A 24-Week, Multicenter, Open-Label, Randomized Study to Compare Changes in Glucose Metabolism in Patients With Schizophrenia Receiving Treatment With Olanzapine, Quetiapine, or Risperidone

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Objective: This randomized, 24-week, flexible-dose study compared changes in glucose metabolism in patients with DSM-IV schizophrenia receiving initial exposure to olanzapine, quetiapine, or risperidone.

Method: The hypothesized primary endpoint was change (baseline to week 24) in area under the curve (AUC) 0- to 2-hour plasma glucose values during an oral glucose tolerance test (OGTT); primary analysis: olanzapine versus quetiapine. Secondary endpoints included mean change in AUC 0- to 2-hour plasma insulin values, insulin sensitivity index, and fasting lipids. The first patient enrolled on April 29, 2004, and the last patient completed the study on October 24, 2005.

Results: Mean weight change (kg) over 24 weeks was +3.7 (quetiapine), +4.6 (olanzapine), and +3.6 (risperidone). Based on data from 395 patients (quetiapine, N = 115 [mean dose = 607.0 mg/day], olanzapine, N = 146 [mean dose = 15.2 mg/day], and risperidone, N = 134 [mean dose = 5.2 mg/day]), mean change in AUC 0- to 2-hour glucose value (mg/dL × h) at week 24 was significantly lower for quetiapine versus olanzapine (t = 1.98, df = 377, p = .048). Increases in AUC 0- to 2-hour glucose values were statistically significant with olanzapine (+21.9 mg/dL × h, 95% CI = 11.5 to 32.4 mg/dL × h) and risperidone (+18.8 mg/dL × h, 95% CI = 8.1 to 29.4 mg/dL × h), but not quetiapine (+9.1 mg/dL × h, 95% CI = –2.3 to 20.5 mg/dL × h). AUC 0- to 2-hour insulin values increased statistically significantly with olanzapine (+24.5%, 95% CI = 11.5% to 39.0%), but not with quetiapine or risperidone. Reductions in insulin sensitivity index were statistically significant with olanzapine (–19.1%, 95% CI = –27.9% to –9.3%) and risperidone (–15.8%, 95% CI = –25.1% to –5.4%), but not quetiapine. Total cholesterol and low-density lipoprotein levels increased statistically significantly with olanzapine (+21.1 mg/dL, 95% CI = 13.0 to 29.2 mg/dL, and +20.5 mg/dL, 95% CI = 13.8 to 27.1 mg/dL, respectively) and quetiapine (+13.1 mg/dL, 95% CI = 4.3 to 21.9 mg/dL, and +13.3 mg/dL, 95% CI = 6.1 to 20.5 mg/dL, respectively), but not risperidone. Statistically significant increases in triglycerides (+30.9 mg/dL, 95% CI = 10.9 to 51.0 mg/dL), total cholesterol/high-density lipoprotein (HDL) ratio (0.5, 95% CI = 0.2 to 0.8), and triglyceride/HDL ratio (0.3, 95% CI = 0.0 to 0.6) were observed with olanzapine only.

Conclusion: The results indicate a significant difference in the change in glucose tolerance during 6 months' treatment with olanzapine versus quetiapine, with significant reductions on olanzapine and risperidone, but not quetiapine; these differential changes were largely explained by changes in insulin sensitivity.

Trial Registration: clinicaltrials.gov Identifier: NCT00214578

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Schizophrenia is a chronic, debilitating, and multidimensional illness that can adversely impact quality of life and significantly reduce lifespan, largely related to premature cardiovascular disease.[1,2] Patients with schizophrenia have an increased prevalence of modifiable cardiometabolic risk factors (e.g., obesity, hyperglycemia, smoking, hypertension, and lipid abnormalities),

compared with that found in the general population.[3–5] Contributions to the increased prevalence of these risk factors are multifactorial, including poverty, poor nutrition, lack of exercise and restricted access to healthcare, and relative underutilization of primary and secondary prevention approaches in this population.[4,6,7]

In addition, there is increasing interest in the effects of antipsychotic treatment on the development or worsening of metabolic disturbances, based on evidence that treatment with specific antipsychotics is associated with changes in weight, plasma lipids, insulin resistance, and glucose tolerance.[6,8–10]

The American Diabetes Association, as well as the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity, sponsored a consensus statement summarizing differences in the risk of weight gain, diabetes, and dyslipidemia associated with different atypical antipsychotics, based on evidence available at the time. The consensus statement recommended that patients undergo baseline screening and follow-up monitoring of weight, plasma glucose, and plasma lipids.[11]

A variety of approaches has been used to study medication-specific risk for adverse effects on glucose and lipid metabolism during antipsychotic treatment. Prospective, randomized, controlled clinical trials provide the gold standard approach for hypothesis testing in this area. A recent, well-publicized example is the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE).[8] Although the trial was designed primarily to compare the time to treatment discontinuation between olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine in patients with schizophrenia, secondary endpoints included several metabolic indicators (e.g., body weight, plasma glucose, lipids, and glycosylated hemoglobin). The results suggested differences between medications with regard to changes in weight, glucose, and lipids, relevant to the prediction of cardiovascular and diabetes risk parameters.[8] However, interpretation of the metabolic findings in the CATIE study is limited by unconfirmed fasting conditions, the confounding effect of variable prior treatments preceding the study, and a lack of sensitive metabolic indicators.[12] Similarly, the interpretation of many other studies evaluating the metabolic effects of antipsychotics is limited by methodological concerns that include use of less sensitive measures, such as unconfirmed fasting plasma glucose measurements at single time points, lack of needed comparator groups, and lack of adequate controls for potentially confounding factors such as underlying medical conditions.[10]

This report provides results from a large-scale, multicenter study evaluating differential changes in glucose tolerance, as well as insulin sensitivity, weight, plasma lipids, and other relevant parameters, in patients with schizophrenia randomly assigned to 24 weeks of treatment with olanzapine, quetiapine, or risperidone. Key design strengths include sensitive primary and secondary measures of glucose metabolism, confirmed fasting conditions, rigorous screening methods, and a patient sample not previously exposed to any of the agents under testing for at least 90 days.

METHOD

Study Design

This was a multicenter, randomized, 24-week, open-label, flexible-dose, parallel-group study (study number D1441C00125) that compared differential changes in glucose metabolism, plasma lipids, and weight-related measures in patients with schizophrenia receiving olanzapine, quetiapine, or risperidone. The first patient enrolled on April 29, 2004, and the last patient completed the study on October 24, 2005.

This study was conducted in 58 participating centers from 9 countries: Bulgaria (8 centers), the Czech Republic (8 centers), Germany (6 centers), Hungary (7 centers), Norway (1 center), Romania (7 centers), Slovakia (12 centers), South Africa (8 centers), and the United Kingdom (1 center). The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP). Patients provided written informed consent before the start of any study-related procedures.

Patients

Male and female patients aged 18–65 years were included in this study if they fulfilled the diagnostic criteria for schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Patients were eligible if they had not received previous antipsychotic treatment or had shown an inadequate response or poor tolerance to previous treatment and could benefit from a change in treatment. Key exclusion criteria included previous treatment with one of the study medications (quetiapine, olanzapine, or risperidone), clozapine, or chlorpromazine within 3 months and/or valproic acid, lithium, or antidepressants within 1 month; treatment with insulin or oral antidiabetic agents; patients who had recently started treatment with agents known to affect insulin sensitivity; patients with a known diagnosis of diabetes; and pregnancy. Patients were also excluded if they had a history of nonadherence, a diagnosis of any other Axis I disorder, any clinically relevant disease (e.g., liver, renal, or heart disease), or had received treatment with a depot antipsychotic within 1 dosing interval.

A small number of patients whose blood glucose rating was in the diabetic range as defined by the American Diabetes Association[13] (≥ 126 mg/dL for fasting glucose

and/or ≥ 200 mg/dL for 2-hour postload glucose) at baseline were incorrectly randomly assigned for participation in the study, despite the fact that they fulfilled exclusion criteria, due to a programming failure in the central laboratory. This affected 20 patients in the primary analysis population (3 patients in the quetiapine group, 10 in the olanzapine group, and 7 in the risperidone group) and 26 patients in the safety population (N = 5, 11, and 10, respectively); these patients were all excluded from the per protocol population (see statistical section for description of defined study samples). Following randomization, no patients were excluded due to development of diabetes during the study.

Treatment

Patients were randomly assigned sequentially, with an equal probability of receiving olanzapine, quetiapine, or risperidone. Patients were stratified according to body mass index (BMI) in 4 groups (< 18.5, 18.5–24.9, 25–29.9, ≥ 30 kg/m^2) and according to age in 2 groups (≤ 50 years, > 50 to ≤ 65 years). Randomization was performed using a validated computer-based system and an interactive voice recording system, which provided the assigned treatment and a randomization code for each patient, after all relevant information was entered by the investigator. Serum glucose and glycosylated hemoglobin (HbA_{1c}) values at screening were required to determine patient eligibility. These values were not blinded, and treatment assignment was open.

Patients entered a 5-day crossover period during which any previous antipsychotic was tapered off and study medication was escalated to the target dose (quetiapine 600 mg/day, olanzapine 15 mg/day, risperidone 6 mg/day). This was followed by a 23-week, flexible-dose, open-label period during which quetiapine was administered in the range of 400–800 mg/day; olanzapine, 10–20 mg/day; and risperidone, 4–8 mg/day. Quetiapine was administered twice daily, olanzapine once daily, and risperidone once or twice daily, depending on local prescribing information.

No other psychoactive medications were allowed during the study. All previous anticholinergic medication had to be withdrawn during the first week of treatment, by which time any residual extrapyramidal symptoms (EPS) from previous medication should have resolved. Benztropine mesylate (≤ 6 mg/day), trihexyphenidyl (≤ 6 mg/day), biperiden (≤ 6 mg/day), or procyclidine (≤ 30 mg/day) could be used to treat any newly emerging EPS-related adverse events; prophylactic use was prohibited. Benzodiazepines (lorazepam ≤ 4 mg/day, oxazepam ≤ 60 mg/day, or alprazolam ≤ 2 mg/day) and sleep medication (zolpidem tartrate ≤ 10 mg/day, chloral hydrate ≤ 2 g/day, zaleplon ≤ 20 mg/day, or zopiclone ≤ 7.5 mg/day) were permitted during the study. Medications considered to potentially affect glucose metabolism and insulin sensitivity (e.g., some antihypertensives) were restricted during the study.

Adherence to treatment was calculated on the basis of the difference between the number of dispensed and returned tablets. Patients were considered adherent if they rated ≥ 70% to ≤ 120%.

Assessments

Area under the curve 0- to 2-hour plasma glucose values during an oral glucose tolerance test. The hypothesized primary objective of the study was to compare the safety and tolerability of olanzapine versus quetiapine treatment in regard to glucose metabolism. The primary outcome variable was the mean change from baseline to week 24 in area under the curve (AUC) values for plasma glucose from 0 to 2 hours during an oral glucose tolerance test (OGTT).[14] A secondary objective was to compare the safety and tolerability of quetiapine and risperidone treatment regarding glucose metabolism by evaluating the mean change from baseline to week 24 in AUC 0- to 2-hour plasma glucose values during the OGTT.

Patients were hospitalized overnight to ensure 8- to 14-hour fasting conditions prior to OGTT.[14] A blood sample was taken prior to the test to determine fasting levels of variables related to glucose and lipid metabolism. The test commenced with the patient drinking 75 g of anhydrous glucose in 250–300 mL of water over 5 minutes. Blood samples were collected at 30, 60, 90, and 120 minutes by venous catheter.

Measures of insulin sensitivity and secretion. Other secondary objectives of the study were to compare the mean changes from randomization to week 24 in plasma insulin AUC 0- to 2-hour values during OGTT; insulin sensitivity index derived from OGTT,[15] fasting insulin values; and homeostasis model assessment of insulin resistance (HOMA-IR).[16] The change in plasma C-peptide levels was an exploratory measure, and mean relative changes in the insulinogenic index[17] were estimated in a post hoc descriptive analysis.

Insulin sensitivity index was calculated as 10,000 ÷ square root of ([fasting glucose (mg/dL) × fasting insulin (μIU/mL)] × [mean glucose (mg/dL) × mean insulin (μIU/mL) during OGTT]). HOMA-IR was calculated as follows: fasting plasma insulin (μIU/mL) × fasting plasma glucose (mmol/L) ÷ 22.5. Insulinogenic index was calculated as the ratio between simultaneous increments in plasma insulin and glucose from 0 to 30 minutes after glucose load (change in insulin at 30 minutes [μIU/mL] ÷ change in glucose at 30 minutes [mg/dL]).

Additional glucose parameters. Other secondary objectives of the study were to compare the changes from randomization to week 24 for fasting and 2-hour postload glucose; incidences of patients with hyperglycemia (fasting plasma glucose ≥ 126 mg/dL and/or 2-hour glucose ≥ 200 mg/dL); incidences of patients with impaired fast-

ing glucose (defined as fasting plasma glucose ≥ 100 and < 126 mg/dL) or impaired glucose tolerance (defined as 2-hour glucose ≥ 140 and < 200 mg/dL); and the change from randomization to week 24 in HbA_{1c} levels. The proportion of patients with $HbA_{1c} \geq 6.05\%$ was an exploratory measure.

Lipid parameters. Additional secondary objectives of the study were to compare the safety/tolerability of quetiapine, olanzapine, and risperidone in regard to blood lipid levels by evaluating fasting plasma lipid levels (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and triglycerides). The change in ratios between total cholesterol and HDL, and triglyceride and HDL levels, as proposed predictors of cardiovascular risk,[18,19] was also estimated as a post hoc analysis.

Body weight. Changes from randomization to week 24 were assessed for body weight, BMI (calculated as weight in kg ÷ height in m^2), and waist circumference.

All of the above assessments were made at the following intervals: baseline (randomization), week 12, and week 24 (±4 weeks). Key laboratory values, including glucose metabolic variables and lipids, were blinded throughout the study.

Other safety and tolerability objectives. In order to compare changes in prolactin levels, the mean change from baseline to week 24 in plasma prolactin (μg/L) was determined. The safety/tolerability profile of quetiapine, olanzapine, and risperidone regarding EPS and other adverse events was also examined by recording the following: mean change from baseline to week 24 in Simpson-Angus Scale[20] total score and Barnes Akathisia Scale[21] total score; incidence of adverse events; sitting and standing systolic and diastolic blood pressure and pulse rate; changes in electrocardiogram; and the proportion of patients using anticholinergic medication.

Efficacy measures. The efficacy of quetiapine, olanzapine, and risperidone was assessed by evaluation of clinical symptoms, using the following outcome variables: the proportion of patients with a Clinical Global Impressions-Improvement (CGI-I) scale rating of "very much improved" or "much improved" at the final assessment (last observation carried forward), and the proportion of patients with a Clinical Global Impressions-Severity of Illness (CGI-S) scale score less than or equal to 3 at week 24.

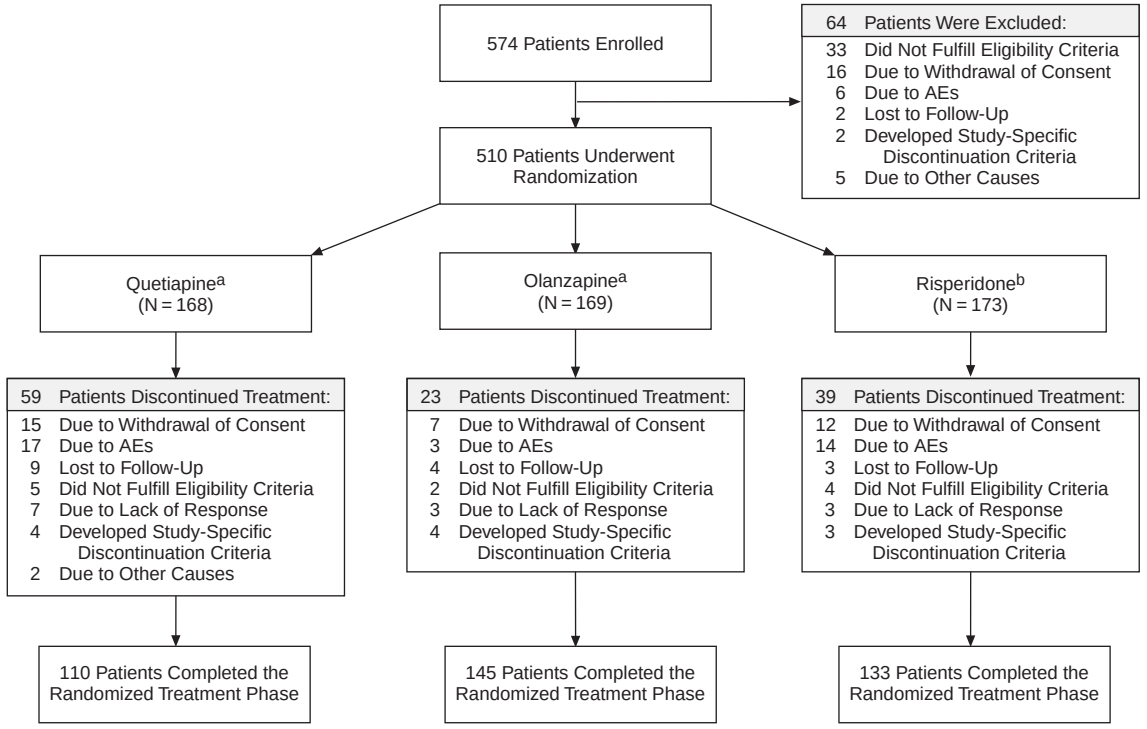
Statistical Analyses and Patient Populations

The power calculation for the sample size determination was based on weight change, due to its anticipated correlation with changes in plasma glucose levels and because there is a lack of published data on the variance of the primary variable. Calculations were based on information from previous long-term trials of quetiapine,[22] as well as on published olanzapine data.[23] The within-patient variability of the change from baseline for weight was assumed to be 6.4 kg. The sample size was calculated as the number of patients needed to find a change of 3 kg in mean weight from baseline to week 24 between the quetiapine and olanzapine groups. It was estimated that 95 patients per group (285 in total) would be required to provide 90% power for a 2-sided test at the 5% α level. After allowing for withdrawals and protocol violations, approximately 500 patients had to be randomly assigned in order to get 285 evaluable patients at week 24.

Primary and secondary endpoints were analyzed using the primary analysis population, which consisted of all randomly assigned patients who were given study treatment and had baseline and week 24 (±4 weeks) assessments. Primary and secondary measures were analyzed using analysis of covariance (ANCOVA) with baseline AUC 0- to 2-hour glucose value, BMI group, age group, and treatment as independent variables. Least squares means (LSMs) and 95% confidence intervals (CIs) were calculated. For the primary analysis, a p value was derived and a significant difference was declared if the p value was not higher than .05. For insulin and insulin sensitivity indices, log-transformed values were analyzed with the ANCOVA model. Least squares means and CIs were exponentially back-transformed. As the protocol stated that only descriptive analyses would be presented for secondary endpoints, post hoc analyses were performed to evaluate between-group differences and changes from baseline within groups, with statistical significance based on CI coverage of zero; no adjustments were made for multiplicity. A post hoc analysis was also carried out to assess the change in ratios between total cholesterol and HDL, and triglyceride and HDL levels, as validated predictors of cardiovascular risk.[18,19] Pearson correlation coefficients were calculated to explore possible correlations between change in weight and change in AUC 0- to 2-hour glucose values, and between change in weight and change in log-transformed insulin sensitivity index.

The per protocol population excluded patients with significant protocol violations or deviations, or patients considered to be nonadherent to treatment, i.e., who took < 70% or > 120% of the tablets. One patient randomly assigned to the olanzapine group actually received treatment with quetiapine; this patient was excluded from the per protocol population and was not included in the primary analysis population because of discontinuation before week 20. Only the primary analysis was repeated on the per protocol sample to test for homogeneity of the treatment changes. Adverse event data and any other safety analyses that were not the focus of the study objectives were analyzed on the safety population, which consisted of all randomly assigned patients who were given study treatment (i.e., who took at least 1 dose of medication), classified according to the treatment actually

Figure 1. Patient Disposition



[a]1 patient randomly assigned to olanzapine actually received quetiapine.
[b]1 patient did not receive treatment.
Abbreviation: AEs = adverse events.

received. Efficacy data were analyzed for the intent-to-treat (ITT) population, which included all randomly assigned patients who were given study treatment, classified according to randomized treatment.

RESULTS

Patients

A total of 574 patients were enrolled, and 510 were randomly assigned: quetiapine, N = 168; olanzapine, N = 169; and risperidone, N = 173. Details of patient disposition and baseline demographics are given in Figure 1 and Table 1, respectively. Overall, the treatment groups were well matched for baseline demographic, clinical, and glucose metabolism characteristics (Table 1). Most patients were male, had paranoid schizophrenia, and were receiving antipsychotic medication at time of randomization. As described in Table 1, less than 30% of patients randomly assigned to each treatment group were receiving no antipsychotics at randomization for an unknown period of time, while the majority of randomly assigned patients who were being treated at baseline were receiving conventional antipsychotics.

A total of 395 patients (quetiapine, N = 115; olanzapine, N = 146; risperidone, N = 134) had data at baseline and at ≥ 20 weeks, and were included in the primary analysis population. The per protocol population consisted of 330 patients (quetiapine, N = 98; olanzapine, N = 126; risperidone, N = 106), the safety population included 509 patients (quetiapine, N = 169; olanzapine, N = 168; risperidone, N = 172), and the ITT population comprised 509 patients (quetiapine, N = 168; olanzapine, N = 169; risperidone, N = 172). Unless otherwise stated, results from the primary analysis population are presented.

Treatment

Following randomization, mean (SD) doses at week 24 were as follows: quetiapine, 607.0 (128.3) mg/day; olanzapine, 15.2 (2.7) mg/day; and risperidone, 5.2 (1.0) mg/day. The corresponding dose ranges were quetiapine, 338–785 mg/day; olanzapine, 10–20 mg/day; and risperidone, 3–8 mg/day.

Use of concomitant medication during the study was similar across the treatment groups. Total use of concomitant benzodiazepines at any time during the study was 17.4% in the quetiapine group, 13.0% in the olanzapine group, and 18.7% in the risperidone group. The use of sleep medication was 16.5% in the quetiapine group, 17.1% in the olanzapine group, and 23.1% in the risperidone group.

Table 1. Key Demographic, Clinical, and Glucose Metabolism Characteristics of Patients With Schizophrenia at Baseline (primary analysis population)

Characteristic	Quetiapine (N = 115)	Olanzapine (N = 146)	Risperidone (N = 134)
Demographic and Clinical			
Age, mean (SD), y	39.4 (11.1)	40.5 (10.4)	38.3 (11.1)
Male:female, %	66:34	66:34	65:35
White, %	90.4	91.8	86.6
Weight, mean (SD), kg	73.6 (15.4)	71.9 (14.6)	72.1 (15.8)
LSM BMI (SE), kg/m^2	24.6 (0.36)	24.8 (0.36)	24.6 (0.36)
BMI, kg/m^2, %			
< 18.5	7.0	6.8	6.7
18.5 to < 25	47.0	49.3	52.2
25 to < 30	32.2	29.5	26.1
≥ 30	13.9	14.4	14.9
Schizophrenia subtype, %			
Paranoid	79.1	71.9	72.4
Residual	10.4	17.1	14.9
Undifferentiated	7.0	6.8	11.9
Disorganized	3.5	3.4	0.7
Catatonic	0.0	0.7	0.0
Years since diagnosis, mean (SD)	11.1 (10.2)	12.6 (10.5)	10.2 (9.7)
No antipsychotic medication at randomization, N (%)	33 (28.7)	42 (28.8)	37 (27.6)
Antipsychotic medication at randomization, N (%)	82 (71.3)	104 (71.2)	97 (72.4)
Conventional antipsychotics, oral, N (%)[a]	62 (53.9)	84 (57.5)	77 (57.5)
Conventional antipsychotics, IM, N (%)[a]	13 (11.3)	13 (8.9)	21 (15.7)
Atypical antipsychotics, N (%)[b]	1 (0.9)	1 (0.7)	0 (0.0)
Other antipsychotics, N (%)[c]	14 (12.2)	20 (13.7)	14 (10.4)
> 1 antipsychotic, N (%)[a–c]	24 (20.9)	25 (17.1)	26 (19.4)
Smoking, N (%)	67 (58.3)	86 (58.9)	86 (64.2)
Glucose metabolism characteristic, mean (SD)			
AUC glucose, mg/dL × h	255.1 (54.4)	260.9 (69.1)	259.3 (65.4)
Fasting glucose, mg/dL	92.6 (12.1)	93.7 (17.8)	93.7 (11.9)
2-h glucose, mg/dL	106.9 (33.6)	111.0 (42.1)	112.9 (38.3)
HbA_{1c}, %	5.3 (0.4)	5.3 (0.4)	5.3 (0.5)
Fasting plasma insulin, μIU/mL[d]	5.2 (79.9)	5.4 (63.7)	5.4 (52.5)
AUC insulin (OGTT) [μIU/mL × h][d]	80.3 (64.9)	71.3 (68.7)	67.6 (56.9)
Fasting C-peptide, ng/mL	2.3 (1.1)	2.2 (0.9)	2.2 (1.1)

[a]Medications with ATC codes N05AA, N05AB, N05AC, N05AD, N05AE, N05AF, N05AG, and N05AH (excluding atypical antipsychotics).
[b]Ziprasidone, aripiprazole, sertindole, or clozapine.
[c]Medications with ATC codes N05A, excluding medications included in footnotes *a* and *b*.
[d]Geometric mean (coefficient of variation).
Abbreviations: AUC = area under the curve, BMI = body mass index, IM = intramuscular, LSM = least squares means, OGTT = oral glucose tolerance test.

Adherence to treatment was similar across treatment groups: 98.3%, 99.3%, and 97.8% for patients receiving quetiapine, olanzapine, and risperidone, respectively.

Body Weight

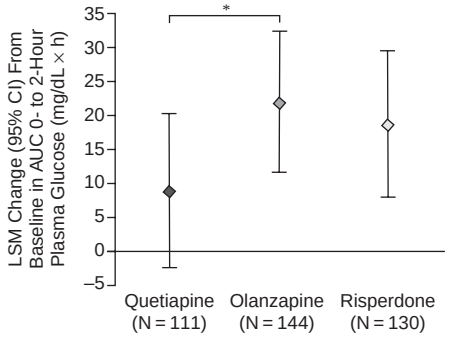
At week 24, mean weight change from baseline was +3.7 kg (95% CI = 2.4 to 4.9 kg) for quetiapine, +4.6 kg (95% CI = 3.5 to 5.7 kg) for olanzapine, and +3.6 kg (95% CI = 2.4 to 4.7 kg) for risperidone. These changes from baseline were statistically significant for all groups. Between-treatment differences were not statistically significant.

The change from baseline in mean BMI (kg/m^2) was +1.3 (95% CI = 0.9 to 1.7) for quetiapine, +1.6 (95% CI = 1.2 to 2.0) for olanzapine, and +1.3 (95% CI = 0.9 to 1.7) for risperidone. The mean change from baseline in waist circumference (cm) was +3.2 (95% CI = 1.9 to 4.6) in the quetiapine group, +4.4 (95% CI = 3.1 to 5.6) in the olanzapine group, and +3.0 (95% CI = 1.7 to 4.3) in the risperidone group. Pairwise comparisons showed that there were no significant differences in change from baseline in BMI or waist circumference between the treatment groups.

AUC 0- to 2-Hour Plasma Glucose Values During OGTT

Mean change from baseline to week 24 in AUC plasma glucose values (mg/dL × h) was +9.1 (95% CI = –2.3 to 20.5) with quetiapine (not statistically significant based on CI coverage of zero) and +21.9 (95% CI = 11.5 to 32.4) with olanzapine (statistically significant based on CI noncoverage of zero). The primary analysis results indicated that the difference in mean change from baseline in AUC 0- to 2-hour plasma glucose values was significantly different between quetiapine and olanzapine (–12.8 mg/dL × h, 95% CI = –25.5 to –0.1 mg/dL × h) (t = 1.98,

Figure 2. Change From Baseline to Week 24 in AUC 0- to 2-Hour Plasma Glucose Values During Oral Glucose Tolerance Test[a]



[a]Statistical significance is based on 95% CI coverage of zero.
*p = .048 versus olanzapine.
Abbreviations: AUC = area under the curve, LSM = least squares means.

df = 377, p = .048) (Figure 2). The mean change from baseline in AUC plasma glucose values with risperidone was +18.8 mg/dL × h (95% CI = 8.1 to 29.4 mg/dL × h) (statistically significant based on CI noncoverage of zero) at week 24. The secondary analysis results indicated that the difference in mean change from baseline in AUC plasma glucose values for quetiapine compared with risperidone was –9.6 mg/dL × h; 95% CI = –22.7 to 3.4 mg/dL × h (not statistically significant based on CI coverage of zero) (Figure 2). The change from baseline to week 24 in mean plasma glucose values over time (0- to 120-minute post–glucose load) for the 3 treatment groups is shown in Figure 3.

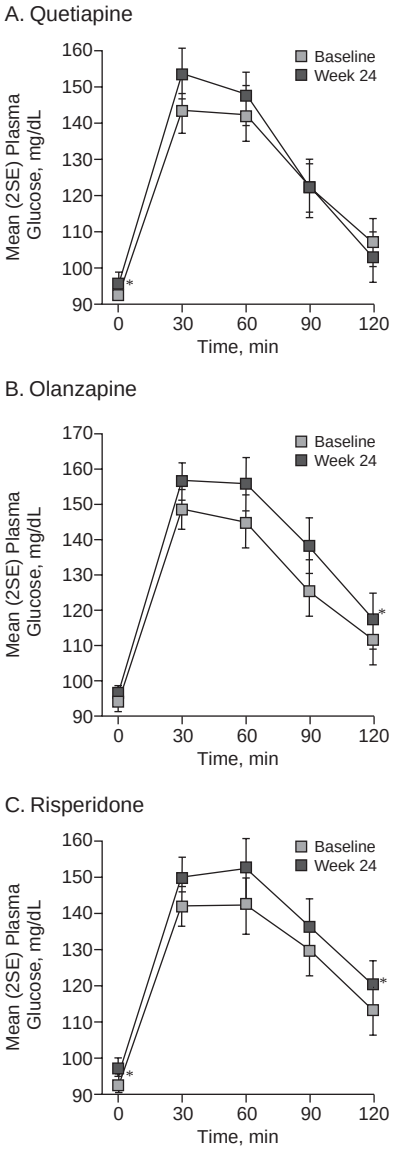
In the per protocol population, the mean change from baseline to week 24 in AUC 0- to 2-hour plasma glucose values (mg/dL × h) was +11.2 (95% CI = –0.1 to 22.6) in the quetiapine group and +26.2 (95% CI = 15.5 to 36.9) in the olanzapine group. The difference between quetiapine and olanzapine was statistically significant (t = 2.34, df = 322, p = .0199), confirming the results in the primary analysis population. Mean change from baseline to week 24 in the per protocol population was +21.0 mg/dL × h (95% CI = 10.3 to 31.7 mg/dL × h) in the risperidone group.

Examination of the within-treatment correlation between change in weight and change in AUC 0- to 2-hour glucose values indicated relatively weak associations for quetiapine, olanzapine, and risperidone (Pearson correlation coefficient: 0.25, 0.14, and –0.10, respectively).

Measures of Insulin Sensitivity and Secretion

Relative increases from baseline in AUC 0- to 2-hour plasma insulin values during OGTT were not statistically significant with quetiapine (+13.2%, 95% CI = –0.1% to 28.2%) or risperidone (+10.7%, 95% CI = –1.2% to

Figure 3. Change From Baseline to Week 24 in Plasma Glucose Values During Oral Glucose Tolerance Test, From 0 to 120 Minutes After Glucose Load[a,b]



[a]Values at 30, 60, and 90 min were not tested for significance.
[b]Mean change from baseline to week 24 in AUC 0- to 2-hour plasma glucose values: p = .048 quetiapine versus olanzapine.
*Significant change from baseline to week 24.

24.1%) but were with olanzapine (+24.5%, 95% CI = 11.5% to 39.0%). Analysis of insulin sensitivity, as assessed by insulin sensitivity index, showed that decreases from baseline were not statistically significant with quetiapine (–10.8%, 95% CI = –21.9% to 1.8%), but were statistically significant with olanzapine (–19.1%, 95% CI = –27.9% to –9.3%) and risperidone (–15.8%, 95% CI = –25.1% to –5.4%) (Figure 4). Within-treatment correlations between change in weight and change in insulin sensitivity index also indicated relatively weak

associations (Pearson correlation coefficient: –0.31, –0.45, –0.15 for quetiapine, olanzapine, and risperidone, respectively).

To further explore insulin secretion, the insulinogenic index, i.e., the early insulin response to oral glucose stimulation during the first 30 minutes of the OGTT, was estimated. The median relative change in insulinogenic index from baseline to week 24 was –0.2% (lower quartile, –41.7%; upper quartile, 40.5%) in the quetiapine group, –9.2% (lower quartile, –45.3%; upper quartile, 32.2%) in the olanzapine group, and –3.3% (lower quartile, –35.2%; upper quartile, 50.2%) in the risperidone group.

Mean changes in fasting insulin from baseline to week 24 were 3.3% (95% CI = –9.2% to 17.6%) for quetiapine, 8.5% (95% CI = –3.3% to 21.7%) for olanzapine, and 11.9% (95% CI = –0.2% to 25.5%) for risperidone.

For HOMA-IR, a measure of insulin resistance, increases of 6.4% (95% CI = –7.6% to 22.7%) and 11.0% (95% CI = –2.2% to 25.9%) from baseline to week 24 were seen for quetiapine and olanzapine, respectively, but were not statistically significant. A statistically significant difference from baseline to week 24 occurred with risperidone (16.8%; 95% CI = 2.9% to 32.4%).

Mean change from baseline to week 24 in plasma C-peptide levels was 0.4 ng/mL (95% CI = 0.1 to 0.6 ng/mL) for quetiapine, 0.4 ng/mL (95% CI = 0.2 to 0.7 ng/mL) for olanzapine, and 0.4 ng/mL (95% CI = 0.2 to 0.7 ng/mL) for risperidone. These increases from baseline were statistically significant for all 3 treatment groups.

Pairwise comparisons of the treatment groups at week 24 did not show any statistically significant difference in terms of mean change from baseline for AUC 0- to 2-hour plasma insulin values, insulin sensitivity index, fasting insulin values, HOMA-IR, or C-peptide values.

Additional Glucose Parameters

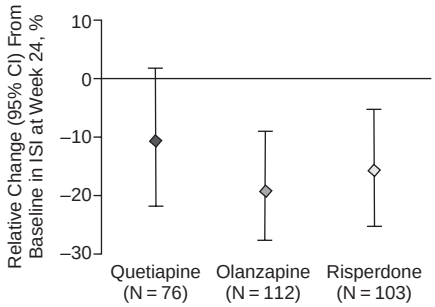
At week 24, small changes from baseline in mean fasting glucose values were seen in all treatment groups: 3.2 mg/dL (95% CI = 0.2 to 6.1 mg/dL) for quetiapine, 2.3 mg/dL (95% CI = –0.4 to 5.1 mg/dL) for olanzapine, and 4.4 mg/dL (95% CI = 1.6 to 7.2 mg/dL) for risperidone (statistically significant for quetiapine and risperidone). All mean changes were within the normal range, and there were no statistically significant differences between the treatment groups.

For 2-hour postload glucose (mg/dL), the mean change from baseline was not statistically significant for quetiapine (–1.9, 95% CI = –10.0 to 6.3), but was statistically significant for olanzapine (+9.8, 95% CI = 2.4 to 17.2), and risperidone (+10.6, 95% CI = 2.9 to 18.2) (Figure 3). The differences between quetiapine and olanzapine and between quetiapine and risperidone were statistically significant.

The proportion of patients in the primary analysis population with a blood glucose value in the diabetic range (fasting plasma glucose ≥ 126 mg/dL and/or 2-hour glucose ≥ 200 mg/dL) at baseline was 2.6% for quetiapine, 6.9% for olanzapine, and 5.2% for risperidone. At week 24, the corresponding values were 4.3%, 6.8%, and 6.8%. Of the 20 patients in the primary analysis population who had high glucose values at baseline (diabetic levels), 6 patients similarly had a high glucose measurement recorded at their following visit. The number (%) of patients with fasting glucose ≥ 126 mg/dL at baseline was 2 (1.8%), 3 (2.1%), and 3 (2.2%) and at week 24 was 3 (2.6%), 5 (3.4%), and 4 (3.0%) for quetiapine, olanzapine, and risperidone, respectively. In total, 8 patients had glucose values below the diabetic range at randomization but then at least 2 consecutive postrandomization values of fasting glucose ≥ 126 mg/dL and/or 2-hour glucose ≥ 200 mg/dL. Of these 8 patients, 2 patients received quetiapine, 2 received olanzapine, and 4 received risperidone. At baseline, 26.3% of patients receiving quetiapine, 20.0% receiving olanzapine, and 32.1% receiving risperidone were defined as having impaired fasting glucose (defined as fasting plasma glucose ≥ 100 and < 126 mg/dL) and/or impaired glucose tolerance (defined as 2-hour glucose ≥ 140 and < 200 mg/dL). At week 24, the corresponding values were 32.2%, 29.5%, and 40.6%. Pairwise comparisons between the treatment groups showed no significant differences between treatments with respect to the frequency of glucose measurements at the impaired fasting glucose, impaired glucose tolerance, or diabetic levels.

Small increases in HbA_{1c} from baseline were seen in each treatment group: quetiapine, 0.12% (95% CI = 0.05% to 0.19%); olanzapine, 0.05% (95% CI = –0.01% to 0.11%); risperidone, 0.07% (95% CI = 0.00% to 0.13%); these changes were statistically significant for quetiapine and risperidone, but were within the normal range and not clinically significant. The proportion of patients with HbA_{1c} ≥ 6.05% at baseline was 4.5% for quetiapine, 4.2% for olanzapine, and 6.8% for risperidone. At week 24, the corresponding values were 5.5%, 3.5%, and 4.7%. There were no statistically significant differences

Figure 4. Change From Baseline to Week 24 in Insulin Sensitivity Index (ISI) During Oral Glucose Tolerance Test[a]



[a]Statistical significance is based on 95% CI coverage of zero.

Table 2. Mean Change From Baseline to Week 24 in Fasting Lipid Levels (primary analysis population) and Lipid Ratios

Measure	Quetiapine	Olanzapine	Risperidone
Total cholesterol, mg/dL			
N[a]	107	142	124
Baseline	193.1	192.4	195.1
Change at week 24	13.1	21.1	4.8
95% CI	4.3 to 21.9	13.0 to 29.2	–3.5 to 13.2
HDL cholesterol, mg/dL			
N[a]	89	116	106
Baseline	41.8	43.4	44.7
Change at week 24	1.0	0.1	1.1
95% CI	–1.4 to 3.3	–2.0 to 2.3	–1.1 to 3.3
LDL cholesterol, mg/dL			
N[a]	108	142	125
Baseline	117.4	121.4	121.1
Change at week 24	13.3	20.5	5.1
95% CI	6.1 to 20.5	13.8 to 27.1	–1.8 to 11.9
Triglycerides, mg/dL			
N[a]	104	142	123
Baseline	166.2	146.1	154.2
Change at week 24	17.6	30.9	11.7
95% CI	–4.6 to 39.8	10.9 to 51.0	–9.2 to 32.5
Total cholesterol/HDL ratio			
N[a]	86	116	104
Baseline	4.9	4.6	4.6
Change at week 24	0.2	0.5	0.1
95% CI	–0.1 to 0.6	0.2 to 0.8	–0.3 to 0.4
Triglycerides/HDL ratio			
N[a]	86	116	104
Baseline	1.8	1.6	1.7
Change at week 24	0.2	0.3	0.2
95% CI	–0.1 to 0.6	0.0 to 0.6	–0.1 to 0.5

[a]Number of patients with nonmissing value.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

between treatments in HbA_{1c} levels or in the proportion of patients with $HbA_{1c} \geq 6.05\%$ at week 24.

Lipid Parameters

Changes from baseline to week 24 in total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides are shown in Table 2. Statistically significant increases from baseline in mean total cholesterol and LDL cholesterol, but not triglycerides, were seen for quetiapine. Increases from baseline in mean total cholesterol, LDL cholesterol, and triglycerides were statistically significant for olanzapine. No significant increases in total cholesterol, LDL cholesterol, or triglycerides were observed with risperidone. Olanzapine showed a statistically significantly greater increase in mean total cholesterol and LDL cholesterol compared with risperidone (difference in total cholesterol increase comparing olanzapine and risperidone: 16.3 mg/dL, 95% CI = 6.7 to 25.9 mg/dL; difference in LDL cholesterol increase comparing olanzapine and risperidone: 15.4 mg/dL, 95% CI = 7.5 to 23.3 mg/dL). No other between-group comparisons were statistically significant.

A post hoc analysis of triglyceride/HDL cholesterol and total cholesterol/HDL cholesterol ratios indicated that changes from baseline to week 24 were statistically significant with olanzapine only (Table 2). There were no statistically significant differences between treatments for triglyceride/HDL ratios. Olanzapine was associated with a statistically significantly greater change in total cholesterol/HDL ratio compared with risperidone (0.4, 95% CI = 0.0 to 0.8), but not quetiapine.

Other Safety and Tolerability Endpoints

Mean (SD) plasma prolactin levels at baseline were high in all treatment groups and probably reflected prior medication with conventional antipsychotics: 36.5 (40.9) μg/L in the quetiapine group, 57.2 (82.1) μg/L in the olanzapine group, and 44.7 (49.9) μg/L in the risperidone group. At week 24, LSM change in prolactin was –32.1 μg/L (95% CI = –42.2 to –22.0 μg/L) and –22.4 μg/L (95% CI = –31.7 to –13.1 μg/L) in the quetiapine and olanzapine treatment groups, respectively. In the risperidone group, prolactin levels increased by +11.7 μg/L (95% CI = 2.1 to 21.3 μg/L). A between-group analysis showed that the increase in prolactin levels with risperidone was statistically significantly greater compared with quetiapine (43.8 μg/L, 95% CI = 32.2 to 55.4 μg/L) and olanzapine (34.1 μg/L, 95% CI = 23.2 to 45.0 μg/L).

Adverse events during the treatment and follow-up period are presented in Table 3. No patients died during the treatment period. Two deaths occurred in the follow-up period in the risperidone group; however, these were not considered treatment related. Discontinuation rates due to adverse events were 10.1% in the quetiapine group, 8.1% in the risperidone group, and 1.8% in the olanzapine group. No unexpected adverse events were reported; the pattern of the most frequently reported adverse events conformed to what was expected from the pharmacologic profiles of each drug.

Treatment-related EPS, as measured by Barnes Akathisia Scale and Simpson-Angus Scale scores, showed statistically significant improvements in all treatment groups. Least squares means change at week 24 in Barnes Akathisia Scale scores was –0.5 (95% CI = –0.6 to –0.4) with quetiapine, –0.5 (95% CI = –0.6 to –0.4) with olanzapine, and –0.2 (95% CI = –0.3 to –0.1) with risperidone. Least squares means change at week 24 in Simpson-Angus Scale scores was –2.9 (95% CI = –3.3 to –2.5) with quetiapine, –2.6 (95% CI = –3.0 to –2.3) with olanzapine, and –1.8 (95% CI = –2.2 to –1.5) with risperidone. The improvements were statistically significantly greater in the quetiapine and olanzapine groups, compared with the risperidone group. During the study, anticholinergic medication was used by 4.2% of patients in the quetiapine group, 5.9% in the olanzapine group, and 25.6% in the risperidone group.

The baseline values for sitting or standing pulse, and systolic or diastolic blood pressure, were comparable across the treatment groups. At week 24, there were no significant increases from baseline in any of these variables in the primary analysis population, apart from

Table 3. Adverse Events (AEs) During the Treatment and Follow-Up Period (safety population)

Category of AE	Quetiapine, N = 169, N (%)	Olanzapine, N = 168, N (%)	Risperidone, N = 172, N (%)
AEs[a]	101 (59.8)	79 (47.0)	116 (67.4)
Serious AEs[a]	17 (10.1)	4 (2.4)	13 (7.6)
Drug-related AEs[a,b]	57 (33.7)	36 (21.4)	87 (50.6)
AEs leading to discontinuation[a]	17 (10.1)	3 (1.8)	14 (8.1)
Common AEs[c] (MedDRA term)			
Extrapyramidal disorder	3 (1.8)	3 (1.8)	42 (24.4)
Insomnia	11 (6.5)	7 (4.2)	25 (14.5)
Somnolence	17 (10.1)	6 (3.6)	8 (4.7)
Akathisia	2 (1.2)	3 (1.8)	22 (12.8)
Schizophrenia	12 (7.1)	2 (1.2)	8 (4.7)
Sedation	11 (6.5)	5 (3.0)	5 (2.9)
Dizziness	9 (5.3)	0 (0.0)	6 (3.5)
Discontinuations due to AEs (MedDRA term)			
Schizophrenia	7 (4.1)	0 (0.0)	2 (1.2)
Psychotic disorder	3 (1.8)	0 (0.0)	1 (0.6)
Depression	0 (0.0)	0 (0.0)	3 (1.7)
Extrapyramidal disorder	0 (0.0)	0 (0.0)	3 (1.7)
Somnolence	2 (1.2)	1 (0.6)	1 (0.6)
Delusion	2 (1.2)	0 (0.0)	0 (0.0)
Hallucination	2 (1.2)	0 (0.0)	0 (0.0)
Headache	1 (0.6)	0 (0.0)	1 (0.6)
Insomnia	1 (0.6)	0 (0.0)	1 (0.6)
Restlessness	1 (0.6)	1 (0.6)	0 (0.0)
Weight increased	0 (0.0)	1 (0.6)	1 (0.6)
Abdominal pain upper	1 (0.6)	0 (0.0)	0 (0.0)
Chest discomfort	1 (0.6)	0 (0.0)	0 (0.0)
Neutrophil count decreased	1 (0.6)	0 (0.0)	0 (0.0)
Sedation	0 (0.0)	1 (0.6)	0 (0.0)
Akathisia	0 (0.0)	0 (0.0)	1 (0.6)
Dyspnea	0 (0.0)	0 (0.0)	1 (0.6)
Dystonia	0 (0.0)	0 (0.0)	1 (0.6)
Hypertension	0 (0.0)	0 (0.0)	1 (0.6)
Panic attack	0 (0.0)	0 (0.0)	1 (0.6)

[a]Patients with multiple events in the same category are counted only once. Patients with events in more than one category are counted once in each category.
[b]As judged by the investigator.
[c]Any AE occurring at an incidence of ≥ 5% in any randomized treatment group.
Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.

sitting pulse rate (b.p.m.), which showed a significant increase with quetiapine (+3.1, 95% CI = 1.1 to 5.1) compared with olanzapine (+0.6, 95% CI = –1.2 to 2.4) and risperidone (+0.6, 95% CI = –1.3 to 2.5). These changes were not considered to be clinically significant. Electrocardiogram abnormalities at week 24 were reported for 12 of 155 patients (7.7%) in the quetiapine group, 13 of 157 patients (8.3%) in the olanzapine group, and 12 of 165 patients (7.3%) in the risperidone group. None of these were considered clinically significant or led to discontinuation of treatment.

Efficacy

Efficacy was assessed by CGI-S and CGI-I scores in the ITT population. The proportion of patients with CGI-S score ≤ 3 at baseline was 28.0% in the quetiapine group, 28.4% in the olanzapine group, and 25.6% in the risperidone group. At week 24, the vast majority of patients showed improvements, i.e., the proportion of patients with a CGI-S score ≤ 3 was 70.2% in the quetiapine group, 75.7% in the olanzapine group, and 74.3% in the risperidone group. Furthermore, the proportion of patients with a CGI-I score of "very much improved" or "much improved" at week 24 was 57.7% for quetiapine, 63.9% for olanzapine, and 55.6% for risperidone.

DISCUSSION

Addressing growing interest in the effect of individual antipsychotic medications on risk for diabetes,[11] this large-scale, multicenter, randomized clinical trial offers the first report to our knowledge of a study using sensitively assessed differential changes in glucose tolerance observed during treatment with various atypical antipsychotics as the primary endpoint. Measuring mean change from baseline in AUC 0- to 2-hour plasma glucose values during 24 weeks of treatment with quetiapine, olanzapine, or risperidone, the primary analysis indicates a significant difference between quetiapine and olanzapine in the change from baseline to week 24 in glucose tolerance, explained by a significant reduction in glucose tolerance during treatment with olanzapine but not quetiapine. Although a statistically significant reduction in glucose tolerance from baseline to week 24 was also observed during treatment with risperidone, the reduction was smaller in magnitude than that observed with olanzapine, and the difference between risperidone and quetiapine in the change in glucose tolerance—although the study was not powered for this comparison—was not significant. Secondary analysis of additional metabolic indices, including mean changes from baseline to week 24 in AUC 0- to 2-hour plasma insulin values, insulin sensitivity (insulin sensitivity index), and a calculated measure of insulin secretion (insulinogenic index), strongly suggests that the changes in glucose tolerance observed in this study were largely related to changes in insulin sensitivity rather than to changes in insulin secretion.

While other studies have contributed to a growing understanding of differential antipsychotic medication changes in metabolic parameters, this study offers several advantages over previous reports. Key strengths include sensitive primary and secondary measures focused on glucose metabolism, confirmed fasting conditions, timely sample collection ensured by overnight hospitalization, rigorous screening methods, and a patient sample not previously exposed for at least 90 days to any of the agents under testing. In particular, the modified 2-hour OGTT method used in this study provided sensitive measures of glucose metabolism, such as AUC 0- to 2-hour plasma glucose and insulin values, which permit a

calculation of insulin sensitivity previously validated against the euglycemic-hyperinsulinemic clamp, a reference methodology.[9,14,15]

Small increases in HbA_{1c} and fasting glucose were observed in all 3 treatment groups; however, these changes remained within the normal range, and there were no statistically significant between-group differences. Results from the CATIE study suggest that HbA_{1c} might be sensitive to differential medication changes under some conditions, but while patients in the CATIE study were instructed to fast, there was limited certainty that fasting was consistently achieved, and no statistically significant effects of treatment group were observed on plasma glucose.[8] However, HbA_{1c} is not generally recommended as a screening tool because of limited sensitivity to early change, and even confirmed fasting plasma glucose values are recognized as less sensitive than postload glucose as a screening method, with clinical practice guidelines recommending postload glucose as the ideal screening tool in higher risk patients[13] and with several guidelines recognizing schizophrenia as a risk state.[24,25]

In this study, there were statistically significant changes in weight for all treatment groups, with the largest change from baseline in the olanzapine group. Whole body or abdominal adiposity, measured directly or estimated by BMI/weight or waist circumference, is an established predictor or correlate of insulin sensitivity in a variety of human populations, including treated patients with schizophrenia,[26] leading to the expectation that treatment-induced weight gain would explain substantial variance in treatment-induced changes in insulin sensitivity or glucose tolerance. However, previous evidence indicates that certain antipsychotic medications can produce adiposity-independent changes in glucose metabolism or insulin sensitivity.[27–29] In this study, the correlation between change in weight and change in insulin resistance or glucose tolerance was relatively weak, which is in part explained by the increased error/residual effect observed in correlations of change scores in comparison to correlations of single time-point values. Despite the known effect of adiposity on insulin sensitivity and glucose metabolism, it remains possible that adiposity-independent mechanisms may be of importance in explaining some portion of the observed treatment-induced changes in insulin sensitivity or glucose tolerance. Such adiposity-independent effects, and/or underlying changes in regional adiposity not captured by observed changes in weight, could contribute to the explanation of differential results for risperidone and quetiapine on baseline to endpoint change in insulin sensitivity and glucose tolerance.

Measurement of plasma lipid changes in this study indicated that olanzapine treatment was associated with significant increases in total cholesterol, LDL cholesterol, and triglyceride levels; quetiapine treatment was associated with numerically smaller but still statistically significant increases in total cholesterol and LDL cholesterol, but not triglyceride levels; and risperidone treatment produced no significant changes in plasma lipid levels. Notably, the quetiapine-related changes in LDL and total cholesterol occurred in the setting of changes in AUC 0- to 2-hour plasma insulin values, insulin sensitivity index, weight, BMI, and waist circumference that were less than or similar to risperidone treatment. Risperidone treatment, however, did not increase plasma lipids, suggesting that the changes in lipid profile observed during treatment with quetiapine can be influenced by mechanisms other than changes in adiposity and insulin sensitivity. With regard to lipid ratios that can be used to predict cardiovascular risk,[18,19] triglyceride/HDL and total cholesterol/HDL ratios increased significantly from baseline in patients treated with olanzapine.

Regarding differences between treatments in the number of discontinuations owing to adverse events, the results did not appear to be biased by a somewhat higher discontinuation rate in the quetiapine treatment group in comparison with the olanzapine and risperidone groups. The majority of discontinuations owing to adverse events in the quetiapine group related to worsening of schizophrenia and did not suggest changes in the glucose metabolism profile. Patients who discontinued and had at least 1 postrandomization OGTT, performed after 8 weeks of treatment or later, were included in the ITT analysis, which showed the same trends as the primary analysis population and per protocol analyses.

Although this study was highly controlled, some of its methodological limitations warrant discussion. For instance, there was no placebo control group, which may restrict the interpretation of the absolute value of changes from baseline. In addition, the patient population was largely European and largely previously treated with conventional antipsychotics, or no known antipsychotic in some cases. The potential effect of this demographic on the study results might include a greater sensitivity to observed adverse effects such as weight gain, in comparison to samples that are already chronically treated with atypical antipsychotics, or in comparison to U.S. patient samples that tend to start with higher mean body weight, BMI, and prevalence of conditions such as metabolic syndrome at baseline,[5,8,30] reducing the ability to detect change or worsening. Moreover, the findings of this study may or may not be generalizable beyond 24 weeks. Taking these limitations and study characteristics into account, this study represents an advance from previously reported trials measuring the observed changes with antipsychotic medications on glucose metabolism, providing further evidence of differential changes with individual medications on the primary endpoint that are largely explained by treatment-related changes in insulin sensitivity.

CONCLUSIONS

This large-scale, randomized, 24-week clinical trial evaluated differential changes in glucose metabolism, insulin sensitivity, and lipid parameters in nondiabetic patients with schizophrenia treated with quetiapine, olanzapine, or risperidone. At clinically relevant doses, a significant difference was observed in the change in glucose tolerance during 6 months of treatment with olanzapine versus quetiapine, with significant reductions in glucose tolerance during treatment with olanzapine and risperidone, but not quetiapine. The observed treatment-related changes on glucose tolerance were largely explained by changes in insulin sensitivity.

Drug names: alprazolam (Xanax, Niravam, and others), biperiden (Akineton), clozapine (FazaClo, Clozaril, and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), procyclidine (Kemadrin), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakene, Stavzor, and others), zaleplon (Sonata and others), ziprasidone (Geodon), zolpidem tartrate (Ambien and others), zopiclone (Lunesta).

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