Briefing Document on Olanzapine and Glucose Homeostasis

[Prepared for the FDA]

Eli Lilly and Company
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1. Introduction

The current literature supports that schizophrenia and bipolar disorder appear to be associated with a higher prevalence of type 2 diabetes. The prevalence of diabetes has been reported to range from 10% to 36% among patients with schizophrenia (Balter 1961; Keskiner et al. 1973; Mukherjee et al. 1989; Mukherjee et al. 1996; Dixon et al. 2000) and from 10% to 26% among patients with bipolar disorder (Lilliker 1980; Cassidy et al. 1999; Regenold et al. 2002). In contrast, the prevalence of diagnosed diabetes in the general population has recently been reported to be 5.1% (Harris et al. 1998). With the widespread uses of atypical antipsychotics, increasing attention has been directed toward the issue of these agents as potential contributors to the development of diabetes.

The identification of a drug-related signal is rendered particularly challenging by the high rate of diabetes among patients with schizophrenia and bipolar disorder, which is superimposed onto an epidemic increase in the prevalence of diabetes in the general population, and finally with an increasing awareness that diabetes in the general population is an underrecognized condition. For instance, approximately 30% of US adults and 50% of Australian adults with diabetes are undiagnosed (Harris et al. 1998; Dunstan et al. 2002). Recently, interest in the issue of antipsychotics and diabetes has extended beyond the scientific and medical arenas to become the object of intense focus in the competitive marketplace and at the level of patient advocacy groups.

An association between diabetes and psychotic disorders was described 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). Subsequent to the advent of antipsychotic drugs in the 1950s and continuing through the 1970s, several reports emerged linking chlorpromazine to glucose dysregulation.[a] Evidence of changes in glucose homeostasis in patients treated with antipsychotics was inconsistent, and little additional information appeared in the literature until the reintroduction of clozapine in the US market,[b] and later following the introduction of olanzapine.[c]

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a Charatan and Bartlett 1955; Klett and Caffey 1960; Korenyi and Lowenstein 1968; Schwarz and Munoz 1968; Thonnard-Neumann 1968; Erle et al. 1975, 1977.

b Korenyi and Lowenstein 1968; Schwarz and Munoz 1968; Erle et al. 1975; Koval et al. 1994; Kostakoglu et al. 1996; Pierides 1997; Popli et al. 1997; Ai et al. 1998; Hagg et al. 1998; Wirshing et al. 1998; Colli et al. 1999; Hauptmann et al. 1999; Maule et al. 1999; Mohan et al. 1999; Smith et al. 1999; Henderson et al. 2000; Isakov et al. 2000; Ramaekers et al. 2000; Wehring et al. 2000.

c Fertig et al. 1998; Gatta et al. 1999; Goldstein et al. 1999; Lindenmayer and Patel 1999; Ober et al. 1999; Von Hayek et al. 1999; Zung et al. 1999; Bettinger et al. 2000; Mendell and Soares-Welch 2000; Bonanno et al. 2001; Kropp et al. 2001; Muench and Carey 2001; Roefaro and Mukherjee 2001; Selva and Scott 2001.

While structural similarities between clozapine and olanzapine may have initially directed greater attention on events of glucose dysregulation observed during treatment with olanzapine, there are now reports of hyperglycemia or diabetes during treatment with risperidone (Melamed et al. 1998; Croarkin et al. 2000; Wirshing et al. 2001b), during treatment with quetiapine (Sobel et al. 1999; Procyshyn et al. 2000), and most recently during treatment with ziprasidone (Yang and McNeely 2002). Although weight gain has been observed during treatment with most of these agents (Allison et al. 1999), in some cases, new-onset diabetes has been reported in patients without weight gain (Popli et al. 1997; Wirshing et al. 1998; Gatta et al. 1999; Goldstein et al. 1999; Rigalleau et al. 2000), leading to hypotheses that, in some cases, atypical antipsychotics may exert a direct effect on glucose homeostasis.

The widespread use of atypical antipsychotics has witnessed a renewed interest in mental disorders and glucose dysregulation, and the potential role that atypical antipsychotics may play in the development of diabetes in psychiatrically-ill patients. Cases of glucose dysregulation have been reported in patients treated with clozapine, olanzapine, risperidone, quetiapine, and ziprasidone. In a systematic search of the literature for the period from May 2000 through September 2002 (presented in Section 5.3), a total of 84 published case reports of glucose dysregulation occurring in temporal association with atypical antipsychotic treatment were identified. These cases included reports of exacerbation of preexisting diabetes, de-novo diabetes, and acute presentations of diabetes (diabetic ketoacidosis or hyperglycemic hyperosmolar coma). Of these, 27 published case reports related to patients treated with clozapine, 49 reports with olanzapine, 4 reports with risperidone, 3 reports with quetiapine, and 1 report with ziprasidone (see list of references in Appendix C).

In a recent series of reviews of glucose dysregulation events from the FDA MedWatch database, Koller and colleagues identified 384 reports for clozapine (January 1990 through February 2001), 289 reports for olanzapine (January 1994 through 15 May 2001), and 132 reports for risperidone (January 1993 through December 2001) (Koller et al. 2001, 2002; Koller and Doraiswamy 2002). In an analysis of the FDA MedWatch database conducted by Lilly for the period ending 31 March 2002 (discussed in Section 3.4), 395 unique reports were identified for clozapine, 434 reports for olanzapine, 57 reports for quetiapine, 244 reports for risperidone, and 5 reports for ziprasidone.

The observed differences in reporting rates among patients treated with atypical antipsychotics must be interpreted within the context of the known limitations of spontaneous report data, including the approximation of drug exposures on the basis of prescription data and potential differences in reporting practices and reporting environment (Goldman 1998). Given these limitations, it is not possible to resolve whether the differences in reporting rates of the magnitudes observed in these analyses reflect a substantial differences in the actual incidence or prevalence of events at the population level.

It is also difficult to determine to what extent the increasing focus in the literature and in the competitive marketplace directed at the issue of diabetes (first with clozapine and later with olanzapine) may have impacted the volume and patterns of reporting (Wallenstein and Fife 2001). While a number of analytical methods have been proposed and are often used to circumvent some of the limitations of spontaneous data, hypotheses generated on the basis of spontaneous data must be tested systematically using multiple study modalities.

The issues of atypical antipsychotics and metabolic dysregulation are not likely to be resolved by any one type of study. Rather, multiple lines of evidence from diverse types of studies must be examined to provide the most comprehensive insight into these issues. To evaluate potential mechanisms of glucose dysregulation that may be associated with atypical antipsychotic treatment, this multimodal approach would include large cohort or case-control studies, retrospective analyses of large integrated clinical trial databases, and clinical pharmacology studies in healthy volunteers or in patients.

Further, these investigations need to be appropriately applied to the multiple lines of evidence relevant to the question of diabetes and antipsychotics, including an epidemic increase in the prevalence of diabetes in the general population, the evolving presentation and natural history of diabetes that has paralleled the epidemic rise of obesity in the general population, the evidence supporting an even greater prevalence of diabetes in patients with schizophrenia and bipolar disorder, and the current state of understanding regarding a potential direct effect of antipsychotic drugs on glucose homeostasis.

As the Division is aware, Lilly has been actively engaged in numerous investigations to evaluate a potential association between treatment with olanzapine and glucose dysregulation, and has submitted data to the Division as it has become available. These investigations have employed multiple modalities and have pursued multiple lines of evidence relevant to the question of diabetes and antipsychotics.

This briefing document has been prepared to:

1) Update the Division on results of relevant Lilly-sponsored investigations that have become available since our last submission of 21 May 2001
2) Briefly summarize data sets previously submitted to the Division as a follow-up to Lilly's response to the original FDA request of 1 May 2000
3) Provide an update of the relevant literature since Lilly's submission of 31 July 2000
4) Obtain the Division's feedback on data gaps in the evaluation of potential contributions of olanzapine and other antipsychotics to glucose dysregulation events in severely mentally ill patients
5) Update the Division on current educational initiatives and obtain the Division's feedback on proposed educational initiatives to improve health care providers' understanding of diabetes and its relationship to psychiatric disorders.

2. Questions for the FDA

In the following questions, Lilly seeks the Division's guidance and feedback regarding the information presented in this briefing document.

2.1. Potential Mechanisms of Glucose Dysregulation

Lilly has conducted two controlled studies in healthy volunteers, designed to investigate potential effects of olanzapine and risperidone on insulin receptor sensitivity (Study S013 in Section 3.1) or pancreatic insulin secretory response (Study HGIM in Section 4.1).

These two studies did not demonstrate a statistically significant decrease in insulin secretion or insulin sensitivity in healthy volunteers after 2.5 to 3 weeks of treatment with olanzapine or risperidone. These results contrast those that have been described for insulin secretion in healthy volunteers following short exposures to diphenylhydantoin (1 week), and for insulin sensitivity after short exposures (1 to 4 weeks) to the HIV protease inhibitor indinavir and the glucocorticoid prednisone.

1] Does the Division agree with Lilly's interpretation of the results from these two studies in healthy volunteers regarding insulin secretion and insulin receptor sensitivity?

2.2. Comparative Risk within Drug Class

Lilly has systematically evaluated multiple types of study data and literature regarding glucose and diabetes in schizophrenic and bipolar patients treated with atypical antipsychotics. These evaluations include:

- Mechanisms of glucose dysregulation (Study S013 in Section 3.1; Study HGIM in Section 4.1)
- Lilly integrated clinical trial database for treatment-emergent diabetes (Section 3.2)
- Spontaneous postmarketing adverse events from Lilly Clintrace database (Section 3.3)
- FDA MedWatch Database (Section 3.4)
- Previously submitted data retrospective analysis of the Lilly integrated database –Allison (Section 4.2), cohort studies –AdvancePCS (Section 4.3.1) and United Kingdom GPRD (Section 4.3.2)
- Review of currently available literature (Section 5)

It is the opinion of Eli Lilly and Company that the cumulative data currently available do not consistently support the presence of differences in the risk for diabetes, or in changes in markers of glucose regulation, in patients treated with olanzapine compared with other atypical antipsychotics.

2] Does the Division agree with Lilly's overall interpretation and conclusions based on the evaluation of the data currently available to Lilly?

2.3. Olanzapine in Context of Overall Data

In summarizing information for this briefing document, Lilly has examined a number of sources of data, including internal Lilly studies and external studies published in the scientific literature (listed in Section 2.2). Lilly recognizes that there may be other data available to FDA that is not currently available to Lilly, which could provide a fuller perspective.

3] Are the conclusions that Lilly is drawing in this briefing document, based on data available to Lilly, consistent with the overall body of data currently available to the Division?

4] Are any additional data anticipated to be available to the Division in the near future, which could provide a more complete perspective on the issues of atypical antipsychotics and glucose homeostasis?

2.4. Providing Additional Information

The FDA correspondence from 1 May 2000 requested information from Lilly to assist in the evaluation of the possible contributions of atypical antipsychotics to disturbances in glucose metabolism. Lilly provided information per that request, and through this briefing document, is continuing to update the Division as data has become available.

5] Does the Division identify any data gaps in the evaluation of a potential contribution of olanzapine and other antipsychotics to glucose dysregulation events in patients with severe mental illness?

2.5. Educational Initiatives

As described in Section 8, Lilly has developed educational initiatives to assist health care providers in providing patients with optimal care. Lilly is considering new initiatives to further educate and provide resources to the medical community on the increased prevalence of diabetes in the schizophrenic and bipolar populations.

6] Could the Division comment on proposed educational initiatives to improve health care providers' understanding of diabetes and its relationship to psychiatric disorders?

3. New Lilly Data

3.1. Study F1D-MC-S013 – Effect of Antipsychotic Therapy on Insulin Sensitivity: A Comparison of Olanzapine, Risperidone, and Placebo in Normal Subjects

A temporal association between atypical antipsychotics, new-onset diabetes, diabetic ketoacidosis, and exacerbation of preexisting diabetes has been described in the literature (Mir and Taylor 2001; Henderson 2002). Although treatment with many psychotropic medications may be temporally associated with weight gain, reports of severe hyperglycemia with ketoacidosis in the absence of weight gain (or shortly after initiation of treatment) have led to speculation that some of the atypical antipsychotics may have a rapid direct effect that impairs insulin secretion or insulin action (Mir and Taylor 2001; Muench and Carey 2001; Sowell et al. 2002b).

Study F1D-MC-S013 was a 3-week, prospective, randomized, single-blind study designed to determine whether treatment with olanzapine or risperidone is associated with a decrease in insulin sensitivity. The abbreviated clinical study report (CSR) has been approved by Lilly and is being prepared for submission to olanzapine IND 28,705. The information below provides a summary of the more detailed data presented in the CSR.

3.1.1. Synopsis

Insulin sensitivity was assessed in healthy volunteers at baseline and again after 21 to 23 days of treatment with olanzapine (10 mg/day), risperidone (4 mg/day), or placebo using the two-step hyperinsulinemic, euglycemic clamp (the most widely accepted method for quantitating insulin sensitivity in humans).

Results of this prospective, randomized study of healthy volunteers did not demonstrate a significant decrease in insulin sensitivity or maximal tissue responsiveness to insulin following 3 weeks of treatment with olanzapine or risperidone. Specifically, in this study there were no significant within-group mean changes in insulin sensitivity or glucose disposal rate at either the low- or high-insulin steady states for olanzapine, risperidone, or placebo.

These results are in contrast to those described for healthy volunteers following exposure to the anti-HIV protease inhibitor indinavir for 4 weeks (Noor et al. 2001; Noor et al. 2002) or the glucocorticoid prednisone for 7 days (Pagano et al. 1983), where insulin sensitivity was found to significantly decrease.

3.1.2. Methods

3.1.2.1. Study Design

Study S013 was a 3-week, randomized, single-blind, placebo-controlled, parallel study of healthy volunteers. Figure 3.1 shows the study design.

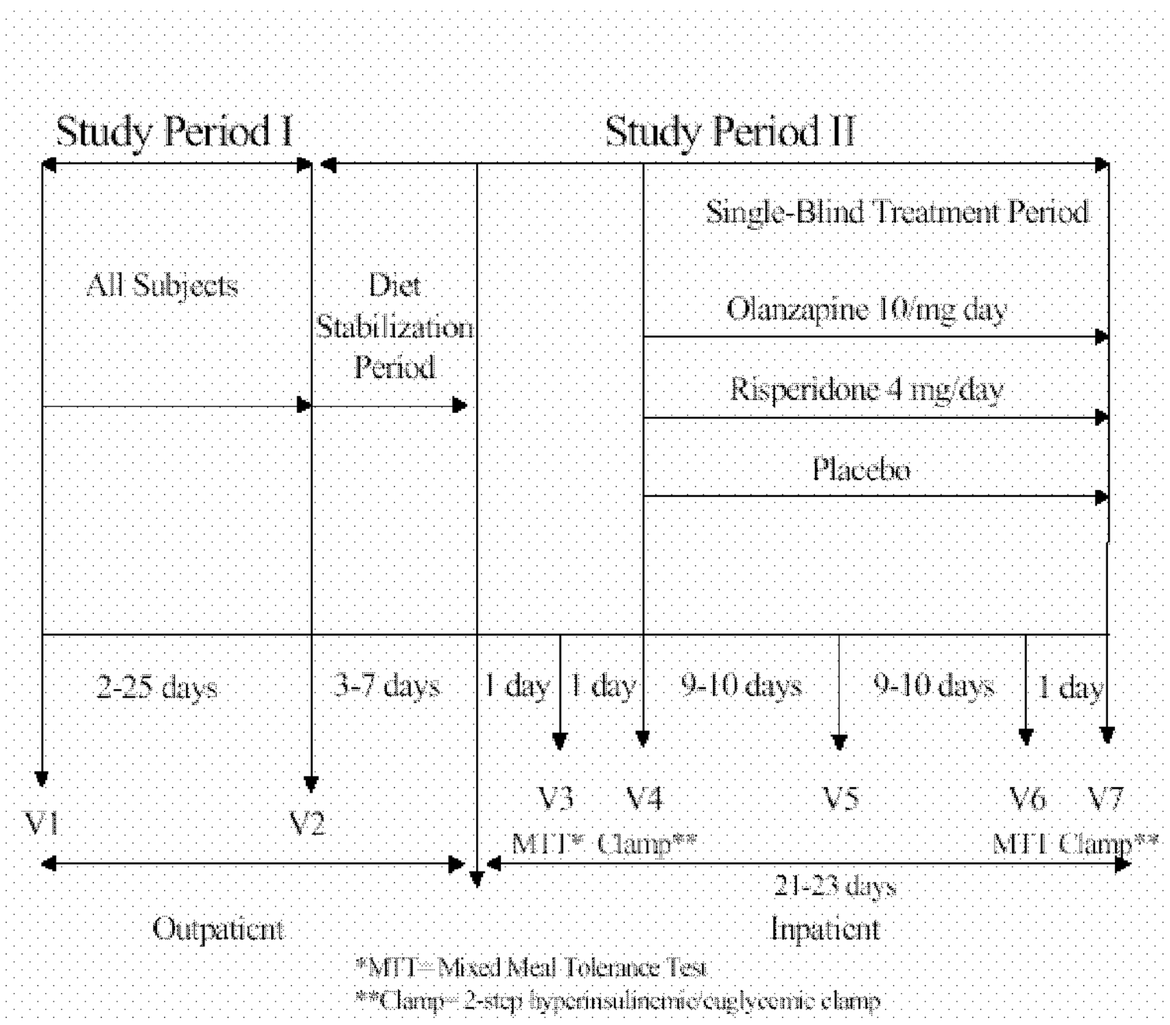


Figure 3.1. Study design for F1D-MC-S013.

Subjects were males or females, between 18 and 65 years of age, body mass index (BMI) between 20 and 27 kg/m^2, fasting glucose ≤100 mg/dL, and no personal or family history of diabetes. All subjects provided written informed consent after study procedures and possible treatment adverse events were explained. The protocol was approved by the University of California-San Diego Institutional Review Board.

Screening tests, physical examination, and laboratory tests were administered and medical history collected to determine eligibility for study enrollment. Subjects underwent a 3- to 7-day outpatient period of diet stabilization followed by hospitalization. After undergoing baseline testing, subjects were randomized at a 1:1:1 ratio for treatment with olanzapine 10 mg/day, risperidone 4 mg/day, or placebo for approximately 3 weeks.

Subjects were allowed up to three passes (72 hours each) during the study, but were required to be readmitted to the inpatient unit 72 hours prior to the final metabolic testing. The Mixed-Meal Tolerance Test (MMTT) and euglycemic clamp was performed on each subject 1 and 2 days after admission, respectively. These measures were repeated sequentially at the end of the treatment period.

The olanzapine dose was titrated by administering 2.5 mg/day for 2 days, 5.0 mg/day for 2 days, and 10 mg/day thereafter. The risperidone dose was titrated by administering 0.5 mg twice a day for 2 days, 1.0 mg twice a day for 2 days, and 2.0 mg twice a day thereafter.

3.1.2.2. Hyperinsulinemic, Euglycemic Clamp

A 5-hour, two-step hyperinsulinemic, euglycemic clamp (Morris et al. 1997) was used to assess peripheral insulin sensitivity in subjects following a 12-hour fast. Blood glucose levels were clamped at approximately 90 mg/dL. Insulin action was assessed at two insulin infusion rates: 20 mU/m^2/min (low dose) and 120 mU/m^2/min (high dose). These insulin infusion rates result in steady-state serum insulin concentrations that approximate the ED50 (low dose) and the maximum (high dose) concentration for stimulation of peripheral glucose uptake in non-obese, non-diabetic subjects. A constant insulin infusion rate was maintained at 20 mU/m^2/min for approximately 180 minutes after which the rate was increased to 120 mU/m^2/min for an additional ~120 minutes. The total duration of the two-step clamp procedure was approximately 300 minutes. For this analysis, steady-states were defined as the 140- to 160-minute interval of the clamp for the low-insulin concentration, and as the 240- to 260-minute interval for the high-insulin concentration. Insulin sensitivity was quantitated as M/I, where M was the steady-state glucose disposal rate during the time interval and I was the steady-state mean insulin concentration during the same time interval.

3.1.2.3. Mixed-Meal Tolerance Test

A Mixed-Meal Tolerance Test (MMTT) was conducted to assess changes in postprandial glucose and insulin levels and the clinical significance of any changes in insulin sensitivity detected by peripheral administration of glucose and insulin during the euglycemic clamp. In the morning following a 12-hour fast, subjects were given two standard meals 4 hours apart with each meal consisting of 33.3% of total daily calories and a caloric distribution of 55% carbohydrate, 30% fat, and 15% protein. Blood glucose and insulin levels were measured hourly beginning 1 hour prior to the first meal and continuing for 3 hours after the second meal.

3.1.2.4. Statistics

The primary objective of this study was to assess whether olanzapine 10 mg/day had an adverse effect on insulin sensitivity, and the primary measure used to assess olanzapine's effect was the percent change from baseline to endpoint in the insulin sensitivity index M/I [calculated as $(100*([M/I]_2 - [M/I]_1)/[M/I]_1)$ at the low-insulin steady state. The anticipated sample distribution of 18 placebo-treated subjects, 18 olanzapine-treated subjects, and 18 risperidone-treated subjects would give the study 80% power to detect at least 25% decrease from baseline in the within-group mean percent change in M/I at the low-insulin steady state. This calculation assumed a one-sided significance level, a type I error rate of 0.05, and an estimated standard deviation (for $100*([M/I]_2 - [M/I]_1)/[M/I]_1$, the primary measurement) of 40.

Analysis of variance (ANOVA) models were used to evaluate continuous data. Count data were analyzed using Fisher's exact test. Unless stated otherwise, all tests of hypotheses were tested at a two-sided level of 0.05.

3.1.3. Results

3.1.3.1. Patient Demographics

The proportion of Caucasian subjects was significantly different (greater) in the olanzapine group compared to placebo (p=.0265), but not compared to the risperidone group (p=.3566). However, ethnicity was not significantly different when all ethnic categories (Caucasian, African, Southeast Asian/Asian, Hispanic, and other) were considered (p=.105 overall). There were no other significant differences in baseline patient demographics of age, gender, or BMI between the treatment groups (Table 3.1).

Table 3.1. Patient Demographics Study F1D-MC-S013

	Olanzapine	Risperidone	Placebo
Number	22	14	19
Age, Mean (SD)	35.6 (15.7)	32.9 (10.4)	31.9 (12.9)
Gender, Male, n (%)	17 (77.3%)	8 (57.1%)	13 (68.4%)
Ethnicity, Caucasian, n (%)	20 (90.9%)	11 (78.6%)	11 (57.9%)
BMI, kg/m^2 (SD)	22.70 (2.26)	22.38 (2.73)	23.83 (2.28)

Abbreviations: BMI = body mass index; SD = standard deviation.
Results are expressed as mean (SD) or as percentage of patients.

3.1.3.2. Patient Disposition

A total of 64 subjects were randomized in the study and 9 subjects discontinued after randomization. A statistically significant difference in overall subject disposition was observed between the olanzapine and risperidone treatment groups, as a relatively large proportion of subjects in the risperidone treatment group (7 of 21) were discontinued from the study. Reasons for discontinuation in the risperidone treatment group were as follows: 1 subject withdrew consent due to anxiety (an adverse event); 1 subject withdrew consent due to a personal decision; 1 subject withdrew consent due to discomfort associated with the intravenous catheter employed during the baseline clamp; and 4 subjects were discontinued for criteria not met/noncompliance with protocol. Two subjects discontinued in the placebo group due to criteria not met/noncompliance with protocol. Of the 55 randomized subjects, 22 received olanzapine, 14 received risperidone, and 19 received placebo treatment for 21 to 23 days.

3.1.3.3. Change in Weight, Fasting Glucose, Insulin, and Free Fatty Acid

Table 3.2 summarizes mean (SD) baseline and mean (SD) changes for weight, fasting glucose, insulin, and free fatty acids.

Table 3.2. Mean Baseline and Mean Change in Weight, Fasting Glucose, Fasting Insulin, and Fasting Free Fatty Acids (FFA) Study F1D-MC-S013

Treatment	Weight, kg (SD)		Glucose, mg/dl (SD)		Insulin, μU/ml (SD)		FFA, mEq/L (SD)	
	Baseline	Change at Endpoint	Baseline	Change at Endpoint	Baseline	Change at Endpoint	Baseline	Change at Endpoint
PLC	70.3 (11.0)	-0.22 (0.90)	87.2 (6.2)	0.3 (5.0)	7.1 (2.8)	2.4 (5.4)	0.56 (0.24)	-0.12 (0.22)
OLZ	69.9 (9.6)	1.95 (1.29)*	86.4 (4.7)	2.3 (4.4)	6.1 (2.1)	2.8 (4.5)	0.48 (0.17)	-0.11 (0.22)
RIS	69.4 (13.8)	1.61 (1.31)*	91.4 (6.7)	-0.8 (6.7)	10.5 (4.7)	-0.6 (3.8)	0.54 (0.20)	-0.16 (0.21)

Abbreviations: FFA = fasting free fatty acids; OLZ = olanzapine; PLC = placebo; RSP = risperidone; SD = standard deviation.
*p <.001 vs placebo.

Patients in both active treatment groups gained significantly more weight during the study period than did those in the placebo group (p<.001 within-group and versus placebo). However, there was no significant difference between the olanzapine and risperidone treatment groups in mean weight gain.

A statistically significant within-group baseline to endpoint increase (2.3 ± 4.4 mg/dL) in fasting glucose was observed within the olanzapine treatment group (p=.023). However, this change was not significantly different from the changes observed in either the placebo (0.3 ± 5.0 mg/dL) or risperidone (-0.8 ± 6.7 mg/dL) groups. A statistically significant within-group change (increase) in fasting insulin (2.8 ± 4.5 μIU/mL) was also observed for the olanzapine treatment group (p=.009). However, this increase was not significantly different from the increase observed in the placebo group (2.4 ± 5.4 μIU/mL; p=.789).

Small, nonsignificant within-group mean decreases in fasting glucose and insulin were observed for the risperidone group. However, at baseline, the mean fasting glucose (p<.05) and fasting insulin (p<.004) levels were significantly different (higher) in the group of patients randomized to risperidone compared with the groups randomized to olanzapine or placebo. Endpoint fasting FFA concentrations decreased significantly within all 3 treatment groups compared to baseline values (p<.031). However, no significant between-group differences were observed in the change in fasting FFA concentration.

3.1.3.4. Hyperinsulinemic, Euglycemic Clamp

3.1.3.4.1. Low-Insulin Phase

In all treatment groups, the mean glucose levels at low-insulin steady state achieved the target glucose level of approximately 90 mg/dL with the mean steady-state insulin level at ~27 μU/mL in both the baseline and endpoint clamp studies. The target insulin concentration at the low steady state approximates the half maximal concentration for stimulation of glucose uptake by peripheral tissues. As a consequence, assessments of insulin sensitivity at the low-insulin steady state are extremely sensitive for detecting even relatively small within-group changes.

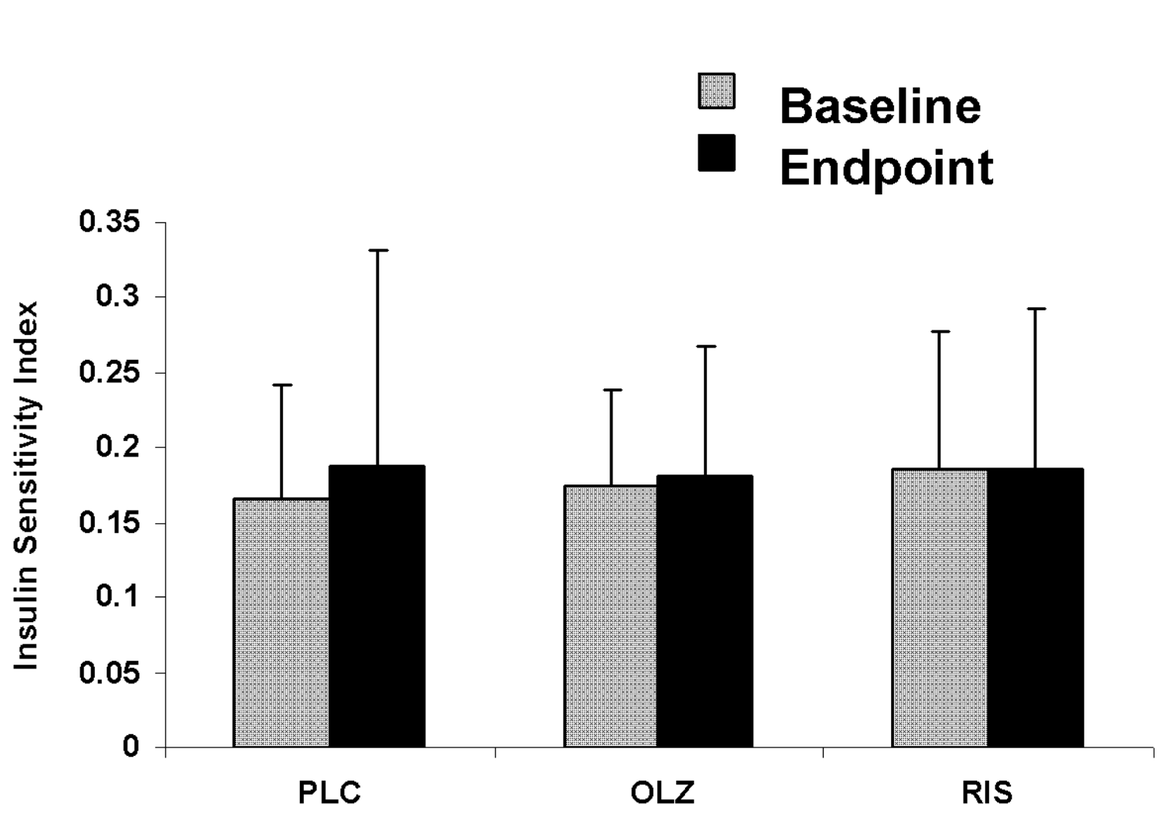
No significant within-group changes were noted in the glucose disposal rate for the olanzapine or risperidone groups at the low-insulin steady state (M, shown in Table 3.3). A small within-group change (increase, p=.019) in M was observed for the placebo group. The baseline to endpoint changes in M for the risperidone and placebo groups achieved borderline significance (p=.453).

Table 3.3. Mean Baseline (SD) and Mean Change (SD) Glucose Disposal Rate (M) at Low and High Insulin Phases Two-Step Euglycemic Clamp

Treatment	Glucose disposal rate (M), mg/kg/min			
	Low Insulin Phase		High Insulin Phase	
	Baseline	Change at Endpoint	Baseline	Change at Endpoint
PLC	4.1 (1.4)	0.5 (0.8)	12.1 (2.0)	-0.3 (1.1)
OLZ	4.8 (1.7)	0.1 (2.0)	12.7 (2.8)	-0.02 (2.0)
RIS	4.9 (2.1)	-0.6 (1.2)	13.3 (2.9)	-0.7 (1.7)

Abbreviations: OLZ = olanzapine; PLC = placebo; RSP = risperidone.

At steady state, the ratio of M (glucose disposal rate) to I (steady state insulin concentration) provides a precise quantitative measure of insulin sensitivity. As shown in Figure 3.2, no significant within- or between-treatment differences were noted in the change (absolute value or percent change from baseline) in insulin sensitivity index (M/I) at the low-insulin concentration after 3 weeks of treatment.



Abbreviations: OLZ = olanzapine; PLC = placebo; RSP = risperidone.

Figure 3.2. Mean baseline (SD) and mean endpoint (SD) insulin sensitivity, M/I at low-insulin steady state.

Ranges for the change in M/I (absolute values) at low-insulin steady state were: olanzapine, 0.147 to –0.212; risperidone, 0.110 to –0.112; and placebo, 0.414 to –0.102 (mg glucose/kg body weight/min per μIU insulin/mL).

Figure 3.3 shows results for individual subjects, expressed as percent change from baseline in M/I. Overall, at the low-insulin steady state, the mean insulin sensitivity actually increased slightly (though not statistically significant) in all treatment groups: olanzapine 4.6% ± 36.1%; risperidone 3.2% ± 33.7%; and placebo 12.4% ± 47.7%. A numerically greater increase in insulin sensitivity was noted for the placebo group; however, this difference appears to be accounted for by 1 subject whose insulin sensitivity increased dramatically (153%). Of note, this subject's baseline insulin sensitivity may have been affected by a concurrent upper respiratory infection. In the absence of this subject, the mean increase in insulin sensitivity measured at the low-insulin steady state for the placebo group was 3.5% ± 34.2%.

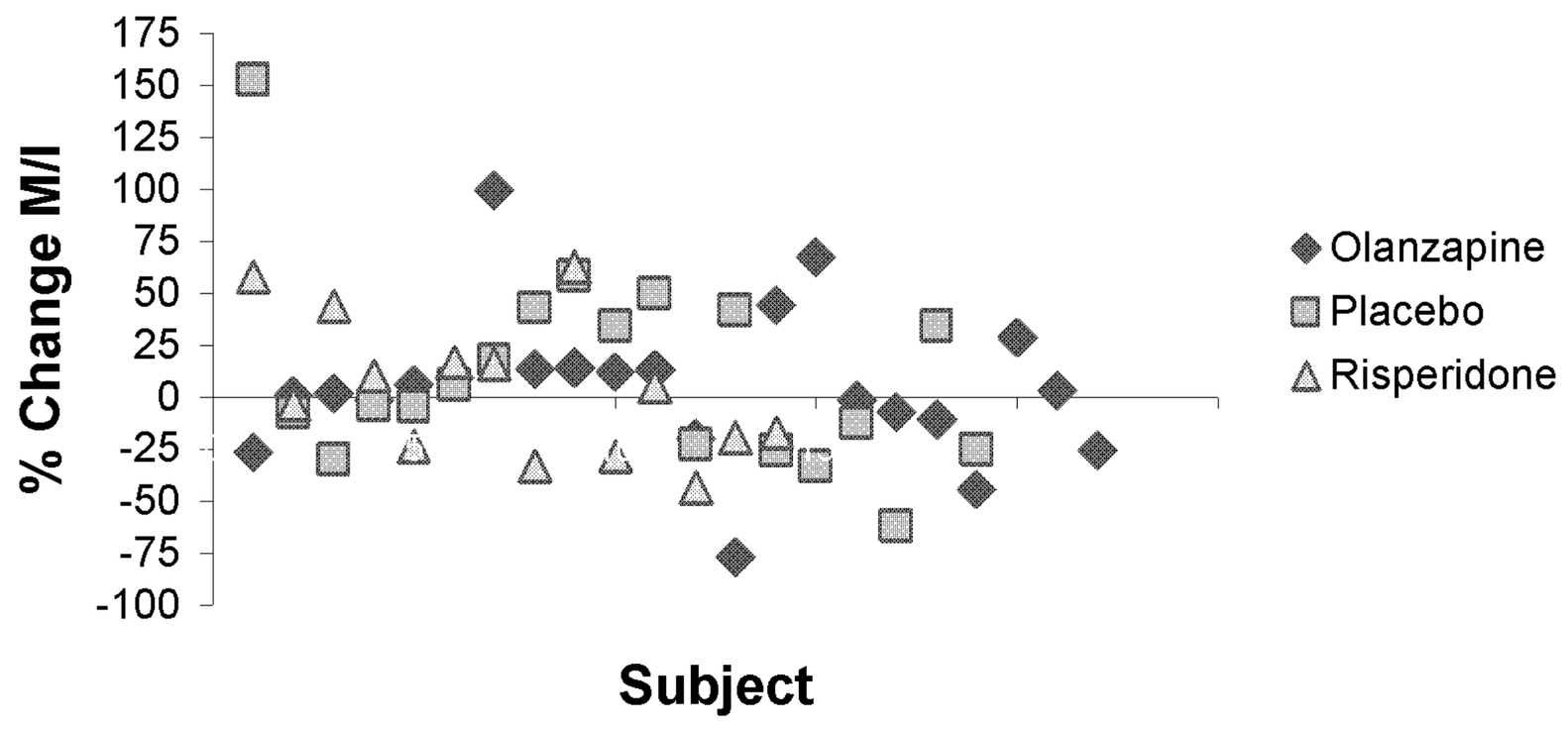
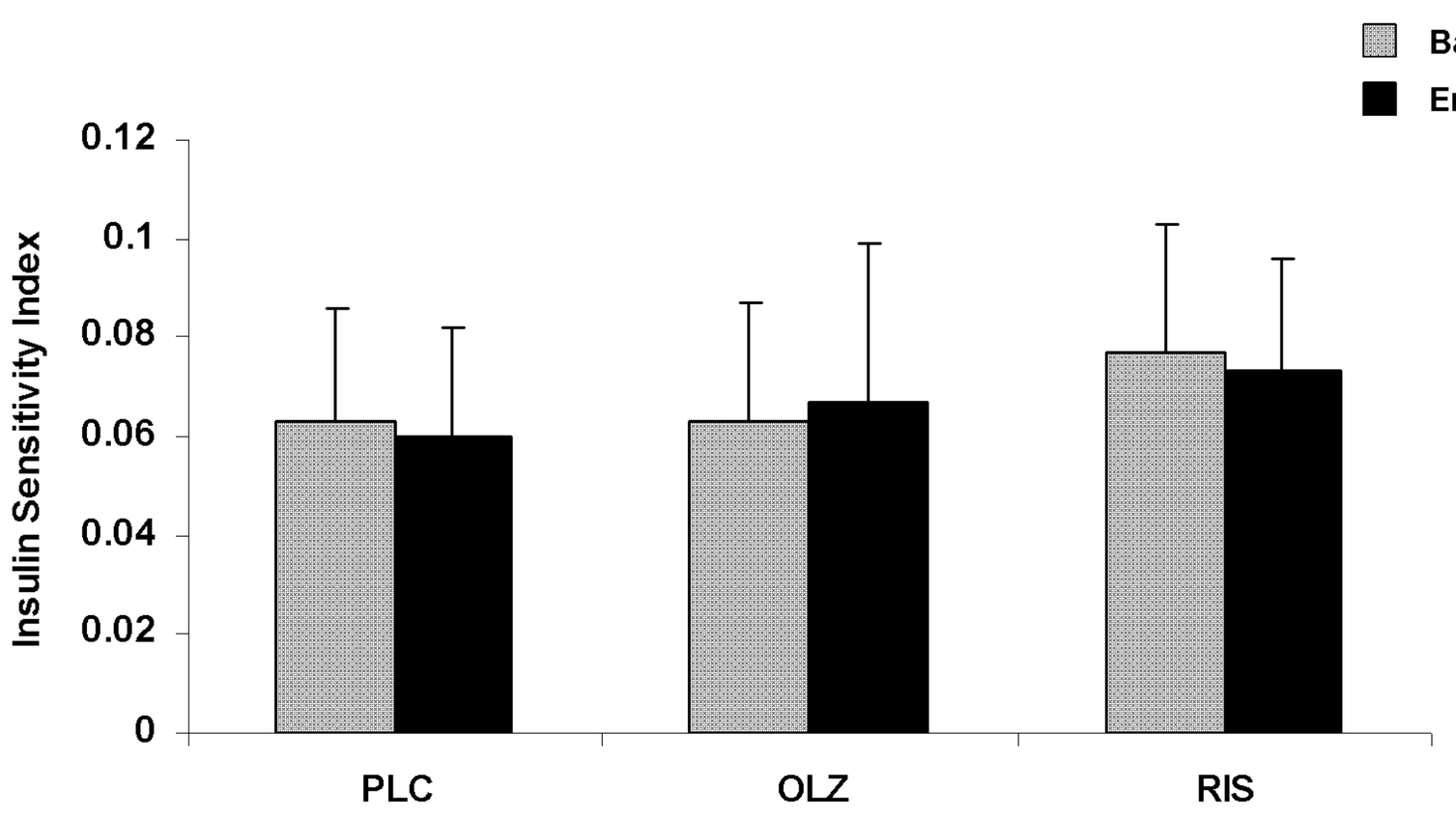


Figure 3.3. **Percent change in M/I (M/I Endpoint – M/I Baseline / M/I Baseline X 100%) at low-insulin steady state for individual subjects.**

Using 48% change as a threshold for categorical assessment (ie, the variability observed within the placebo group), 3 patients (15.7%) in the placebo group, 2 patients (9.1%) in the olanzapine group, and 2 patients (14.3%) in the risperidone group exhibited increases in percent change in M/I greater than 48%. In a categorical assessment of decreases in percent change in M/I at the low-insulin steady state, 1 patient (5.3%) in the placebo group, 1 patient (4.5%) in the olanzapine group, and no patients in the risperidone group exhibited decreases in percent change in M/I greater than 48%.

3.1.3.4.1. High-Insulin Phase

The mean glucose levels at high-insulin steady state achieved the target glucose level of approximately 90 mg/dL, with mean steady-state insulin levels of ~200 μU/mL in both the baseline and endpoint clamp studies. The target insulin concentration at the high-insulin steady state is in the range for maximal stimulation of peripheral glucose uptake, and therefore should provide information regarding possible drug effects on maximal tissue responsiveness to insulin. There were no significant within-group changes or between-group differences in the change in glucose disposal rate (M, Table 3.3). There were also no significant within-group or between-group differences in the mean change (absolute value or percent change from baseline) in M/I at the high-insulin steady state (Figure 3.4).



Abbreviations: OLZ = olanzapine; PLC = placebo; RSP = risperidone.

Figure 3.4. Mean baseline (SD) and mean endpoint (SD) insulin sensitivity, M/I at high insulin phase.

The changes in M/I (absolute values) ranged from: olanzapine, 0.072 to –0.039; risperidone, 0.023 to –0.036; and placebo, 0.014 to –0.026 (mg glucose/kg body weight/min per μIU insulin/mL).

The mean percent change in M/I at the high-insulin steady state was as follows: olanzapine, 6.89% ± 24.54%; risperidone, -0.67% ± 21.38%; and placebo, -4.66% ± 17.88%. Figure 3.5 shows results for individual subjects expressed as percent change from baseline.

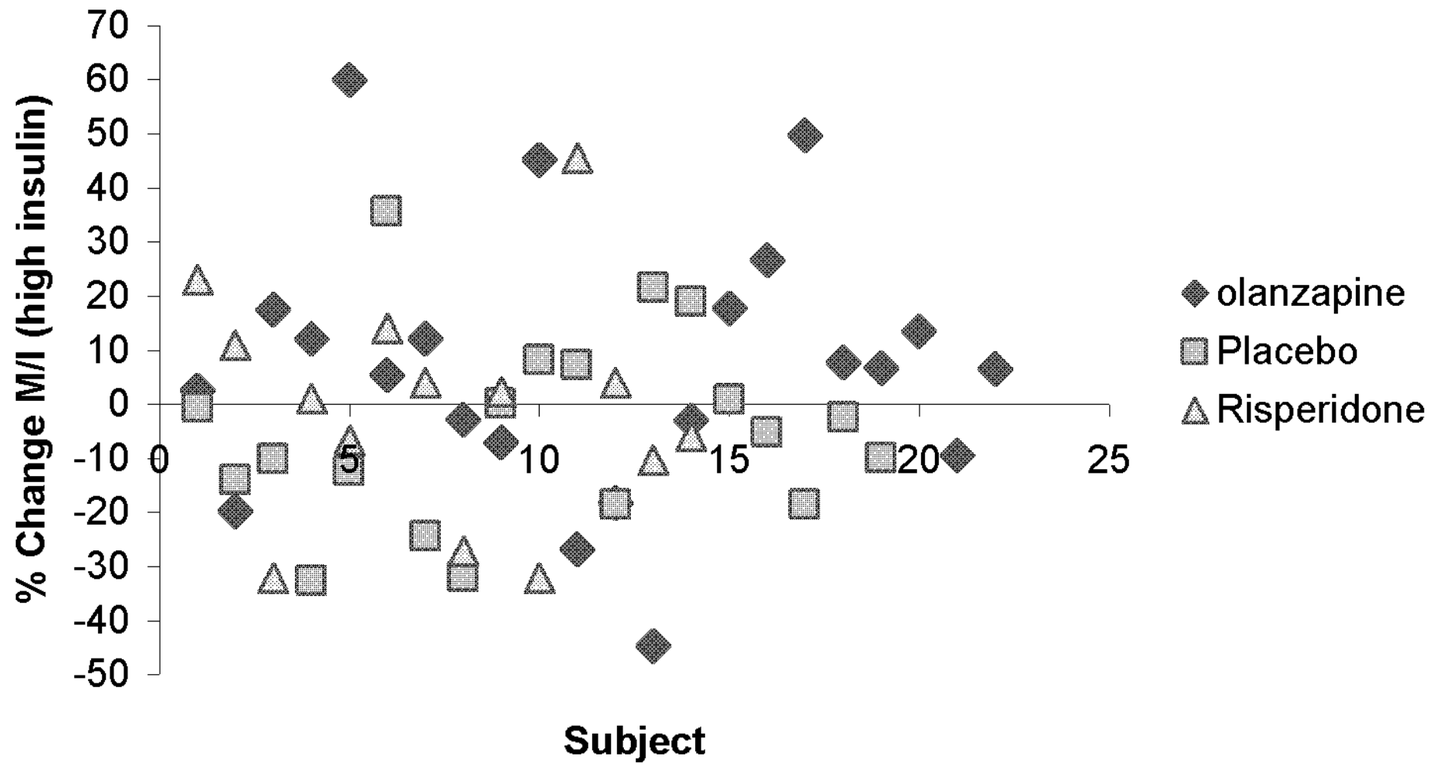
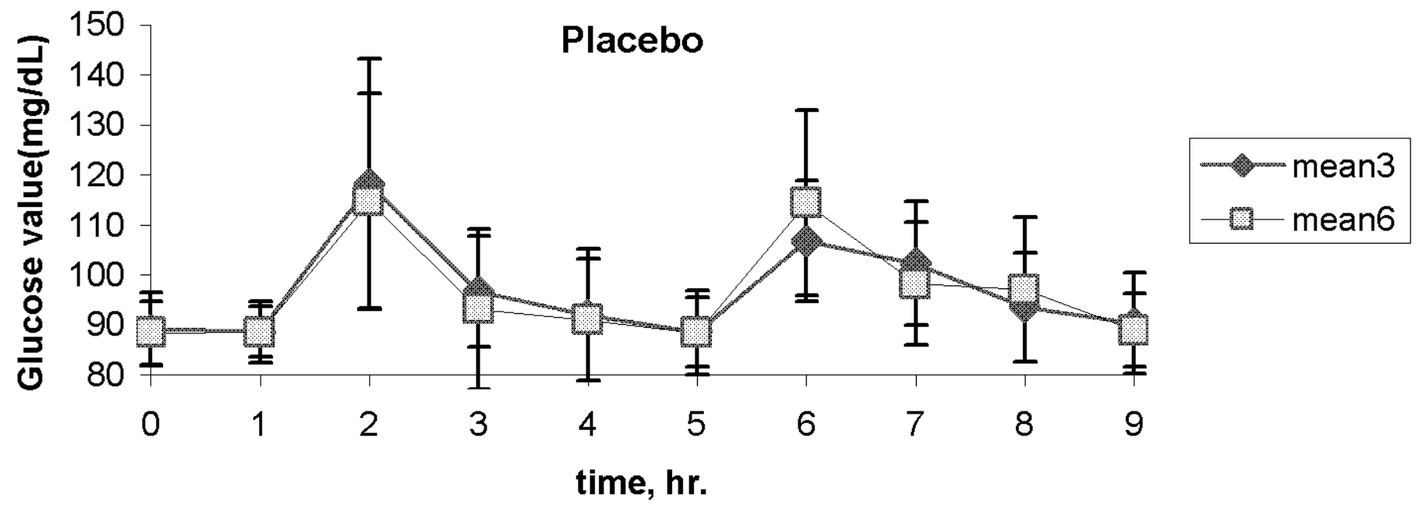


Figure 3.5. **Percent change in M/I (M/I endpoint – M/I baseline / M/I baseline X 100%) at high-insulin steady state for individual subjects.**

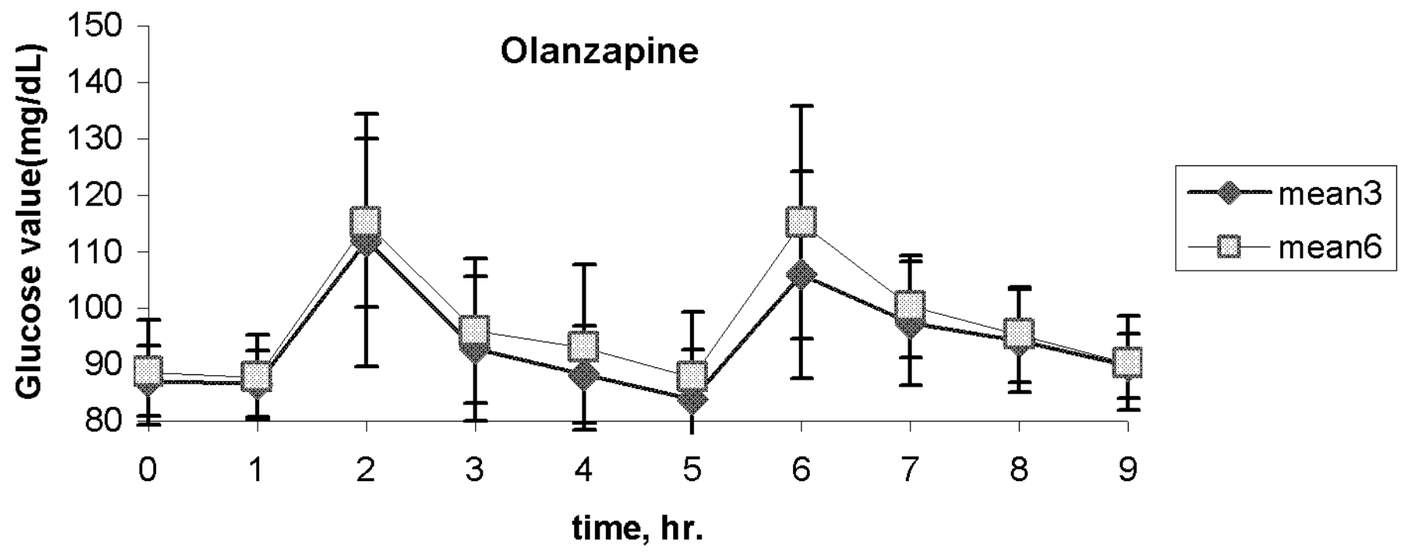
3.1.3.5. Mixed-Meal Tolerance Test

Mean glucose at each time point sampled during the MMTT are shown in Figure 3.6a (placebo), Figure 3.6b (olanzapine), and Figure 3.6c (risperidone), respectively. Mean insulin responses at each time point sampled during the MMTT are shown in Figure 3.7a (placebo), Figure 3.7b (olanzapine), and Figure 3.7c (risperidone), respectively.



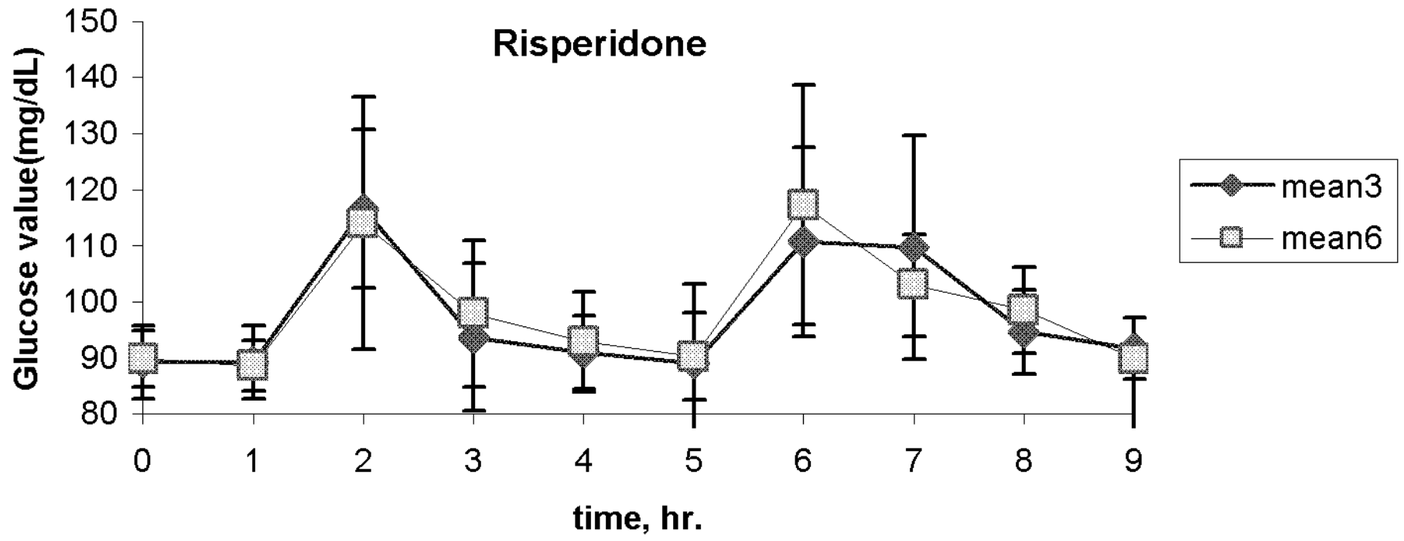
Note: Mean 3 represents baseline; mean 6 represents endpoint.

Figure 3.6a. Mean glucose levels (SE) during MMTT for placebo.



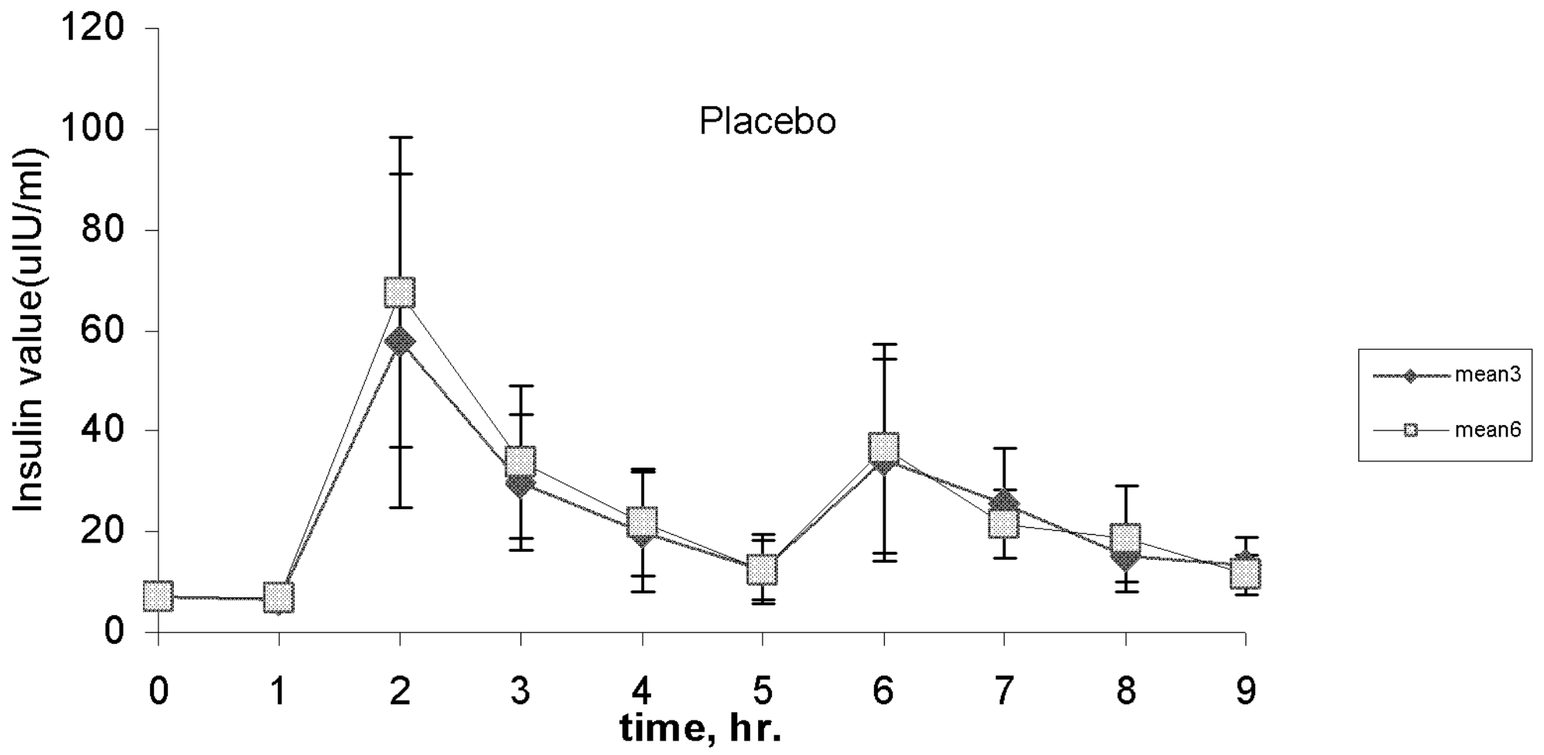
Note: Mean 3 represents baseline; mean 6 represents endpoint.

Figure 3.6b. Mean glucose levels (SE) during MMTT for olanzapine.



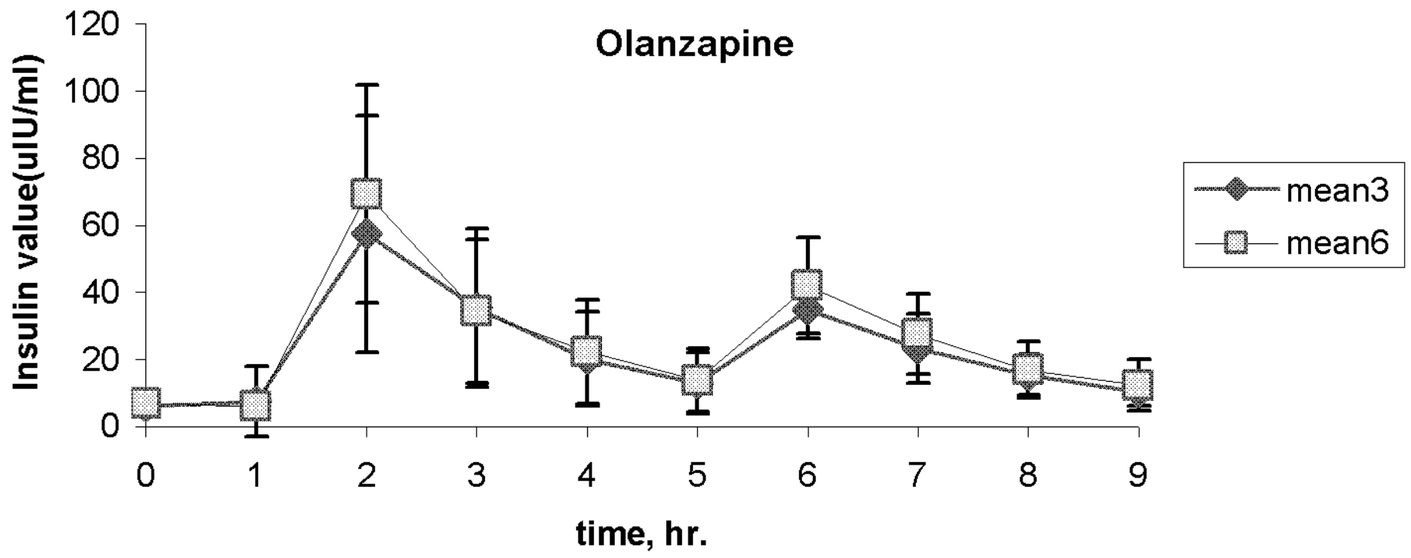
Note: Mean 3 represents baseline; mean 6 represents endpoint.

Figure 3.6c. Mean glucose levels (SE) during MMTT for risperidone.



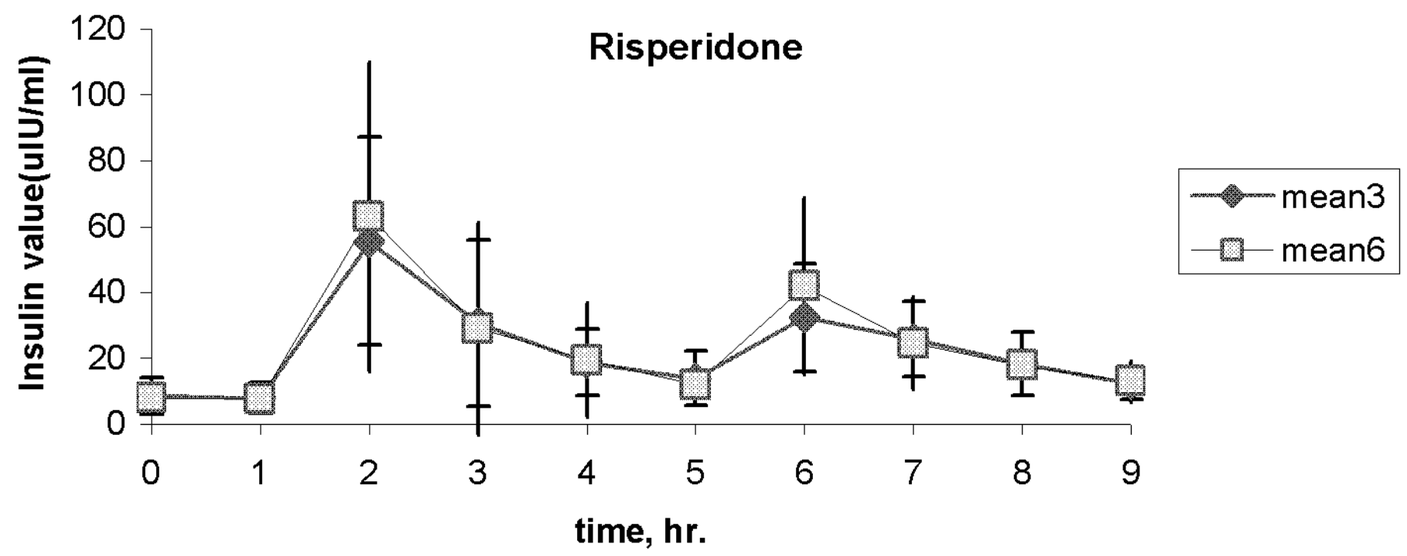
Note: Mean 3 represents baseline; mean 6 represents endpoint.

Figure 3.7a. Mean insulin levels (SE) during MMTT for placebo.



Note: Mean 3 represents baseline; mean 6 represents endpoint.

Figure 3.7b. Mean insulin levels (SE) during MMTT for olanzapine.



Note: Mean 3 represents baseline; mean 6 represents endpoint.

Figure 3.7c. Mean insulin levels (SE) during MMTT for risperidone.

No significant changes in glucose peak levels were observed following the first meal in any treatment group. Following the second meal, peak glucose levels were slightly higher in all treatment groups. Although the mean within-group increase (7.32 mg/dL) in peak glucose during Meal 2 for the olanzapine group was statistically significant ($p=.039$), this change was not different ($p>.4$) from the mean increases observed for either the risperidone (2.36 mg/dL) or placebo (5.74 mg/dL) groups.

The mean glucose area under the curve (AUC) was slightly lower at endpoint for the placebo group (Table 3.4). Small within-group increases in the glucose AUC were noted for both olanzapine (3.7%; p=.018 within-group) and risperidone (~1.0%, p=.439 within-group). The between-group comparison in mean change in glucose AUC for active therapies was not significant (p=.181). However, the change observed for the olanzapine group did achieve statistical significance compared to that observed in the placebo group (p=.033). Evaluation of glucose responses as the net AUC (total area above the fasting level) did not demonstrate any significant withi- group or between-group differences in the mean net change in glucose AUC.

Table 3.4. Integrated Glucose and Insulin Responses During MMTT Results Expressed as Mean (SD) AUC without Adjusting for Differences in Fasting Glucose and Insulin Levels

Treatment	Mixed Meal Tolerance Test			
	Glucose AUC mg/dl x min ($x10^3$)		Insulin AUC µUI/ml x min ($x10^3$)	
	Baseline	Change at Endpoint	Baseline	Change at Endpoint
PLC	52.7 (3.5)	-0.2 (2.9)	12.7 (4.7)	1.0 (3.8)
OLZ	50.9 (3.0)	1.9 (3.4)*	12.9 (4.9)	1.4 (4.9)
RIS	53.1 (3.1)	0.5 (2.3)	12.8 (6.2)	0.7 (4.4)

* p=0.033 vs PLC

Abbreviations: AUC = area under the curve; OLZ = olanzapine; PLC = placebo; RSP = risperidone; vs = versus.

The insulin responses during the MMTT were also similar among the treatment groups. Peak insulin levels following Meal 1 were unchanged in all groups. The mean changes in insulin levels following the second meal were significantly increased within both the olanzapine (7.64 µIU/mL, p=.009) and risperidone (9.27 µIU/mL, p=.036) groups; however, these increases were not different from the increase observed with placebo (olanzapine p=.194 versus placebo, risperidone p=.138 versus placebo). Further, insulin AUCs were slightly increased in all treatment groups at endpoint (olanzapine, 10.9%; risperidone, 5.6%; and placebo, 7.9%), although none of the changes achieved statistical significance. There were no significant within-group or between-treatment differences in the net insulin AUC (total area above the fasting level).

3.1.4. Discussion

The absence of a statistically significant decrease in insulin sensitivity during olanzapine or risperidone treatment in this study is in contrast to results reported for a number of other medications that have been associated with treatment-emergent diabetes. For example, euglycemic clamp studies of patients with hypertension treated with beta-adrenergic antagonists revealed a 22% to 23% decrease in the insulin sensitivity with atenolol (Pollare et al. 1989b; Reneland et al. 2000) and a 28% decrease in insulin sensitivity with metaprolol (Reneland et al. 2000). A similar study found a 16% decrease in insulin sensitivity with hydrochlorothiazide (Pollare et al. 1989a). A marked (2-fold) decrease in insulin sensitivity as assessed by glucose disposal rate at steady state was detected using the euglycemic clamp after only 7 days of exposure to prednisone (15 mg/day) in a study of 10 healthy normal weight volunteers (Pagano et al. 1983).

Treatment of healthy men with the anti-HIV protease inhibitor indinavir was also shown to decrease insulin sensitivity between 17% after 4 weeks of oral therapy (Noor et al. 2001) and 34% after a single intravenous dose (Noor et al. 2002) using euglycemic clamps.

Results of Study S013 suggest that olanzapine and risperidone, unlike medications described above, do not have an acute direct effect that promotes insulin resistance. The absence of a significant change in glucose disposal rate (M) at the high-insulin steady state further suggests that neither olanzapine nor risperidone cause a decrease in the maximal glucose response of peripheral tissues.

One limitation of Study S013 is the relatively short duration (~3 weeks) of exposure. At the time this study protocol was drafted, 6 of 35 published case reports of diabetes associated with atypical antipsychotic treatment occurred within 30 days of exposure. Also noted above, marked effects on insulin sensitivity have been detected with prednisone and indinavir after short exposures. Therefore, a 3-week exposure seemed reasonable, particularly with the use of the highly sensitive, two-step, hyperinsulinemic, euglycemic clamp to quantitate insulin action. These results cannot address potential effects of either agent following longer-term treatment.

In addition, effects of olanzapine and risperidone were examined in a relatively small number of healthy subjects. While the olanzapine treatment group was sufficiently populated to achieve the intended statistical power, caution is warranted in extrapolating these results to larger groups or to groups with different characteristics.

The inclusion of non-psychotic, non-diabetic subjects in this study, rather than patients with schizophrenia, might also be questioned. The use of healthy volunteers is important for the evaluation of changes in insulin sensitivity during treatment with these antipsychotics, an effect that may be independent from changes in insulin sensitivity associated with underlying mental illness (Lorenz 1922; Freeman 1946).

For patients with major depressive illness, there is reasonable evidence supporting a state-related decrease in insulin sensitivity (Winokur et al. 1988; Okamura et al. 2000; Weber et al. 2000). While specific data are lacking for patients with psychotic illnesses, it is reasonable to hypothesize that acute illness states in schizophrenia and bipolar disorder may impact insulin sensitivity. In addition, there are likely difficulties associated with compliance when studying patients with schizophrenia, given the demands of the study protocol and potential confounding effects of concomitant and previous medications on measures of insulin sensitivity. For these reasons, examination of potential drug effects in healthy volunteers was considered appropriate. In fact, this same rationale was applied in studies of healthy volunteers designed to evaluate the impact on insulin sensitivity of the HIV protease inhibitor indinavir (Noor et al. 2001, 2002).

Nonetheless, results of this prospective study using healthy volunteers appear to be consistent with results of a cross-sectional study examining patients with schizophrenia. Using the hyperinsulinemic, euglycemic clamp, Newcomer et al. (2002b) found no significant difference in glucose disposal rates (M) among matched groups of overweight patients with schizophrenia treated with olanzapine, risperidone, or typical antipsychotic medications.

3.1.5. Conclusions

Results of this prospective, randomized study of healthy volunteers did not demonstrate a significant decrease in insulin sensitivity or maximal tissue responsiveness to insulin following 3 weeks of treatment with olanzapine or risperidone. These results are in contrast to results that have been described for healthy volunteers using the euglycemic clamp to assess insulin sensitivity following similarly short exposures to the anti-HIV protease inhibitor indinavir (Noor et al. 2001, 2002) or the glucocorticoid prednisone (Pagano et al. 1983). Further, results of the MMTT did not support a marked effect of these medications on gluco-regulatory endpoints following ingestion of a mixed-composition meal.

3.2. Analysis of Treatment-Emergent Diabetes (TED) in Lilly Integrated Clinical Trial Database

This retrospective analysis examined the impact of baseline variables, mean random glucose, number of preexisting risk factors for diabetes, treatment-emergent weight gain, and therapy assignment on the risk of being identified with treatment-emergent diabetes (TED).

3.2.1. Synopsis

From a large (n=5013) non-diabetic cohort of patients with schizophrenia, 94 patients were identified with TED and 282 patients were identified as possessing uncertain glucose tolerance (UGT). The relationship between baseline risk factors for diabetes, treatment-emergent weight gain, and therapy assignment on the risk of TED were assessed. At study entry, patients subsequently identified with TED and UGT were significantly different compared to patients who appeared to maintain normal glucose tolerance (NGT). Specifically, TED and UGT patients had higher baseline random glucose levels, were older, more obese, and more likely to possess multiple risk factors for diabetes at entry into the clinical trials than NGT patients. Results of this analysis suggest that many of the patients with schizophrenia who were identified with TED were likely to have preexisting unrecognized glycemic abnormalities or possessed a greater burden of preexisting risk factors for diabetes than did patients who appeared to maintain normoglycemia. Treatment-emergent weight gain or therapy assignment appeared to have a relatively smaller impact on the short-term risk of TED.

3.2.2. Methods

3.2.2.1. Patient Population and Study Design

From the olanzapine clinical trial database, 24 studies were identified in which patient weight and post-randomization plasma glucose measurements were available at multiple time points. For many of the studies, the details of the study designs, patient characteristics (ie, age, sex, race, illness characteristics), and efficacy and safety results have been previously published (Beasley et al. 1996a, 1996b; Tollefson et al. 1997, 1999, 2001; Tran et al. 1997; Chengappa et al. 2000; Baker et al. 2002). Briefly, study participants were inpatients or outpatients, ages 18 to 65 years, diagnosed with DSM-III-R or DSM-IV schizophrenia or related disorders, and had provided written informed consent after the details of the study design and possible adverse events were completely described.

Participation criteria were similar among the pooled trials, except that studies examining clozapine were limited to patients with treatment-refractory disease (Tollefson et al. 1999, 2001). In several studies comparing olanzapine to risperidone, patients with cardiovascular disease including hypertension may have been excluded (Tran et al. 1997). All studies included a 2- to 9-day medication washout period and a 6- to 52-week double-blind treatment period, followed by an olanzapine open-label extension phase in some cases. For those studies with medication crossover, only the initial monotherapy treatment period was included in the analyses. During the double-blind treatment period, all patients received therapeutic doses of a single antipsychotic medication (olanzapine 5 to 25 mg/day, haloperidol 5 to 20 mg/day, risperidone 4 to 12 mg/day, clozapine 200 to 600 mg/day), or placebo.

3.2.2.2. Random Glucose Measurements

Random plasma glucose levels were analyzed by Covance, Inc., using a photometric chemistry analyzer (Hitachi 747-200; Roche Diagnostics, Indianapolis, IN). The frequency of sample collection was specified by each study protocol. In general, two samples were obtained prerandomization and after that, usually weekly for the first 6 weeks, and monthly or biweekly thereafter. In case of multiple glucose measurements for the same visit, only the maximum observation was considered. The analyses included all measurements up to and including the day after the last day of treatment.

3.2.2.3. Classification of Patients

Patients with missing glucose data (ie, only baseline glucose values) and those with preexisting diabetes at entry (clinical diagnosis of diabetes, taking antidiabetic medications at baseline [ie, insulin, sulfonylurea, metformin, thiazolidinediones, or alpha-glucosidase inhibitor], or two prerandomization glucose values of ≥200 mg/dL) were excluded from the analyses. Patients (n=27) with a single glucose measurement ≥200 mg/dL at entry were not excluded because these individuals lacked a confirmatory second value prior to drug assignment. A single glucose value of ≥200 mg/dL at entry was, however, considered suggestive of underlying dysglycemia in the assessment of preexisting risk factors for diabetes (see below).

Postbaseline random glucose values were used to classify or categorize patients as exhibiting: 1) treatment-emergent diabetes (TED), defined as two random glucose values ≥200 mg/dL at any time after baseline, or final glucose ≥200 mg/dL, or initiation of antidiabetic medication, or a new clinical diagnosis of diabetes; 2) uncertain glucose tolerance (UGT), defined as two or more random glucose values ≥140 mg/dL but one or no glucose values ≥200 mg/dL at any time prior to endpoint; or 3) normal glucose tolerance (NGT).

A random glucose value of 140 mg/dL was chosen as the threshold for UGT based on several lines of evidence: 1) postprandial glucose levels of individuals with normal glucose tolerance rarely exceeds 140 mg/dL (ADA 2000a); 2) individuals with glucose values 140 mg/dL or greater in a standard 2-hour oral glucose tolerance test (OGTT) are considered to have impaired glucose tolerance (ADA 2002a); and 3) random capillary glucose values 140 mg/dL or higher, have reasonable sensitivity (62% to 65%) and specificity (95% to 96%) for identifying individuals with diabetes confirmed by OGTT or fasting blood sugar (FBS) (Rolka et al. 2001).

3.2.2.4. Categorical Risk Factors

Patients possessing one or more of the following risk factors for diabetes at baseline were identified: age ≥45 years, baseline BMI ≥27 kg/m2, non-Caucasian ethnicity, hypertension based on clinical diagnosis or use of anti-hypertensive medication, or random glucose levels suggestive of underlying dysglycemia (eg, single prerandomization glucose ≥200 mg/dL [ADA 2002]). Height was available for BMI calculation for ~80% of the patients. Where BMI was not available, patients were considered to be non-obese.

3.2.2.5. Statistical Methods

Data were pooled from 24 studies for these analyses. The prevalence of baseline risk factors within the TED versus the NGT group were compared by Fisher's exact test. Imbalance in risk factors that are continuous variables such as age, mean baseline glucose, maximum baseline glucose, and baseline BMI were tested by F-test. Weight gain was analyzed by a last observation carried forward (LOCF) method. To account for variation in observation times for individual therapy groups, a time-to-event analysis using the Cox proportional hazards model was employed to assess the risk of TED. Specifically, the Cox model assessed the impact of mean random glucose or the presence of preexisting risk factors for diabetes on the subsequent risk of being identified with TED. The Cox proportional hazards model was also used to assess the impact of weight gain and therapy assignment on the risk of being identified with TED versus "not TED" (UGT plus NGT cohorts). Due to the small number of events in individual therapy groups, the therapy effect was compared between olanzapine and non-olanzapine groups including haloperidol, risperidone, or placebo. Unless otherwise specified, the Cox proportional hazards model included a single test covariate (baseline mean random glucose, baseline risk factors for diabetes, treatment-emergent weight gain, or therapy) along with study protocol. Study protocol was also included as a stratification variable in the model to control for effects of pooling multiple clinical trials.

3.2.3. Results

3.2.3.1. Categorization of Patients

Of the 5529 patients enrolled, 149 patients were identified with preexisting diabetes and were excluded from the TED analysis. Postrandomization glucose values were available for 5013 patients not known to be diabetic by diagnosis or prerandomization glucose values (shown in Table 3.5). The majority (60%) of these patients received olanzapine, followed by haloperidol (24%), risperidone (8%), placebo (4%), and clozapine (4%). The mean postrandomization observation time was 205 ± 283 days (median 86 days), with the maximum observation time of 1775 days, but varied among the individual therapy assignments.

Postrandomization, most patients (n=4637, 92.5%) appeared to maintain normoglycemia and were considered to possess NGT. Of the remaining patients, 94 (1.9%) were identified with TED and 282 (5.7%) exhibited an intermediate level of hyperglycemia and were considered to possess UGT.

Table 3.5. Postrandomization Glycemic Categories Shown as Number of Patients and Percentage of Patients Randomized at Study Entry

Therapy	Number of subjects	Post Randomization Glycemic Category			
		Normal Glucose Tolerance (NGT)	Uncertain Glucose Tolerance (UGT)	Treatment-emergent Diabetes (TED)	Median of days of Observation Time (maximum)
Olanzapine	3068	2799 91.2%	198 6.4%	71 2.3%	123 (1775)
Haloperidol	1164	1122 96.4%	33 2.8%	9 0.8%	43 (861)
Risperidone	364	346 95.0%	13 3.6%	5 1.4%	169 (804)
Clozapine	211	172 81.5%	33 15.6%	6 2.8%	121 (202)
Placebo	206	198 96.1%	5 2.4%	3 1.4%	32 (555)
Total	5013	4637 92.5%	282 5.6%	94 1.9%	86 (1775)

Note: Median and maximum observation time is shown in days.

3.2.3.2. Risk Factors for Treatment-Emergent Diabetes

3.2.3.2.1. Risk Factors at Study Entry

At study entry, mean random glucose levels for TED patients were significantly higher than for NGT patients (Table 3.6). Further comparisons of TED and NGT patients demonstrated that at study entry, patients subsequently identified with TED were significantly older, more obese and, more likely to be hypertensive, non-Caucasian, or have baseline dysglycemia (eg, single baseline glucose ≥200 mg/dL) than NGT patients.

Table 3.6. Entry Characteristics of Patients

Characteristic	Glycemic Category				
	TED (N=94)	**UGT (n=282)**	**NGT (N=4637)**	**p-Value TED vs NGT**	**p-Value UGT vs NGT**
Mean entry glucose (mg/dL ± SD)	127.4 ± 36.3	108.3 ± 23.0	94.1 ± 16.2	<.001	<.001
Age (years ± SD)	44.4 ± 10.3	42.4 ± 11.4	37.1 ± 10.8	<.001	<.001
Body Mass Index (kg/m^2 ± SD)	31.5 ± 6.4	28.1 ± 5.6	25.8 ± 5.3	<.001	<.001
Hypertension (% patients)	23%	15%	9%	<.001	0.002
Non-Caucasian Ethnicity (% patients)	38%	21%	27%	0.026	0.027
Baseline Dysglycemia (% patients)	10%	2%	0.3%	<.001	0.003

Abbreviations: NGT = normal glucose tolerance TED = treatment-emergent diabetes;
UGT = uncertain glucose tolerance.

Over half (61%) of the patients subsequently identified with TED had mean glucose values ≥110 mg/dL and over 30% had values ≥140 mg/dL at entry (Figure 3.8). In comparison, 13% of NGT patients had mean glucose values ≥110 mg/dL at entry and only 1.5% had values ≥140 mg/dL.

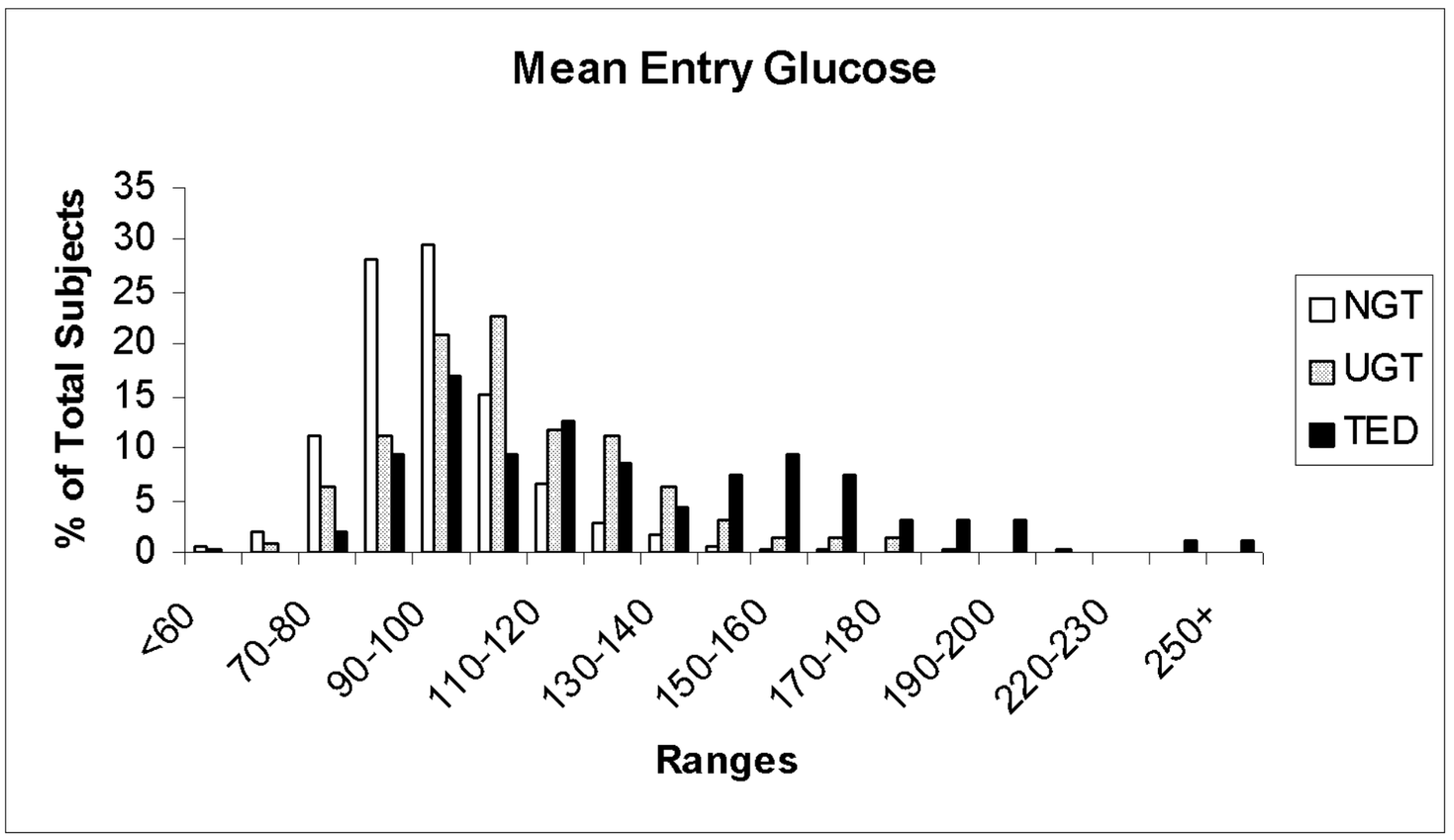


Figure 3.8. Distribution of mean random glucose levels at baseline for the three postrandomization glycemic categories.

As shown in Figure 3.9, 64% of TED patients possessed multiple risk factors for diabetes compared to 21% of NGT patients.

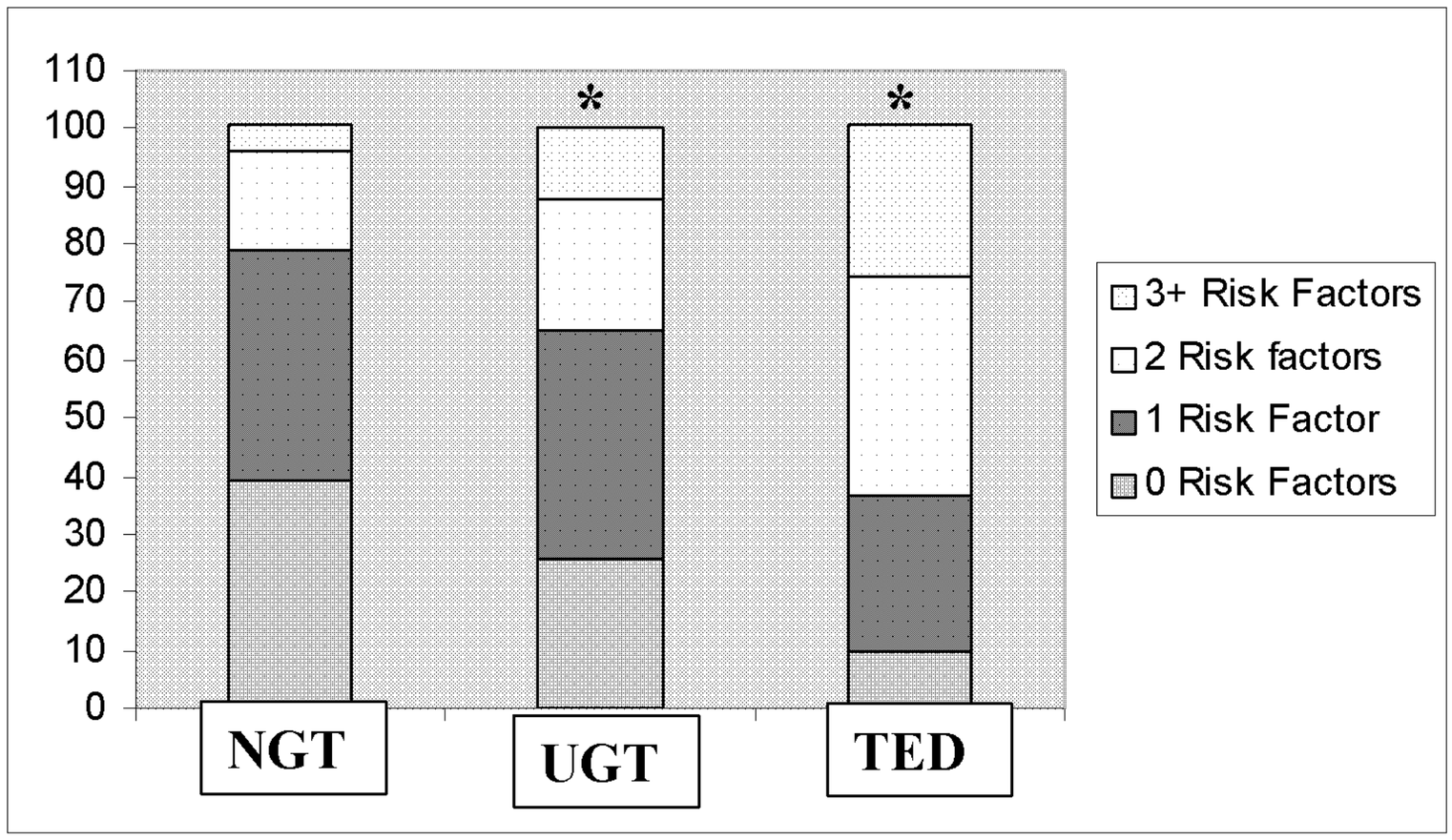


Figure 3.9. **Percentage of patients within each postrandomization glycemic category identified with designated number of baseline risk factors for diabetes.**

Baseline characteristics (Table 3.7) of patients subsequently identified with TED demonstrated that substantial numbers possessed mean baseline random glucose levels ≥140 mg/dL or multiple preexisting risk factors for diabetes in each of the individual treatment groups.

Table 3.7. Number (and Percentage) of Treatment-Emergent Diabetes Patients with Mean Entry Glucose Values ≥140 mg/dL or ≥2 Preexisting Risk Factors within Each Treatment Group

Treatment (N)	Mean Entry Glucose ≥140 mg/dl n (%)	≥2 Pre-existing Risk Factors n (%)
Olanzapine (71)	25 (35%)	44 (62%)
Haloperidol (9)	3 (33%)	5(55%)
Clozapine (6)	2 (33%)	5 (83%)
Risperidone (5)	2 (40%)	4 (80%)
Placebo (3)	2 (67%)	2 (67%)
Total (94)	34 (33%)	60 (64%)

Approximately half of the cases of TED were identified within 3 months of trial entry. For these "early" TED patients, the mean entry glucose was 142.9 ± 38.9 mg/dL and 71% possessed at least two risk factors for diabetes at entry.

As expected, entry mean random glucose had a highly significant impact on the risk of TED. The risk of being identified with TED was markedly greater for patients with mean entry random glucose ≥140 mg/dL (HR 31.9; 95% CI=19.6-52.0; p<.001) compared to those with lower glucose levels. Even at lower entry glucose levels the risk for TED was markedly increased. For example, for patients with mean random glucose ≥120 mg/dL (Figure 3.10), the risk of TED was nearly 12 times greater compared to patients with baseline glucose levels <120 mg/dL (HR 11.85; 95% CI=7.7-18.3; p<.001). Further, the risk for TED was 9 times greater for patients with entry mean random glucose ≥110 mg/dL (HR 9.57; 95% CI=6.18-14.82; p<.001).

The presence of baseline risk factors for diabetes (age, BMI, non-Caucasian ethnicity, hypertension, and dysglycemia) also had a highly significant impact on the risk of being identified with TED. Without adjusting for entry random glucose in the Cox model, patients with 2 or more risk factors at entry were nearly 6 times more likely to be identified with TED (HR 5.7; 95% CI=3.6-9.0; p<.001) than those with 1 or fewer risk factors.

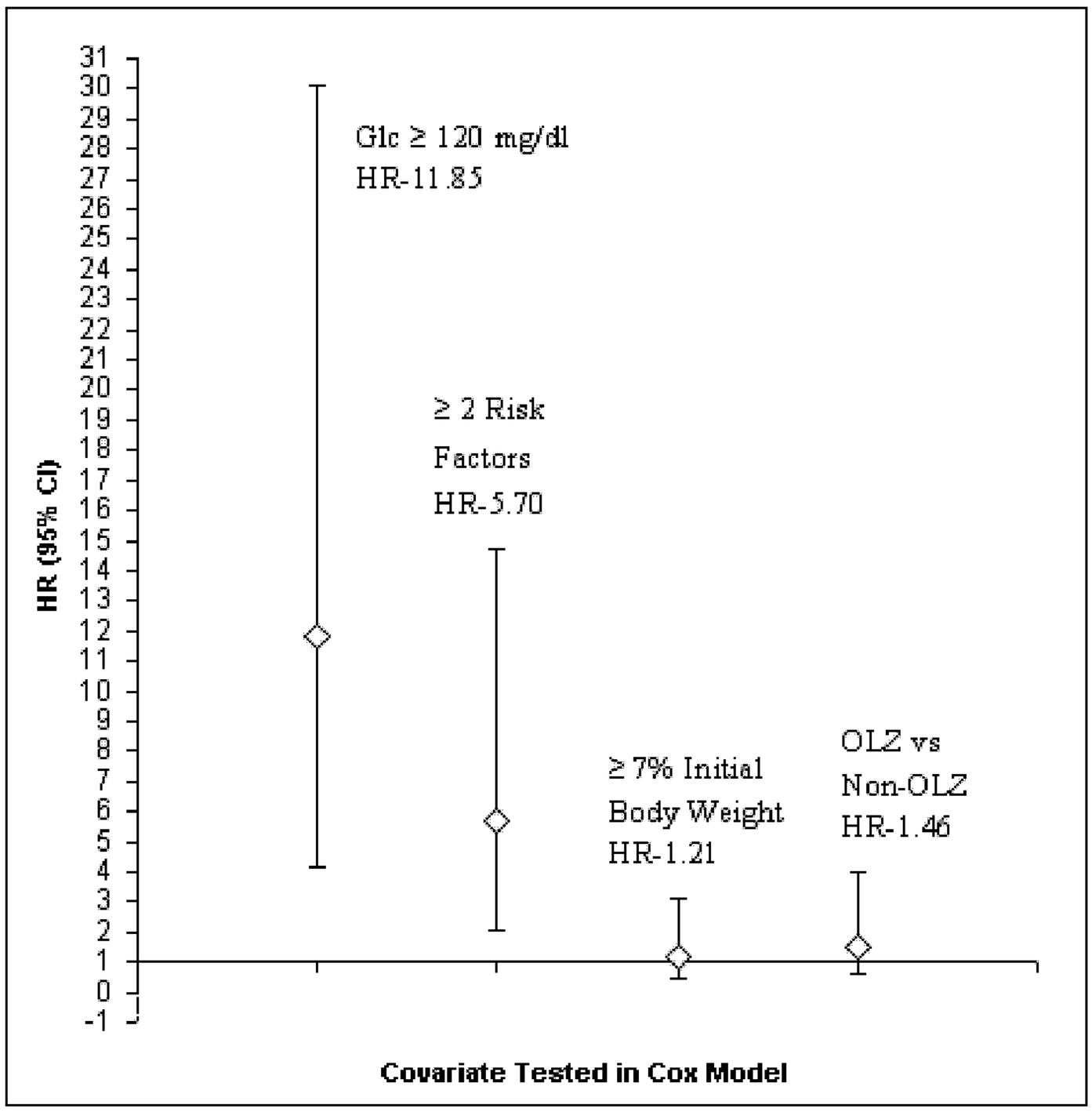


Figure 3.10. HR from Cox proportional Hazards Model evaluating the risk for TED.

Figure 3.11 illustrates the interaction between entry mean random glucose and number of preexisting diabetes risk factors. Among patients with entry glucose values ≥140 mg/dL and 2 or more baseline risk factors for diabetes, 40% (26 out of 64 patients) were identified with TED. In contrast, less than 1% (26 out of 3795) of patients with ≤1 risk factor and an entry glucose <140 mg/dL were identified with TED during the observation period. Furthermore, for patients with mean entry glucose <140 mg/dL, the likelihood of being identified with TED was greater if multiple (two or more) baseline risk factors were present; 3.2% (34 out of 1068) of patients with normal glucose and multiple risk factors were identified with TED.

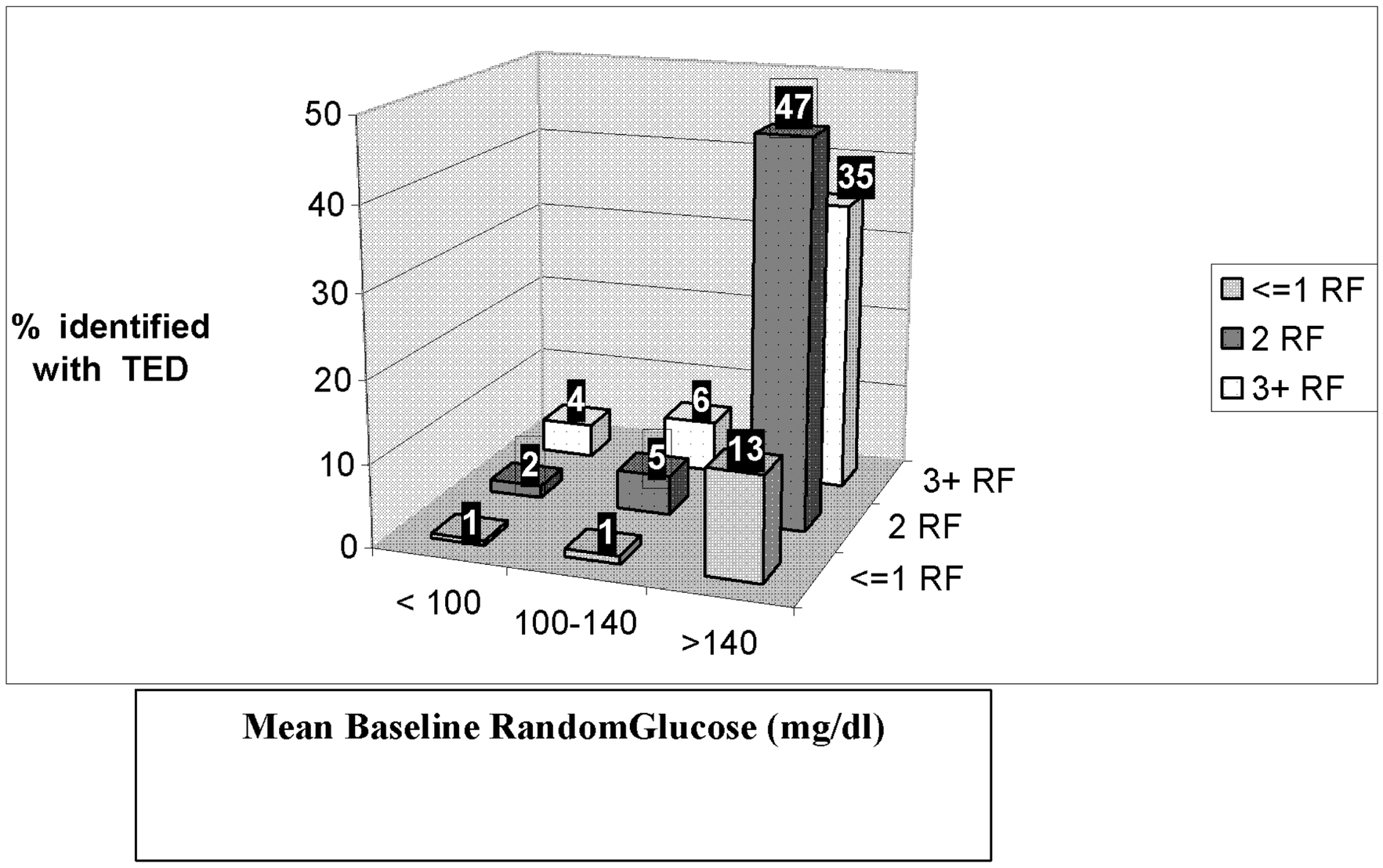


Figure 3.11. Interaction between baseline mean random glucose and preexisting risk factors for diabetes.

Of the 94 TED patients, 9 appeared to lack risk factors for diabetes at study entry. However, within this subgroup, detailed review revealed that 7 patients were overweight (BMI 26.5 to 26.9 kg/m^2 or weight >260 lbs), over 35 years of age, or had questionable random glucose levels (range, 140 to 180 mg/dL) at entry. The 2 remaining patients experienced substantial weight gain (>13 kg) prior to identification with TED.

A subset of patients (n=282) with repeated postrandomization glucose levels ≥140 mg/dL, but insufficient hyperglycemia to meet criteria for TED, were identified. This appeared to be a heterogeneous group in terms of glycemic control. Because confirmatory testing data (eg, fasting glucose or OGTT) were not available to more precisely define glycemic status, these patients were considered to possess uncertain glucose tolerance (UGT) and were analyzed separately.

Overall, this group possessed entry characteristics (Table 3.6) and risk factor profiles (Figure 3.11) intermediate to those of the TED and NGT groups. At study entry, the mean glucose value of UGT patients was significantly higher than NGT patients and 37% of the UGT patients had entry glucose values ≥110 mg/dL, with 7% ≥140 mg/dL (Table 3.6 and Figure 3.8). The number and percentage of patients identified with UGT with mean entry random glucose ≥140 mg/dL or with 2 or more baseline risk factors for diabetes are presented in Table 3.8 for individual therapy groups.

Table 3.8. Number (and Percentage) of Patients Identified as UGT with Mean Entry Glucose Values ≥140 mg/dL or ≥2 Preexisting Risk Factors within Each Treatment Group

Treatment	Mean Entry Glucose, ≥ 140 mg/dl n (%)	≥ 2 Pre-existing Risk Factors n (%)
Olanzapine (198)	17 (9%)	76 (38%)
Haloperidol (33)	1 (3%)	12 (36%)
Clozapine (33)	3 (9%)	5 (15%)
Risperidone (13)	3 (23%)	5 (38%)
Placebo (5)	0 (0%)	2 (67%)
Total (282)	24 (8%)	99 (35%)

3.2.3.2.2. Postrandomization Risk Factors

Weight gain is an established risk factor for diabetes (Chan et al. 1994; Colditz et al. 1995). Patients identified with TED gained more weight than NGT patients (3.95 kg versus 2.7 kg, baseline to endpoint). However, observation times were longer for TED patients compared to the overall NGT group (data not shown). To adjust for differences in observation time, a time to event analysis was performed using a Cox proportional hazards model (Figure 3.10). In this analysis, the impact of weight gain as a categorical covariate on the risk of being identified with TED did not achieve statistical significance (without adjusting for baseline glucose or number of preexisting risk factors). The relative risk (HR) of being identified with TED was 1.21 (95% CI=0.77-1.90; p=.4143) for patients that gained ≥7% of their initial body weight (IBW). The risk of TED for patients receiving olanzapine versus non-olanzapine interventions was also assessed using the Cox proportional hazards model (Figure 3.10). As there were relatively few TED events in individual non-olanzapine treatment groups, the risk of TED was evaluated between patients receiving olanzapine and a pooled cohort of patients receiving other interventions (haloperidol, risperidone, and placebo, but not clozapine; see Table 3.5). In the Cox model (without adjusting for baseline random glucose, baseline number of risk factors, or weight gain), the risk for TED was not significantly different between patients receiving olanzapine versus non-olanzapine (HR 1.46; 95% CI=0.83-2.57; p=.1863).

In a separate analysis that included baseline glucose, number of baseline risk factors, and weight gain as continuous covariates in the Cox proportional hazards model, the risk for TED was not significantly different between the olanzapine and non-olanzapine treatment groups (p=.2200). In this multivariate analysis, both baseline glucose and number of preexisting risk factors remained highly significant covariates (p<.001), while weight gain (as a continuous covariate) was not significant (p=.3111).

3.2.4. Discussion

In this retrospective analysis of a large clinical trial database of patients with schizophrenia, 94 cases of TED (~2% of the patient population) were identified. At entry into the clinical trials, patients subsequently identified with TED possessed significantly higher random plasma glucose levels and were much more likely to possess multiple risk factors for diabetes than patients who maintained NGT. In general, TED patients were significantly older, more obese, and more likely to be non-Caucasian, hypertensive, or have random glucose levels suggestive of preexisting dysglycemia (eg, single prerandomization glucose greater than 200 mg/dL) at study entry than did patients who appeared to maintain normal glucose levels (NGT patients). Results of this analysis suggest that many of the patients with schizophrenia who were identified with TED were likely to have preexisting unrecognized glycemic abnormalities or possessed a greater burden of preexisting risk factors for diabetes than did patients who appeared to maintain normoglycemia.

The mean random plasma glucose at entry was higher (~100 mg/dL) in clinical trials of patients with treatment-refractory schizophrenia (eg, studies of olanzapine versus clozapine) than observed in any of the other comparator studies (mean baseline random glucose range 93 to 96 mg/dL). The significance of this finding must be considered when evaluating the numerically higher incidence of TED in the clozapine group.

Weight gain has been established as a risk factor for diabetes (Chan et al. 1994; Colditz et al. 1995), yet reports have failed to demonstrate an association between weight gain and new-onset diabetes temporally associated with atypical antipsychotic medications (Henderson 2002). In the current analysis, although patients identified with TED gained slightly more weight than those who maintained NGT, weight gain during the trials did not have a statistically significant effect on the risk for TED. It should be noted that evaluation of the relationship between weight gain and risk of diabetes may be confounded if significant numbers of individuals with unrecognized preexisting diabetes are present (Wannamethee and Shaper 1999). Even among individuals without preexisting diabetes but who are at high risk for the disorder, it may be difficult to measure a significant impact of further weight gain (Wannamethee and Shaper 1999).

In the current analysis, a substantial number of TED patients appeared to have a high likelihood of underlying glucose abnormalities or to possess multiple risk factors for diabetes at baseline (eg, ~1/3 of the TED group possessed mean entry random plasma glucose values ≥140 mg/dL and ~2/3 possessed 2 or more baseline risk factors). This, coupled with the relatively short duration of observation, may have contributed to the nonsignificant impact of weight gain in the Cox proportional hazards analysis.

In this analysis, treatment with olanzapine was not associated with a significantly different risk for TED compared to non-olanzapine treatment. However, retrospective analyses have inherent limitations, and several limitations specific to the current study warrant discussion. Random glucose measurements have limited sensitivity for detecting diabetes (Rolka et al. 2001). Consequently, the current analysis likely represents a minimal estimate of the number of cases of TED. Inclusion of the UGT postrandomization category may ameliorate this limitation to some extent in terms of the descriptive findings; however, without definitive diagnostic testing, limited conclusions regarding the true frequency of abnormal glycemic events can be drawn from this heterogeneous group. The clinical trials database also lacked information for a number of important risk factors for diabetes as this data was not collected in a systematic fashion. Therefore, the risk factor assessment may well represent an under-estimate of the true preexisting risk burden. In addition, evaluation of between-group comparisons for patients receiving different treatments were limited by differences in sample sizes and duration of observation.

It must also be acknowledged that reasonable alternative classification paradigms for identifying patients with TED or UGT could be employed. Finally, a major limitation is that the clinical trials were not intended to assess risk factors for diabetes or to look for treatment-emergent diabetes, and caution is warranted when extrapolating results of this analysis to a more general practice setting.

3.2.5. Conclusions

Overall, results of this analysis suggest that many of the patients with schizophrenia who were identified with TED were likely to have preexisting unrecognized glycemic abnormalities or possessed a greater burden of preexisting risk factors for diabetes than did patients who appeared to maintain normoglycemia. Treatment-emergent weight gain or therapy assignment appeared to have a relatively smaller impact on the short-term risk of TED.

3.3. Analysis of Postmarketing Spontaneous Adverse Events in Lilly Clintrace Database

A search of postmarketing spontaneous adverse events in the Lilly Clintrace database identified all adverse event reports of possible hyperglycemia or diabetes mellitus during treatment with commercially marketed olanzapine through 31 March 2002. Table 3.9 shows the MedDRA preferred terms used for this search. The scope of the search was intentionally broad in order to include all possible adverse event reports possibly suggestive of a glucose dysregulation adverse event.

Table 3.9. MedDRA Search Terms for Postmarketing Glucose Dysregulation Adverse Events Lilly Clintrace Database 31 Mar 2002 Data Cutoff

Diabetic Ketoacidosis	Diabetes Mellitus Non Insulin-dependent	Diabetic Complication NOS
Ketoacidosis	Gestational Diabetes	Hyperglycaemia NOS
Ketosis	Glucose Tolerance Impaired in Pregnancy	Blood Glucose Increased
Ketonuria	Diabetes Mellitus NOS	Blood Glucose Abnormal
Metabolic Acidosis NOS	Insulin Resistant Diabetes	Blood Glucose Fluctuation
Lactic Acidosis	Diabetes Mellitus Aggravated	Glucose Tolerance Decreased
Blood Lactic Acid Increased	Diabetes Mellitus Inadequate Control	Glucose Tolerance Impaired
Acetone Abnormal	Diabetes Mellitus Reactivated	Insulin Resistance
Acidosis NOS	Increased Insulin Requirement	Hyperinsulinemia
Non-Ketotic Hyperglycaemic-Hyperosmolar Coma	Glycosuria	Blood Insulin Increased
Diabetic Hyperglycaemic Coma	Glucose Urine Present	Blood Insulin C peptide Increased
Diabetic Coma NOS	Glucose Urine	Blood Insulin Abnormal NOS
Diabetes Mellitus Insulin-Dependent	Glycosylated Haemoglobin Increased	Blood Insulin C peptide Abnormal NOS
Insulin-requiring Type II Diabetes Mellitus		
Diabetes Mellitus Non Insulin-dependent		

Note: Search was performed 30 April 2002

A total of 945 adverse event reports were identified. Of these 945 reports, 38 adverse event reports failed to meet the criteria for a glucose dysregulation adverse event because the patient was found not to be receiving olanzapine at the onset of the reported adverse event, the patient was reported to have a peak glucose <126 mg/dL, or the report did not have a definitive MedDRA preferred-term identifier listed in the adverse event report and also lacked a description of a glucose dysregulation adverse event in the report narrative.

The remaining 907 adverse event reports were categorized as cases suggestive of hyperglycemia or diabetes mellitus. Out of these, a total of 716 adverse event reports were identified through clinical evaluation to be non-severe cases of glucose dysregulation, as they did not involve death, coma, or acidosis. The remaining 191 cases were identified to be potentially severe glucose adverse events involving death, coma, or acidosis. A detailed clinical evaluation was undertaken for these 191 potentially severe glucose adverse events. A majority (142/191) of these severe spontaneous adverse event reports ascertained to be cases of glucose dysregulation were confounded by the presence of definite other etiologic factors (54/191) or possible other etiologic contributing factors (88/191) known to affect glucose homeostasis (including risk factors for diabetes, concurrent medical conditions that have been established to affect glucose homeostasis, or concomitant treatment with drugs known be associated with glucose dysregulation). In 47/191 cases of potentially severe glucose adverse events, a lack of information in the adverse event report precluded the assessment of any etiologic factors.

For 2 cases out of 191, potentially severe glucose-related adverse events, no apparent etiology other than treatment with olanzapine was identified. Both these cases were nonfatal and resolved after discontinuation of olanzapine. The first case was reported as hyperglycemia (NOS) and ketoacidosis, with positive dechallenge following discontinuation of olanzapine. There were no previous medical problems or concurrent medications reported. The report stated that no concomitant medications or prior history of glucose dysregulation were present. Peak glucose levels were not reported. The second case was reported as panceatitis (NOS) and diabetic ketoacidosis, with positive dechallenge following discontinuation of olanzapine. Reported laboratory values were: lipase 2399 U/L, amylase 577 U/L, triglycerides 1441 mg/dL, peak glucose 517 mg/dL. The patient had risk factors for diabetes (non-caucasian ethnicity and dyslipidemia), and was reported as non-compliant with olanzapine use.

Out of 907 adverse event reports that were categorized as cases suggestive of hyperglycemia or diabetes mellitus, 48 reports of death were ascertained to be actual cases of glucose dysregulation. These cases underwent detailed clinical evaluation. All 48 cases were either confounded by the presence of definite or possible other etiologic contributing factors known to affect glucose homeostasis (including baseline risk factors for diabetes, medical conditions that have been established to affect glucose homeostasis, or concomitant treatment with drugs known be associated with glucose dysregulation), or a lack of information in the adverse event report precluded the assessment of any etiologic factor. In addition, the reported cause of death in 66.7% (32/48) of the death cases was either not diabetes- or glucose dysregulation-related, or the cause was unknown.

As of March 2002, approximately 9,070,000 patients had been treated with commercially marketed olanzapine. Thus, the reporting rate for the *total* of all adverse event categories of possible glucose dysregulation (907 reports) observed in temporal association with commercially marketed olanzapine was 0.01% (907 of 9,070,000). The reporting rate for all cases of potentially severe glucose adverse events involving death, coma, and/or acidosis (191 cases) was <0.01%.

In summary, cases of potentially severe spontaneous adverse events of glucose dysregulation involving death, coma and/or acidosis have been reported very rarely (<0.01%). Almost all of these severe adverse events (189/191 cases were either confounded by the presence of definite or possible other etiologic contributing factors, or a lack of information in the adverse event report precluded the assessment of any etiologic factor. Given the limitations of spontaneous adverse event data (eg, incomplete reporting of essential information; selective reporting based on literature or competitive marketplace activities; approximation of drug exposure calculations) definitive conclusions as to causality or actual incidence cannot be made on the basis of spontaneous adverse event reports.

A detailed report containing the finding described above, with detailed case summaries for the cases of potentially severe glucose dysregulation, is available upon request.

3.4. Lilly Analysis of FDA MedWatch Database

Under the Freedom of Information Act (FOIA), Lilly queried the FDA MedWatch database for spontaneous adverse events suggestive of glucose dysregulation reported during treatment with all atypical antipsychotics currently marketed in the US (clozapine, olanzapine, risperidone, quetiapine, and ziprasidone).

The most recent available adverse event information from the FDA database at the time the search was completed was for adverse event reports received through the end of September 2001. All *unique* MedDRA event terms in the MedWatch adverse event database for the five atypical antipsychotics were reviewed. A total of 41 MedDRA event terms were selected as suggestive of an adverse event (refer to list of MedDRA terms in Table 3.9). All adverse event reports coded with 1 or more of these terms were identified, and duplicate reports were identified for the MedDRA terms within the FDA MedWatch database in the same manner for all five drugs.

Using comparable Lilly proprietary algorithms based on drug utilization data, the patient-years of exposure for the five atypical antipsychotics were calculated and applied to an estimation of adverse event reporting rates. A comparison of the reporting rates of the total number of identified reports for patients treated with clozapine, olanzapine, quetiapine, risperidone, or ziprasidone are displayed in Table 3.10 below.

Table 3.10. Reporting Rate (Per 100,000 Patient-Years) for All Glucose Dysregulation-Related Reports
FDA MedWatch Database through 30 September 2001

	Clozapine[a]		Olanzapine		Quetiapine		Risperidone		
MedDRA Preferred Term	Freq	Reporting Rate	Freq	Reporting Rate	Freq	Reporting Rate	Freq	Reporting Rate	
Diabetic ketoacidosis	31	1.51	72	1.94	11	1.47	13	0.20	(
Ketoacidosis	31	1.51	32	0.86	1	0.13	18	0.27	(
Ketonaemia present	1	0.05	0	0.00	0	0.00	0	0.00	(
Ketonuria present	5	0.24	5	0.13	3	0.40	1	0.02	(
Metabolic acidosis NOS	7	0.34	14	0.38	7	0.93	8	0.12	(
Lactic acidosis	1	0.05	9	0.24	1	0.13	7	0.11	(
Blood lactic acid increased	0	0.00	2	0.05	0	0.00	0	0.00	(
Acetonaemia	0	0.00	0	0.00	0	0.00	0	0.00	(
Acetone increased	0	0.00	0	0.00	0	0.00	0	0.00	(
Acetone	0	0.00	1	0.03	0	0.00	0	0.00	(
Acidosis NOS	9	0.44	5	0.13	1	0.13	9	0.14	(
Blood pH decreased	0	0.00	2	0.05	0	0.00	1	0.02	(
Nonketotic hyperglycaemic-hyperosmolar coma	0	0.00	4	0.11	0	0.00	0	0.00	(
Diabetic hyperosmolar non-ketoacidosis	2	0.10	1	0.03	0	0.00	0	0.00	(
Diabetic hyperosmolar coma	0	0.00	3	0.08	0	0.00	0	0.00	(
Diabetic hyperglycaemic coma	4	0.19	2	0.05	1	0.13	0	0.00	(
Diabetic coma NOS	12	0.58	10	0.27	1	0.13	2	0.03	(

(continued)

Table 3.10. Reporting Rate (Per 100,000 Patient-Years) for All Glucose Dysregulation-Related Reports
FDA MedWatch Database through 30 September 2001 (concluded)

	Clozapine[a]		Olanzapine		Quetiapine		Risperidone		
MedDRA Preferred Term	Freq	Reporting Rate	Freq	Reporting Rate	Freq	Reporting Rate	Freq	Reporting Rate	
Diabetes mellitus insulin-dependent	16	0.78	5	0.13	0	0.00	2	0.03	(
Diabetes mellitus non insulin-dependent	27	1.31	10	0.27	2	0.27	4	0.06	(
Gestational diabetes	1	0.05	4	0.11	0	0.00	0	0.00	(
Diabetes mellitus NOS	143	6.96	63	1.70	11	1.47	54	0.82	1
Diabetes mellitus aggravated	17	0.83	11	0.30	2	0.27	13	0.20	2
Diabetes mellitus inadequate control	0	0.00	6	0.16	0	0.00	6	0.09	(
Glycosuria present	6	0.29	4	0.11	0	0.00	4	0.06	(
Glucose urine	0	0.00	0	0.00	0	0.00	0	0.00	(
Glycosylated haemoglobin increased	1	0.05	3	0.08	0	0.00	0	0.00	(
Diabetic complication NOS	0	0.00	1	0.03	0	0.00	0	0.00	(
Hyperglycaemia NOS	71	3.45	128	3.45	10	1.34	92	1.40	1
Blood glucose increased	8	0.39	34	0.92	6	0.80	7	0.11	1
Blood glucose abnormal	0	0.00	2	0.05	0	0.00	0	0.00	(
Glucose tolerance decreased	0	0.00	0	0.00	0	0.00	3	0.05	(
Glucose tolerance impaired	2	0.10	1	0.03	0	0.00	0	0.00	(
Insulin resistance	0	0.00	0	0.00	0	0.00	0	0.00	(
Blood insulin decreased	0	0.00	0	0.00	0	0.00	0	0.00	(
Totals	**395**	**19.22**	**434**	**11.70**	**57**	**7.61**	**244**	**3.72**	5
Total Patient-Years Exposure	***2,055,000***		***3,708,000***		***749,000***		***6,565,000***		2

Abbreviations: Freq = frequency; NOS = not otherwise specified.

[a] Only clozapine reports included from 1 Jan 1996 thru 30 Sep 2001, as clozapine utilization data was not available to Lilly for the period prior to 1 Jan 1996.

Note: Reports manually reviewed and duplicate reports were removed

Note: Reporting rate = frequency / total patient-years exposure

Table 3.11 show a comparison of the reporting rates of the total number potentially *severe* events of glucose dysregulation, including all MedDRA terms suggestive of presence of diabetic ketoacidosis or diabetic hyperosmolar states with or without coma for patients treated with clozapine, olanzapine, quetiapine, and risperidone. In contrast to Table 3.9, ziprasidone is not included in the following table because no such severe adverse events were reported to the FDA MedWatch database during treatment with this drug.

**Table 3.11. Reporting Rate (Per 100,000 Patient-Years)
Potentially Severe Events of Glucose Dysregulation
Suggestive of Diabetic Ketoacidosis or Diabetic Hyperosmolar States with or without Coma
FDA MedWatch Database through 30 September 2001**

	Clozapine[a]		Olanzapine		Quetiapine		Risperidone	
MedDRA Preferred Term	**Freq**	**Reporting Rate**	**Freq**	**Reporting Rate**	**Freq**	**Reporting Rate**	**Freq**	**Reporting Rate**
Diabetic Ketoacidosis	30	1.46	69	1.86	11	1.47	15	0.23
Ketoacidosis	31	1.51	32	0.86	1	0.13	19	0.29
Non-Ketotic Hyperglycemic-Hyperosmolar Coma	0	0.00	5	0.13		0.00	0	0.00
Diabetic Hyperosmolar Non-Ketoacidosis	2	0.10	1	0.03		0.00	0	0.00
Diabetic Hyperosmolar Coma	0	0.00	3	0.08		0.00	0	0.00
Diabetic Hyperglycemic Coma	4	0.19	1	0.03	1	0.13	0	0.00
Diabetic Coma NOS	12	0.58	10	0.27	1	0.13	2	0.03
Totals	**79**	**3.84**	**121**	**3.26**	**14**	**1.87**	**36**	**0.55**
Total Patient-Years Exposure	***2,055,000***		***3,708,000***		***749,000***		***6,565,000***	

[a] Only clozapine reports included from 1 Jan 1996 thru 30 Sep 2001, as clozapine utilization data was not available to Lilly for the period prior to 1 Jan 1996.

Note: Reports manually reviewed and duplicate reports were removed.

3.4.1. Summary of Lilly FDA MedWatch Database Analysis

This analysis of the FDA MedWatch database shows that postmarketing events of glucose dysregulation have been reported during treatment with all currently marketed atypical antipsychotic drugs. The total number of events was greatest during treatment with olanzapine, followed by clozapine, risperidone, quetiapine, and ziprasidone. However, when patient-years exposures were taken into consideration, the highest reporting rate was observed during treatment with clozapine, followed by ziprasidone, olanzapine, quetiapine, and risperidone. When only potentially severe events of glucose dysregulation (all MedDRA terms suggestive of diabetic ketoacidosis or diabetic hyperosmolar states with or without coma) were taken into consideration, the greatest reporting rate was observed during treatment with clozapine, followed by olanzapine, quetiapine, and risperidone.

In some instances, taking the number of drug exposures into consideration markedly affected the magnitude of differences observed between drug groups. For instance, the absolute number of events reported during treatment with olanzapine was approximately 8 times the total number of events reported during treatment with quetiapine. When only severe events of glucose dysregulation (all MedDRA terms suggestive of diabetic ketoacidosis or diabetic hyperosmolar states with or without coma) were taken into consideration, the absolute number of events in the olanzapine group was approximately 9 times greater than the quetiapine group. However, given that patient-years exposures to olanzapine were approximately 4 times greater than quetiapine, the reporting rate during treatment with olanzapine was only 1.5 times greater than quetiapine for total number of events, and 1.7 times quetiapine for severe events of glucose dysregulation.

The overall reporting rate for the olanzapine group was approximately 3 times greater than the lowest reporting rate in the analysis, which was observed with risperidone (11.7 versus 3.7). When only severe events of glucose dysregulation (all MedDRA terms suggestive of diabetic ketoacidosis or diabetic hyperosmolar states with or without coma) were taken into consideration, the reporting rate for the olanzapine group was approximately 6 times greater than the lowest reporting rate (risperidone) observed in the analysis (3.26 versus 0.55). In the context of the limitations of spontaneous event reporting, it is difficult to establish what magnitude of differences in reporting rates may point to a signal worthy of further evaluation.

Finally, spontaneous adverse event report rates can be very sensitive to small increases in the number of events with relatively limited numbers of drug exposures. This may explain the relatively high reporting rate observed in the ziprasidone group (17.24 on the basis of 5 events), second in magnitude only to the clozapine group (19.22 on the basis of 395 events).

3.4.2. Discussion and Conclusions of Lilly FDA MedWatch Database Analysis

The observed differences in reporting rates among patients treated with antipsychotics must be interpreted within the context of the known limitations of spontaneous report data, including the approximation of drug exposures on the basis of prescription data, and potential differences in reporting practices and reporting environment (Goldman 1998). Given these limitations, it is not possible to resolve whether the differences in reporting rates of the magnitudes observed in these analyses reflect substantial differences in the actual incidence or prevalence of events at the population level. In addition, differences in target patient populations (eg, differences in illness severity and chronicity; or use as first-break versus treatment-refractory schizophrenia) are important factors to consider when evaluating these data. It is also difficult to determine to what extent the increasing focus in the literature and in the competitive marketplace directed at the issue of diabetes (first with clozapine and later with olanzapine) may have effected the volume and patterns of reporting (Wallenstein and Fife 2001).

In summary, Lilly analyses of the FDA MedWatch database indicate that glucose-related events have been reported during treatment with all currently marketed atypical antipsychotics. Given the limitations of spontaneous adverse event reporting, these data cannot be used to make definitive conclusions in regard to causality or to differences in the incidence or prevalence of glucose-dysregulation events in patients who have been treated with atypical antipsychotics currently marketed in the US.

4. Summary of Previously Submitted Lilly Data

The following sections summarize previous data sent by Lilly to the FDA regarding olanzapine and glucose metabolism.

4.1. Study F1D-MC-HGIM – Effect of Antipsychotic Therapy on Glycemic Control: A Comparison of Olanzapine, Risperidone, and Placebo in Healthy Subjects

Study F1D-MC-HGIM was designed to determine if atypical antipsychotics have an acute direct effect on pancreatic beta cell function causing decreased insulin secretion. The hyperglycemic clamp, the "gold standard" for quantitating insulin secretion, was used for this study. Glucose is infused over an extended period of time, and plasma glucose is maintained in a hyperglycemic range that stimulates insulin secretion. Clamp studies are very sensitive instruments for detecting impaired capacity to secrete insulin in response to glucose challenge.

The study report for this trial was submitted to the FDA on 6 September 2001 as serial submission #791 to olanzapine IND 28,705. In post-hoc analyses, changes in study variables in the absence of weight gain were calculated from linear regression analyses with therapy and change in BMI as covariates (Sowell et al. 2002b, attached as Appendix A).

This study assessed insulin secretory capability as measured by changes (baseline to endpoint) in insulin levels during a hyperglycemic clamp in healthy subjects treated (15 to 17 days) with olanzapine 10 mg/day (n=17), in comparison to risperidone 4 mg/day (n=13) or placebo (n=18). Insulin secretion was quantitatively assessed at baseline and endpoint using the hyperglycemic clamp.

Weight increased significantly ($p<.01$) in both the olanzapine (2.8 ± 1.7 kg) and risperidone (3.1 ± 2.1 kg) treatment groups. Fasting insulin levels were also increased significantly ($p<.05$) compared to placebo during treatment with olanzapine (40%) or risperidone (36%). Fasting glucose was not changed in either active treatment group (Table 4.1).

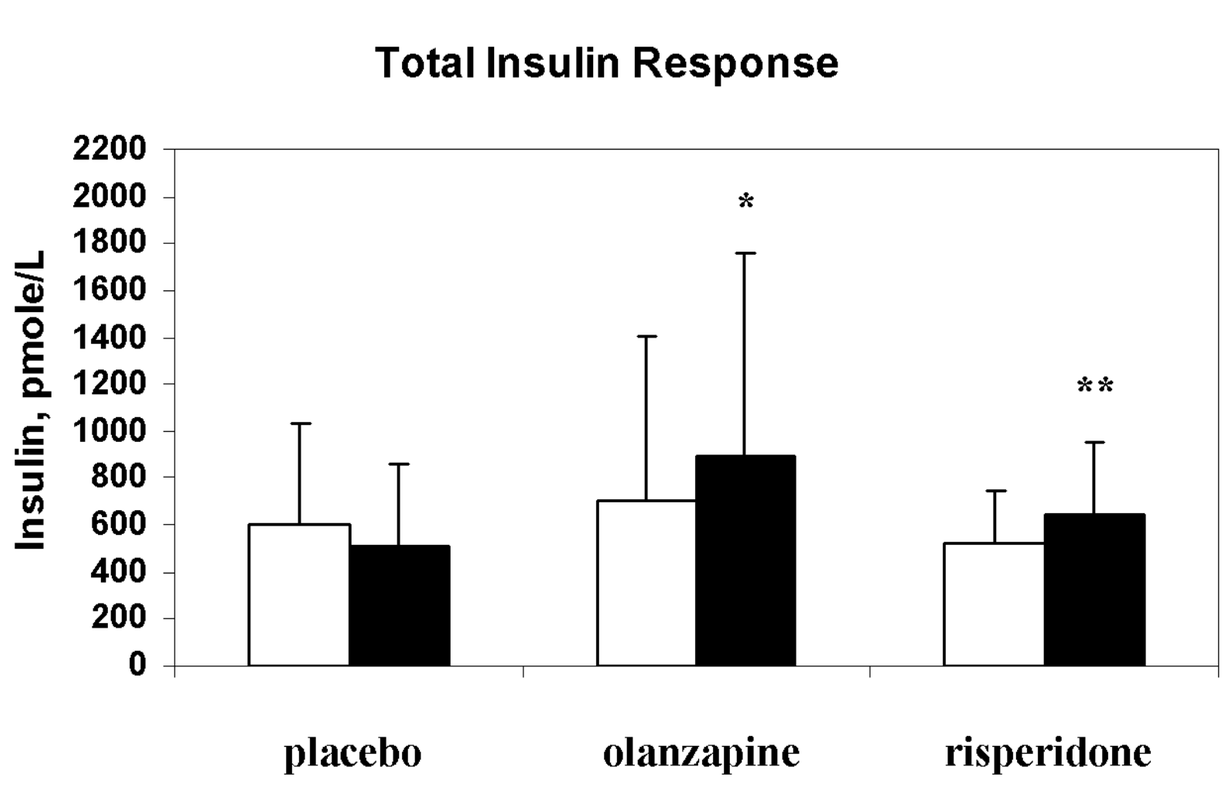
Table 4.1. Changes in Weight and Fasting Measures of Glucose and Insulin

Therapy Group	Weight (kg)	Glucose (mmole/L)	Insulin (pmole/L)
Olanzapine	2.8 (1.7)[a, *]	0.02 (0.53)	19.8 (54.6)[b, **]
Risperidone	3.1 (2.1)[a, *]	0.14 (0.44)	15.0 (28.2)[c]
Placebo	0.5 (1.2)	–0.08 (0.31)	–13.8 (17.4)

[a] p<.001 vs placebo
[b] p≤.02 vs placebo
[c] p<.05 vs placebo
*p<.01 within group
**p≤.04 within group

Within-individual baseline to endpoint change in weight and fasting values were calculated and results expressed as mean (standard deviation [SD]) for each therapy group.

Using the hyperglycemic clamp, an increase in the total insulin response to hyperglycemia was observed after treatment with olanzapine or risperidone. Further, the magnitude of the increase (~25%) in the total insulin response (weighted mean insulin level, 0 to 240 minutes) was similar for the active therapy groups (Figure 4.1).



Note: The total insulin response (TIR, 0 to 240 minutes,) to hyperglycemia was evaluated and is expressed as pmole/L insulin. Results from the baseline (white bars) and endpoint (black bars) hyperglycemic clamps are shown and are expressed as means (SD).
*p<.01 within-group; p<.001 vs placebo
**p=.054 within-group; p=.014 vs placebo

Figure 4.1. Total insulin response in patients treated with placebo, olanzapine, or risperidone.

Figure 4.2 illustrates the relationship between change in the total insulin response (TIR) during the hyperglycemic clamp and change in weight (BMI) during the study. Change in TIR was significantly correlated with BMI change (r=.5576, p=.019).

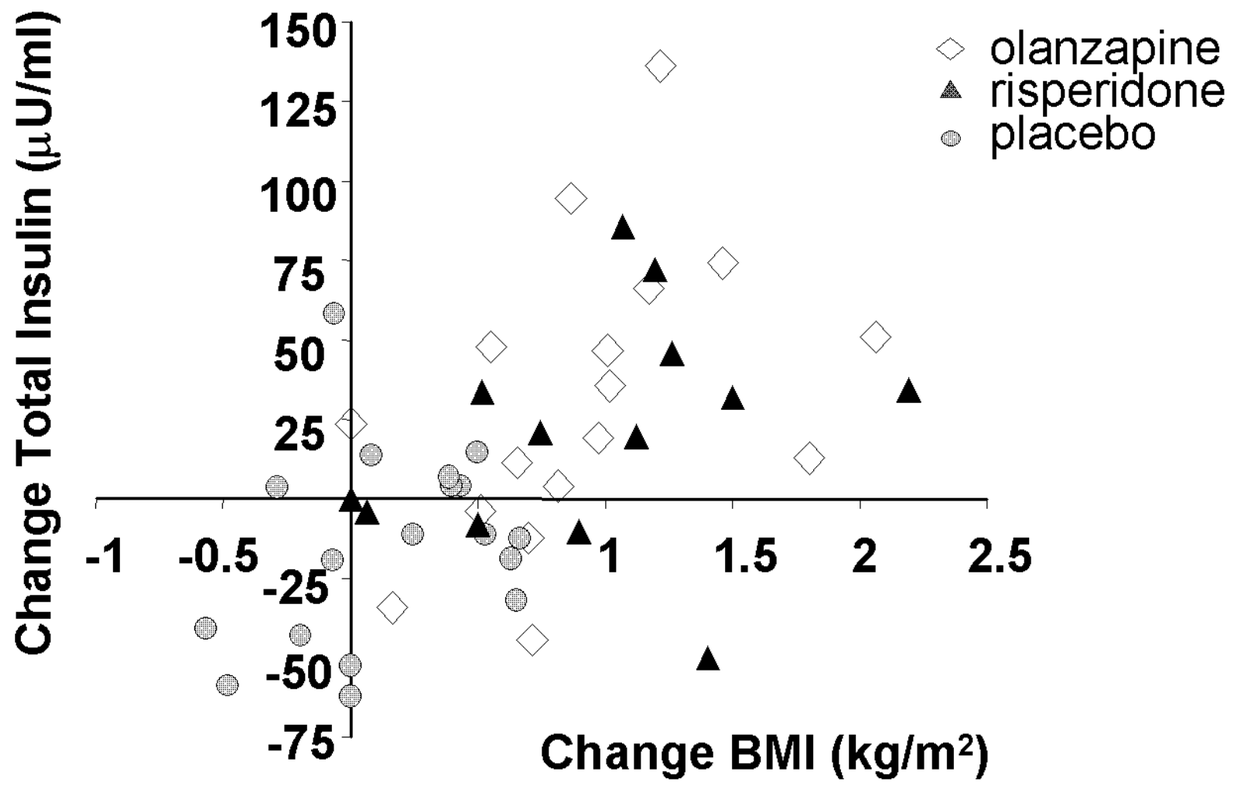


Figure 4.2. **Relationship between change in total insulin response and change in BMI. Values for individual subjects are shown.**

Further, using linear multivariate regression analysis (with BMI change = 0) to adjust for the impact of weight gain, no significant changes were observed in the olanzapine or risperidone groups for TIR, total C peptide response, fasting insulin, or the insulin sensitivity index (M/I) derived from steady-state measures during the hyperglycemic clamp (Table 4.2).

Table 4.2. Least Square (LS) Mean (SD) Change from Baseline to Endpoint Fasting Insulin, TIR, TCR, and M/I Where BMI Change = 0

Treatment Group	Change Fasting Insulin μU/mL	Change TIR μU/mL	Change TCR μU/mL	Change M/I
Olanzapine	0.4 (9.1)	7.1 (54.6)	-0.54 (5.86)	0.02 (0.14)
Risperidone	-0.6 (4.7)	-4.0 (51.8)	0.51 (5.57)	0.03 (0.13)
Placebo	-2.8 (2.9)	-18.6 (36.9) *	-0.32 (3.97)	0.03 (0.09)

Abbreviations: BMI = body mass index; M/I = insulin sensitivity index; SD = standard deviation; TCR = total C peptide response; TIR = total insulin response.
*p<.05 within-group

Limitations of this study are similar to those discussed for the euglycemic clamp (Section 3.1.4) and include a small number of individuals examined, a relatively short exposure time, and use of healthy volunteers rather than patients with psychiatric illnesses.

Results of this study found similar changes in body weight, fasting insulin, and insulin secretion during hyperglycemia in healthy volunteers treated with olanzapine or risperidone. An increase in total insulin response during the clamp was seen with both drugs and was most likely related to weight gain observed during therapy. Weight-related increases in insulin response and decreases in the insulin sensitivity index calculated from steady-state measures during the hyperglycemic clamp were observed and are consistent with the known effects of weight gain and short-term overfeeding on glucose and insulin homeostasis. However, after accounting for the impact of weight gain in linear regression analyses, results of this study do not suggest that subjects treated with olanzapine or risperidone experienced decreased insulin or C peptide responses during the hyperglycemic challenge.

In summary, results of this study did not suggest an acute weight-independent effect of olanzapine or risperidone to decrease insulin secretion or insulin sensitivity during a prolonged hyperglycemic challenge (15 to 17 days of treatment) in healthy subjects. These results are in contrast to a decrease in insulin secretion that has been noted in healthy volunteers and pregnant women after short exposure (3 to 7 days) to therapeutic doses of oral diphenylhydantoin (Draznin et al. 1977; Spellacy et al. 1975).

4.2. Analysis of Integrated Clinical Trial Database

In a manuscript included with Lilly's May 2001 hyperglycemia update to the FDA, Lilly presented a retrospective analysis of pooled data from olanzapine-integrated database, which included double-blind, randomized, direct-comparator-controlled olanzapine clinical trials of schizophrenia-spectrum disorders (Allison et al.).

These analyses compared the mean change in random plasma glucose, which was measured periodically during head-to-head clinical trials of olanzapine in patients with schizophrenia over an observation period of 18 to 52 weeks. Mean random glucose increases of 0.8 to 4.6 mg/dL were observed in olanzapine-treated patients. This increase was significantly more than that observed with haloperidol or placebo, not significantly different from that seen with risperidone, and significantly less than observed with clozapine. These analyses controlled for a number of factors, including age, time of exposure to antipsychotic therapy, baseline BMI, baseline glucose, and change in BMI during treatment (Table 4.3).

Table 4.3. Mean* Change in Baseline to Endpoint Random Blood Glucose Concentrations

	Mean Change ± S.E. (mg/dL)				
Database	**Olz**	**Comp**	**d.f.**	**F**	**p-value**
Haloperidol-controlled	4.56 ± 0.57	0.22 ± 0.93	1	20.47	0.0001
Placebo-controlled	0.77 ± 1.12	-1.28 ± 1.5	1	8.68	0.0035
Risperidone-controlled	4.51 ± 1.79	2.58 ± 1.12	1	3.50	0.0626
Clozapine-controlled	3.17 ± 1.36	13.22 ± 2.19	1	16.48	0.0001

*Mean refers to least-squares mean.
Abbreviations: Comp = comparator; d.f. = degrees of freedom; F = f statistic; Olz = olanzapine; S.E. = standard error.

These analyses of the olanzapine-integrated clinical trial data indicate that, although greater than what was observed with haloperidol or placebo, increases in glucose during treatment with olanzapine were relatively small in magnitude across all databases, and were not significantly different from the mean glucose increase observed during treatment with risperidone. Overall, treatment-emergent glycemic changes were most pronounced in patients treated with clozapine, as indicated by a significantly greater mean glucose increase.

In a separate study (summarized in Section 3.2), the olanzapine-integrated schizophrenia clinical trial database was analyzed to evaluate the frequency and predictors of treatment-emergent diabetes during treatment with olanzapine, haloperidol, clozapine, risperidone, or placebo.

4.3. Cohort Studies

Lilly's May 2001 hyperglycemia update to the FDA provided results from two cohort studies of large prescription claim or health care practitioner databases:

- Analysis of data from the AdvancePCS prescription claims database to estimate the risk of developing diabetes during treatment with antipsychotic exposure relative to the general AdvancePCS patient population in the United States
- Analysis of data from the General Practice Research Database (GPRD) to determine the hazard ratio of diabetes in patients prescribed antipsychotics compared with the general adult population in the United Kingdom.

4.3.1. AdvancePCS Prescription Claims Database

A retrospective cohort study of diabetes during antipsychotic treatment was conducted using prescription claim data from the AdvancePCS database in the US covering the period from 1 December 1997 to 31 August 2000 (refer to manuscript in Appendix B).

The Advance Prescription Card Services (AdvancePCS) prescription claims database processes over 300 million prescription claims per year for over 50 million members covered by over 2000 employers and managed care plans within the US. This database was used to identify large cohorts of patients treated with antipsychotic monotherapy, regardless of indication. Prescription claims for antipsychotics were used to identify and select adult subjects that began antipsychotic monotherapy between 1 December 1998 and 29 February 2000. The AdvancePCS general patient population (N=5,816,473) included all adult AdvancePCS members who had made at least one prescription claim (other than an antipsychotic) between 1 January 2000 and 29 February 2000. Prescription claims for diabetes medications were used to identify subjects with diabetes. Those with antipsychotic prescription claim(s) 6 months prior to starting antidiabetic therapy, or those with antidiabetic prescription claims any time prior to starting antipsychotic therapy, were excluded. Cox proportional hazards regression (controlling for age and gender) was used to determine the hazard ratio (HR) of diabetes in the antipsychotic cohorts relative to the general PCS patient population and relative to other selected antipsychotic cohorts.

Results showed that compared to the general AdvancePCS patient population, the incidence of diabetes was substantially increased in both the conventional and atypical antipsychotic groups (Table 4.4).

Table 4.4. Incidence and Hazard Ratio of Diabetes in Patients During Treatment With Antipsychotics

COHORT	No. of new cases	No. of patients	No. of patient-years	Incidence (per 1000 patient-years)		Hazard ratio[a]		
				Rate	95% CI	Ratio	95% CI	p-value
CONVENTIONAL ANTIPSYCHOTICS								
All combined	307	19,782	3,645.57	84	75 - 94	3.5	3.1 - 3.9	≤.0001
Haloperidol	133	8,476	1,568.39	85	70 - 100	3.1	2.6 - 3.7	≤.0001
Thioridazine	62	3,133	654.28	95	71 - 119	4.2	3.2 - 5.5	≤.0001
ATYPICAL ANTIPSYCHOTICS								
All combined	641	38,969	9,571.18	67	62 - 72	3.1	2.9 - 3.4	≤.0001
Clozapine	7	277	103.95	67	16 - 118	3.3	1.4 - 8.0	0.0070
Olanzapine	194	13,863	3,374.57	58	49 - 66	3.0	2.6 - 3.5	≤.0001
Quetiapine	40	4,196	1,025.75	39	27 - 51	1.7	1.2 - 2.4	0.0020
Risperidone	400	20,633	5,066.90	79	71 - 87	3.4	3.1 - 3.8	≤.0001
GENERAL PATIENT POPULATION								
	45,513	5,816,473	2,908,236.5	15.7	15.5-15.8	--	--	--

Abbreviations: CI = Confidence Interval; No. = number.

[a] Cox proportional hazards regression analysis adjusted for age, gender, and duration of antipsychotic exposure.

Note: HR and 95% CI values were rounded to first decimal place except where such rounding obscured significance cut-off points."

When the entire quetiapine cohort was analyzed, the risk of diabetes was lower (HR=.67; 95% CI=0.46–0.97; p=.033) (Table 4.6). However, this included patients treated with a range of doses, reflected in the relatively low mean quetiapine dose. When additional analyses were conducted comparing the 25% of subjects receiving the highest dose ranges (Q4, or 4th dose quartile) of each of the treatments being considered, the risk of diabetes was found to be comparable across all treatments, including quetiapine, and ranging between 3 to 4 times the risk observed in controls not receiving antipsychotic medications (Table 4.5).

Table 4.5. Hazard Ratios for Antipsychotic Cohort Dose Quartiles Relative to the AdvancePCS General Patient Population

Cohort [a]	Mean dose/quartile ± SD [b]	Mean age ± SD	Hazard ratio[c]		
			Ratio	95% CI	p-value
Conventional					
Haloperidol Q1	0.5 ± 0.3	77.1 ± 30.6	2.6	1.9 - 3.7	≤.0001
Q2	0.9 ± 0.3	75.8 ± 31.5	2.9	2.0 - 4.2	≤.0001
Q3	1.7 ± 0.7	72.6 ± 34.1	2.9	2.0 - 4.1	≤.0001
Q4	7.0 ± 17.5	61.5 ± 39.5	4.3	3.1 - 5.9	≤.0001
Thioridazine Q1	9.9 ± 6.3	66.1 ± 39.6	2.1	1.0 - 4.5	0.0453
Q2	20.1 ± 6.3	63.6 ± 38.8	3.0	1.7 - 5.4	≤.0001
Q3	37.3 ± 14.4	60.2 ± 37.9	2.9	1.6 - 5.2	0.0005
Q4	110.8 ± 151.1	54.9 ± 37.0	8.9	6.2 - 12.7	≤.0001
Atypical					
Olanzapine Q1	1.7 ± 0.9	60.1 ± 42.2	3.4	2.6 - 4.5	≤.0001
Q2	3.1 ± 0.7	55.0 ± 41.0	2.6	1.9 - 3.6	≤.0001
Q3	5.3 ± 2.0	53.4 ± 39.6	2.5	1.9 - 3.3	≤.0001
Q4	11.3 ± 9.8	50.0 ± 37.1	3.6	2.8 - 4.7	≤.0001
Risperidone Q1	0.4 ± 0.2	70.9 ± 40.6	3.7	3.0 - 4.5	≤.0001
Q2	0.7 ± 0.1	65.1 ± 43.5	3.0	2.4 - 3.8	≤.0001
Q3	1.1 ± 0.3	63.6 ± 43.0	3.0	2.5 - 3.7	≤.0001
Q4	2.5 ± 2.4	56.0 ± 42.2	4.0	3.3 - 4.8	≤.0001
Quetiapine Q1	17.0 ± 8.6	60.2 ± 40.7	1.8	0.9 - 3.4	0.0957
Q2	34.5 ± 11.3	57.1 ± 41.2	1.4	0.7 - 2.9	0.3347
Q3	64.5 ± 24.4	53.3 ± 37.8	0.6	0.2 - 1.8	0.3938
Q4	203.7 ± 245.1	49.8 ± 36.4	3.1	1.9 - 5.1	≤.0001

Abbreviations: CI = Confidence Interval; SD = Standard Deviation.

[a] The sample size of the clozapine cohort (277 subjects with 7 cases of diabetes) was too small for a meaningful quartile analysis.

[b] The 21 May 2001 submission to FDA contained errors in these numbers. The data herein are the corrected data.

[c] Cox proportional hazards regression analysis adjusted for age and gender.

Note: HR and 95% CI values were rounded to first decimal place except where such rounding obscured significance cut-off points."

Comparison between individual atypical antipsychotic cohorts and the haloperidol cohort revealed a statistically significant but small increase in risk of diabetes during treatment with risperidone (HR=1.2; 95% CI=1.0-1.5; p=.04), but not during treatment with olanzapine (HR=1.09; 95% CI=0.86-1.37; p=.479). The risk of diabetes in the quetiapine cohort was lower than the risk in the haloperidol cohort (HR=0.67; 95% CI=0.46-0.97; p=.033). On comparison of the olanzapine cohort relative to the risperidone cohort, no statistically significant difference in risk of diabetes was observed (HR=0.90; CI=0.76-1.07; p=.23 [data on file]). Please refer to Table 4.6 below.

Table 4.6. Hazard Ratio of Developing Diabetes Comparing Selected Antipsychotic Cohorts to Other Antipsychotic Cohorts

TREATMENT COHORT	No. of new cases	No. of subjects in cohort	Hazard ratio[a]		
			Ratio	95% CI	p-value
Atypical	641	38,969	0.97	0.84 - 1.11	0.626
vs Conventional	307	19,782	-	-	-
Clozapine	7	277	1.31	0.60 - 2.86	0.496
Olanzapine	194	13,863	1.09	0.86 - 1.37	0.479
Quetiapine	40	4,196	0.67	0.46 - 0.97	0.033
Risperidone	400	20,633	1.23	1.01 - 1.50	0.040
vs Haloperidol	133	8476	-	-	-

Abbreviations: CI = Confidence Interval; No. = number; vs = versus.

[a] Cox proportional hazards regression analysis adjusted for age, gender, and duration of antipsychotic exposure.

Note: HR and 95% CI values were rounded to first decimal place except where such rounding obscured significance cut-off points."

Limitations of this analysis of the AdvancePCS database include lack of information on psychiatric diagnosis; identification of incident cases of diabetes solely on the basis of prescription of antidiabetic medications; inclusion of all indications for antipsychotic prescriptions regardless of psychiatric illness spectrum or severity; a relatively short average duration of antipsychotic exposure (68 to 37 days); lack of information on risks for diabetes; lack of adjustment for concomitant use of other drugs that may be temporally associated with glucose dysregulation.

In summary, an increased risk of developing diabetes was observed in the AdvancePCS prescription claim patient cohorts during treatment with either conventional or atypical antipsychotics compared to a general reference population, with no substantial differences in risk of diabetes observed on direct comparison of the overall conventional and atypical antipsychotic cohorts or olanzapine and other atypical (including risperidone) cohorts.

4.3.2. United Kingdom General Practice Research Database (GPRD)

In this retrospective cohort study (Cavazzoni et al. 2002), data from the United Kingdom (UK) General Practice Research database (GPRD) was analyzed to determine the HR of diabetes for patients prescribed antipsychotics compared with the GPRD general patient population in the UK.

The study included a GPRD general patient population cohort, a combined antipsychotic cohort, and individual antipsychotic monotherapy cohorts. The GPRD general patient population cohort (N=269,049) consisted of a random sample of subjects registered continuously between 1 January 1996 and 31 December 1997 who had received at least one prescription for any medication other than an antipsychotic during this 2-year period. The study population was comprised of adults 18 years of age or older as of 1994, who were registered in standard general practices, and were prescribed an antipsychotic between 1 January 1994 and 31 December 1999. The combined antipsychotic cohort included patients exposed to either conventional or atypical antipsychotics (N=46,111). Individual antipsychotic cohorts were comprised of patients exposed to a single antipsychotic during the study period.

Any patient with a recorded diagnosis of type 1 or type 2 diabetes (as defined by one or more of the Oxford Medical Information System diagnostic codes for diabetes) or prescribed any antidiabetic agent was considered diabetic. Patients with a personal history of diabetes prior to the first prescription of antipsychotic(s) were excluded from the analysis.

A Cox proportional hazards regression model was used to determine the HR of diabetes development among the GPRD general patient population, combined antipsychotic, and individual antipsychotic cohorts. The covariates included in the model were age, gender, and the presence or absence of obesity.

Results showed that compared to the GPRD general patient population cohort, patients in the combined antipsychotic cohort (conventional and atypical antipsychotics combined) had a higher risk of developing diabetes (HR=1.5; CI=1.1-1.9; p=.007). The risk of diabetes in the combined atypical cohort was greater than the risk of diabetes in the conventional antipsychotic cohort (HR=2.6; CI=1.3-5.3).

The risk of developing diabetes during exposure to thioridazine (HR=1.5; CI=1.009-2.3; p=.045) and risperidone (HR=3.2; CI=1.4-7.1; p=.006) was significantly higher than that of the GPRD general patient population. Assessment of some individual antipsychotic cohorts, including the olanzapine cohort, was limited by small sample size (Table 4.7).

Table 4.7. Incidence and Hazard Ratio of Diabetes in Patients During Treatment With Antipsychotics

Cohort	No. of new cases	No. of patients	Mean days of exposure (SD)	No. of patient-years	Incidence (per 1000 patient-years)		Hazard ratio		
					Rate	95% CI	Ratio	95% CI	
All antipsychotics combined[b]	170	46,111	156 (244)	19,720	8.6	7.3 - 9.9	1.5	1.1 - 1.9	
CONVENTIONAL ANTIPSYCHOTICS									
Thioridazine only	56	15,008	175 (245)	7,172	7.8	5.7 - 9.9	1.5	1.009 - 2.3	
Fluopenthixol only	13	7,950	116 (174)	2,538	5.1	2.3 - 8.0	0.86	0.4 - 2.0	
Trifluoperazine only	12	3,848	159 (250)	1,675	7.2	3.0 - 11.3	1.2	0.5 - 3.0	
Chlorpromazine only	5	3,294	128 (217)	1,156	4.3	0.5 - 8.2	0.37	0.05 - 2.6	
Haloperidol only	13	3,550	109 (178)	1,059	12.3	5.5 - 19.1	1.6	0.7 - 4.0	
ATYPICAL ANTIPSYCHOTICS									
Risperidone only	16	1,702	229 (296)	1,067	15.0	7.5 - 22.5	3.2	1.4 - 7.1	
Olanzapine only	2	528	194 (188)	279	7.2	0 - 17.3	2.0	0.3 - 14.5	
GENERAL PATIENT POPULATION									
	1,589	269,049	--	430,892	3.7	3.4 - 4 .0	1.0	--	

Abbreviations: CI = Confidence Interval; No. = number; SD = Standard Deviation.

[a] Results from Cox proportional hazards analyses with age, gender, and obesity as covariates. Reference group was the general patient population cohort. Three age categories were included as a covariate in the model for the antipsychotic combined cohort, but only two age categories were included for individual antipsychotic monotherapy cohorts.

[b] Includes antipsychotics not listed in this table that were less commonly prescribed in the UK.

The main limitation of this analysis of the UK GPRD was the relatively small number of patients treated with atypical antipsychotics compared to the size of conventional antipsychotic cohorts. This is reflected in the very small number of incident cases of diabetes in the atypical antipsychotic cohorts. This problem was also present in other recent independent analyses of the UK GPRD (Kornegay et al. 2002; Koro et al. 2002), and reflects the limited use of atypical antipsychotics among primary care practitioners in the UK. Finally, information on some risk factors for diabetes (obesity, family history, weight gain) was not consistently available for all patients.

In conclusion, the results of this study suggest that the risk of diabetes is greater among users of antipsychotic drugs compared to a control group of patients not taking antipsychotics. These analyses also suggest that the risk of diabetes may be greater among users of atypical antipsychotics compared to conventional drugs. These findings are not inconsistent with the results of other recent retrospective cohort or case-control studies (see Section 5.3).

5. Literature Review

5.1. Overview of Diabetes

5.1.1. Pathophysiology of Hyperglycemia and Diabetes

Type 2 diabetes mellitus is a complex metabolic disorder characterized by hyperglycemia and frequently accompanied by dyslipidemias. The phenotype recognized as type 2 diabetes mellitus appears to reflect a spectrum of disorders with variable degrees of pancreatic beta cell dysfunction and tissue (skeletal muscle, fat, and liver) insulin resistance. Expression of the phenotype is dependent upon genetic factors and is substantially impacted by lifestyle and behavior. This is evidenced by the epidemic increase in the prevalence of diabetes in parallel with the increase in overweight and obesity in the general population.

Although the overall clinical course of classic type 2 diabetes is one of slow progression (Brown JB et al. 1999; Riddle 2000), a number of factors can acutely or subacutely impact glycemic control. Acute medical illness, psychological stresses, diet, activity, weight changes, hormonal changes, and medications are among the variables that can impact glucose homeostasis. Indeed, the phenomenon of stress hyperglycemia is well recognized and has led the World Health Organization (WHO) to urge caution in applying the diagnosis of diabetes to cases of severe hyperglycemia detected under conditions of acute stress that may be transitory (WHO 1999).

The fluctuating nature of glucose homeostasis may also be relevant in consideration of the 11% to 12% spontaneous reversion rate to a non-diabetic status that has been reported for patients diagnosed by fasting glucose or oral glucose tolerance test (OGTT) criteria. Available data suggest that those who revert have shorter duration of hyperglycemia and fewer risk factors for diabetes (Burke et al. 1998).

The American Diabetes Association (ADA) defines major risk factors for diabetes as follows: older age (45 or older), non-Caucasian ethnic background, body mass index (BMI) $\geq$25 kg/m^2, hypertension, elevated triglycerides, low (high-density lipoprotein) HDL, history of impaired glucose tolerance or insulin resistance, family history of diabetes, or sedentary lifestyle, polycystic ovary syndrome, delivery of an infant greater than 9 pounds, or history of gestational diabetes (ADA 2002).

In addition, other variables significantly associated with increased risk for diabetes include: lower income, education, and social class (Rewers and Hamman 1995); "westernization"; urban dwelling; cigarette smoking; longer duration of overweight and obesity; low birth weight; or depression (Rubin and Peyrot 2002).

As noted above, the phenotype classified as type 2 diabetes appears to reflect a spectrum of disorders and there is a growing appreciation for subgroups of patients within the clinical phenotype of type 2 diabetes. For example, one subset of adult patients classified on clinical grounds with type 2 diabetes appears upon specific testing to have a slowly progressive auto-immune form of the disease more akin to type 1 diabetes (ECDCDM 1998).

Another distinctive subset of adult patients, those with idiopathic type 1 diabetes, are characterized by episodic insulin deficiency frequently without an identifiable precipitant and present with diabetic ketoacidosis (DKA) as the first manifestation (Pinero-Pilona et al. 2001; Pinero-Pilona and Raskin 2001). These patients lack evidence of the auto-immune process characteristic of the juvenile type 1 diabetes mellitus and the more slowly progressive adult form of type 1. In general, the physical characteristics and subsequent clinical course for this subgroup is more characteristic of patients with type 2 diabetes mellitus, leading to alternative terminology such as ketosis-prone type 2 diabetes mellitus, Flatbush diabetes, atypical diabetes, and "soft drink ketosis." In the United States (US), this subgroup appears to represent between 16% and 60% (depending upon the specific criteria applied) of the adult patients that present with DKA as the first manifestation of diabetes (Westphal 1996; Umpierrez et al. 1997; Wilson et al. 1997; Balasubramanyam et al. 1999; Pinero-Pilona and Raskin 2001).

Many of these adult patients (24% to 100%, again depending upon specific criteria applied) are subsequently managed without insulin or other anti-diabetic medications after resolution of the acute event and some may have rather prolonged (months to years) remissions before recurrent hyperglycemia is evident (Westphal 1996; Tan et al. 2000; Pinero-Pilona et al. 2001). In a series described out of Dallas, Texas (Pinero-Pilona et al. 2001), patients identified with idiopathic type 1 diabetes mellitus were predominantly male, of African or Hispanic descent, and had a mean age 35 years. All patients reported being overweight prior to the event but many had noted substantial weight loss, and at presentation, 18% of the patients had a BMI < 26 kg/m^2. All patients were initially discharged from the hospital on insulin therapy and after 5 years of follow-up, 38% of these patients were on diet or oral therapy with a median of 8 months (range 1 to 36 months) to discontinuation of insulin.

Although initially described in African-American and Hispanic-American groups in the US, a similar presentation and clinical course has been described for adult patients in other countries with different ethnic backgrounds. These reports suggest that 10% to 34% of cases of new-onset diabetes that present with DKA in adulthood may follow a similar clinical course (Zouvanis et al. 1997; Nagasaka et al. 1998; Tanaka et al. 1999; Pitteloud and Philippe 2000; Yan et al. 2000; Rheeder et al. 2001).

In summary, type 2 diabetes mellitus in the general population is an increasingly prevalent health problem and represents a heterogeneous group of disorders characterized by variable clinical presentations, and in some cases, a fluctuating course of illness. It is important to take this information into consideration when evaluating causality in cases of glucose dysregulation that occur in temporal association with antipsychotic therapy.

5.1.2. Prevalence of Diabetes in the General Population

Over the last decade, diabetes has been increasing in the general population at an alarming rate, and currently diabetes represents a major worldwide public health issue (Amos et al. 1997; King et al. 1998; Mokdad et al. 2001a). The prevalence of diabetes in the general US population has been steadily increasing, in parallel to an epidemic increase in the rates of obesity (Mokdad et al. 2000, 2001a, 2001b). In 1998, the prevalence of diabetes in the US was 5.1% (Harris et al. 1998), with subsequent data demonstrating a continued increase, particularly in the younger adult age groups and in children and adolescents (ADA 2000b).

Similar findings been reported from other countries (King and Rewers 1993; Cockram 2000; Mokdad et al. 2000; Zargar et al. 2000), including a very recent national survey in Australia (Dunstan et al. 2002). These surveys have also found that many patients with diabetes are undiagnosed (approximately one-third of patients with diabetes in the US population [Harris et al. 1998] and approximately one-half of patients with diabetes in the Australian survey [Dunstan et al. 2002]). The prevalence of patients with less marked dysglycemia is also quite high (approximately 7% Impaired Fasting Glucose [IFG] alone in the US [Harris et al. 1998], and 16% in Australia for IFG or Impaired Glucose Tolerance [IGT] [Dunstan et al. 2002]). Individuals with IFG or IGT have very high rates of conversion to diabetes, 3% to 16% per year (Yudkin et al. 1990; Edelstein et al. 1997; Knowler et al. 2002) compared with the general population (0.3% to 0.4% new cases per year in the US) (Harris et al. 1998).

5.2. Diabetes and Psychiatric Disorders

An association between abnormalities in glucose homeostasis and serious mental illness, including schizophrenia, bipolar disorder, and depression, were first described in the early part of the 20th century (Raphael and Parsons 1921; Lorenz 1922; Cowie 1924; Braceland et al. 1945). A possible role for medications in this association was postulated shortly after the introduction of phenothiazines (Charatan and Bartlett 1955). However, results of studies investigating potential drug effects of conventional antipsychotics have been largely inconsistent (Korenyi and Lowenstein 1968; Schwarz and Munoz 1968; Erle et al. 1977; Zumoff 1979; Ohwovoriole et al. 1992).

There is mounting evidence that the prevalence of diabetes and diabetes-related events is greater among patients with serious mental illness including schizophrenia, major depressive disorder, and bipolar disorder, and may be as much as several times the prevalence observed in the general population (Dixon et al. 2000). The reasons for these observations remain unresolved. However, likely factors include common genetic or environmentally-induced vulnerability, including greater family history of diabetes than in the general population (Mukherjee et al. 1989), greater rates of obesity (Allison et al. submitted for publication; Thakore et al. 2002), sedentary lifestyle (Brown S et al. 1999), and impulsive eating behavior.

There is also evidence that diabetic patients suffering from psychiatric disorders are at greater risk of poor glycemic control (Lustman et al. 2000) and of experiencing complications of diabetes. In a recent study, the presence of psychiatric disorders was found to markedly increase the risk of ketoacidosis in children with type 1 diabetes mellitus (Rewers et al. 2002). It is also well recognized that patients with serious mental illnesses such as schizophrenia are less likely to receive adequate care for non-psychiatric illnesses or to be actively engaged in preventive medicine activities with their health care providers (Osborn 2001; Desai et al. 2002).

The risk of developing diabetes may be related to the severity of a psychiatric disorder and not necessarily to a specific disorder itself. Stress hyperglycemia is well defined in the literature as an increase in blood glucose during acute physiologic stress, and is thought to be related to more severe illness (Umpierrez et al. 2002). This hyperglycemic effect is mediated by an elevated response to stress resulting in excess production of cytokines and counterregulatory hormones that produce insulin resistance (Hirsh 2002).

Stress hyperglycemia often goes unrecognized in critically ill or acutely hospitalized patients in the medical setting. In a study of 397 subjects with acute myocardial infarction, the prevalence of undiagnosed diabetes was 4.3%, with undiagnosed diabetes accounting for 9.6% of hospital mortality (Oswald and Yudkin 1987). In a survey of 1034 hospitalized patients, 66% had one or more plasma glucose measurements over 200 mg/dL, and the mean glucose for the surveyed sample was 299 mg/dL. However, diabetes was formally documented as a diagnosis in only 7.3% of these patients (Levetan et al. 1998). A number of other reports have described the complications and high mortality rates of stress hyperglycemia in acute medical settings (Evans 2001; van den Berghe et al. 2001).

Psychiatric illness severity has been correlated with glucose intolerance and insulin resistance. In a 5-hour oral glucose tolerance study in patients with major depression, Winokur and colleagues (1988) found a significant correlation between the severity of depression and glucose cumulative response. A potential mechanism for such an effect may be that more severe illness triggers a stress response such as an increase in cortisol, which may alter normal metabolism of glucose and fat (Cassidy et al. 1999).

Despite these reports, stress hyperglycemia appears to be a variable that has not been adequately considered in the research on the effect of antipsychotics on glucose homeostasis. It seems reasonable to consider that acute illness states in schizophrenia and bipolar disorder may be important confounding factors in the evaluation of events of glucose dysregulation.

5.2.1. Diabetes and Schizophrenia

Studies in populations with schizophrenia have shown a prevalence of elevated blood glucose levels 2 to 4 times higher than in the general population (Keskiner et al. 1973; McKee et al. 1986; Tabata et al. 1987; Mukherjee 1995; Mukherjee et al. 1996). Mukherjee and colleagues found a prevalence of diabetes of 15.8% in 95 patients with schizophrenia (Mukherjee 1996). Keskiner and colleagues found a greater incidence of an elevated 2-hour oral glucose tolerance test in patients treated with thioridazine (11.6%) and chlorpromazine (10.6%), compared with haloperidol (2.9%) and fluphenazine (4.3%) (Keskiner et al. 1973). Tabata and colleagues found an incidence of diabetes of 8.8% in a schizophrenic population compared with an incidence of 5% in controls (Tabata et al. 1987). In a landmark study, Dixon and colleagues (2000) examined a large US healthcare database cohort from 1991 onward. The study found that the prevalence of diabetes among patients with schizophrenia was approximately 12%, over twice the prevalence reported in the US general population in similar types of studies (Figure 5.1).

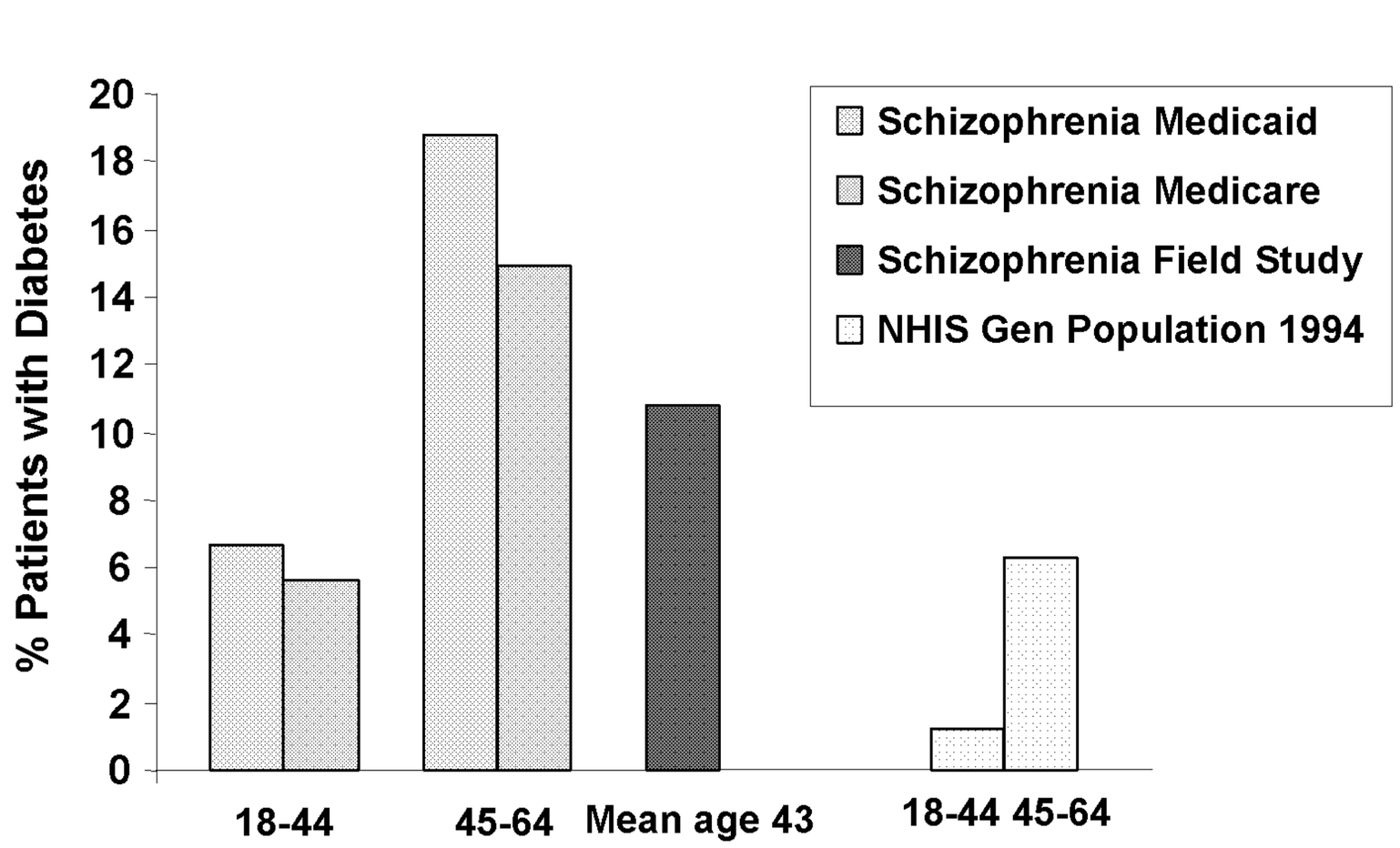


Figure 5.1. Prevalence and correlates of diabetes in national schizophrenia samples.

5.2.2. Diabetes and Bipolar Disorder / Major Depression

Similar rates of diabetes as seen in schizophrenic samples have also been reported in patients with 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.

In a recent investigation, the potential relationship between altered glucose metabolism and serious mental illness was evaluated while controlling for several known risk factors for diabetes including race, age, body mass, and psychotropic medication use (Regenold et al. 2002). This study was a retrospective chart review of 243 inpatients (50 to 74 years of age) with a diagnosis of schizophrenia, schizoaffective disorder, bipolar I disorder, major depression, or dementia. A diagnosis of type 2 diabetes mellitus was determined from documentation on the discharge summaries or the prescription of an oral hypoglycemic medication or insulin.

Results from this investigation showed that the rate of type 2 diabetes mellitus was significantly different between treatment groups with patients diagnosed, with schizoaffective disorder and bipolar I disorder having the highest incidence (50% and 26%, respectively). Diabetic patients were noted to have a higher mean BMI compared with non-diabetics (p=.021), but not to have a significantly higher use of antipsychotic medications. Psychiatric diagnosis and body mass were the only significant, independent predictors of risk of developing type 2 diabetes mellitus. The authors concluded that their findings suggest an intrinsic relationship between abnormal glucose metabolism and bipolar I and schizoaffective disorder.

Major depression has also been shown to be associated with altered glucose tolerance. Winokur and colleagues (1988) evaluated glucose, insulin, and glucagon responses in 28 patients meeting Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) criteria for major depression and 21 healthy controls using a 5-hour oral glucose tolerance test. Patients with depression had significantly higher basal glucose levels, larger cumulative glucose responses, and greater cumulative insulin responses after the glucose tolerance test compared with controls. The authors concluded the results were consistent with a relative insulin-resistant state in the depressed patients.

Similar findings were also demonstrated by Weber and colleagues (2000) who evaluated insulin, glucose, and cortisol levels over a 26-hour period in 26 patients meeting DSM-IV depression and 33 age- and sex-matched controls. Insulin and glucose responses were also measured after a standardized meal was provided. Glucose and insulin responses after the standard meal were significantly higher in the depressed patients compared with controls. The authors concluded that patients with major depression may have an impaired insulin sensitivity. Further, a study by Okamura and colleagues (2000) showed improvement of insulin sensitivity following treatment of the acute depressive episode.

In addition, two prospective studies have provided data suggesting that the risk of future diabetes may be increased as much as two-fold in patients with depression (Rubin and Peyrot 2002).

5.2.3. Studies of Parameters of Glucose Regulation in Antipsychotic-Naïve Patients

While the studies conducted to date evaluating the potential relationship between serious mental illness and altered glucose metabolism have had fairly consistent conclusions, they have had some methodological limitations, including inconsistent diagnostic criteria for diabetes mellitus and failure to control for all known risk factors for diabetes mellitus (eg, age, diet, antipsychotic medication use). In a recent study, Thakore and colleagues attempted to address some of these limitations by evaluating fasting blood glucose levels in first episode, antipsychotic-naïve, schizophrenic patients (Thakore et al. 2002, in press).

Patients included in this 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). Patients were found to have higher mean glucose, insulin, and cortisol levels, as well as decreased insulin sensitivity compared with controls (Table 5.1).

Table 5.1. Glucose and Insulin Levels

Characteristic	Patients	Controls	p-Value
Glucose (mg/dL)*	95.8 ± 16.9	88.2 ± 5.4	(t=2.17, df=48, p<.03)
Insulin (μU/mL)*	9.8 ± 3.9	7.7 ± 3.7	(t=2.07, df=48, p<.05)
Insulin Resistance (IR)*	2.3 ± 1.0	1.7 ± 0.7	(t=2.56, df=48, p<.01)
Cortisol levels (nmol/L)*	499.0 ± 161	303.0 ± 110	(t=5.11, df=48, p<.005)

* Signifies significant difference between patients and controls.
IR = Calculated using Homeostasis Model Assessment (HOMA) (insulin mM/L x glucose in mU/L / 22.5).

5.3. Diabetes and Antipsychotics

While it has been established that type 2 diabetes mellitus is more common in patients with mental illness, debate persists over whether this can be attributed solely to the underlying disease or to pharmacotherapy. Several reports have been unable to demonstrate a definitive association between diabetes and the use of antipsychotics (Schwarz 1968; Waitzkin 1970; Keskiner et al. 1973; Mukherjee 1995;).

More recently, there has been interest in a possible link between atypical antipsychotic medications and hyperglycemia and diabetes mellitus (diabetes) (Henderson 2002; Sernyak et al. 2002). Although, as with the conventional agents, this potential association is not clearly defined (Regenold et al. 2002).

5.3.1. Glucose Dysregulation during Treatment with Drug Classes other than Atypical Antipsychotics – Protease Inhibitors

Concerns about certain classes of drugs being associated with dysregulation of glucose-insulin homeostasis are not new to the medical or regulatory arenas. Drug classes that have been implicated include beta-blockers, thiazide diuretics, and corticosteroids (Pandit 1993; Luna 2001). While there is limited understanding of the mechanisms by which some of these drugs may exert an effect on glucose homeostasis, some agents have received greater scrutiny from the scientific community.

The anti-HIV protease inhibitors have been the focus of systematic multimodal investigations (Tsiodras et al. 2000; Mulligan et al. 2000; Noor et al. 2001, 2002), following spontaneous adverse event reports of new-onset diabetes, hyperglycemia, or exacerbation of preexisting diabetes in patients infected with HIV. As with the atypical antipsychotic drug class, cases of glucose dysregulation have been reported with protease inhibitors (Dybul et al. 2002).

Analogous to investigations conducted with some of the atypical antipsychotics, studies have been conducted to measure the effect of protease inhibitors (PI) treatment on insulin sensitivity in patients with AIDS that had been previously treated with PI, in AIDS patients that were PI-naïve, and in uninfected healthy controls. These studies found that PI treatment was associated with a lower insulin sensitivity in PI-naïve patients with AIDS compared with healthy controls but higher insulin sensitivity compared with PI-treated AIDS patients (Carr et al. 1998, 1999). Using a euglycemic, hyperinsulinemic clamp to assess insulin sensitivity in healthy men, PI were shown to clearly decrease insulin sensitivity between 17% and 35% (Noor et al. 2000, 2002). This finding is in contrast with findings of similar studies conducted in healthy volunteers treated with atypical antipsychotics (olanzapine and risperidone), where no evidence was found of an acute direct detrimental drug effect on insulin secretion or on insulin receptor sensitivity (see Section 3.1).

5.3.2. Published Literature on Glucose Dysregulation During Treatment with Atypical Antipsychotics (May 2000 through September 2002)

A comprehensive review of the recent literature pertinent to the issue of glucose homeostasis, mental illness, and psychotropics was conducted. Relevant literature was identified by searching the following bibliographic databases: Biosis Previews, Derwent Drug Files, Embase, Medline, PsychInfo, and SciSearch from 1 May 2000 through 4 September 2002. The databases were searched using the terms blood glucose, hyperglycemia, diabetes, ketoacidosis, or non-ketotic hyperosmolar syndrome in conjunction with schizophrenia, bipolar disorder, depression, olanzapine, risperidone, clozapine, quetiapine, ziprasidone, or aripiprazole. Appendix C contains a list of references returned for all published case reports of glucose dysregulation during treatment with atypical antipsychotics during this time period.

Of the atypical antipsychotics, case reports demonstrating a temporal association with glucose dysregulation (diabetic ketoacidosis, hyperosmolar coma, and new diagnosis or exacerbation of previously diagnosed diabetes) have been reported for clozapine, olanzapine, risperidone, quetiapine, and ziprasidone. Many patients in these case reports had risk factors for type 2 diabetes mellitus based on race, obesity, or personal family history (Hua et al. 2002).

The following sections represent an update to the extensive literature review provided to the Division on 31 July 2000. Table 5.2 summarizes recently published manuscripts (excluding review papers) or referenced abstracts for the time period of 1 May 2000 through 4 September 2002 on the issue of glucose homeostasis and atypical antipsychotics.

Table 5.2. Summary of Recently Published Literature/Studies Excluding Review Papers
1 May 2000 through 4 September 2002
Glucose Homeostasis and Atypical Antipsychotics

Author	Title	Study Design	N	Reported Findings/Conclusi
Allison DB	Random blood glucose concentrations in patients treated with typical and atypical antipsychotic agents: an analysis of pooled data from double-blind, randomized, controlled trials.	Double-blind, randomized active controlled trials. Max exposure 52 weeks. Posthoc analysis of random blood glucose levels.	Olz 2238 Ris 164 Hal 792 Cloz 85	Mean random glucose increas Increase in glucose with olz si not significantly different fron greater than hal.
Ardizzone TD	Inhibition of glucose transport in PC12 cells by the atypical antipsychotic drugs risperidone and clozapine, and structural analogs of clozapine.	Evaluation of 3H-2-deoxyglucose uptake by rate pheochromocytoma PC12 cells and rat L6 cells.		Ris and cloz decrease glucose differentiated PC12 cells, and may directly interact with gluc decreasing glucose uptake.

Table 5.2. Summary of Recently Published Literature/Studies Excluding Review Papers 1 May 2000 through 4 September 2002 Glucose Homeostasis and Atypical Antipsychotics (continued)

Author	Title	Study Design	N	Reported Findings/Conclusi
Cavazzoni P	A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United Kingdom.	Retrospective cohort study used UK GPRD database to determine hazard ratio of DM for patients prescribed APs compared to adult gen pop in the UK.	Conv APs 43,561 Atypical APs 2550 Gen Pop 269,049	Compared with gen pop cohor APs had higher risk of develo developing DM during exposu was significantly higher than other APs was limited by sam
Chae BJ and Kang BJ	The effect of clozapine on blood glucose metabolism.	Blood glucose metabolism evaluated in patients on cloz or hal.	34	Patients in the cloz group had tolerance (35%) and glycemic compared with hal patients wh glucose tolerance and 10% wh delay.
Gianfrancesco F	Association of new-onset diabetes and antipsychotics: findings from a large health plan database.	Evaluated prescription claims from large mixed indemnity and managed health care plans in the US and determined hazard ratios for developing DM during exposure to AP medications.	High potency Conv APs 1376 Low potency Conv APs 480 Olz 1047 Ris 1368 Cloz 63	Increased risk of developing D both high and low potency co compared with AP non-users. subanalyses, the conclusion w statistically significant increas DM in patients treated with ris
Henderson DC	Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study.	Retrospective chart review.	82	36.6% of patients were diagnc 5-year follow-up. Weight gai total daily dose of cloz were n for developing DM.

(continued)

Table 5.2. Summary of Recently Published Literature/Studies Excluding Review Papers 1 May 2000 through 4 September 2002 Glucose Homeostasis and Atypical Antipsychotics (continued)

Author	Title	Study Design	N	Reported Findings/Conclusi
Howes DO and Pilowsky L	Does clozapine treatment cause diabetes mellitus? A prospective longitudinal study.	Prospective, observational study.	23	Cloz therapy can alter glucose changes in BMI. After 8 weel was a statistically significant i OGTT glucose levels (p<.01). developed impaired glucose tc therapy. There was no signifi during the study (p=.89).
Hua J	Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: an analysis of 45 published cases.	Retrospective analysis of published case reports.	45 published cases for all atypical APs	87% of patients were male, 47 42% presented with DKA, 50 time of presentation, and 84% starting AP therapy. Patients significantly younger, less ove had a greater proportion of wc those who presented with DM
Koller E	Clozapine-associated diabetes.	Analysis of FDA MedWatch database.	384 reports	New-onset DM definitely diag had exacerbation of current di metabolic acidosis or ketosis. hyperglycemic episode. Mear male to female ratio was 2.0. within 6 months of starting cl

(continued)

Table 5.2. Summary of Recently Published Literature/Studies Excluding Review Papers 1 May 2000 through 4 September 2002 Glucose Homeostasis and Atypical Antipsychotics (continued)

Author	Title	Study Design	N	Reported Findings/Conclusi
Koller EA and Doraiswamy PM	Olanzapine-associated diabetes mellitus.	Analysis of FDA MedWatch database.	237 reports	New-onset DM diagnosed in 1 current disease, 5 could not be was 40.7 years. The male to f newly diagnosed hyperglycem appeared within 6 months of s had metabolic acidosis or ketc
Koro CE	Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study.	Nested case-control study using UK GPRD database.	Typical APs 18,443 Olz 970 Ris 1683 Other 578	229 incident cases of DM witl olz, 7 cases with ris, 1 case wi Greater increase in DM in ma taking olz had significantly in developing DM vs non-users Patients taking ris had nonsigı developing DM than non-user conv APs. Given small numb atypical groups, olz and ris no
Lage MJ and Kemner JE	Use of atypical antipsychotics and the incidence of diabetes: evidence from a claims database.	Retrospective analysis of IMS Lifelink claims database.	Conv APs 3381 Atypical APs 3377	The probability of developing following treatment with atypi Within atypicals, the probabili was less during treatment witl but the difference was not stat

(continued)

Table 5.2. Summary of Recently Published Literature/Studies Excluding Review Papers 1 May 2000 through 4 September 2002 Glucose Homeostasis and Atypical Antipsychotics (continued)

Author	Title	Study Design	N	Reported Findings/Conclusi
Lund BC	Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension.	Retrospective cohort study. Pharmacy and medical claims from the Iowa Medicaid program were evaluated to determine the incidence rates of DM in patients with schizophrenia who received cloz compared to patients with schizophrenia who received conv APs.	Cloz 552 Conv APs 2461	No statistically significant difl incidence rate of DM between who received cloz vs schizopl received conv APs. However, DM was found to be statistica in the younger cohort (20-34 y risk of 2.5 (95% CI=1.2–5.4).
Melkersson KI	Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses.	Cross-sectional evaluation of glucose and a variety of metabolic factors in patients treated with olz.	14	Olz was associated with weigl and elevated levels of insulin,

(continued)

Table 5.2. Summary of Recently Published Literature/Studies Excluding Review Papers 1 May 2000 through 4 September 2002 Glucose Homeostasis and Atypical Antipsychotics (continued)

Author	Title	Study Design	N	Reported Findings/Conclusi
Melkersson KI	Different effects of antipsychotic drugs on insulin release in vitro.	In vitro experiment. Studied laboratory responses of isolated rat pancreatic islets during exposure to one of 7 different APs or without addition (control). They measured basal-(unstimulated) and glucose-stimulated insulin release during 1 or 4 hours of exposure.		In the 4-hour exposure experi effect compared with controls or glucose-stimulated insulin r tested medications (olz, chlorp zuclopenthixol, or ris). Islets hours released less insulin in r did controls. Basal insulin rel incubated with cloz for 4 hour greater than controls, while gl by islets incubated with cloz v controls.
Meyer JM	A retrospective comparison of weight, lipid, and glucose changes between risperidone- and olanzapine-treated inpatients: metabolic outcomes after 1 year.	Retrospective chart review.	94	Patients <60 yr old (n=37) hac increase at 1 yr in all metaboli with ris. Neither weight chan valproate was associated with lipids for either drug in patien significant difference between with respect to weight gain.

(continued)

Table 5.2. Summary of Recently Published Literature/Studies Excluding Review Papers 1 May 2000 through 4 September 2002 Glucose Homeostasis and Atypical Antipsychotics (continued)

Author	Title	Study Design	N	Reported Findings/Conclusi
Newcomer JW	Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia.	Cross-sectional non-standard OGTT, plasma sampled up to 75 min.	48 schizophr. 31 controls	Olz-treated patients had signif elevations at all time periods c APs and untreated healthy cor patients had statistically signif elevations compared with con to healthy controls. There we significantly greater elevation compared with healthy contro patients treated with conv APs subjects. There were no statis differences between the ris an
Sernyak MJ	Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia.	Cross-sectional cohort study in **VA database** prevalence of DM in schizophrenia patients receiving typical vs atypical APs.	Conv APs 15,984 Atypical APs 22,648	Patients receiving atypicals w have DM compared with typic was significantly increased fo olz, and quet, but not ris. For old, all of the atypical AP trea significantly increased prevale with typical APs.
Singer B	Weight gain, diabetes mellitus and the pharmacotherapy of schizophrenia.	Retrospective analysis of a state hospital's records from July 1992 to May 1999 for development of DM on atypical APs.	Atypical APs 34 Conv APs 22	Of the 34 patients who receive DM onset while taking the aty 23 had onset of DM prior to a

(continued)

Table 5.2. Summary of Recently Published Literature/Studies Excluding Review Papers 1 May 2000 through 4 September 2002 Glucose Homeostasis and Atypical Antipsychotics (continued)

Author	Title	Study Design	N	Reported Findings/Conclusi
Smith RC	A prospective cross-sectional of glucose and lipid metabolism with atypical and conventional antipsychotics.	Prospective, cross-sectional evaluation of fasting glucose and lipid parameters in conv vs atypical APs.	101	No consistent difference in me values among the 4 drug grou cloz). No significant differen groups on glucose, glycohemc peptide, fructosamine, cholest LDL, chol/HDL ratio, leptin. treated with ris, had fasting gl
Sowell MO	Hyperglycemic clamp assessment of insulin secretory responses in normal subjects treated with olanzapine, risperidone, or placebo.	Randomized, single-blind, healthy volunteers.	48	Results of this study found sin weight, fasting insulin, and in hyperglycemia in healthy volu ris. The study found no evide healthy volunteers with olz or decrease in the insulin secreto prolonged hyperglycemic resp
Wang PS	Clozapine use and risk of diabetes mellitus.	Case-control **government-sponsored drug benefit programs in New Jersey.**	7227 cases 6780 controls	The authors found no significa developing DM with cloz use CI=0.74-1.31). They found n associated with higher doses c of cloz therapy. A significant was seen with use of chlorpro CI=1.09-1.56) and perphenazi CI=1.11-1.62).

(continued)

Table 5.2. Summary of Recently Published Literature/Studies Excluding Review Papers 1 May 2000 through 4 September 2002 Glucose Homeostasis and Atypical Antipsychotics (concluded)

Author	Title	Study Design	N	Reported Findings/Conclusi
Wilson D	Glucose intolerance with atypical antipsychotics.	Retrospective chart review of state hospital records.	Olz 2542	The overall rate of DM among was 10.9% with 5% being nev
Wirshing DA	Antipsychotic medication: impact on coronary artery disease risk factors.	Retrospective chart review.	Cloz 39 Olz 32 Ris 49 Quet 13 Hal 41 Fluphenazine 41	Cloz-, olz-, and hal-treated sul significant increases in glucos

Abbreviations: APs = antipsychotics; BMI = body mass index; CI = confidence interval; Cloz = clozapine; conv = conventional; DKA = diabetic ketoacidosis; DM = diabetes mellitus; Gen Pop = general population; Hal = haloperidol; OGTT = oral glucose tolerance test; Olz = olanzapine; Quet = quetiapine; Ris = risperidone; UK GPRD = United Kingdom General Practice Research Database; vs = versus; yrs = years.

5.3.3. Studies of Mechanisms of Glucose Dysregulation

Treatment-emergent glucose dysregulation has been reported in patients treated with atypical antipsychotics. These reports include newly identified cases of diabetes, hyperglycemia, diabetic ketoacidosis (DKA), and hyperosmolar, hyperglycemic, nonketotic syndromes (Mir and Taylor 2001; Henderson 2002). In some cases, newly identified cases of diabetes were reported in the absence of weight gain or other known risk factors for diabetes (see Section 3.2). In addition, a majority of the reported cases of glucose dysregulation occurred within 3 to 6 months of initiating or switching antipsychotic therapies. These observations have led to a suggestion that some of the atypical antipsychotic medications may have a direct effect on pancreatic function or insulin sensitivity.

5.3.3.1. In Vitro Study of Effect of Antipsychotics on Pancreatic Insulin Release

A recently published study (Melkersson et al. 2001) investigated the in vitro effects of antipsychotic medications on pancreatic insulin release. Based on reports that older antipsychotic medications (chlorpromazine, pimozide, haloperidol) may decrease insulin secretion, Melkersson and colleagues studied laboratory responses of isolated rat pancreatic islets during exposure to one of seven different antipsychotics or without addition (control). They measured basal (unstimulated) and glucose-stimulated insulin release during 1 or 4 hours of exposure. No significant effects on insulin release were observed for any drug during 1 hour of exposure. In the 4-hour exposure experiments, no significant effect compared with controls was observed for basal or glucose-stimulated insulin release with five of the tested medications (olanzapine, chlorpromazine, perphenazine, zuclopenthixol, or risperidone). Islets incubated with haloperidol for 4 hours released less insulin in response to glucose than did controls. Basal insulin release from islets incubated with clozapine for 4 hours was significantly greater than controls while glucose stimulated release by islets incubated with clozapine was not different from controls. The authors speculate that if clozapine similarly stimulates insulin release in vivo, the elevated insulin levels might stimulate appetite, promote weight gain, and thereby predispose to developing diabetes. Caution is warranted, however, in extrapolating these findings to humans, as data from in vitro studies of rodent islet preparations may not adequately reflect in vivo human homeostatic mechanisms for regulating insulin release and production.

A study evaluating the effects of risperidone and clozapine on glucose transport in rat PC12 cells suggested that clozapine and risperidone directly interact with glucose transporters, thus inhibiting the uptake of glucose into cells (Ardizzone et al. 2001). However, the relevance of these findings to human glucose homeostasis is unclear as noted above, and PC12 cells are a transformed cell line which further complicates analysis of glucose transporter function.

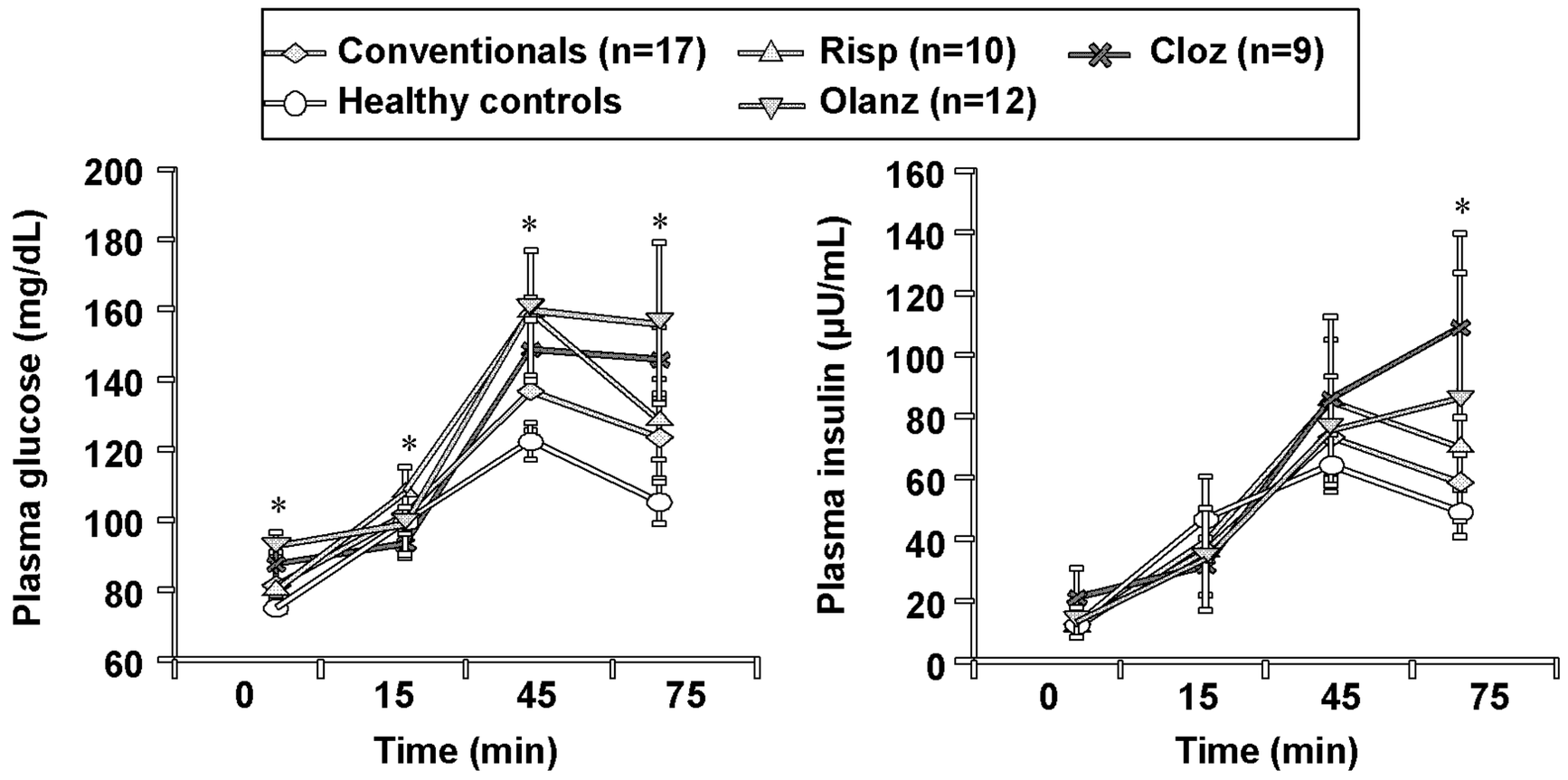
5.3.3.3. Glucose Challenge Studies in Psychiatric Patients Treated with Antipsychotics

Glucose challenge studies (OGTT, IVGTT, hyperglycemic, and hyperinsulinemic clamp) have the potential to provide a more sensitive assessment of glucose regulation, and conducting these studies in psychiatrically-ill patients may be viewed as having greater clinical relevance. However, given the evidence linking dysglycemia and psychiatric disorders, studies conducted in patients with mental illnesses, as opposed to healthy volunteers, are limited in their ability to distinguish potential drug effects from glucose dysregulation intrinsic to the psychiatric disorder.

Henderson (2000) used frequently sampled intravenous glucose tolerance testing (FSIVGTT). Glucose and insulin levels were collected after glucose challenge, and the Bergman's Minimal Modal Analysis (MINMOD) is used for glucose effectiveness and insulin sensitivity. Patients on established treatment with several atypical antipsychotics were compared. No statistically significant differences were found on glucose effectiveness, but rank ordering on insulin sensitivity was clozapine < olanzapine < risperidone. While this study did not include an untreated control group, historical norms for results of this test appear to fall between results for olanzapine- and risperidone-treated patients.

Newcomer and colleagues (2002a) used a modified glucose tolerance test (GTT) consisting of 50 gm of dextrose and glucose measurements at baseline (fasting), 15, 45, and 75 minutes. Thirty-one healthy untreated patients were compared with 48 patients with schizophrenia treated with olanzapine (n=12), risperidone (n=10), clozapine (n=9), and conventional antipsychotic drugs (n=17). Compared with patients receiving conventional antipsychotics or healthy controls, significant glucose elevations were observed in olanzapine-treated patients at all time points, and in patients treated with clozapine at fasting and at 75 minutes post-load glucose. Risperidone-treated patients had significant elevations in fasting and post-load glucose compared with untreated healthy controls, but not in comparison with patients receiving conventional antipsychotics. There were no differences in fasting or post-load glucose levels between patients treated with conventional antipsychotics and untreated healthy controls by means of a single OGTT. In this study, an association was reported between use of clozapine and olanzapine and decreased insulin sensitivity. This study was limited by small sample size, use of nonrandomized, open-label, cross-sectional design (with potential for sampling bias), and the need for extensive statistical modeling to control for confounding factors (for example, ethnic differences or concomitant medications).

Figure 5.2 shows effects of an oral 50 g dextrose challenge in patients with schizophrenia (n=48) and healthy controls (n=31), with treatment groups matched for age and BMI (Newcomer et al. 2001).



* Significant effect of treatment condition, p<.05

Figure 5.2. Medication-related abnormalities in glucose regulation in schizophrenia.

In a more recent study also conducted by Newcomer et al. (2002c), insulin sensitivity in patients treated with antipsychotics was evaluated using the hyperinsulinemic euglycemic clamp. The euglycemic clamp method is considered the most reliable measure of insulin sensitivity in humans.

In this study, Newcomer compared patients with schizophrenia under chronic antipsychotic therapy to healthy controls (Table 5.3). Patients were required to be on their current antipsychotic regimen for at least 3 months prior to study entry. Antipsychotic treatment groups were matched for age and adiposity (BMI) and were compared with 1) a non-obese group of average weight and 2) a control group of lean young healthy controls.

Table 5.3. Characteristics of Control Subjects and Patients Exposed to Conventional or Atypical Antipsychotics

Cohort	BMI	M/F	Age	BPRS	# of Admits
Olanzapine N = 10	30.8	8/2	35.7	28.7 ± 3	6.1 ± 4.15
Risperidone N = 10	30.1	7/3	38	27.8 ± 7	3.4 ± 2.91
Conventionals N = 10	28.9	8/2	37.7	23.3 ± 3	5.4 ± 3.78
Slim Controls N = 12	20.5	4/8	21.5	NA	NA
Average Controls N = 16	27.5	11/5	40	NA	NA

Abbreviations: BMI = body mass index; BPRS = Brief Psychiatric Rating Scale; M/F = male/female; NA = non-applicable.

Insulin sensitivity (as indicated by the dextrose infusion rate) was significantly lower in the three drug cohorts (risperidone, olanzapine, and conventional antipsychotics) compared with slim controls. However, there was no statistically significant difference in insulin sensitivity compared with the average weight control group (Figure 5.3). The observed reduction in insulin sensitivity could be due to a variety of factors, including a schizophrenia disease-related effect, an obesity-related effect, or a possible drug treatment effect. To the extent that a direct drug effect may be implicated, the lack of a statistically significant difference in insulin sensitivity among the risperidone, olanzapine, and conventional antipsychotic treatment cohorts does not support a differential drug effect.

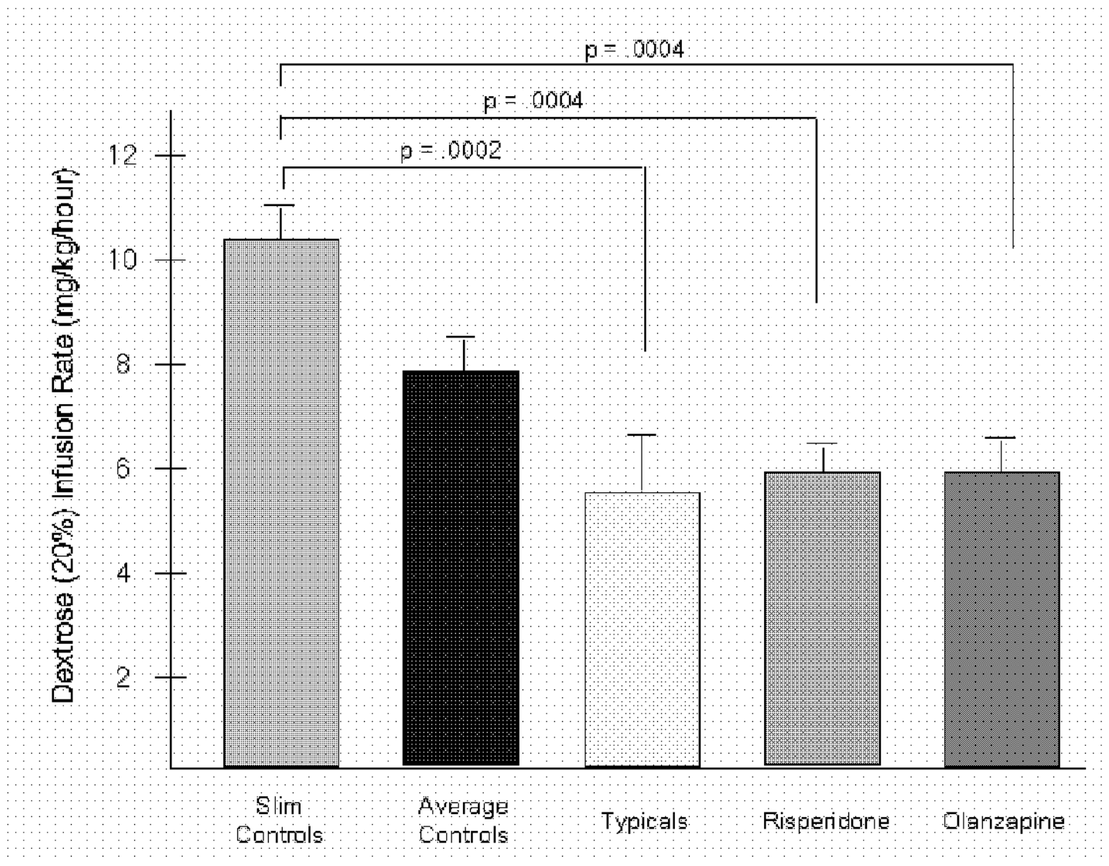


Figure 5.3. **Insulin sensitivity in control subjects versus patients exposed to either conventional or atypical antipsychotics.**

5.3.4. Postmarketing Spontaneous Adverse Events

Koller and colleagues have performed separate analyses of the FDA MedWatch database on patients that have been exposed to clozapine, risperidone, and olanzapine (Koller et al. 2001, 2002; Koller and Doraiswamy 2002). The goal of these analyses was to assess the frequency of diabetes; the clinical severity of diabetes; frequency of new-onset diabetes versus exacerbation of preexisting disease; time-to-onset of hyperglycemia; and the effect of drug discontinuation and rechallenge. The authors found that the average age of these patients was lower than is typical of patients with type 2 diabetes mellitus. The authors found a gender imbalance in their results, with more females than males experiencing glucose dysregulation events. In addition, the majority of new-onset diabetes occurred within 6 months of therapy initiation. Overall, the analyses showed that glucose abnormalities were seen in patients treated with any of the three atypical antipsychotics (Table 5.4).

Table 5.4. Characteristics of Control Subjects and Patients Exposed to Conventional or Atypical Antipsychotics

	Clozapine	Olanzapine	Risperidone
Total	384	237	132
New-onset DM	242	188	83
Exacerbation	54	44	40
Metabolic Acidosis/Ketosis	80	80	36
Death	25	15	5
Average Age (years)	40.0 ± 12.0	40.7 ± 12.9	39.0 ± 17.4
Male:Female Ratio	2.0	1.8	1.5

Abbreviations: DM = diabetes mellitus.

5.3.5. Cohort Studies

Several large, population-based, cohort studies have been conducted comparing the risk of developing diabetes mellitus between users of antipsychotics and non-users, conventional and atypical antipsychotics, or between different atypical antipsychotics. The three largest cohort studies performed to date evaluated data from the AdvancePCS database (summarized in Section 4.3), the recently published study by Sernyak et al. (2002) reporting analyses of the US Veterans Affairs healthcare system database, and the United Kingdom (UK) General Practice Research Database (GPRD) (summarized in Section 4.3). The methodology and results of the US Veterans Affairs study and some smaller epidemiological studies are also described.

5.3.5.1. Association of Diabetes Mellitus with Use of Atypical Neuroleptics in the Treatment of Schizophrenia (Sernyak et al. 2002)

A recently published study using the US Veterans Administration claims database examined 38,632 outpatients with schizophrenia treated with antipsychotics over a 4-month period in 1999. The proportion of patients diagnosed with diabetes (or receiving prescription for anti-diabetic medication) was compared between patients who received conventional antipsychotic medications and those who received atypical antipsychotic medications, and again between patients who received conventionals versus those who received a specific atypical antipsychotic (clozapine, olanzapine, quetiapine, and risperidone), adjusted and unadjusted for age (five age groups).

The study showed an increase in the likelihood of concomitant diagnosis of diabetes among patients with schizophrenia (specifically those in the younger age groups) who were using atypical antipsychotics compared with conventional agents (9% greater risk, OR =1.09; 95% CI=1.03-1.15; p=.002). A significantly greater prevalence of diabetes in patients less than 40 years old was observed in all of the individual atypical antipsychotic groups (clozapine, olanzapine, quetiapine, or risperidone) compared with conventional antipsychotics. The authors concluded that schizophrenia patients who received atypicals were more likely to have a concomitant diagnosis of diabetes than those who received a conventional agent, and that the likelihood of a concomitant diagnosis of diabetes was significantly increased compared with the cohort receiving a conventional agent for those patients who received clozapine, olanzapine, and quetiapine, but not risperidone. However, as shown in Figure 5.4 below, careful examination of the data reveals that while the comparisons that attained statistical significance vary across age ranges, the odds ratios are overall quite similar among all the atypical agents (clozapine, olanzapine, quetiapine, and risperidone).

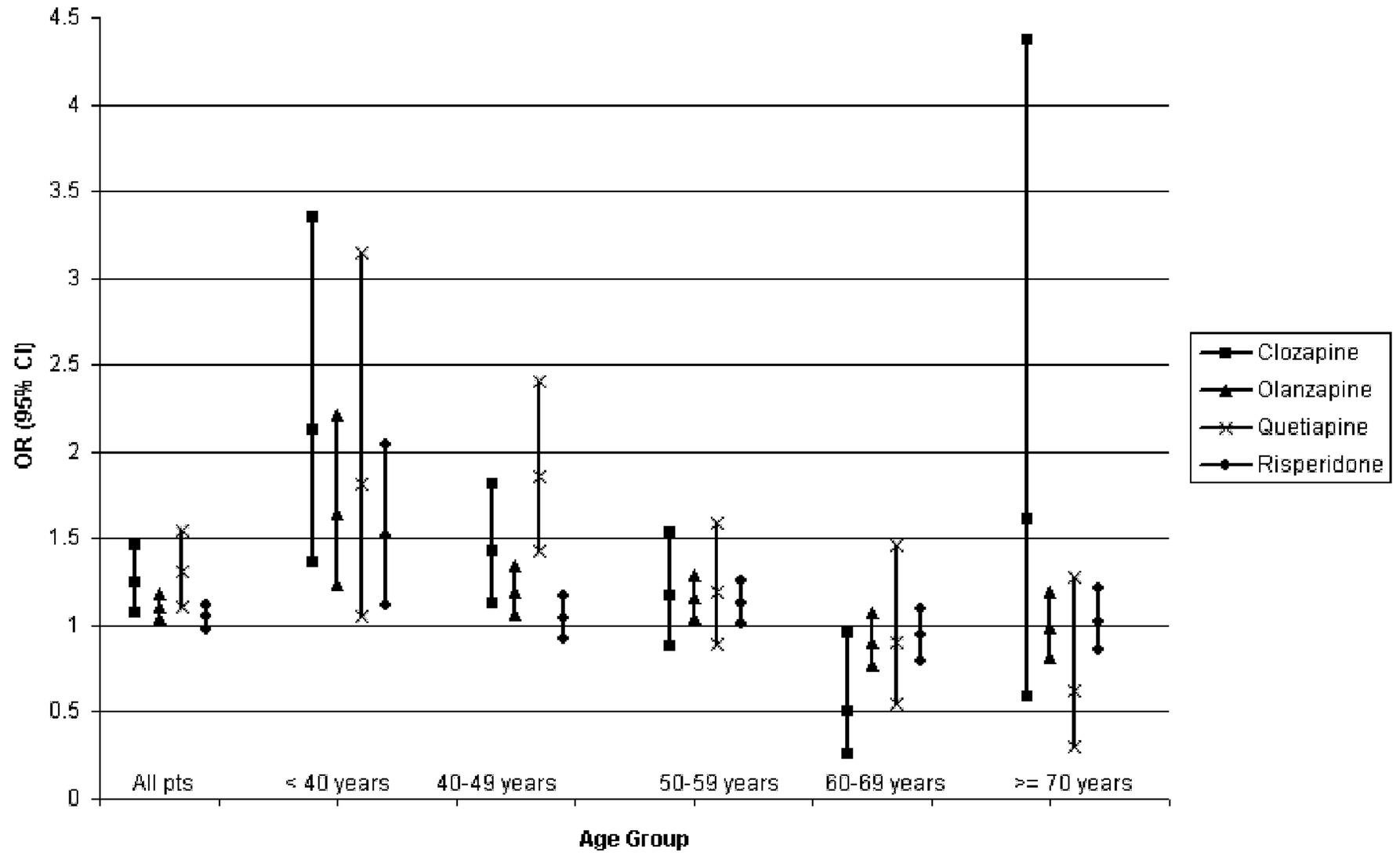


Figure 5.4. **Prevalence of diabetes in schizophrenia: odds ratios during treatment with atypical compared with conventional antipsychotics.**

Methodological limitation of the study by Sernyak et al. (2002) include the narrow time frame (4 months) during which incident cases of diabetes were identified, lack of information on body weight, the potential for less compliance to treatment in the conventional antipsychotic group due to their less favorable side-effect profile, and the use of ICD-9 codes contained in an administrative database to identify cases of diabetes. Also, patients receiving atypical antipsychotic drugs were markedly different from those receiving conventional agents in terms of comorbid psychiatric diagnoses (more prevalent among patients receiving atypical antipsychotics) and days of hospitalization (2 to 3 times greater among patients receiving atypical antipsychotics). Therefore, it is difficult to determine the extent to which the observed results may reflect differences in patient characteristics which were not accounted for in the analysis, including greater chronicity or acute psychiatric illness severity in patients receiving atypical agents.

5.3.5.2. Other Cohort Studies

Gianfrancesco and colleagues (2001) examined prescription claims data from two large mixed indemnity and managed health care plans in the US and determined the odds ratios for developing diabetes during exposure to antipsychotic medications. Over the 4- and 8-month periods preceding the time of observation, the study showed an increased risk of developing diabetes in patients exposed to high- or low-potency conventional antipsychotics (clozapine or olanzapine) but not in patients exposed to risperidone compared with patients not treated with antipsychotics. The authors then performed a series of subanalyses where the odd ratios for antipsychotic treatment duration were converted to 12 months. These subanalyses also showed that that the odds of diabetes were increased during treatment with high-potency or low-potency conventional antipsychotics, olanzapine, or clozapine compared with no treatment, but were not increased during treatment with risperidone. However, the confidence intervals for the two conventional antipsychotic groups (clozapine and olanzapine) overlapped the confidence interval for risperidone. The 12-month subanalyses also showed that the odds of diabetes were significantly increased in patients treated with low-potency conventional antipsychotics, clozapine, or olanzapine compared with patients treated with risperidone. On the basis of these results, the authors concluded that clozapine and olanzapine had a greater association with diabetes than risperidone.

In another report yet to be published, Caro and colleagues retrospectively examined treatment-emergent diabetes during exposure to either risperidone or olanzapine from prescription claims and physician diagnosis from the Regie de l'Assurance Maladie de Quebec (RAMQ). The study showed no significant difference in the risk of diabetes during treatment with olanzapine compared with risperidone (crude OR 1.08, CI=0.89-1.31); age and gender adjusted (HR 1.2, CI=1.0-1.43). The risk of diabetes in the olanzapine cohort was numerically slightly greater than the overall cohort, and was statistically significant compared with risperidone (HR 1.31, CI=1.05-1.65). On the basis of these results, the authors concluded that the risk of treatment-emergent diabetes was higher among patients treated with olanzapine versus risperidone. Limitations of this study included the lack of reference population not using antipsychotics, the absence of control for concomitant medications or severity of illness, and the fact that patients receiving olanzapine concurrently with risperidone were assigned to the olanzapine cohort.

Similar analyses have been performed comparing clozapine with conventional antipsychotics. Lund et al. (2001) compared the incidence rates of diabetes in 552 patients with schizophrenia who received clozapine with 2461 patients with schizophrenia who received conventional antipsychotics using pharmacy and medical claims from the Iowa Medicaid program. The authors found no statistically significant differences in the overall incidence rate of diabetes between schizophrenic patients who received clozapine versus schizophrenic patients who received conventional antipsychotics. However, the incidence rate of diabetes was found to be statistically significantly increased in the younger cohort (20 to 34 years old) with a relative risk of 2.5.

5.3.6. Case-Control Studies

Using medical and prescription records from the UK GPRD database, Koro and colleagues (2002) assessed the risk of diabetes in patients with schizophrenia treated with conventional antipsychotics, risperidone, olanzapine, or other newer agents. The authors identified patients who had been diagnosed as having and being treated for schizophrenia (n=19,637) between June 1987 and September 2000. Of the study population, the number of patients being treated with the antipsychotics of interest were: conventional antipsychotics (n=18,443), olanzapine (n=970), risperidone (n=1683), and other newer agents (n=578). In a nested case-control design, incident cases of diabetes were identified from this patient group as the earliest date of a diagnosis of diabetes or treatment of diabetes, occurring at least 3 months after the start of the study (n=451). Each case was matched to six controls matched by age and sex only (n=2696).

During the observation period, the authors identified 229 incident cases of diabetes during treatment with conventional antipsychotics, 7 incident cases of diabetes with olanzapine, 7 incident cases with risperidone, and 1 incident case of diabetes with other newer agents. Results showed that patients taking olanzapine had a significantly increased risk of developing diabetes than non-users of antipsychotics (odds ratio: 5.8; CI=2.0-16.7) and those taking conventional antipsychotics (odds ratio: 4.2; CI=1.5-12.2). Patients taking risperidone had a non-significant increased risk of developing diabetes than non-users of antipsychotics (odds ratio: 2.2; CI=0.9-5.2) and those taking conventional antipsychotics (odds ratio: 1.6; CI=0.7 –3.8). The risk of developing diabetes was also significantly increased in patients treated with conventional antipsychotics compared with no antipsychotic use (odds ratio: 1.4; CI=1.1-1.7). The authors noted that the study lacked power to compare the odds ratios between olanzapine and risperidone users.

Further, given the limitations of the UK GPRD database, the analysis could not control for important variables potentially related to the risk of diabetes, including severity of schizophrenia or important risk factors for diabetes such as race, social class, or weight gain. Finally, the results of the study represent a 3-month period within a 3-year study, with no information provided as to how this period was selected or as to how representative this 3-month window was of the remainder of the study period.

In a similarly designed nested-case control study, Kornegay and colleagues (2002) also used the UK GPRD database to compare the odds ratio of current (within the prior 6 months) or recent (within the prior 7 to 12 months) antipsychotic exposure among patients diagnosed with incident diabetes compared with those without incident diabetes. The study population included all patients who had received at least one prescription for an antipsychotic for any indication between January 1994 and December 1998 (n=73,428). In a nested, case-control design, each incident case of diabetes (n=424) was matched to four controls on age, gender, and general practice (n=1522). Of the cases in the currently exposed group, there were 8 patients on atypical (5 risperidone, 3 olanzapine) and 152 patients on conventional antipsychotics. Among cases in the recently exposed group, there were 26 patients on conventional and no patients on atypical antipsychotics. Odds ratios were adjusted for any number of additional variables, including primary psychiatric diagnosis, some medical conditions (myocardial infarction, stroke, angina, hypertension), BMI, smoking status, and alcoholism.

The adjusted odds ratio for current use of any antipsychotic drug compared with no use in the past year among those with diabetes was 1.7 (CI=1.3-2.3). The adjusted odds ratio for current use of atypical and conventional antipsychotic drugs compared with no use in the past year among those with diabetes was 4.7 (CI=1.5-14.9) and 1.7 (CI=1.2-2.3), respectively. The adjusted odds ratio for recent use of conventional antipsychotic drugs compared with no use in the past year among those with diabetes was 1.0 (CI=0.6-1.6). The odds ratio for recent atypical antipsychotic drug use could not be calculated due to no study subjects had this exposure. The authors concluded that there is an increased risk of incident diabetes among current users of conventional and atypical antipsychotics which were independent of other risk factors. However, they cautioned that the numerically larger odds ratio observed among users of atypical antipsychotics should be viewed as preliminary, in light of the fact that the current atypical antipsychotic use group contained very few incident cases of diabetes.

Another case-control study compared the risk of developing diabetes in patients with psychiatric disorders who used clozapine compared with non-users of clozapine or use of other antipsychotics (Wang 2002). The data was obtained using medical and pharmacy claims data from the New Jersey Medicaid program. Using a case-control design, 7227 cases of newly treated diabetes and 6780 controls were identified. The authors found no significant increase in risk of developing diabetes with clozapine use (odds ratio: 0.98; CI=0.74-1.31). They found no increased risk of diabetes associated with higher doses of clozapine or longer duration of clozapine therapy. A significantly increased risk of diabetes was seen with use of chlorpromazine (odds ratio: 1.31; CI=1.09-1.56) and perphenazine (odds ratio: 1.34; CI=1.11-1.62).

5.3.6.4. Summary of Results and Interpretations of Cohort and Case-Control Studies

Table 5.5 summarizes the results of cases control and retrospective cohort studies involving olanzapine-treated patients that have examined a possible association between the use of antipsychotic medications and diabetes.

Table 5.5. Summary of Case-Control and Retrospective Cohort Studies Comparing Risk of Diabetes During Treatment with Antipsychotics

Author / Title	Database/ Study Design/ Sponsor	Sample Size	Antipsychotics (Conventional or Atypical) > Non-Use	Atypical > Conventional	Olanzap Other A
Cavazzoni P: A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United Kingdom.	**UK GPRD database;** Retrospective cohort study Sponsor: Eli Lilly and Company	Conv APs 43,651 Atypical APs 2550 Gen Pop 266,272	**YES** Combined conv + atypical cohort > non-use (HR=1.5; CI=1.1-1.9) Combined conv > non-use (HR=3.5; CI=3.1-3.9) Combined atypical > non-use (HR=3.1; CI=2.9-3.4)	**YES** Combined atypical cohort > combined conv (HR=3.3; CI=1.7-6.5)	**Not dire**
Koro CE: Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study.	**UK GPRD database;** Nested case-control study Sponsor: Bristol-Meyers Squibb	Conv APs 18,443 Atypical APs Ris 1683 Olz 970 Other 578	**YES** Conv AP group > non-use (OR 1.4; CI=1.1-1.7) Olz group > non-use (OR=5.8; CI=2.0-16.7) **NO** Ris group not significantly different from non-use OHR 2.2; CI=0.9-5.2)	**YES** Olz group > combined conv (OR=4.2; CI=1.5-12.2) **NO** Ris group not significantly different from combined conv (OR 1.6; CI=0.7-3.8)	**Not dire**

(continued)

Table 5.5. Summary of Case-Control and Retrospective Cohort Studies Comparing Risk of Diabetes During Treatment with Antipsychotics (continued)

Author / Title	Database/ Study Design/ Sponsor	Sample Size	Antipsychotics (Conventional or Atypical) > Non-Use	Atypical > Conventional	Olanzap Other A
Kornegay CJ: Incident diabetes associated with antipsychotic use in the United Kingdom General Practice Research Database.	**UK GPRD database;** Case control Sponsor: Boston Collaborative Drug Surveillance Program, supported by grants from AstraZeneca, Berlex, Bristol-Meyers Squibb, Glaxo-Wellcome, Hoffman-LaRoche, Janssen Pharmaceutica, McNeil, Novartis	Any AP 73,428 Incident cases of DM 424 Controls 1522	**YES** Combined conv > non-use (OR=1.7; CI=1.2-2.3) Combined atypical > non-use (OR=4.7; CI=1.5-14.9)	**Not directly compared**	**Not dire**

(continued)

Table 5.5. Summary of Case-Control and Retrospective Cohort Studies Comparing Risk of Diabetes During Treatment with Antipsychotics (continued)

Author / Title	Database/ Study Design/ Sponsor	Sample Size	Antipsychotics (Conventional or Atypical) > Non-Use	Atypical > Conventional	Olanzap Other A
Caro J: The risk of developing diabetes in users of atypical antipsychotics.	**Quebec Medicare database;** Retrospective cohort study Sponsor: Janssen Pharmaceutica	Olz 19,153 Ris 14,792	**Not directly compared**	**Not directly compared**	**NO (ove** Olz coh differen (HR=1.2 **YES (w** **only)** Olz coh (HR=1.3

(continued)

Table 5.5. Summary of Case-Control and Retrospective Cohort Studies Comparing Risk of Diabetes During Treatment with Antipsychotics (continued)

Author / Title	Database/ Study Design/ Sponsor	Sample Size	Antipsychotics (Conventional or Atypical) > Non-Use	Atypical > Conventional	Olanzap Other A
Buse J: A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States	**AdvancePCS database;** Retrospective cohort study Sponsor: Eli Lilly and Company	Conv APs 19,782 Hal 8476 Atypical APs 38,969 Olz 13,863 Ris 20,633 Quet 4186 Cloz 277	**YES** Combined conv cohort > non-use (HR=3.5; CI=3.1-3.9) Combined atypical cohort > non-use (HR-3.1; CI=2.9-3.4)	**NO** Combined conv cohort not significantly different from atypical cohort (HR=0.966; CI=0.8-1.1) Olz not significantly different from hal cohort (HR=0.9; CI=0.8-1.1) Cloz not significantly different from hal cohort (HR=1.31; CI=0.60-2.86) Quet < hal cohort (HR=0.67; CI=0.46-0.97) **YES** Ris > hal cohort (HR=1.23; CI=1.01-1.50)	**NO** Olz coh different (HR=0.9 [data on

(continued)

Table 5.5. Summary of Case-Control and Retrospective Cohort Studies Comparing Risk of Diabetes During Treatment with Antipsychotics (continued)

Author / Title	Database/ Study Design/ Sponsor	Sample Size	Antipsychotics (Conventional or Atypical) > Non-Use	Atypical > Conventional	Olanzap Other A
Lage MJ, Kemner JE: Use of atypical antipsychotics and the incidence of diabetes: evidence from a claims database.	**IMS Lifelink claims database**; Retrospective cohort study Sponsor: Eli Lilly and Company	Conv APs 3381 Atypical APs 3377	**Not directly compared**	**NO** Combined atypical cohort not significantly different from combined conv cohort (OR=1.03; p=.82) Olz not significantly different from combined conv cohort (OR=.98; p=.9) Ris not significantly different from combined conv cohort (OR=1.17; p=.35)	**NO** Olz not different (OR=0.8

(continued)

Table 5.5. Summary of Case-Control and Retrospective Cohort Studies Comparing Risk of Diabetes During Treatment with Antipsychotics (continued)

Author / Title	Database/ Study Design/ Sponsor	Sample Size	Antipsychotics (Conventional or Atypical) > Non-Use	Atypical > Conventional	Olanzap Other A
Gianfrancesco F: Association of new-onset diabetes and antipsychotics: findings from a large health plan database.	**Large mixed indemnity and managed health care plans in the US;** Retrospective cohort study Sponsor: Janssen Pharmaceutica	High potency Conv APs 1376 Low potency Conv APs 480 Olz 1047 Ris 1368 Cloz 63	**YES** **8-month results**:[a] High-potency conv > non-use (OR=1.065; p=.025) Low-potency conv > non-use (OR=1.109; p=.003) Olz > non-use (OR=1.099; p=.0006) Cloz > non-use (OR=1.182; p=.01) **NO** Ris not significantly different from non-users (OR=.989; p=.765)	**NO** **12-month results** Low-potency conv > ris (OR=3.93; p<.05) Olz > ris (OR=3.53; p<.05) Cloz > ris (OR=8.45; p<.05) High-potency conv not significantly different from ris (OR=2.42; p=NS)	**YES** **12-mont** Olz > ris

a Gianfrancesco results at 4 months were comparable with 8-month results.
b Subanalyses converted the odds ratios for AP duration to 12 months.

(continued)

Table 5.5. Summary of Case-Control and Retrospective Cohort Studies Comparing Risk of Diabetes During Treatment with Antipsychotics (concluded)

Author / Title	Database/ Study Design/ Sponsor	Sample Size	Antipsychotics (Conventional or Atypical) > Non-Use	Atypical > Conventional	Olanzap Other A
Sernyak MJ: Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia.	**VA database;** Cross-sectional cohort study Sponsor: Department of Veterans Affairs	Conv APs 15,984 Atypical APs 22,648 Cloz 1207 Olz 10970 Quet 955 Ris 9903	**Not directly compared**	**YES** Any atypical > any conv (all ages) (OR=1.09; CI=1.03-1.15) Also, any atypical significantly > any conv age <40, 40-49, and 50-59 years Cloz significantly > conv for all ages, <40, 40-49, and 60-69 years Olz > any conv for all ages, <40, 40-49, and 50-59 years Quet > any conv all ages, <40 and 40-49 years Ris > any conv for age <40 and 50-59 years	**Not dire**

Abbreviations: APs = antipsychotics; Cloz = clozapine; conv = conventional; DM = diabetes mellitus; Gen Pop = general population; Hal = haloperidol; Olz = olanzapine; Ris = risperidone; UK GPRD = United Kingdom General Practice Research Database.

Note: Table summarizes all studies which included olanzapine-treated patients in the analysis, published or presented, up to 30 September 2002.

A number of retrospective cohort studies examining a possible association between antipsychotic medications and diabetes have been reported. These studies vary in study design, sample size, methods, and specific comparisons. Overall, the results suggest that patients treated with antipsychotics may have a greater likelihood of diabetes than patients who are not treated with these medications. Conclusions regarding an increased risk of diabetes between patients treated with atypical and patients treated with conventional antipsychotics are more tentative. Finally, these data do not appear sufficient to support any conclusions regarding differences in likelihood of diabetes between patients treated with specific atypical antipsychotic medications.

5.3.7. Other Studies

A retrospective chart review evaluated changes in weight, glucose, and lipids after 1 year of treatment with olanzapine (n=47, mean dose 16.7 mg/day) or risperidone (n=47, mean dose 4.5 mg/day) (Meyer 2002). At endpoint, both the olanzapine and risperidone treatment groups experienced a statistically significant increase in weight, with no significant difference between treatment groups. Risperidone-treated patients had a non-significant increase from baseline in fasting glucose (0.68 mg/dL; p=.762), while the olanzapine-treated patients experienced a significant increase from baseline (7.3 mg/dL; p=.031) in the sample as a whole. There was no statistically significant difference between olanzapine and risperidone groups in the sample as a whole; however, there was a significant difference in fasting glucose values in the non-elderly subpopulation (patients <60 years) (risperidone 0.74, olanzapine 10.8, p=.030). No apparent correlation was found between weight gain and changes in fasting glucose for either treatment group. Limitations of this study include the retrospective nature of the data collected; absence of a control group receiving atypical antipsychotics; predominantly male, Caucasian demographic; and the fact that the population of interest comprised long-term hospital patients. Small sample sizes in this study also limited the ability to detect significant differences, especially among clinically important subgroups such as patients ≥60 years of age and those patients receiving lithium or valproate. The authors report that dose correlations calculated for this study may not be as useful as those performed in a more stable outpatient cohort due to the significant and frequent dose adjustments performed during the first year of treatment with both agents in this severely mentally ill state hospital population.

Melkersson et al. (2001) measured glucose and a variety of metabolic factors in 14 patients treated with olanzapine. However, this study adds little to the understanding of effects of the drug on glucose homeostasis. Three of the patients had fasting glucose levels above the normal range, and one of the three patients had a glucose level >126 mg/dL, suggestive of diabetes. The study also reported weight increase and elevated insulin levels in many subjects. However, interpretation of these results is made difficult by the cross-sectional design, the lack of a control group, and the failure to assure fasting status at the time glucose was measured.

Henderson and colleagues conducted a naturalistic observational study of 82 outpatients with schizophrenia or schizoaffective disorder who had been treated with clozapine over a 5-year time period (Henderson et al. 2000). Data were collected from review of medical records. A diagnosis of diabetes was made based on a fasting glucose >126 mg/dL. By the end of the 5-year observation period, 36.6% of patients were diagnosed with diabetes and treated by their primary care physicians. Patients gained an average of 1.16 pounds per month. Weight gain appeared to plateau after Month 46 from initiation of clozapine, and was not a significant risk factor for the development of diabetes in this population. Total daily dose of clozapine and use of valproate were also not significant risk factors for the development of diabetes. While this series provides important longitudinal data, conclusions as to a potential role of clozapine on the development of diabetes are limited by the retrospective design and the lack of a parallel control group with similar pre-treatment characteristics as the clozapine cohort.

6. Overall Summary

Reports of glucose dysregulation in association with severe psychiatric disorders predate the advent of antipsychotics in clinical practice. The introduction of chlorpromazine led to the first series of reports associating antipsychotic use with abnormalities in glucose homeostasis. The widespread use of atypical antipsychotics has witnessed a renewed interest in mental disorders and glucose dysregulation, and the potential role that atypical antipsychotics may play in the development of diabetes in psychiatrically-ill patients.

The recent interest in a possible role for atypical antipsychotic agents to increase the risk for diabetes in patients suffering from severe psychiatric disorders has occurred in the context of a global epidemic of diabetes in the general population. In parallel, there is substantial evidence that many individuals with diabetes are undiagnosed and that the onset of diabetes is occurring at a younger age in the general population.

There is mounting evidence that the prevalence of diabetes and diabetes-related events is greater among patients with schizophrenia and bipolar disorder. The reasons for this observation remain unresolved; however, likely factors include common genetic or environmentally-induced vulnerability, as well as factors potentially associated with the use of psychotropic drugs, including antipsychotics.

In a comparative analysis of the FDA MedWatch database conducted by Lilly, the total number of glucose dysregulation events was greatest with olanzapine, followed by clozapine, risperidone, quetiapine, and ziprasidone. When total patient-years exposures were taken into consideration, the highest reporting rate for the total number of events was observed with clozapine, followed by ziprasidone, olanzapine, quetiapine, and risperidone. When only severe events of glucose dysregulation (all MedDRA terms suggestive of diabetic ketoacidosis or diabetic hyperosmolar states with or without coma) were taken into consideration, the greatest reporting rate was observed with clozapine, followed by olanzapine, quetiapine, and risperidone.

In the Lilly Clintrace spontaneous event database, a majority of severe spontaneous adverse events of hyperglycemia and diabetes reported during treatment with olanzapine were confounded by the presence of baseline risk factors for diabetes, medical conditions that have been established to affect glucose homeostasis, or concomitant treatment with drugs known be associated with glucose dysregulation.

The evaluation of a potential contribution of olanzapine or other antipsychotics to the development of diabetes, as well as possible differences during treatment with antipsychotics to the relative risk of diabetes, requires systematic research using a multimodal approach. Further, distinctions need to be made between changes in glucose homeostasis mediated by treatment-emergent weight gain and changes potentially related to direct drug effects on known pathways of glucose regulation.

Large cohort studies in discrete patient populations (eg, the VA hospital system) or using prescription benefit data can be designed to evaluate the relative risk of diabetes in patients treated with antipsychotics. A number of cohort studies (including two studies sponsored by Eli Lilly and Company) have been conducted to compare the relative risk of diabetes during treatment with specific atypical antipsychotics or classes of antipsychotics (conventional versus atypical). The results of these studies have yielded inconsistent results. Some studies suggest that the risk of diabetes may be greater in patients treated with atypical compared to conventional antipsychotics. Other studies suggest that, while the risk of diabetes may be greater in patients treated with antipsychotics compared to untreated controls, there may not be substantial differences in the risk of diabetes among patients treated with most atypical and conventional antipsychotics.

A crucial step in the investigation of a potential effect of olanzapine or other antipsychotics in the development of diabetes is a systematic assessment of baseline characteristics for those patients who develop treatment-emergent diabetes (TED). An analysis of the integrated olanzapine schizophrenia clinical trial database suggested that risk factors for TED in patients participating in the studies were similar to established risk factors for diabetes in the general population, and that the risk factor profiles of TED patients were similar across patients treated with various antipsychotics. Further, this analysis suggests that any impact of treatment assignment to olanzapine, or treatment-emergent weight gain, on the risk for TED over the relatively short observation periods available from these clinical analyses may be relatively small when compared to the impact of baseline characteristics of random glucose and the number of major risk factors for diabetes.

Finally, careful consideration must be given to potential direct drug effects on specific mechanisms involved in glucose homeostasis. Pancreatic insulin secretory response to a hyperglycemic challenge and insulin receptor sensitivity represent two critical functions of glucose regulation, and are best evaluated with hyperglycemic and euglycemic clamp procedures, respectively, within the context of a controlled, randomized, prospective study design. Studies in healthy volunteers allow for control of potential effects of the psychiatric disorder (both as a trait or as a state) on glucose homeostasis. The results of two prospective, randomized studies in healthy volunteers did not demonstrate significant decrease in insulin secretion or insulin sensitivity after 2.5 to 3 weeks of treatment with olanzapine or risperidone. These results are in contrast with the decrease in insulin secretion observed in healthy volunteers following short exposures to diphenylhydantoin (1 week), and for the decrease in insulin sensitivity reported after short exposures (1 to 4 weeks) to the HIV protease inhibitor indinavir and the glucocorticoid prednisone.

7. Overall Conclusions

A potential etiological contribution of olanzapine to the development of diabetes was extensively evaluated on the basis of available data, including results of studies conducted by Lilly, and a review of the relevant scientific literature available to date. While anecdotal clinical observations, spontaneous adverse event reports, and uncontrolled studies are important for hypothesis generation, these hypotheses must then be tested using a systematic, multimodal, scientific approach.

To this date, results of systematic evaluations of a potential association between diabetes and use of antipsychotic medications support the following statements:

1. Two prospective, randomized studies in healthy volunteers did not demonstrate a significant decrease in insulin secretion or insulin sensitivity after 2.5 to 3 weeks of treatment with olanzapine or risperidone. These results contrast those that have been described for insulin secretion in healthy volunteers following short exposures to diphenylhydantoin (1 week), and for insulin sensitivity after short exposures (1 to 4 weeks) to the HIV protease inhibitor indinavir and the glucocorticoid prednisone.

2. Evaluations of characteristics of patients with treatment-emergent diabetes (TED) from case reports and Lilly retrospective analysis of clinical trials database suggest that many of these patients represent a subgroup with a high baseline burden of risk for diabetes or have evidence suggestive of preexisting unrecognized glycemic abnormalities.

3. Analyses of the FDA MedWatch database conducted by Lilly indicate that glucose-related events have been reported during treatment with all currently marketed atypical antipsychotics. Given the limitations of spontaneous adverse event reporting, these data cannot be used to make definitive conclusions in regard to causality or to differences in the incidence or prevalence of glucose-dysregulation events in patients who have been treated with atypical antipsychotics currently marketed in the US.

4. In the Lilly Clintrace postmarketing database, a majority of severe glucose-related adverse events reported during treatment with olanzapine are confounded by baseline risk factors for diabetes, and by medical conditions and concomitant medications that are known to affect glucose homeostasis.

5. A number of retrospective cohort studies examining a possible association between antipsychotic medications and diabetes have been reported. These studies vary in study design, sample size, methods, and specific comparisons. Overall, the results suggest that patients treated antipsychotics may have a greater likelihood of diabetes than patients who are not treated with these medications. Conclusions regarding an increased risk of diabetes between users of atypical and conventional antipsychotics are more tentative. Finally, these data do not appear sufficient to support any definitive conclusions regarding differences in likelihood of diabetes between users of specific atypical antipsychotic medications.

In conclusion, it is the opinion of Eli Lilly and Company that the cumulative data currently available do not consistently support the presence of differences in the risk for diabetes, or in changes in markers of glucose regulation, in patients treated with olanzapine compared with other atypical antipsychotics.

8. Educational Initiatives

Lilly has initiated educational programs and information sources designed to educate health care professionals on the health and metabolic issues faced by patients with severe mental illness. Lilly has provided unrestricted education grants toward the sponsorship of Continuing Medical Education programs, has developed programs that focus on fitness and nutrition, and maintains a toll-free 800 line for information on Zyprexa.

The Solutions for Wellness program, which focuses on healthy eating, fitness, sleep, and stress factors, has been made available by Lilly to physicians, regardless of the medication prescribed. Physicians can use this program to develop a personalized fitness and nutrition program for the functional outpatient. The program includes follow-up phone calls with the patient for continued motivation to complete the 24-week program. For patients in a community health setting, a modular, group approach can be used with this program to educate patients about fitness and nutrition. This program is in the early phase (Summer 2002) of execution.

The Continuing Medical Education Programs have consistently received high ratings by attendees, with 90% to 95% of survey respondents identifying that these educational activities enhance their ability to treat and manage their patients. In addition to providing unrestricted grants to Continuing Medical Education providers, materials from these programs have been made available to health care providers in the form of video and audio tapes. Printed materials based on the content of the Continuing Medical Education programs have been published in journals such as the Journal of Clinical Psychiatry.

In order to provide a ongoing source of easily accessible information, Lilly has a toll-free 800 line where physicians can speak to health care professionals about questions regarding Zyprexa. In addition, the Lilly Global Medical Information group provides answers to health care provider questions through medical letters on a variety of topics.

Lilly has generated new ideas regarding possible future educational initiatives such as:

- Development of consensus guidelines with the American Diabetes Association for awareness of comorbidity of diabetes with serious and persistent mental illness.
- Development of a group of certified diabetes educators who could offer perspectives to psychiatrists on the comorbidity of psychiatric illness and the role of the psychiatrist in assessment of patients and linking patients with health and fitness programs.
- Develop a health care professional staff who have specialized training regarding the issues of comorbid disease in patients with schizophrenia and bipolar disorder and have them operate a toll-free 800 line.
- Continue to provide unrestricted grants to Continuing Medical Education providers to educate physicians on topics related to metabolic disorders and comorbid disease in people with schizophrenia and bipolar disorder.

In summary, education initiatives can play a vital role in informing physicians about health, fitness, nutrition and diabetes as they treat patients with schizophrenia and bipolar disorder. These initiatives can help provide optimal care for patients with psychiatric disorders.

9. References

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Appendix A: HGIM Manuscript

Appendix B: AdvancePCS Manuscript

Appendix C: List of Published Case Reports of Glucose Dysregulation during Treatment with Atypical Antipsychotics (May 2000 through September 2002)

This Appendix contains a list of published case reports, including cases of diabetic ketoacidosis, type 1 diabetes mellitus (DM), and/or type 2 DM in temporal association with clozapine, olanzapine, risperidone, quetiapine, and ziprasidone as of September 2002. The diagnosis and baseline obesity (ie, classification of obesity and ideal body weight) are reported as defined by the respective report authors.

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