.814
ZIP	233	3.01	(1.01)	-0.25	(0.70)		
HDL CHOLESTEROL-DEXTRAN PRECIP.							
Olz	246	1.24	(0.36)	-0.07	(0.27)	<.001	.423
ZIP	239	1.21	(0.33)	0.03	(0.25)		
PROLACTIN							
Olz	251	0.74	(0.98)	0.19	(1.13)	.293	.833
ZIP	242	0.67	(0.75)	0.35	(1.38)		

N - Number of patients having both baseline and endpoint.

\*1 - P-values are from Type III Sum of Squares ANOVA :

Model = THERAPY INV THERAPY\*INV.

Inv with < 2 pat per therapy were pooled within country

Report HJDF733

RMP.F1DSHGJ.SASPGM(LABX01DB) RMX8636

MACRO: RMP.F1DSHGJ.SASPGM(MEANS)

**Table A.5. Fasting Glucose**  
**Percent of Patients with Change from Normal Baseline (< 6.993 SI or 126 mg/dL)**  
**to Abnormal Postbaseline (>= 6.993 SI or 126 mg/dL) at Anytime**  
**All Randomized Patients, Double-Blind Phase**  
**Study F1D-MC-HGHJ**

Name of Lab Test	Direction	Therapy						P-val
		Olz		Zip		Abnrm		
		N	n (%)	N	n (%)	N	n (%)	P-value
GLUCOSE, FASTING	HIGH (>=6.993)	244	28 11.5%	229	17 7.4%			0.159

RMP.F1DSCRT3.SASPGM (GLUE01HJ) C015848

**Table A.6.** **Fasting Glucose**  
**Percent of Patients with Change from Normal Baseline (< 6.993 SI or 126 mg/dL)**  
**to Abnormal Postbaseline (>=6.993 SI or 126 mg/dL) at Endpoint**  
**All Randomized Patients, Double-Blind Phase**  
**Study F1D-MC-HGHJ**

Name of Lab Test	Direction	Therapy						P-value
		Olz		Zip		Endabn		
		N	n (%)	N	n (%)	N	n (%)	
GLUCOSE, FASTING	HIGH (>=6.993)	244	13 5.3%	229	6 2.6%			0.163

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Olanzapine (LY170053)  
Confidential

Update to Olanzapine and Glucose Homeostasis  
20 June 2003 (Internal 24 June 2003)

**Table A.7. Percent of Patients with Baseline Fasting Glucose < 6.1050 SI (110 mg/dL)  
Excluding Known Baseline Diabetics  
Double-Blind Phase  
Study F1D-MC-HGHJ**

Therapy	N	%
Olz	189	51.08
ZIP	181	48.92

RMP.F1DSCRT3.SASPGM (GLUE02HJ) C015848

**Table A.8. Fasting Glucose  
Incidence of Treatment-Emergent Abnormal Values ( $\geq 6.9930$  SI or 126 mg/dL) at Anytime  
Excluding Patients with Fasting Glucose  $\geq 6.1050$  (110 mg/dL) or Known Diabetes at Baseline  
Double-Blind Phase  
Study F1D-MC-HGHJ**

Name of Lab Test	Olanzapine		Ziprasidone		p-val
	N	%	N	%	
GLUCOSE, FASTING	189	6.9%	181	5.5%	.669

RMP.F1DSCRT3.SASPGM(GLU02HJ) C015848

Note: Excluding baseline fasting glucose  $\geq 6.1050$ ; known baseline diabetics; patients with 2 glucose  $\geq 6.9930$  at baseline patients with DM medication at baseline; patients with DM as adverse event at baseline

**Table A.9. Fasting Glucose  
Incidence of Treatment-Emergent Abnormal Values ( $\geq 6.9930$  SI or 126 mg/dL) at Endpoint  
Excluding Patients with Fasting Glucose  $\geq 6.1050$  (110 mg/dL) or Known Diabetes at Baseline  
Double-Blind Phase  
Study F1D-MC-HGHJ**

Name of Lab Test	Olanzapine		Ziprasidone		p-val
	N	%	N	%	
GLUCOSE, FASTING	189	3.2%	181	2.8%	1.000

RMP.F1DSCRT3.SASPGM(GIUE02HJ) C015848

Note: Excluding baseline fasting glucose  $\geq 6.1050$ ; known baseline diabetics; patients with 2 glucose  $\geq 6.9930$  at baseline; patients with DM medication at baseline; patients with DM as adverse event at baseline