A 24-WEEK, MULTICENTER, OPEN-LABEL, RANDOMIZED STUDY TO COMPARE CHANGES IN GLUCOSE METABOLISM IN PATIENTS WITH SCHIZOPHRENIA RECEIVING TREATMENT WITH OLANZAPINE, QUETIAPINE AND RISPERIDONE

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Abstract

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

Methods: Primary endpoint was change (baseline to Week 24) in area under the curve (AUC) 0-2h plasma glucose during oral glucose tolerance test (OGTT); primary analysis: olanzapine versus quetiapine. Secondary endpoints included change in AUC 0-2h plasma insulin, insulin sensitivity index (ISI), and fasting lipids.

Results: Mean weight change over 24 weeks was +3.65 kg (quetiapine), +4.58 kg (olanzapine), and +3.57 kg (risperidone). Based on data from 395 patients (quetiapine n=115 [mean 607.0 mg/day], olanzapine n=146 [15.2 mg/day], and risperidone n=134 [5.2 mg/day]), change in AUC 0-2h glucose (mg/dL×h) at Week 24 was significantly lower for quetiapine versus olanzapine (t=1.98; DF=377; p=0.048). Increases in AUC 0-2h glucose were statistically significant with olanzapine (+21.9 mg/dL, 95% CI 11.5, 32.4) and risperidone (+18.8, CI 8.1, 29.4), but not quetiapine (+9.1, CI -2.3, 20.5). AUC 0-2h insulin increased statistically significantly with olanzapine, but not quetiapine or risperidone. Reductions in ISI were statistically significant with olanzapine and risperidone, but not quetiapine. Total cholesterol and LDL increased statistically significantly with olanzapine and quetiapine, but not risperidone. Statistically significant increases in triglycerides, cholesterol/HDL, and triglyceride/HDL ratios 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.

Word count: 250/250

Keywords: glucose, insulin, lipids, olanzapine, quetiapine, risperidone, schizophrenia.

Introduction

Schizophrenia is a chronic, debilitating, and multidimensional illness that can adversely impact on 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 (obesity, hyperglycemia, smoking, hypertension, 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.[3;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.[7-10]

The American Diabetes Association (ADA), 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 have 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).[10] 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.[10] However, interpretation of the metabolic findings in the CATIE study are 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 are limited by methodological concerns that include use of less sensitive measures, such as unconfirmed fasting plasma glucose measurements at single timepoints, lack of needed comparator groups, and lack of adequate controls for potentially confounding factors such as underlying medical conditions.[8]

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 randomized 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 for at least 90 days to any of the agents under testing.

Methods

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 29 April 2004 and the last patient completed the study on 24 October 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, 4th Edition (DSM-IV). 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 three months and/or valproic acid, lithium, or antidepressants within one 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 one dosing interval.

A small number of patients whose blood glucose rating was in the diabetic range as defined by the ADA (≥126 mg/dL for fasting glucose and/or ≥200 mg/dL for 2-h post-load glucose) at baseline were incorrectly randomized 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 (PAP) [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 excluded from the per-protocol (PP) population. Following randomization, no patients were excluded due to development of diabetes during the study.

Treatment

Patients were randomized sequentially, with an equal probability of receiving olanzapine, quetiapine, or risperidone. Patients were stratified according to body mass index (BMI) in four groups (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m^2) and according to age in two 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 HbA_{1c} values at screening were required to determine patient eligibility. These values were not blinded, and treatment assignment was open.

Patients entered a five-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 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 new emerging EPS-related adverse events (AEs); 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 ≤2mg/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.

Assessments

AUC 0-2 h plasma glucose during an oral glucose tolerance test

The primary objective of the study was to compare the safety/tolerability effect profile of olanzapine versus quetiapine on glucose metabolism. The primary outcome variable was the change from baseline to Week 24 in area under the curve (AUC) for plasma glucose from 0-2 h (AUC 0-2 h), during an oral glucose tolerance test (OGTT).[13] A secondary objective was to compare the safety/tolerability of quetiapine and risperidone on glucose metabolism, by evaluating the change from baseline to Week 24 in AUC 0-2 h of plasma glucose values during the OGTT.

Patients were hospitalized overnight to ensure 8-14 h fasting conditions prior to OGTT.[13] 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 min. Blood samples were collected at 30, 60, 90, and 120 min by venous catheter.

Measures of insulin sensitivity and secretion

Other secondary objectives of the study were to compare the changes from randomization to Week 24 in: plasma insulin AUC 0-2 h during OGTT; insulin sensitivity index (ISI) derived from OGTT,[14] fasting insulin; and homeostasis model assessment (HOMA-IR).[15] The change in plasma C-peptide levels was an exploratory measure, and mean relative changes in the insulinogenic index (IGI)[16] were estimated in a post hoc descriptive analysis.

ISI was calculated as the 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: fasting plasma insulin (μIU/mL) × fasting plasma glucose (mmol/L)/22.5. IGI was calculated as the ratio between simultaneous increments in plasma insulin and glucose from 0 to 30 min after glucose load (change in insulin at 30 min [μIU/mL] / change in glucose at 30 min [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-h post-load glucose; incidences of patients with hyperglycemia (fasting plasma glucose ≥126 mg/dL and/or 2-h glucose ≥200 mg/dL); incidences of patients with impaired fasting glucose (IFG, defined as fasting plasma glucose ≥100 and <126 mg/dL) or impaired glucose tolerance (IGT, defined as 2-h 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} ≥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 on blood lipid levels by evaluating fasting plasma lipid levels (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides). The change in ratios between total cholesterol and HDL, and triglyceride and HDL levels, as proposed predictors of cardiovascular risk,[17;18] was also estimated as a post hoc analysis.

Bodyweight

Changes from randomization to Week 24 were assessed for bodyweight, 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 change from baseline to Week 24 in plasma prolactin (μg/L) was determined. The safety/tolerability profile of quetiapine, olanzapine, and risperidone on EPS and other AEs was also examined, by recording the following: change from baseline to Week 24 in Simpson-Angus Scale (SAS) total score and Barnes Akathisia Rating Scale (BARS) total score; incidence of AEs; sitting and standing systolic and diastolic blood pressure and pulse rate; changes in electrocardiogram (ECG); 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 Impression-Improvement (CGI-I) rating of "very much improved" or "much improved" at the final assessment (last observation carried forward, [LOCF]), and the proportion of patients with a Clinical Global Impression Severity of Illness rating scale (CGI-S) 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,[19] as well as on published olanzapine data.[20] 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 two-sided test at the 5% alpha level. After allowing for withdrawals and protocol violations, approximately 500 patients had to be randomized in order to get 285 evaluable patients at Week 24.

Primary and secondary endpoints were analyzed using the PAP, which consisted of all randomized 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 0-2 h glucose, 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. For insulin and insulin sensitivity indices, log-transformed values were analyzed with the ANCOVA model. LSMs 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.[17;18] Pearson correlation coefficients were calculated to explore possible correlations between change in weight and change in AUC 0-2 h glucose, and between change in weight and change in log-transformed ISI.

The per-protocol (PP) 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 randomized to the olanzapine group actually received treatment with quetiapine; this patient was excluded from the PP population and was not included in the PAP population because of discontinuation before Week 20. Only the primary analysis was repeated on the PP sample to test for homogeneity of the treatment changes. AE 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 randomized patients who were given study treatment (i.e. who took at least one dose of medication), classified according to the treatment actually received. Efficacy data were analyzed for the intent-to-treat (ITT) population, which included all randomized patients who were given study treatment, classified according to randomized treatment.

Results

Patients

A total of 574 patients were enrolled, and 510 were randomized: 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 and glucose metabolism characteristics (Table 1). Most patients were male, had paranoid schizophrenia, and were receiving antipsychotic medication at time of randomization. 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 PAP. The PP 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 PAP are presented.

Treatment

Following randomization, mean (SD) doses at Week 24 were: 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.

Bodyweight

At Week 24, mean weight change from baseline was +3.65 kg (95% CI 2.43, 4.87) for quetiapine, +4.58 kg (95% CI, 3.46, 5.71) for olanzapine, and +3.57 kg (95% CI 2.42, 4.73) 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: +1.29 (95% CI 0.87, 1.72) for quetiapine, +1.64 (95% CI 1.25, 2.03) for olanzapine, and +1.28 (95% CI 0.88, 1.68) for risperidone. The mean change from baseline in waist circumference (cm) was +3.24 (95% CI 1.87, 4.60) in the quetiapine group, +4.37 (95% CI 3.11, 5.63) in the olanzapine group, and +2.99 (95% CI 1.71, 4.27) 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 0-2 h plasma glucose during OGTT

Mean change from baseline to Week 24 in AUC plasma glucose (mg/dL × h) was +9.1 (95% CI -2.3, 20.5) with quetiapine (not statistically significant based on CI coverage of zero) and +21.9 (95% CI 11.5, 32.4) with olanzapine (statistically significant based on CI non-coverage of zero). The primary analysis results indicated that the difference in mean change from baseline in AUC 0-2 h plasma glucose was significantly different between quetiapine and olanzapine (-12.8 mg/dL × h; 95% CI -25.5, -0.11) (t=1.98; DF=377; p=0.048) [Figure 2]. The mean change from baseline in AUC plasma glucose with risperidone was +18.8 mg/dL (95% CI 8.1, 29.4) (statistically significant based on CI non-coverage of zero) at Week 24. The secondary analysis results indicated that the difference in mean change from baseline

in AUC plasma glucose for quetiapine compared with risperidone was -9.6 mg/dL × h; 95% CI -22.7, 3.4 (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 (0-120-min post-glucose load) for the three treatment groups is shown in Figure 3.

In the PP population, the mean change from baseline to Week 24 in AUC 0-2 h plasma glucose (mg/dL × h) was +11.24 (95% CI -0.08, 22.56) in the quetiapine group and +26.2 (95% CI 15.49, 36.92) in the olanzapine group. The difference between quetiapine and olanzapine was statistically significant (t=2.34; DF=322; p=0.0199), confirming the results in the PAP. Mean change from baseline to Week 24 in the PP population was +20.97 (95% CI 10.25, 31.68) in the risperidone group.

Examination of the within-treatment correlation between change in weight and change in AUC 0-2 h glucose 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 0-2 h plasma insulin during OGTT were not statistically significant with quetiapine (+13.15%; 95% CI, -0.14, 28.22) or risperidone (+10.74%; CI, -1.2, 24.13), but were with olanzapine (+24.45%; CI, 11.46, 38.96). Analysis of insulin sensitivity, as assessed by ISI, showed that decreases from baseline were not statistically significant with quetiapine (-10.8%, 95% CI -21.9, 1.85), but were statistically significant with olanzapine (-19.1%, CI -27.9, -9.33) and risperidone (-15.8%, CI -25.1, -5.41) [Figure 4]. Within-treatment

correlations between change in weight and change in ISI 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 IGI, i.e. the early insulin response to oral glucose stimulation during the first 30 min of the OGTT, was estimated. The median relative change in IGI from baseline to Week 24 was -0.20% (lower quartile [LQ] -41.73, upper quartile [UQ] 40.49) in the quetiapine group, -9.15% (LQ -45.28, UQ 32.23) in the olanzapine group, and -3.27% (LQ -35.17, UQ 50.16) in the risperidone group.

Mean changes (95% CIs) in fasting insulin from baseline to Week 24 were 3.324% (-9.2, 17.58) for quetiapine, 8.475% (-3.33, 21.73) for olanzapine, and 11.9% (-0.2, 25.47) for risperidone.

For HOMA-IR, a measure of insulin resistance, increases of 6.44% (CI -7.63, 22.65) and 10.97% (CI -2.22, 25.94) 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 (16.75%; 95% CI 2.95, 32.41).

Change from baseline to Week 24 in plasma C-peptide levels was 0.36 ng/mL (95% CI, 0.11, 0.62) for quetiapine, 0.43 (CI 0.20, 0.67) for olanzapine, and 0.42 (CI 0.19, 0.66) for risperidone. These increases from baseline were statistically significant for all three 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 0-2 h plasma insulin, ISI, fasting insulin, HOMA-IR, or C-peptide.

Additional glucose parameters

At Week 24, small changes from baseline in fasting glucose were seen in all treatment groups: 3.18 mg/dL (95% CI 0.24, 6.12) for quetiapine; 2.33 (CI -0.40, 5.06) for olanzapine; 4.40 (CI 1.62, 7.18) 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-h post-load glucose (mg/dL), the mean change from baseline was not statistically significant for quetiapine (-1.88, 95% CI -10.01, 6.26), but was statistically significant for olanzapine (+9.77, 95% CI 2.37, 17.17) and risperidone (+10.58, 95% CI 2.91, 18.24) [Figure 3]. The differences between quetiapine and olanzapine and between quetiapine and risperidone were statistically significant.

The proportion of patients in the PAP with a blood glucose value in the diabetic range (fasting plasma glucose $\geq$126 mg/dL and/or 2-h glucose $\geq$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 PAP 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 post-randomization values of fasting glucose ≥126 mg/dL and/or 2-h 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 IFG (defined as fasting plasma glucose ≥100 and <126 mg/dL) and/or IGT (defined as 2-h 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 IFG, IGT, or diabetic levels.

Small increases in HbA_{1c} from baseline were seen in each treatment group: quetiapine 0.12% (95% CI 0.05, 0.19), olanzapine 0.05% (CI -0.01, 0.11), risperidone 0.07% (CI 0.00, 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 between treatments in HbA_{1c} levels or in the proportion of patients with HbA_{1c} ≥6.05% at Week 24.

Lipid parameters

Changes from baseline to Week 24 in total cholesterol, HDL, LDL, and triglycerides are shown in Table 2. Statistically significant increases from baseline in mean total cholesterol and LDL, but not triglycerides, were seen for quetiapine. Increases from baseline in mean total cholesterol, LDL, and triglycerides were statistically significant

for olanzapine. No significant increases in total cholesterol, LDL, or triglycerides were observed with risperidone. Olanzapine showed a statistically significantly greater increase in mean total cholesterol and LDL compared with risperidone. No other between-group comparisons were statistically significant.

A post hoc analysis of triglyceride/HDL and total cholesterol/HDL 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, but not quetiapine.

Other safety and tolerability endpoints

Mean (SD) plasma prolactin levels at baseline were: 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, -22.0) and -22.4 μg/L (CI -31.7, -13.1) in the quetiapine and olanzapine treatment groups, respectively. In the risperidone group, prolactin levels increased by +11.7 μg/L (95% CI 2.1, 21.3). A between-group analysis showed that the increase in prolactin levels with risperidone was statistically significant compared with quetiapine and olanzapine.

AEs 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. No

unexpected AEs were reported; the pattern of the most frequently reported AEs conformed to what was expected from the pharmacological profiles of each drug.

Treatment-related EPS, as measured by BARS and SAS scores, showed statistically significant improvements in all treatment groups. LSM change at Week 24 in BARS scores was: -0.5 (95% CI -0.61, -0.39) with quetiapine; -0.48 (95% CI -0.58, -0.38) with olanzapine; and -0.21 (95% CI -0.31, -0.11) with risperidone. LSM change in SAS scores was: -2.89 (95% CI -3.27, -2.5) with quetiapine; -2.63 (95% CI -2.99, -2.28) with olanzapine; and -1.84 (95% CI -2.2, -1.48) 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 PAP, apart from sitting pulse rate (bpm), which showed a significant increase with quetiapine (+3.12; 95% CI 1.13, 5.10) compared with olanzapine (+0.62, 95% CI -1.19, 2.44) and risperidone (+0.60, 95% CI -1.27, 2.46). These changes were not considered to be clinically significant. ECG abnormalities at Week 24 were reported for 12 (7.7%) patients in the quetiapine group, 13 (8.3%) in the olanzapine group, and 12 (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 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 individual antipsychotic medication changes 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 0-2 h plasma glucose 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 changes from baseline to Week 24 in AUC 0-2 h plasma insulin, insulin sensitivity (ISI), and a calculated measure of insulin secretion (IGI), strongly suggest that the changes in glucose tolerance observed in this study were largely related to changes in insulin sensitivity rather than 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, and 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-h OGTT method used in this study provided sensitive measures of glucose metabolism, such as AUC 0-2 h plasma glucose and insulin, which permit a calculation of insulin sensitivity previously validated against the euglycemic-hyperinsulinemic clamp, a reference methodology.[9;13;14]

Small increases in HbA_{1c} and fasting glucose were observed in all three 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.[10] 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 post-load glucose as a screening method, with clinical practice guidelines recommending post-load glucose as the ideal screening tool in higher risk patients[21] and several guidelines recognizing schizophrenia as a risk state.[22;23]

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,[24] 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.[25-27] 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 timepoint 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, and triglyceride, quetiapine treatment was associated with numerically smaller but still statistically significant increases in total cholesterol and LDL, but not triglyceride, 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 0-2 h plasma insulin, ISI, 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,[17;18] triglyceride/HDL and total cholesterol/HDL ratios increased significantly from baseline in patients treated with olanzapine.

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. Moreover, the findings of this study may or may not be generalizable beyond 24 weeks. Despite these limitations, 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 medication 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 non-diabetic 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 on olanzapine and risperidone, but not quetiapine. The observed treatment-related changes on glucose tolerance were largely explained by changes in insulin sensitivity.

Clinical trials registration: ClinicalTrials.gov identifier NCT00214578

References

1. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. Prev Chronic Dis 2006;3:A42

2. Newcomer JW, Hennekens CH. Severe mental illness and risk of cardiovascular disease. JAMA 2007;298:1794–1796

3. Dixon L, Weiden P, Delahanty J, et al. Prevalence and correlates of diabetes in national schizophrenia samples. Schizophr Bull 2000;26:903–912

4. McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr Res 2005;80:19–32

5. Cohen D, Stolk RP, Grobbee DE, et al. Hyperglycemia and diabetes in patients with schizophrenia or schizoaffective disorders. Diabetes Care 2006;29:786–791

6. Van Gaal LF. Long-term health considerations in schizophrenia: Metabolic effects and the role of abdominal adiposity. Eur Neuropsychopharmacol 2006;16 (suppl 3):S142–S148

7. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 2005;19 (suppl 1):1–93

8. Newcomer JW, Haupt DW. The metabolic effects of antipsychotic medications. Can J Psychiatry 2006;51:480–491

9. Newcomer JW, Haupt DW, Fucetola R, et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. Arch Gen Psychiatry 2002;59:337–345

10. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353:1209–1223

11. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27:596–601

12. Nasrallah HA, Meyer JM, Goff DC, et al. Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: Data from the CATIE schizophrenia trial sample at baseline. Schizophr Res 2006;86:15–22

13. Mari A, Pacini G, Murphy E, et al. A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. Diabetes Care 2001;24:539–548

14. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462–1470

15. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419

16. Seltzer HS, Allen EW, Herron AL, Jr., et al. Insulin secretion in response to glycemic stimulus: relation of delayed initial release to carbohydrate intolerance in mild diabetes mellitus. J Clin Invest 1967;46:323–335

17. Castelli WP. Cholesterol and lipids in the risk of coronary artery disease--the Framingham Heart Study. Can J Cardiol 1988;4 (suppl A):5A–10A

18. Dobiasova M. Atherogenic index of plasma [log(triglycerides/HDL-cholesterol)]: theoretical and practical implications. Clin Chem 2004;50:1113–1115

19. Brecher M, Leong R, Stening G, et al. Quetiapine and long-term weight change: a comprehensive data review of patients with schizophrenia. J Clin Psychiatry 2007;68:597–603

20. Kinon BJ, Basson BR, Gilmore JA, et al. Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia. J Clin Psychiatry 2001;62:92–100

21. Standards of medical care in diabetes--2007. Diabetes Care 2007;30 (suppl 1):S4–S41

22. Howlett MC, Lillie D. The Canadian Diabetes Association guidelines: putting the evidence first. CMAJ 2006;174:333–334

23. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract 2007;13 (suppl 1):1–68

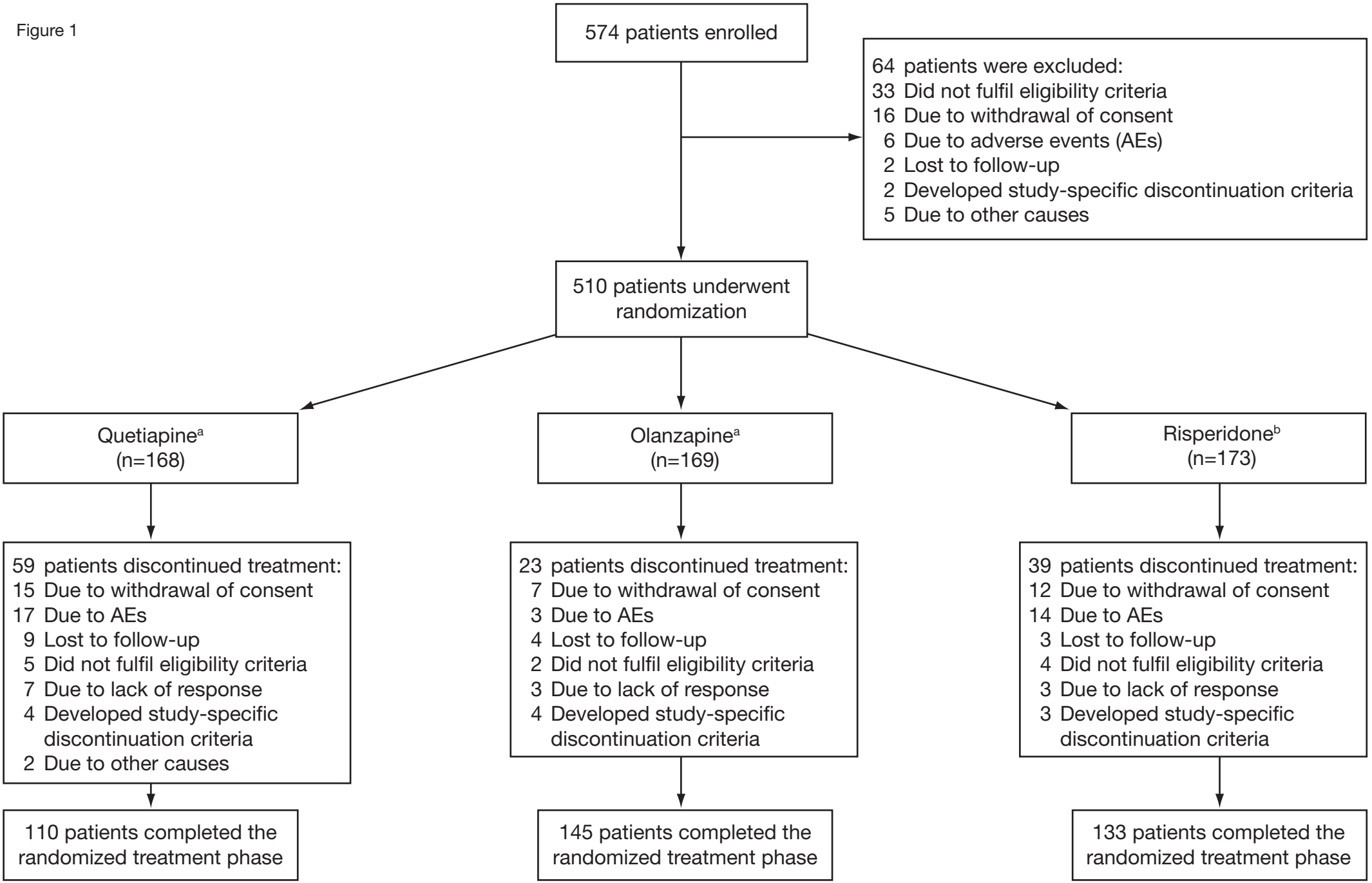
24. Haupt DW, Fahnestock PA, Flavin KA, et al. Adiposity and insulin sensitivity derived from intravenous glucose tolerance tests in antipsychotic-treated patients. Neuropsychopharmacology 2007;32:2561–2569

25. Bonaccorsi A, Garattini S, Jori A. Studies on the hyperglycaemia induced by chlorpromazine in rats. Br J Pharmacol Chemother 1964;23:93–100

26. Houseknecht KL, Robertson AS, Zavadoski W, et al. Acute effects of atypical antipsychotics on whole-body insulin resistance in rats: implications for adverse metabolic effects. Neuropsychopharmacology 2007;32:289–297

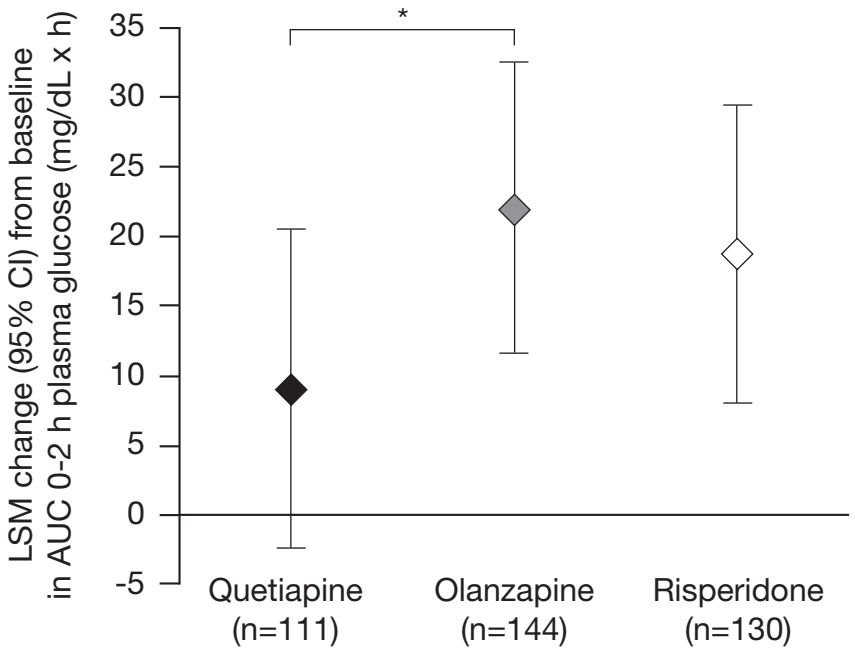
27. Dwyer DS, Lu XH, Bradley RJ. Cytotoxicity of conventional and atypical antipsychotic drugs in relation to glucose metabolism. Brain Res 2003;971:31–39

Figure 1



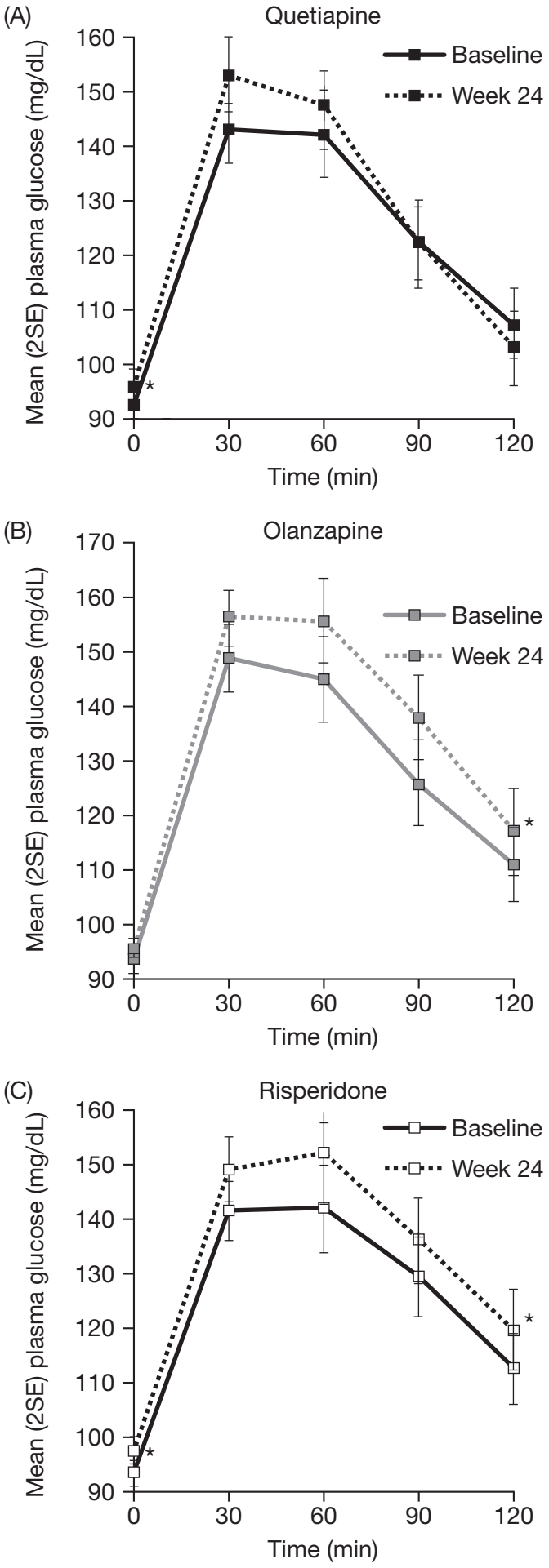
[a]1 patient randomized to olanzapine actually received quetiapine
[b]1 patient did not receive treatment

Figure 2



*p=0.048 vs olanzapine

Figure 3



*Significant change from baseline to Week 24.
Values at 30, 60, and 90 min were not tested for significance.
Change from baseline to Week 24 in AUC 0-2 h plasma glucose:
p=0.048 quetiapine vs olanzapine

Figure 4

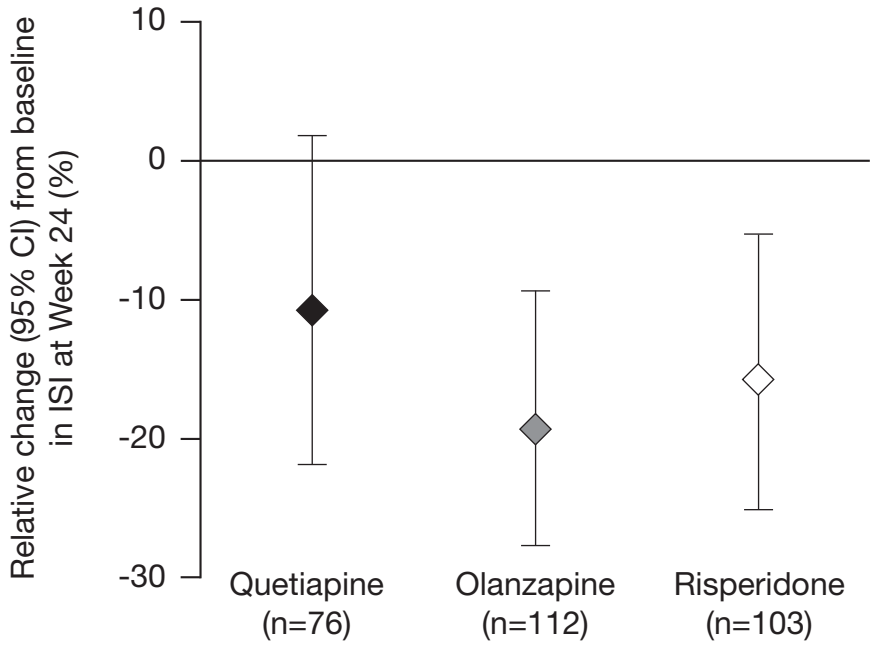

Relative change (95% CI) from baseline in ISI at Week 24 (%)
10
0
-10
-20
-30
Quetiapine (n=76)
Olanzapine (n=112)
Risperidone (n=103)

Table 1. Key demographic and glucose metabolism characteristics at baseline (PAP).

	Quetiapine (N=115)	**Olanzapine (N=146)**	**Risperidone (N=134)**
Mean (SD) age, years	39.4 (11.1)	40.5 (10.4)	38.3 (11.1)
Male:female, %	66:34	66:34	65:35
Caucasian, %	90.4	91.8	86.6
Mean (SD) weight, 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, %			
<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)
Antipsychotic medication at randomization, n (%)	82 (71.3)	104 (71.2)	97 (72.4)
Smoking, n (%)	67 (58.3)	86 (58.9)	86 (64.2)
Glucose metabolism characteristics, mean (SD)			
AUC glucose, mg/dL × h	255.11 (54.43)	260.89 (69.08)	259.34 (65.44)
Fasting glucose, mg/dL	92.59 (12.12)	93.65 (17.78)	93.73 (11.93)
2-h glucose, mg/dL	106.90 (33.59)	111.03 (42.05)	112.87 (38.29)
HbA_{1c}, %	5.33 (0.43)	5.32 (0.39)	5.33 (0.49)
Fasting plasma insulin, µIU/mL[a]	5.21 (79.9)	5.36 (63.7)	5.44 (52.50)
AUC insulin (OGTT) [µIU/mL × h][a]	80.28 (64.9)	71.26 (68.7)	67.58 (56.90)
Fasting C-peptide, ng/mL	2.27 (1.11)	2.23 (0.91)	2.25 (1.05)

[a]Geometric mean (coefficient of variation).

AUC = area under the curve; BMI = body mass index; LSM = least squares means; OGTT = oral glucose tolerance test; PAP = primary analysis population; SD = standard deviation; SE = standard error.

Table 2. Mean change from baseline to Week 24 in fasting lipid levels (PAP), and lipid ratios.

	Quetiapine	**Olanzapine**	**Risperidone**
Total cholesterol, mg/dL			
n[a]	107	142	124
Baseline	193.05	192.41	195.05
Change at Week 24	13.11	21.09	4.82
95% CI	4.29, 21.93	13.02, 29.17	-3.54, 13.18
HDL, mg/dL			
n[a]	89	116	106
Baseline	41.83	43.38	44.68
Change at Week 24	0.98	0.11	1.07
95% CI	-1.36, 3.32	-2.04, 2.26	-1.12, 3.27
LDL, mg/dL			
n[a]	108	142	125
Baseline	117.42	121.42	121.13
Change at Week 24	13.29	20.47	5.07
95% CI	6.05, 20.53	13.82, 27.12	-1.78, 11.93
Triglycerides, mg/dL			
n[a]	104	142	123
Baseline	166.24	146.12	154.20

Change at Week 24	17.61	30.93	11.66
95% CI	-4.57, 39.79	10.86, 51.00	-9.19, 32.51
Total cholesterol/HDL ratio			
n[a]	86	116	104
Baseline	4.86	4.59	4.62
Change at Week 24	0.23	0.48	0.06
95% CI	(-0.12, 0.58)	(0.16, 0.79)	(-0.27, 0.38)
Triglycerides/HDL-ratio			
n[a]	86	116	104
Baseline	1.80	1.59	1.72
Change at Week 24	0.24	0.32	0.18
95% CI	(-0.11, 0.58)	(0.01, 0.63)	(-0.14, 0.50)

[a]Number of patients with non-missing value.

CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PAP = primary analysis population.

Table 3. Adverse events (AEs) during the treatment and follow-up period (safety population).

Category of AE	**Quetiapine N=169**		**Olanzapine N=168**		**Risperidone N=172**	
	n	**(%)**	**n**	**(%)**	**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)

[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.