Effects of Olanzapine and Risperidone on Glucose Metabolism and Insulin Sensitivity in Chronic Schizophrenic Patients With Long-Term Antipsychotic Treatment: A Randomized 5-Month Study

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Background: Comparisons of diabetic potential, glucose related metabolic levels, and insulin resistance between olanzapine and risperidone have produced variable results in cross-sectional and epidemiologic studies. Randomized prospective studies of metabolic effects during treatment with these drugs may provide results that are more informative.

Method: Hospitalized patients with chronic schizophrenia (*DSM-IV*), most of whom had been treated with multiple antipsychotics in the past, were randomly assigned to treatment with a single antipsychotic, olanzapine or risperidone, for a period of 5 months. At baseline and every treatment month thereafter, fasting glucose, insulin, insulin-related metabolic measures, and prolactin were assessed, and an oral glucose tolerance test (OGTT) was performed during baseline and months 1, 2, and 5 of treatment. Weight was assessed monthly, and waist and hip measures were taken at baseline and month 5. Data were analyzed on 23 patients randomly assigned to risperidone and 23 patients randomly assigned to olanzapine. The study was conducted from February 2003 to August 2007.

Results: Most patients were overweight or obese at baseline (mean body mass index [BMI] = 29.4), but there were no differential drug effects on weight change and no differences between drug groups at the 5-month time point. There were no overall drug treatment differences in fasting glucose or glycohemoglobin or 2-hour glucose levels in OGTT and no differences between the two drug groups at the 5-month time point. There were no consistent drug treatment differences in the number of patients who developed borderline or diabetic glucose levels. Olanzapine-treated patients showed a significantly greater increase than risperidone-treated patients in a fasting measure of insulin resistance ($P = .041$), and olanzapine patients showed greater decreases in insulin sensitivity during OGTT ($P = .023$) compared to risperidone-treated patients. Olanzapine-treated patients had a significantly greater increase in 1-hour glucose and insulin levels during OGTT in subsequent months compared to baseline and greater increase in glucose and insulin area under the curve over time than the risperdone-treated patients. Prolactin levels decreased in olanzapine patients and increased in risperidone patients (P values ≈ .02). There were no significant drug treatment differences in C-peptide levels or 2 indices proposed as measures of insulin secretion or β-cell function (homeostasis model assessment of β-cell function [HOMA-B], BIGTT-acute insulin response surrogate measure [BIGTT-AIR]). Changes in insulin resistance over time were not strongly related to changes in BMI or waist circumference during study drug treatment.

Conclusions: The increase in insulin levels during olanzapine treatment may compensate for the increase in insulin resistance and serve to reduce fasting and postprandial glucose levels. This may contribute to the lack of differences between olanzapine and risperidone in indices of diabetic or prediabetic glucose levels or glycohemoglobin. How many years this compensatory mechanism will persist needs further investigation. Periodic OGTT tests measuring glucose and insulin levels would be helpful in assessing the status of β-cell insulin reserve in patients treated with olanzapine and other second-generation antipsychotics and assessing an individual patient's risk for conversion to type 2 diabetes.

Trial Registration: clinicaltrials.gov Identifier NCT00287820

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Diabetes and impaired glucose tolerance are more prevalent in schizophrenics,[1,2] and this increased prevalence may be due to both genetically linked characteristics as well as to induction or exacerbation of this type of side effect by treatment of schizophrenia with antipsychotic medication.[3–5] There has been much debate about the extent to which specific antipsychotics contribute more to the increased risk of developing diabetes and hyperglycemia. Olanzapine and risperidone are widely used

second-generation antipsychotics. Although an increase in diabetes potential has been proposed as an important side effect for all second-generation antipsychotic drugs, especially for clozapine and olanzapine, the results of epidemiologic[6–8] and cross-sectional studies have been variable. Some published cross-sectional metabolic studies have shown higher glucose or insulin levels and higher values for insulin resistance in clozapine- and olanzapine-treated schizophrenic patients compared to those treated with risperidone or first-generation antipsychotics,[9,10] whereas others have found no statistically significant differences between antipsychotic drug effects in glucose levels, glycohemoglobin, or insulin levels or insulin resistance.[11–15] Prospective randomized controlled trials comparing metabolic effects of olanzapine and risperidone are the "gold standard" for providing accurate information on comparing these metabolic side effects and may provide more definitive information on which to base sound scientific evaluations and clinical recommendations. Only one such randomized controlled trial of metabolic effects of olanzapine and risperidone has been recently published,[16] which showed no overall differences between patients treated with olanzapine and risperidone for up to 6 months in glucose or insulin levels or insulin sensitivity indices (see Discussion section for details). Patients with chronic schizophrenia, even those previously treated with several antipsychotics, often remain on the same medication for relatively short times[17] and are frequently switched to another antipsychotic, as recent studies illustrate.[9] Some recent studies suggest that olanzapine may be somewhat more efficacious than other antipsychotics in chronic schizophrenic outpatients and in treatment resistant schizophrenics.[18–21] This makes it clinically relevant to examine the metabolic effects of olanzapine and risperidone, in patients treated with antipsychotics for many years, in a randomized control trial. The current study reports glucose- and insulin-related metabolic effects, and indices of insulin sensitivity and resistance and β-pancreatic cell function, in a randomized controlled trial of olanzapine versus risperidone in longer term hospitalized patients with chronic schizophrenia.

METHOD

Subjects

Patients eligible for the study were men or women, 18 to 65 years of age, residing in one of the inpatient units of a tertiary care psychiatric hospital, who had a diagnosis of *DSM-IV* schizophrenia or schizoaffective psychosis. Their doctors did not object to the patient potentially being switched to another antipsychotic (olanzapine or risperidone), since it was possible that the patient had not obtained the complete remission of all symptoms or the most optimal response with their current antipsychotic treatment. Patients currently treated with clozapine were excluded from the study, except if they had to be discontinued from clozapine for medical reasons or intolerable side effects. Patients currently treated with antidiabetic drugs were excluded from the study because treatment with these drugs may mask the glucose and insulin responses to antipsychotic medication. Patients were allowed to be on statin drugs if these were started more than 2 months prior to the start of the study and if the dosage had not been changed recently. Most of the patients were relatively stable in their psychopathology, either chronically psychotic with long established stable psychotic symptoms or partially improved with decreases in their psychotic symptoms and working though a long program toward eventual discharge. All subjects signed written informed consent for the protocol approved by the Nathan Kline Institute Institutional Review Board.

Study Design

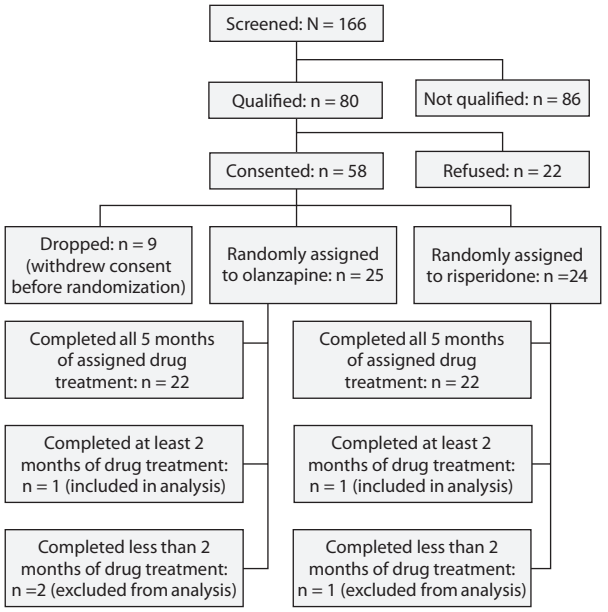
This was a 5-month open-label study of random assignment to treatment with olanzapine or risperidone in hospitalized patients with chronic schizophrenia. A few patients discharged in the middle of the study completed the study as outpatients. The study was conducted from February 2003 to August 2007.

Figure 1 presents a flow diagram of study screening and entry as well as reasons for rejection or termination from the study. Forty-nine patients were randomly assigned to olanzapine or risperidone. Twenty-three patients assigned to each drug were used in this analysis. Three patients (2 olanzapine, 1 risperidone), who were randomly assigned and did not complete at least 2 months of study treatment, were not included in the analysis. Patients who were randomly assigned to olanzapine and included in the analysis received a mean dose of 25.2 mg/d (SD = 10.1; range, 5–40 mg/d). Patients who were randomly assigned to risperidone and included in the analysis received a mean dose of 6.1 mg/d (SD = 1.8; range, 2–10 mg/d).

Procedures

Randomization and cross-tapering. After completing baseline assessments, patients were assigned to receive their study drug, olanzapine or risperidone, based on a stratified random assignment procedure. Doses of olanzapine (5–40 mg/d) or risperidone (2–12 mg/d) could be adjusted for reasons of clinical response or side effects by the research psychiatrist. There was no antipsychotic drug washout period. Lists of random sequence assignments for each drug in each stratification group (factors: type of prior antipsychotic treatment, length of treatment, baseline body mass index [BMI]), drawn up at the beginning of the experiment, utilized a random number table for each stratification group. They were organized so there was equalization of assignment to olanzapine or risperidone on that stratification page over groups of 4 consecutive subjects. If the patient's antipsychotic drug treatment was changed for the study, subjects were cross-tapered onto the new antipsychotic and cross-tapered off the baseline antipsychotic(s) over a 1.5- to 4-week

Figure 1. Subject Flow Through Study of Metabolic Effects of Olanzapine Versus Risperidone[a]



[a]Subjects who were randomly assigned but did not complete the 5 months of study either withdrew consent (n = 2) or had an intercurrent illness unrelated to the drug treatment that led to their removal by administrative decision (n = 2). One patient was terminated before 2 months because of abnormal glucose/lipid profile and excessive weight gain (assigned to olanzapine, completed less than 2 months). Randomization was organized so there was equalization of assignment to olanzapine or risperidone over each of several stratification factors over groups of 4 consecutive subjects. Stratification factors included: (a) antipsychotic drug at baseline—olanzapine, risperidone, or other antipsychotic; (b) if the patient was on either olanzapine or risperidone treatment at baseline, additional stratification by: (b1) treatment with olanzapine greater or less than 6 months prior to entry or (b2) treatment with risperidone (oral or depot) for greater or less than 6 months prior to entry; (c) body mass index (BMI)—within each of the above group stratifications, subjects were further stratified by baseline BMI ≥ 28 versus baseline BMI < 28. Three patients deviated from their initial random assignment, for safety or clinical-administrative reasons.

period, with time for cross-tapering depending on dose and number of antipsychotics they were treated with at baseline. Because of the long cross-tapering for some subjects, we believed we needed at least 2 months of drug treatment to be able to attribute any changes in metabolic effects to the study drug. Therefore, subjects who withdrew consent or were discontinued from the study before 2 months were replaced and are not included in the final analysis. Patients were maintained on the accessory psychotropic and medical medications they were receiving at baseline except if emergency medical conditions or severe side effects warranted immediate adjustments. All psychotropic medication orders were written by the research psychiatrist.

Metabolic assessments. Patients had fasting metabolic assessments at baseline and during every month of treatment with the study drug. These assessments included serum glucose, insulin, C-peptide, serum lipids and related measures, and prolactin, as well as additional chemical measures in selected months. This report will concentrate on the measures of glucose metabolism (glucose, insulin, C-peptide, glycohemoglobin) and prolactin. In addition to these fasting glucose measurements, patients had an oral glucose tolerance test (OGTT), performed in the morning after a 9- to 12-hour fast, at baseline and during months 1, 2, and 5 of study drug treatment. After collection of baseline glucose and insulin, a 75 g glucose load was administered, and subjects' blood samples were drawn at 1 and 2 hours postingestion for glucose and insulin determination.

Anthropomorphic assessments. Other assessments relevant to the current report included weight, height, and waist and hip circumference. Weight was measured with clothes and shoes on. Waist circumstance was measured with a tape measure at the level of the naval. Hip circumference was measured at the level of the iliac crest, usually where a pair of pants would sit on the waist.

Clinical assessments. Patients were administered the Positive and Negative Syndrome Scale (PANSS) monthly and other scales not directly relevant to the current report. The PANSS ratings were performed by the same rater (R.C.S.) for the entire study.

Chemical assays. All chemical analyses were done at the regional clinical chemistry laboratory of Nathan Kline Institute or its contract laboratory (BioReference Laboratories for insulin and C-peptide). Serum glucose was determined by enzymatic procedures using the Roche/Hitachi Kits (Roche Diagnostics, Indianapolis, Indiana). Glycohemoglobin (HbA1c) was assayed by the turbidimetric inhibition immunoassay (TINIA) using Roche/Hitachi Cobas kits. Serum insulin was assayed by 2-site chemiluminescence radioimmunoassay with the Immulite 2000 kits (Siemens Medical Solutions, Los Angeles, California), interassay coefficient of variation 4.2%–7.3%. The insulin assay has no cross-reactivity with C-peptide or glucagon and 8% cross-reactivity with proinsulin. C-peptide was assayed by a 2-site sandwich immunoassay using direct chemiluminescent technology with ADVIA Centaur kit (Siemens Healthcare Diagnostics Ltd, Tarrytown, New York); this assay has no appreciable cross-reactivity with insulin and proinsulin. Prolactin was assayed by Prolactin II Elecsys radioimmunoassay with Roche Cobas kits.

Statistical Analysis

Statistical analysis was performed with SPSS 12 (SPSS, Inc, Chicago, Illinois) and SAS 8.2 and 9.1 (SAS Institute Inc, Cary, North Carolina). Estimates of required sample size were computed using N-Query 3 (Statistical Solutions, Ltd, Cork, Ireland). The primary hypothesis was equivalence of drug effects on serum glucose—ie, that there would not be a large difference in change in glucose values between olanzapine and risperidone groups (≤ 15 mg/dL). Based on our own previous estimates of interpatient variance in glucose values, a sample size of 23 patients

per group was determined sufficient to have 80% power to detect such differences. Secondary hypotheses related to differences in glycohemoglobin, diabetic glucose levels, insulin levels, and insulin sensitivity indices. Variables were examined for normality. If histograms and Kolmogorov-Smirnov or Shapiro-Wilk statistics showed significant deviation from normality, a log transformation was performed. If the log-transformed values showed a substantially better approximation to a normal distribution, using the above criteria, the main analysis of these variables was performed on the log-transformed values (insulin, C-peptide, homeostasis model assessment of insulin resistance [HOMA-IR], homeostasis model assessment of β-cell function [HOMA-B], glucose tolerance test insulin sensitivity, BIGTT-acute insulin response surrogate measure [BIGTT-AIR]). The primary analysis used to compare the metabolic effects of olanzapine versus risperidone over time was a mixed model repeated measures analysis of variance (ie, Covariance Pattern Model also called mixed model with time as categorical variable) with correlation pattern either unstructured or using other variance-covariance structures, when there was a convergence problem, after examining the data correlations over time. The model also produces least mean squares estimates of the value at each time point (ie, baseline to month 5) and statistical significance tests between specific time points within or between the two drug treatments at different time points. Drug (olanzapine vs risperidone) and stay-switch (whether the randomized study drug was the same as the one patients were taking at baseline or whether they were switched to the study drug) were fixed factors, and baseline BMI was covariate. Body mass index was significantly correlated with the metabolic measures except for serum prolactin. In diabetes research, several other measures are standardly used to assess glucose metabolism and pancreatic functioning. These include (1) measures of insulin sensitivity or resistance (ie, a measure related to the amount of insulin needed to effect a change in serum glucose or glucose metabolism) and (2) measures reflecting the ability of the pancreas to produce or secrete insulin under baseline or challenge conditions. Measures and equations have been developed by various authors to assess these parameters from fasting glucose and insulin values (such as HOMA-IR [resistance] and HOMA-B [secretion]), as well as challenge indices from measures derived from an OGTT or an intravenous insulin-glucose frequently sampled glucose tolerance test (FSIVGTT) developed by Bergman and associates.[22,23] In the current study, measures of insulin resistance and secretion were calculated using HOMA-IR and HOMA-B calculations from baseline and monthly fasting glucose and insulin values using the revised insulin sensitivity and resistance estimates from the HOMA2 model and program.[24] A measure of insulin sensitivity, based on the glucose tolerance tests, was calculated using procedures and equations developed by Matsuda and Defronzo.[25] Surrogate measures from the OGTT of insulin sensitivity (BIGTT-insulin sensitivity; BIGTT-S_I) and acute insulin secretory response (BIGTT-AIR) were calculated using equations developed by Hansen and associates[26] for the 0-, 60-, and 120-minute OGTT time points; these authors present data showing that these BIGTT measures are highly correlated with those assessed in the same patients using the FSIVGTT and Bergman's minimal model.[27] Bergman and associates have also proposed another measure, the disposition index (DI), which they believe more accurately reflects pancreatic insulin secretory functioning because it takes into account the degree of insulin resistance present in calculating the relative pancreatic insulin secretion.[28] A surrogate measure of DI from OGTT was calculated as a product of BIGTT-AIR × BIGTT-S_I . For those variables that produced a significant effect of drug × time, a completer statistical analysis was also conducted using those subjects who had complete values over time for the specific metabolic variable.

RESULTS

Subject Background Characteristics

Table 1 presents the baseline demographic, diagnostic, and metabolic characteristics, as well as psychopathology, drug treatment, and 3-year glucose history characteristics of the subjects assigned to olanzapine versus risperidone. There were no statistically significant differences between the two drug groups on any characteristic. Only 12 patients had a history of glucose ≥ 100 mg/dL in the past 3 years, and only 2 had a prior chart diagnosis of diabetes. However, slightly more patients randomly assigned to olanzapine were previously treated with olanzapine at baseline and more patients randomly assigned to risperidone had been previously treated with risperidone at baseline, a result that may appear somewhat inconsistent with our design for random assignment. This imbalance is probably due to several factors. First, the multiple substratification groups in the random assignment procedure each had a separate randomization table. However, some of these groups wound up with only a few patients in the stratification group, and equalization of assignment between the two drugs, which would have occurred in a larger group, was not achieved in the small number of patients in the substratification group. Second, some of the treating clinicians were hesitant to give consent to the study if their patient was to be changed in primary medication. This may have led to some bias in the patient characteristics of those who eventually consented and entered the study. Third, 3 patients had to be assigned outside of strict random order for reasons described in the legend to Figure 1. Because of this potential bias in previous antipsychotic treatment in study drug assignment, we included the variable of switching versus remaining on the same antipsychotic in all analyses (stay vs switch) and performed further analysis on statistically significant interaction effects.

Table 1. Comparison of Baseline Characteristics of Patients Randomly Assigned to Olanzapine or Risperidone

Measure	Olanzapine (n = 23)	Risperidone (n = 23)	Statistical Comparison	*P*
Age, mean ± SD, y	41.22 ± 7.27	42.52 ± 9.10	$t = -0.537$	.594
Sex, male/female, n	23/0	22/1	$\chi^2 = 1.022$	.312
Race, n			$\chi^2 = 1.091$	.580
White	1	0		
Black, non-Hispanic	17	17		
Hispanic surname	5	6		
Other	0	0		
BMI, mean ± SD	29.96 ± 6.50	28.85 ± 5.71	$t = 0.612$	.544
DSM-IV diagnosis, n			$\chi^2 = 1.596$	.660
Schizophrenia	17	15		
Schizoaffective disorder	6	8		
DSM-IV Axis III diagnosis, n	18	17	$\chi^2 = 0.119$	.730
PANSS total score, mean ± SD	64.04 ± 17.00	61.78 ± 13.71	$t = 0.496$	.622
No. of years hospitalized, mean ± SD	2.47 ± 3.04	3.16 ± 5.25	$t = -0.545$	.689
No. of years ill, mean ± SD	21.26 ± 11.42	23.17 ± 11.72	$t = -0.561$	.578
Antipsychotics at baseline, n			$\chi^2 = 2.661$	.264
Olanzapine	13	8		
Risperidone	6	11		
Neither olanzapine or risperidone	4	4		
No. of antipsychotics at baseline, n			$\chi^2 = 4.525$	.104
1	8	14		
2	10	8		
3	5	1		
Type of antipsychotics at baseline, n			$\chi^2 = 4.404$	.111
Second generation	14	12		
First generation	0	4		
Combination first and second generation	9	7		
History of diagnosis of diabetes, n	0	2	FET = 2.310	.221
Family history of diabetes, n	1	2	FET = 0.244	1.000
Concomitant treatment, n				
Antidepressants	3	4	FET = 0.168	1.000
Antiparkinsonian	4	6	FET = 0.511	.722
Lithium	4	4	FET = 0.000	1.000
Valproate	11	9	$\chi^2 = 0.354$	.552
Statins	6	5	$\chi^2 = 0.119$	.730
Antihypertensive drugs	5	2	FET = 1.516	.414
Metabolic status				
Glucose at baseline, mean ± SD, mg/dL	84.48 ± 12.54	86.09 ± 10.18	$t = -0.478$	.635
Glucose over last 3 y, mean ± SD	84.10 ± 10.24	84.82 ± 11.16	$t = -0.218$	.829
No. of patients with glucose ≥ 100 mg/dL in last 3 y, n	5	7	$\chi^2 = 0.451$	.502
Glycohemoglobin at baseline, mean ± SD	5.48 ± 0.42	5.37 ± 0.40	$t = 0.898$	.374
Insulin at baseline, mean ± SD, uIU/mL	10.46 ± 8.97	11.76 ± 12.21	$t = -0.411$	.683
Cholesterol at baseline, mean ± SD, mg/dL	174.48 ± 28.48	170.83 ± 49.98	$t = 0.304$	.762
Triglycerides at baseline, mean ± SD, mg/dL	140.43 ± 103.30	167.96 ± 104.40	$t = -0.899$	.374

Abbreviations: BMI = body mass index; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; FET=Fisher exact test; PANSS = Positive and Negative Syndrome Scale; *t* = 2-sample *t* test.

Fasting Metabolic and Prolactin Values

Main differences between olanzapine and risperidone. Statistical analysis of fasting metabolic values showed that olanzapine-treated patients had a significantly ($P < .05$) higher increase in insulin resistance (HOMA-IR) over time than risperidone-treated patients, although estimated values at 5 months did not differ between the two drug groups. Risperidone-treated patients had a higher increase in serum prolactin ($P < .02$) than olanzapine-treated patients, and risperidone patients' prolactin values were significantly ($P < .01$) higher than olanzapine at the 5-month time point.

Detailed findings. There were no differences in the effects of assignment to 5 months' treatment with olanzapine versus risperidone on fasting glucose, glycohemoglobin, or C-peptide values (drug × time interaction, Table 2). Overall, there was no significant increase in fasting glucose over time in the combined total sample, and there were no significant differences between the two drugs in the mean values at the 5-month treatment time point. However, for the olanzapine-treated patients considered separately, the least mean squares difference of month 5 and baseline values (month 5 – baseline) showed a small but significant increase ($P < .05$). There were no significant differences in the number of patients who showed borderline (≥ 100 mg/dL) or diabetic (≥ 126 mg/dL) fasting glucose values at any time point, except at 2 months, in which slightly more olanzapine patients had borderline fasting glucose. Only 1 patient (assigned to olanzapine) developed a fasting glucose level classified as diabetic during the study period. The main analysis showed a trend ($P = .06$) for olanzapine patients to have increased insulin levels compared to risperidone

Table 2. Glucose-Insulin Metabolic and Other Effects of Olanzapine (n = 23) and Risperidone (n = 23) During 5 Months of Treatment[a,b]

	Baseline, Mean ± SEM		5 Months, Mean ± SEM		Difference (5 months vs baseline), Mean ± SEM		Mixed Model ANOVA
Metabolic or Other Measure	Olanzapine	Risperidone	Olanzapine	Risperidone	Olanzapine	Risperidone	Drug × Time Interaction[c]
BMI (log BMI)	30.15 ± 1.22	28.80 ± 1.21	31.54 ± 1.22	29.39 ± 1.21	1.39 ± 0.51**	0.59 ± 0.50	$F^L = 1.37$, $P = .235$
	(1.47 ± 0.017)	(1.45 ± 0.016)	(1.49 ± 0.017)	(1.46 ± 0.016)	(0.020 ± 0.008)*	(0.010 ± 0.008)	
Fasting metabolic measures							
Glucose fasting, mg/dL	83.91 ± 2.13	86.55 ± 2.11	91.25 ± 2.57	88.92 ± 2.53	7.34 ± 3.15*	2.37 ± 3.11	$F = 0.50$, $P = .774$
Insulin fasting (log insulin fasting), uIU/mL	9.41 ± 1.60	12.27 ± 1.58	16.22 ± 2.49	9.57 ± 2.46	6.81 ± 2.73*	−2.70 ± 2.69	$F^L = 2.32$, $P = .061$
	(0.83 ± 0.06)	(0.94 ± 0.06)	(1.02 ± 0.06)	(0.86 ± 0.06)	(0.19 ± 0.07)**	(−0.08 ± 0.07)	
C-peptide fasting (log C-peptide), ng/mL	2.04 ± 0.20	2.01 ± 0.20	2.17 ± 0.21	1.84 ± 0.21	0.13 ± 0.21	−0.17 ± 0.20	$F^L = 0.66$, $P = .653$
	(0.24 ± 0.03)	(0.25 ± 0.03)	(0.27 ± 0.04)	(0.22 ± 0.04)	(0.03 ± 0.03)	(−0.03 ± 0.03)	
Glycohemoglobin fasting	5.45 ± 0.09	5.37 ± 0.09	5.43 ± 0.12	5.50 ± 0.12	−0.02 ± 0.11	0.14 ± 0.11	$F = 1.47$, $P = .220$
Glucose tolerance test							
1-hour glucose, mg/dL	123.80 ± 6.85	148.30 ± 6.77	143.75 ± 7.41	145.18 ± 7.31	19.94 ± 7.86*	−3.12 ± 7.76	$F = 1.51$, $P = .227$
2-hour glucose, mg/dL	107.48 ± 6.20	116.03 ± 6.13	120.57 ± 5.46	127.44 ± 5.38	13.09 ± 5.05*	11.41 ± 4.98*	$F = 0.70$, $P = .557$
1-hour insulin (log 1-hour insulin), uIU/mL	64.63 ± 12.52	89.87 ± 12.39	103.47 ± 11.32†	67.42 ± 11.16†	38.83 ± 12.40**	−22.44 ± 12.24	$F^L = 3.88$, $P = .016$
	(1.59 ± 0.07)	(1.81 ± 0.07)	(1.89 ± 0.05)	(1.77 ± 0.05)	(0.30 ± 0.08)**	(−0.03 ± 0.07)	
2-hour insulin (log 2-hour insulin), uIU/mL	51.76 ± 8.35	65.44 ± 8.23	76.62 ± 8.95	59.42 ± 8.77	24.86 ± 8.40	−6.02 ± 8.22	$F^L = 1.83$, $P = .157$
	(1.53 ± 0.07)	(1.66 ± 0.07)	(1.74 ± 0.07)	(1.65 ± 0.07)	(0.21 ± 0.08)	(−0.006 ± 0.08)	
AUC glucose, mg/dL × h	51.00 ± 8.01	77.70 ± 7.92	120.96 ± 12.61†	83.99 ± 12.41†	69.96 ± 14.25**	6.29 ± 14.05	$F = 3.58$, $P = .022$
AUC insulin (log AUC insulin), uIU/mL × h	71.67 ± 15.04	103.65 ± 14.84	119.81 ± 12.55†	82.34 ± 12.36†	48.14 ± 15.09**	−21.31 ± 14.87	$F^L = 4.49$, $P = .024$
	(1.68 ± 0.07)	(1.88 ± 0.07)	(1.97 ± 0.05)	(1.88 ± 0.05)	(0.28 ± 0.07)**	(−0.003 ± 0.07)	
Insulin sensitivity–resistance and β-cell function indices							
HOMA-IR fasting (log HOMA-IR)	1.14 ± 0.20	1.58 ± 0.20	1.95 ± 0.30	1.25 ± 0.29	0.81 ± 0.33*	−0.33 ± 0.32	$F^L = 2.57$, $P = .041$
	(−0.09 ± 0.06)	(0.06 ± 0.05)	(0.11 ± 0.06)	(−0.02 ± 0.06)	(0.20 ± 0.07)**	(−0.08 ± 0.06)	
HOMA-B (log HOMA-B)	118.57 ± 11.21	125.30 ± 0.98	143.38 ± 17.90	108.72 ± 17.49	24.80 ± 19.91	−16.58 ± 19.45	$F^L = 1.42$, $P = .238$
	(2.01 ± 0.04)	(2.06 ± 0.14)	(2.06 ± 0.05)	(1.99 ± 0.05)	(0.06 ± 0.05)	(−0.07 ± 0.05)	
GTT insulin sensitivity (log insulin sensitivity) (Matsuda)	9.18 ± 1.14	6.42 ± 1.13	6.19 ± 0.81	6.64 ± 0.79	−2.99 ± 1.25*	0.22 ± 1.23	$F^L = 3.53$, $P = .023$
	(0.82 ± 0.05)	(0.72 ± 0.05)	(0.64 ± 0.06)	(0.76 ± 0.05)	(−0.17 ± 0.06)**	(0.04 ± 0.06)	
BIGTT-S_I	7.34 ± 0.65	5.90 ± 0.64	5.31 ± 0.61	6.07 ± 0.60	−2.03 ± 0.56**	0.17 ± 0.55	$F = 3.14$, $P = .0353$
BIGTT-AIR (log BIGTT-AIR), pmol/L insulin	6811 ± 1311	6398 ± 1293	8164 ± 1362	4547 ± 1341	1353 ± 1126	−1852 ± 1108	$F^L = 1.31$, $P = .127$
	(3.66 ± 0.05)	(3.67 ± 0.05)	(3.73 ± 0.05)	(3.61 ± 0.05)	(0.07 ± 0.05)	(−0.06 ± 1.05)	
BIGTT-DI	27073 ± 2184	22431 ± 2156	20035 ± 1809	22134 ± 1780	−7039 ± 2014**	−297 ± 1983	$F = 2.11$, $P = .114$
Prolactin							
Prolactin fasting (log prolactin fasting), ng/mL	41.85 ± 7.61	57.02 ± 7.60	33.43 ± 8.64‡	69.01 ± 8.55‡	−8.41 ± 4.71	11.98 ± 4.71*	$F^L = 3.18$, $P = .016$
	(1.54 ± 0.06)	(1.62 ± 0.06)	(1.47 ± 0.05)‡	(1.78 ± 0.05)‡	(−0.08 ± 0.06)	(0.16 ± 0.06)*	

[a]Each number represents estimated mean ± SEM from mixed model analysis, which included drug (olanzapine vs risperidone) and stay-switch (randomly assigned to same antipsychotic or switched to different antipsychotic) as factors and BMI baseline as covariate. In prolactin analysis, BMI was not included as covariate because there was no correlation between BMI and prolactin levels at baseline or end of study.

[b]BIGTT (ie, β-cell acute insulin response and insulin sensitivity calculations from OGTT, as per Hansen and associates' abbreviation[26]): S_I = insulin sensitivity; AIR = acute insulin response, often represented in FSIVGTT as AIR_G; DI = disposition index. Values for BIGTT and HOMA are calculated from units expressed in pmol/L insulin and mmol/L glucose, whereas the Matsuda insulin sensitivity equality uses insulin uIU/mL and mg/dL glucose. Adjusted least squares means from mixed model, significance of differences: (1) mean difference of *5 months value minus baseline value*, for olanzapine and risperidone groups *considered separately*: *$P < .05$, **$P < .01$; (2) difference between mean values of olanzapine versus risperidone groups *at the 5-month time point*: †$P < .05$, ‡$P < .01$.

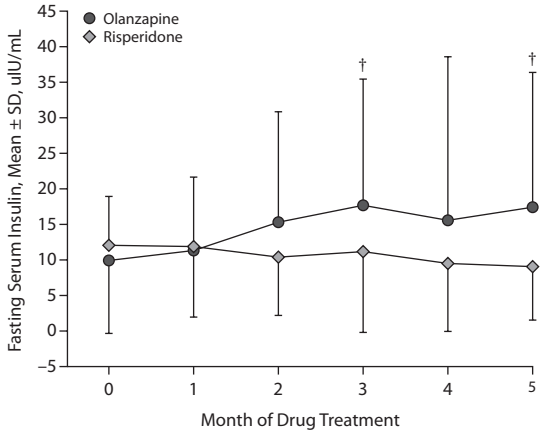
[c]Drug × time interaction effect (F) is from type 3 sum of squares ($df = 5,41$; except for prolactin $df = 5,42$). When distribution of original values deviated substantially from normality (see Method section), results and analyses (F^L) are presented on log transformed values that more closely approximated a normal distribution. The statistical analyses used values from all 6 months (baseline and each of 5 months of drug treatment) in the mixed model repeated ANOVA; however, only baseline and 5-month values are presented in the table.

Abbreviations: ANOVA = analysis of variance, AUC = area under the curve, BIGTT-AIR = BIGTT-acute insulin response surrogate measure, BMI = body mass index, FSIVGTT = frequently sampled intravenous glucose tolerance test, GTT = glucose tolerance test, HOMA-B = homeostasis model assessment of β-cell function, HOMA-IR = homeostasis model assessment of insulin resistance, OGTT = oral glucose tolerance test, SEM = standard error of the mean.

patients. A completer repeated measures analysis of raw insulin levels (not corrected for BMI or other factors) also showed increased insulin levels with olanzapine during the 5 months of treatment ($P = .025$), although comparison at any single time point only reached trend levels ($P < .10$) (Figure 2). A measure of insulin resistance or lack of sensitivity to insulin's effect on glucose, HOMA-IR, showed an overall drug effect, increasing in the olanzapine patients and decreasing in the risperidone patients (drug × time, $P = .04$; Table 2), but the estimated HOMA-IR means of the two drug groups showed no significant difference at the 5-month time point (ie, $P > .05$). HOMA-B, an index putatively related to pancreatic β-cell function and insulin secretion, showed no drug effect or overall change, although the olanzapine-treated patients had a slight increase at month 3 ($P = .04$). Treatment with olanzapine decreased and treatment with risperidone increased serum prolactin (Table 2). Completer analysis using the same covariates and factors showed generally similar overall results to the mixed model analysis presented in Table 2.

There were no significant interaction effects on the metabolic values between drug effects and staying on the baseline drug or being switched to a new antipsychotic (drug × time × stay vs switch), except for serum prolactin (interaction, $P = .005$). Those switched to olanzapine had a greater decrease in prolactin, and those switched to risperidone had a greater increase in prolactin, than those who remained on the same medication. Although there was no overall interaction effect of switch versus stay for drug effects on fasting insulin or HOMA-IR, for risperidone-treated patients considered separately there was a statistically significant interaction effect (interaction effect – time × switch vs stay: insulin $P = .006$, HOMA-IR $P < .004$). Those who stayed on risperidone treatment had a slightly greater increase in insulin and less of a decrease in HOMA-IR than those who were switched to risperidone from another antipsychotic.

Figure 2. Insulin Values at Baseline and During 5 Months of Treatment With Olanzapine or Risperidone, Completer Analysis in Subjects With All Values Recorded[a]



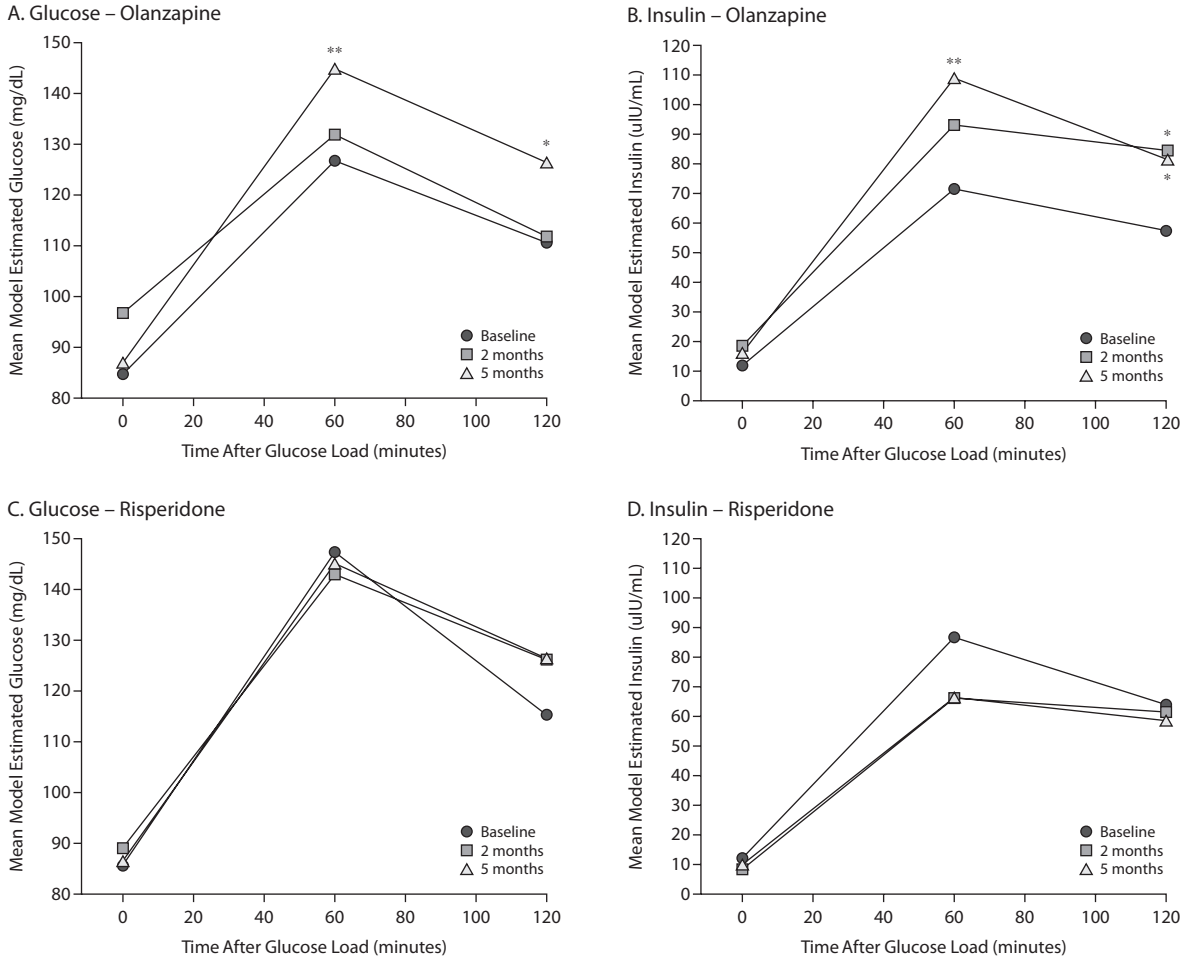
[a]Olanzapine n = 20, risperidone n = 22. Statistical analysis performed on $\log_{10}$ transformed insulin values, which more closely approximated a normal distribution. Analysis of variance, drug × time interaction: $F = 2.638$, $df = 5,200$; $P = .025$. 2-sample T test at specific time points: † = $P < .10$.

Glucose Tolerance Test

Main differences between olanzapine and risperidone. In the glucose tolerance test results, olanzapine patients showed a significant decrease in insulin sensitivity compared to risperidone patients who showed no change (P values range from .02–.03 on different indices); however, there were no statistically significant differences (ie, $P > .05$) in the estimated mean values of insulin sensitivity at the 5-month time point between the two drug groups. Over time, olanzapine patients showed a relative increase in glucose and insulin response at the 1-hour time point after receiving a 75 g glucose load, whereas risperidone patients did not change in these parameters over time. Olanzapine patients had a larger increase in glucose and insulin area under the curve (AUC) over time than risperidone patients ($P = .02$), and the AUC differences between risperidone and olanzapine patients were all significantly different ($P < .05$) at the 5-month treatment time point.

Detailed results. Glucose tolerance tests (OGTT) conducted at baseline and after 1 month, 2 months, and 5 months of treatment showed significant differences over time on some measures between olanzapine and risperidone and increasing glucose and insulin levels in olanzapine-treated patients (Table 2, Figure 3). Serum insulin at 1-hour post–glucose load became significantly higher over time in the olanzapine-treated patients, whereas it decreased in the risperidone-treated patients (Table 2). Overall insulin response to 75 g glucose load increased over months of olanzapine treatment, whereas it remained the same or decreased slightly in risperidone-treated patients. This was also reflected in a significant increase in insulin AUC in the olanzapine-treated patients compared to the risperidone-treated patients (Figure 3, Table 2). There was no overall mean difference in 1- or 2-hour glucose levels in olanzapine- versus risperidone-treated patients. There was also no difference in the number of patients achieving 2-hour glucose levels that were borderline (≥ 140 mg/dL) or diabetic (≥ 200 mg/dL) between the olanzapine- and risperidone-treated patients when analyzed by either mixed model analysis or completer analysis. At baseline, 4 of the olanzapine patients and 3 of the risperidone patients had borderline or abnormal 2-hour glucose levels, and after 5 months of treatment, 5 of the olanzapine and 5 of the risperidone patients had borderline or abnormal 2-hour glucose levels. However, the time course of glucose levels during the OGTT was significantly different over the 5 months of treatment in the olanzapine versus risperidone patients. Glucose levels, especially 1-hour OGTT glucose levels, rose over months of olanzapine treatment, and the

Figure 3. Mean Serum Glucose and Insulin Values During Glucose Tolerance Test at Baseline and After 2 and 5 Months of Treatment With Either Olanzapine or Risperidone[a]



[a]Means are estimated values from mixed model analysis (olanzapine n = 23, risperidone n = 23). See Method section for details of covariate and factors included in the mixed model analysis. For clarity, the graph only shows results at baseline, 2 months, and 5 months, but overall mixed model analysis was performed using values at baseline,1 month, 2 months, and 5 months and yielded the following results for the relevant interaction term effects: (a) month × time (0, 60, 120 minutes) × drug and (b) month × drug. Serum glucose: month × time × drug $F = 2.23$, $df = 12,41$; $P = .028$; month × drug $F = 1.39$, $df = 3,41$; $P = .259$. Serum insulin ($\log_{10}$): month × time × drug $F = 1.04$, $df = 12,254$; $P = .412$; month × drug $F = 5.03$, $df = 3,128$; $P = .003$. Individual comparisons of differences between least squares means from the mixed model analysis showed significant differences at several time points, for glucose or insulin respectively, comparing mean values at month 5 versus baseline and month 2 versus baseline: $^{**}P < .01$, $^{*}P < .05$.

glucose AUC increased more over time in the olanzapine patients than in the risperidone patients (Figure 3, Table 2). We computed 2 measures of insulin sensitivity based on the glucose and insulin values during the OGTT. The olanzapine patients had a significant decrease in these measures of insulin sensitivity (P values, baseline vs 5 month $< .01$), whereas the risperidone patients remained about the same or showed a slight increase in insulin sensitivity that was not statistically different from baseline (drug × time effects: Matsuda OGTT insulin sensitivity, $P = .023$; BIGTT-S_I, $P = .035$; Table 2). We also calculated 2 indices from the OGTT putatively related to pancreatic β-cell function, acute insulin secretion response (BIGTT-AIR), and insulin DI. There was no overall difference between the effects of olanzapine versus risperidone over time, as assessed from serial OGTTs, either in the measure of BIGTT-$AIR_{(0,60,120)}$ or in the DI index. Olanzapine patients did not show any statistically significant overall changes in these measures over time using the analysis of variance (ANOVA) for repeated measures mixed model, completer analysis, or additional nonparametric tests. However, in the mixed model analysis, the least squares mean difference of the DI value for the olanzapine patients for 5 months versus baseline showed a significant decrease ($P < .002$).

Completer analysis, using only those subjects who completed 5 months and had complete values for glucose or insulin, showed a generally similar pattern of results as the mixed model analysis presented above, with some increases

Table 3. Multiple Linear Regression Prediction of HOMA-IR and Change in HOMA-IR[a]

Dependent (predicted) Variable (and regression AVOVA)	Final R^2	Variables in Final Regression Equation (step-down method)	Standardized Regression Coefficient β (significance)
HOMA-IR baseline (log_{10}) ($F = 30.40$, $df = 1,45$; $P < .001$)	.408	Waist circumference (cm)	.639 ($P < .001$)
HOMA-IR month 5 (log_{10}) ($F = 17.44$, $df = 1,43$; $P < .001$)	.293	BMI month 5 (log_{10})	.542 ($P < .001$)
HOMA-IR change (month 5 – month 1) ($F = 6.61$, $df = 2,43$; $P = .014$)	.241	Study drug (olanzapine vs risperidone)	.369 ($P = .008$)

[a]Results based on completer analysis. Independent predictor variables (or their logarithmic transformation) entered into the step-down multiple regression procedure were study drug, BMI at indicated time point or change in BMI, waist circumference at indicated time point or change in waist circumference, and waist-hip ratio at indicted time point or change in waist-hip ratio.
Abbreviations: ANOVA = analysis of variance, BMI = body mass index, HOMA-IR = homeostasis model assessment of insulin resistance.

or decreases in statistical significance compared to the mixed model analysis. For example, completer analysis of olanzapine versus risperidone glucose AUC showed a significant effect of drug × time ($F = 5.253$, $P = .007$), with olanzapine-treated patients having higher AUC glucose in later months of treatment than risperidone-treated patients. One-hour insulin levels in the OGTT were significantly increased over time in the olanzapine- compared to the risperidone-treated patients ($F = 4.201$, $P = .007$)

None of the analyses based on the OGTT showed a significant interaction of drug effect with stay-switch for study drug assignment (drug × time × stay vs switch). For the olanzapine patients considered separately, those who stayed on olanzapine treatment had a slightly greater increase in glucose 1-hour post glucose load than those who were switched to olanzapine.

Factors Predicting Insulin Sensitivity or Resistance

Previous research had reported that insulin sensitivity during antipsychotic treatment is significantly correlated with BMI and waist circumference. There was no differential drug effect of olanzapine versus risperidone on change in BMI (drug × time, Table 2) or changes in weight or waist circumstances over time, although in both drug groups, BMI, weight (baseline, 90.8 ± 19.3 kg; month 5, 93.8 ± 19.5 kg), and waist circumference (baseline, 39.6 ± 5.5 cm; month 5, 40.6 ± 6.0 cm) all increased slightly over time (mean percent increase 2%–4%). For the olanzapine-treated patients, adjusted least squares means showed a significant ($P < .01$) increase in BMI for the 5 month versus baseline difference (Table 2). Multiple linear regression, using step-down procedures for entry, showed that baseline waist circumference significantly predicted HOMA-IR at baseline and month 5 BMI significantly predicted HOMA-IR at month 5, but only study drug assignment predicted change in HOMA-IR from baseline to month 5 (Table 3). Similar regression analysis for the OGTT insulin sensitivity showed that the measure of waist circumference significantly ($P = .007$) predicted insulin sensitivity at baseline ($r^2 = .152$). BMI (log_{10}) and waist-hip ratio at month 5 significantly ($P < .01$) predicted OGTT insulin sensitivity at month 5 ($r^2 = .464$). In contrast, the multiple linear regression, for the dependent variable of change in OGTT insulin sensitivity from baseline to 5 months, showed that no factor related to BMI, adiposity, or antipsychotic drug assignment was significantly predictive. Graphical plots did not suggest an alternative curvilinear relationship.

Another way of assessing the relative independence of drug effects on metabolic changes from the drugs' effects on weight is to include BMI every month as a time-dependent covariate and examine whether drug × time interaction effects in the mixed model are substantially modified from the original results when we include covariates related to weight change. If the significance of the drug × time interaction effects were wiped out or much reduced, or the estimated means are substantially reduced, this could indicate a strong dependence of the metabolic changes on weight changes. When the time-dependent BMI covariates were added to the model, the results were essentially similar to the main analysis, although the significance of the drug × time interaction effect (F) was reduced very slightly in most analyses.

These 2 approaches to the analyses of BMI effects suggest that changes in patients' BMI during study drug treatment with olanzapine or risperidone did not have a large influence on changes in 2 measures of insulin sensitivity, or on differential change in insulin or glucose values during the OGTT, but does not rule out a small contribution of increased adiposity.

Changes in Clinical Ratings

Overall, PANSS total scores decreased slightly (mean 7.2% decrease) but significantly over the course of the study ($F = 5.115$, $P = .008$, completer analysis), with baseline PANSS score (mean ± SD; 62.5 ± 15.1) significantly higher than the month 5 score (58.0 ± 11.5) (contrast month 5 vs baseline, $P = .003$). There was no differential drug effect of olanzapine versus risperidone treatment on PANSS total scores or positive or negative symptoms. Changes in PANSS score were not related to changes in weight, waist circumference, BMI, or changes in glucose, insulin, or HOMA-IR, neither when analyzed for the total sample or separately for olanzapine-treated patients.

DISCUSSION

The main results of this study show that over a 5-month treatment period, olanzapine treatment resulted in significant differences in glucose and insulin metabolism compared to risperidone with differences between the drugs more clearly evident in postprandial glucose metabolism

after a glucose load. There were no drug differences in fasting measures of glucose and glycohemoglobin in the ANOVAs, but there was a strong trend for fasting insulin measures to increase in the olanzapine group and decrease in the risperidone group. It took several months of treatment of these differences in postprandial glucose metabolism to become evident, and the strongest differences were often found at 4 to 5 months. At the 5-month time point, there were significant ($P < .05$) differences in glucose and insulin AUC during an OGTT. However, there were no differences between the two drug groups in standard clinical criteria for diagnosing diabetes or impaired glucose tolerance. There were no significant increases in borderline or diabetic glucose levels over the 5 months of study drug treatment, in either fasting glucose or 2-hour glucose levels in OGTT, and no consistent differences between the number of olanzapine versus risperidone patients meeting these criteria. The increase in insulin secretion may have prevented any clinically significant increase in glucose levels from becoming evident. Whether treatment with olanzapine over a longer term would lead to clinically significant glucose and glycohemoglobin abnormalities in a greater number of patients is uncertain.

Although the number of patients who were treated with olanzapine or risperidone immediately prior to the study was slightly unbalanced between the two random assignment groups, our statistical analysis showed that this did not have a significant effect on metabolic outcome variables. There were no significant interactions of drug effects on glucose or insulin changes dependent on whether the study drug was the same drug the patient was being treated with at baseline or whether the study drug was newly initiated (switched). Length of prior treatment with olanzapine was also not related to change in metabolic indices. Among the olanzapine-treated patients, those who stayed on olanzapine treatment during the study had been taking the drug for a mean of 13.8 months prior to the study (range, 4–36). For these patients, there were no significant correlations between length of prior treatment with olanzapine and fasting glucose levels, the extent of the increase in fasting glucose over time, or increase in 1- or 2-hour glucose values during the glucose tolerance tests; most of the correlations were small and/or negative in direction. There were also no consistent correlations of length of prior treatment with olanzapine and increase in fasting insulin, HOMA-B, increase in insulin during an OGTT test, change in insulin sensitivity, or change in BIGTT-AIR or BIGTT-DI. Our statistical and correlational analyses are consistent with the suggestion that in chronic schizophrenic patients without a history of diabetic metabolic abnormalities who have previously been treated for years with first- and second-generation antipsychotic drugs, treatment with olanzapine over a period of 1 to 3 years is unlikely to result in clinically significant metabolic manifestations of diabetes as reflected in glucose and glycohemoglobin values, although insulin values may be significantly increased, especially postprandial insulin values.

There may be multiple physiologic mechanisms underlying the changes in glucose and insulin levels seen in the olanzapine-treated group, including both physiologic effects increasing primary insulin secretion and glucogenesis. Several studies suggest that olanzapine increases both basal and glucose stimulated insulin release in humans and animals.[29,30] Although our results showed no overall significant change in HOMA-B, which may reflect pancreatic insulin secretion, there was a trend for olanzapine treatment to increase HOMA-B, which was significant ($P = .04$) at the 3-month time point. The insulin increases could also be secondary to stimuli by signals of increased blood glucose, which could be generated by increases in glucogenesis by up-regulation of glycogen phosphorylase, decreases in the effectiveness of insulin's molecular mechanisms on lowering blood glucose, or up-regulation of genes associated with increased glucose production in brain and muscle, all of which have been reported in published studies.[31] For example, olanzapine inhibits some of the cascade of insulin actions, such as insulin stimulated IRS-1 tryosine and IRS-1 associated P13K activity, the net effect leading to a decrease in glycogen production and an increase in glucose.[32] These mechanisms suggest that the increase in serum insulin produced by olanzapine may also be a compensatory response to the higher glucose levels resulting from increased glucogenesis and decreased effectiveness of the cascade of insulin's cellar action to reduce glucose.

Obesity and especially visceral adiposity are related to the increase in insulin resistance and diabetes. In prior studies, olanzapine has been associated with significant weight gain, especially during the first 6 to 8 months of treatment.[33] In a study in a dog model, Ader and associates[34] reported that olanzapine prevented the increase in insulin secretion in obesity-induced insulin resistance, although this may be specific to hepatic insulin resistance. However, a study by Haupt and associates[12] did not report a lack of insulin response to a glucose load in moderately obese patients (BMI = 30–32). They reported that in schizophrenic patients treated with antipsychotics, measures of adiposity, BMI, or waist circumference were significantly negatively associated with insulin sensitivity and positively associated with insulin response to glucose load; there was no difference between patients treated with olanzapine compared to 2 other antipsychotics, risperidone and ziprasidone. In the current study, in which patients' mean BMIs (29–30) were similar to those of the Haupt study, there was also a significant association of BMI, waist circumference, and/or waist-hip ratio with fasting measures of HOMA-IR, as well as OGTT derived insulin sensitivity, measured both at baseline and month 5 of study drug treatment. However, only study drug treatment, and not factors related to adiposity, was significantly predictive of an increase in HOMA-IR from baseline to month 5. This suggests that in this group of

chronically treated patients with schizophrenia, the change in insulin resistance caused by olanzapine was not strongly related to any changes in adiposity produced by the drugs during the study period. This interpretation is also consistent with the lack of any significant drug differences on changes in BMI, weight, or waist circumference. It is possible that more sensitive measures of increase in total or visceral adiposity measured by dual energy x-ray absorptiometry and magnetic resonance imaging or computed tomography abdominal adiposity could reveal a different relationship between drug effects on changes in adiposity and changes in insulin sensitivity.

There have been variable results in previous cross-sectional or prospective studies measuring metabolic effects of olanzapine versus risperidone in schizophrenic patients. (Some of these studies have also utilized patients treated with other antipsychotics.) In a cross-sectional study of closely matched lean patients, Henderson and associates,[9] using a FSIVGTT, found higher fasting insulin levels and higher insulin resistance measures in the olanzapine-treated patients compared to risperidone-treated patients but did not report any difference in indices reflecting β-cell pancreatic function (acute insulin response to glucose [AIR_G] or DI). Newcomer and associates,[10] in a cross-sectional study using an abbreviated oral OGTT (50 mg), reported that patients treated with olanzapine had higher glucose levels and higher insulin resistance than those treated with conventional antipsychotics. Our own prior cross-sectional study using OGTT (75 g)[13] reported that risperidone-treated patients had higher glucose levels at 1 hour than patients treated with olanzapine, and there were more patients taking risperidone who met American Diabetes Association glucose metabolic criteria for diagnosis of diabetes. Van Winkel and associates[35] recently reported significant differences in both fasting and OGTT glucose levels after 3 months of treatment in schizophrenic patients started on or switched to olanzapine, when compared to patients treated with aripiprazole, but there were no significant differences between olanzapine- and risperidone-treated patients. A recent prospective 6-month study of olanzapine and risperidone treatment of schizophrenic patients using fasting measures and FSIVGTT[16] found no significant differences in fasting glucose or insulin between the two drug groups at any time point and no difference in measures of insulin sensitivity or pancreatic β-cell function (AIR_G, DI). In a subset of African American and Hispanic patients in their sample (which is more similar to the main population of this current study), they also found no statistically significant differences in insulin sensitivity between olanzapine and risperidone groups, but a decrease in DI in the olanzapine group after 5 months of treatment. They interpret this change in DI to represent a decrease in compensating pancreatic β-cell function in olanzapine-treated patients. In contrast, the current study, which also used relatively obese patients with similar BMIs to the Ader and associates study,[34] showed differences in insulin sensitivity/resistance both in an index calculated on fasting measures and 2 insulin sensitivity indices calculated from OGTT. However, we found no overall differences in indices of β-cell secretory function derived from fasting measures or OGTT, although the olanzapine patients did have a significant decrease in our imputed measure of DI at 5 months of treatment. It is possible that our HOMA-B and BIGTT-AIR and BIGTT-DI measures of pancreatic β-cell function are less sensitive or accurate than the FSIVGTT measures using the Bergman minimal model,[28] although Hansen and associates[26] reported a strong relationship between BIGTT-AIR and FSIVGTT-AIR indices measured in the same patients. Whether the DI measure we computed from the BIGTT parameters correlates highly with the DI from FSIVGTT has not been evaluated. In addition to differences in assessment methods between Ader and associates[16] versus the current study (ie, FSIVGTT vs OGTT), other differences in subject population (outpatients vs inpatients, mixed sex vs mostly male subjects, multiple sites vs single site) and differences in statistical analysis (last observation carried forward vs mixed model, and controlling for baseline BMI in our analysis) may have contributed to the differences in results, on changes in insulin levels and insulin sensitivity over time, between the two drug treatment groups.

Our sample selection criteria could have biased our ability to find clinically meaningful increases in glucose levels or diabetes during olanzapine treatment. Our sample consisted of overweight patients with chronic schizophrenia, most of whom had been treated with conventional and second-generation antipsychotics for many years and who were not currently being treated with antidiabetic drugs, although 2 patients had a diabetic history and 12 had a history of at least 1 borderline or abnormal glucose in the past 3 years. These patients, who have survived years of treatment with second-generation antipsychotics without developing persistent diabetes, may represent a lower risk for developing diabetes than the general schizophrenic population in which the rate of diabetes has been estimated at 10%–14%. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study,[17] in which 9%–11% of the sample had diabetes and 25% had borderline or abnormal glucose levels at baseline, assignment to olanzapine treatment did produce a significant increase in glycosylated hemoglobin. It is possible that more striking increases in glucose levels and diabetes, and stronger differences between olanzapine and risperidone, might occur in younger, drug-naive patients or those who had no or very limited exposure to second-generation antipsychotics. For example, Davis (J.M.D., manuscript submitted) has reported that increases in weight with second-generation antipsychotics are quite variable and tend to occur most strongly in younger patients with low BMI who have less exposure to second-generation antipsychotics. However, a review of published first-episode schizophrenia studies involving olanzapine or clozapine

generally showed changes in insulin and lipids during treatment but no consistent changes in glucose or statistically significant increase in diabetes incidence.[36–39] These results are fairly similar to the type of metabolic changes reported in this and other studies of chronically treated schizophrenic patients. A recent review of prospective randomized trials of antipsychotics and glucose abnormalities found no consistent significant drug differences in treatment-emergent glucose abnormalities or clinical diabetes in patients treated with different antipsychotics.[40]

Limitations of this study include the relatively small sample size and characteristics of the patient populations studied, which may limit the interpretations of our findings. Although our sample was powered to detect a 15 mg/dL difference in fasting glucose between 2 drugs, it may have lacked the power to detect small differences in fasting glucose between the groups. It may also have lacked the power to detect drug group differences in the propensity to convert to glucose criteria for diagnosis of diabetes, especially if this occurs at a low rate in olanzapine patients. Extrapolation of our results to the general population of schizophrenic patients, who may have a 10%–14% rate of diabetes, or to younger patients who have not been treated with multiple second-generation antipsychotics, or to nonobese, lean schizophrenic patients may also not be fully warranted.

In summary, our study found that 5 months of olanzapine treatment in chronic schizophrenic patients previously treated with multiple antipsychotics produced increases in serum insulin and measures of insulin resistance as compared to risperidone treatment but no drug differences in the emergence of diabetes as indicated by abnormal glucose or glycohemoglobin levels. Our analysis suggested that longer prior treatment with olanzapine (up to 3 years) did not lead to greater effects of olanzapine on increasing glucose, insulin levels, or insulin resistance. Whether the effect of olanzapine on insulin resistance will increase over many years and lead to exhaustion of the β-cell insulin reserve and a subsequent increase in the incidence of clinical diabetes is unclear. In classical type 2 diabetes, elevations in insulin and insulin resistance often precede diabetic hyperglycemia by 5 to 10 years. Yearly OGTT tests measuring both glucose and insulin at 30 minute intervals in patients treated with olanzapine would be helpful in determining the status of the β-cell insulin reserve response and the risk of developing diabetes with long-term olanzapine treatment in this group of patients. Adjunctive antidiabetic medication, which would increase insulin sensitivity, should also be considered in clinical trials to reduce long-term risk. Since the weight increase produced by olanzapine is relatively small in these patients and the significant increase in insulin resistance is not related to drug effects on weight, treatment with drugs that specifically target improving insulin sensitivity, such as peroxisome proliferator-activated receptor γ agonist activators like pioglitazone, may be appropriate to consider in adjunctive clinical therapy trial studies. Pioglitazone significantly reduces postprandial glucose increase and increases insulin sensitivity both during OGTT and euglycemic insulin clamp studies.[41,42] There is also the suggestion that pioglitazone and other thiazolidinediones may be useful in prevention or delay of conversion from impaired fasting glucose into diabetes.[43] However, the risks of blood volume expansion and peripheral edema, which may increase the risk of congestive heart failure with this class of drugs, need to be concomitantly evaluated to assess prospective risk/benefit ratios for patients at increased risk of congestive heart failure. An alternative adjunctive treatment could be metformin, which has also been shown to decrease olanzapine-induced weight gain and prevent increases in insulin resistance in first-episode schizophrenic patients treated with olanzapine,[44] although this drug has not been shown to specifically increase insulin sensitivity or delay conversion to diabetes in patients with impaired glucose tolerance.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), lithium (Lithobid, Eskalith, and others), metformin (Riomet, Fortamet, and others), olanzapine (Zyprexa), pioglitazone (Actos), risperidone (Risperdal and others), ziprasidone (Geodon).

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Author contributions: Dr Smith designed the study and all study procedures, statistical analyses, and manuscript preparation were carried out independently by Dr Smith and his coauthors.

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REFERENCES

1. Dixon L, Weiden P, Delahantry J, et al. Prevalence and correlation of diabetes in national schizophrenia samples. *Schizophr Bull.* 2000;26(4):903–912.
2. Lindenmayer JP, Nathan AM, Smith RC. Hyperglycemia associated with the use of atypical antipsychotics. *J Clin Psychiatry.* 2001;62 (suppl 23):30–38.
3. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs.* 2005;19(suppl 1):1–93.

4. Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. *Am J Psychiatry.* 2003;160(2):284–289.
5. Saddichha S, Manjunatha N, Ameen S, et al. Diabetes and schizophrenia: effect of disease or drug? results from a randomized, double-blind, controlled prospective study in first-episode schizophrenia. *Acta Psychiatr Scand.* 2008;117(5):342–347.
6. Buse JB, Cavazzoni P, Hornbuckle K, et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiol.* 2003;56(2):164–170.
7. Caro JJ, Ward A, Levinton C, et al. The risk of diabetes during olanzapine use compared to risperidone use: a retrospective database analysis. *J Clin Psychiatry.* 2002;63(12):1135–1139.
8. Citrome L, Jaffe A, Levine J, et al. Relationship between antipsychotic medication treatment and new cases of diabetes among psychiatric inpatients. *Psychiatr Serv.* 2004;55:1006–1013.
9. Henderson DC, Cagliero E, Copeland PM, et al. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *Arch Gen Psychiatry.* 2005;62(1):19–28.
10. Newcomer JW, Haupt DW, Fucetola R, et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry.* 2002;59(4):337–345.
11. Cohen D, Stolk R, Grobbee D, et al. Hyperglycemia and diabetes in patients with schizophrenia or schizoaffective disorders. *Diabetes Care.* 2006;29:786–791.
12. Haupt DW, Fahnestock PA, Flavin KA, et al. Adiposity and insulin sensitivity derived intravenous glucose tolerance tests in antipsychotic-treated patients. *Neuropsychopharmacology.* 2007;32(12):2561–2569.
13. Smith RC, Lindenmayer JP, Bark N, et al. Clozapine, risperidone, olanzapine, and conventional antipsychotic drug effects on glucose, lipids, and leptin in schizophrenic patients. *Int J Neuropsychopharmacol.* 2005;8(2): 183–194.
14. Sowell MO, Mukhopadhyay N, Cavazzoni P, et al. Hyperglycemic clamp assessment of insulin secretory responses in normal subjects treated with olanzapine, risperidone, or placebo. *J Clin Endocrinol Metab.* 2002;87(6): 2918–2923.
15. Sowell M, Mukhopadhyay N, Cavazzoni P, et al. Evaluation of insulin sensitivity in healthy volunteers treated with olanzapine, risperidone, or placebo: A prospective, randomized study using the 2-step hyperinsulinemic, euglycemic clamp. *J Clin Endocrinol Metab.* 2003;88(12):5875–5880.
16. Ader M, Garvey T, Phillips L, et al. Ethnic heterogeneity in glucoregulation function during treatment with atypical antipsychotics in patients with schizophrenia. *J Psychiatr Res.* 2008;42(13):1076–1085.
17. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005;353(12):1209–1223.
18. Gasquet I, Haro JM, Tcherny-Lessenot S, et al. Remission in the outpatient care of schizophrenia: 3-year results from the schizophrenia outpatients health outcomes (SOHO) study in France. *Eur Psychiatry* 2008;23(7):491–496
19. Meltzer HY, Bobo WV, Roy A, et al. A randomized double-blind comparison of clozapine and high-dose olanzapine in treatment-resistant patients with schizophrenia. *J Clin Psychiatry.* 2008;69(2):274–285.
20. Novick D, Haro J, Suarez D, et al. Clinical consequences of switching antipsychotics drugs in outpatients with schizophrenia: 36-month results from the European schizophrenia outpatient health outcomes study. *Int Clin Psychopharmacol.* 2008;23(4):203–208.
21. Volavka J, Czobor P, Sheitman B, et al. Clozapine, olanzapine, risperidone, and haloperidol in treatment of patients with chronic schizophrenia and schizoaffective disorder. *Am J Psychiatry.* 2002; 159(2):255–262.
22. Bergman RN, Ider YZ, Bowden CR, et al. Quantitative estimation of insulin sensitivity. *Am J Physiol.* 1979;236(6):E667–E677.
23. Pacini G, Bergman R. MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsibly from the frequently sampled intravenous glucose tolerance test. *Comput Methods Programs Biomed.* 1986;23(2):113–122.
24. Wallace TM, Levy JC, Mathews DR. Use and abuse of HOMA modeling. *Diabetes Care.* 2004;27(6):1487–1495.
25. Matsuda M, Defronzo F. Insulin sensitivity indices obtained from oral glucose tolerance testing. *Diabetes Care.* 1999;22:1462–1470.
26. Hansen T, Drivshoem T, Urhammer S, et al. The BIGTT test: a novel test for simultaneous measurement of pancreatic β-Cell function, insulin sensitivity and glucose tolerance. *Diabetes Care.* 2007;30:257–262.
27. Boston RC, Stefanovski D, Moate PJ, et al. MINMOD millennium: a computer program to calculate glucose effectiveness and insulin sensitivity from the frequently sampled intravenous glucose tolerance test. *Diabetes Technol Ther.* 2003;5(6):1003–1015.
28. Bergman RN, Ader M, Huecking K, et al. Accurate assessment of beta-cell function: the hyperbolic correction. *Diabetes.* 2002;51 (suppl 1):S212–S220.
29. Melkersson K. Clozapine and olanzapine, but not conventional antipsychotics, increase insulin release in vitro. *Eur Neuropsychopharmacol.* 2004;14:115–119.
30. Melkersson KI, Hulting AL, Brismar KE. Elevated levels of insulin, leptin and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. *J Clin Psychiatry.* 2000;61(10):742–749.
31. Fatemi SH. Olanzapine increases glucogenesis by multiple pathways in brain and muscle [letter]. *Mol Psychiatry.* 2006;11(6):524–525.
32. Engl J, Laimer M, Niederwanger A, et al. Olanzapine impairs glycogen synthesis and insulin signaling in L6 skeletal muscle cells. *Mol Psychiatry.* 2005;10:1089–1096.
33. 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(2):92–100.
34. Ader M, Kim S, Catalano K, et al. Metabolic dysregulation with atypical antipsychotics occurs in absence of underlying disease: a placebo controlled study of olanzapine and risperidone in dogs. *Diabetes.* 2005;54(3):862–871.
35. Van Winkel R, De Hert M, Wampers M, et al. Major changes in glucose metabolism, including new-onset diabetes, within 3 months after initiation of or switch to atypical antipsychotic medication in patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry.* 2008;69: 472–479.
36. Graham KA, Perkins DO, Edwards LJ, et al. Effects of olanzapine on body composition and energy expenditure in adults with first-episode psychosis. *Am J Psychiatry.* 2005;162(1):118–123.
37. Green AI, Liegherman JA, Hamer RM, et al. Olanzapine and haloperidol in first-episode psychosis: 2-year data. *Schizophr Res.* 2006; 86(1-3):234–243.
38. Lieberman JA, Phillips M, Gu H, et al. Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. *Neuropsychopharmacology.* 2003;28(5):995–1003.
39. Perez-Igelsias R, Crespo-Facoro B, Amado JA, et al. A 12-week randomized clinical trial to evaluate metabolic changes in drug-naive, first-episode psychosis patients treated with haloperidol, olanzapine, or risperidone. *J Clin Psychiatry.* 2007;68(11):1733–1740.
40. Bushe CJ, Leonard BE. Blood glucose and schizophrenia: a systematic review of prospective randomized clinical trials. *J Clin Psychiatry.* 2007;68(11):1682–1690.
41. Miyazaki Y, Mahankali A, Matsuda M, et al. Improved Glycemia control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. *Diabetes Care.* 2001;24:710–719.
42. Miyazaki Y, Matsuda M, DeFronzo R. Dose-response effect of pioglitazone on insulin secretion in type 2 diabetes. *Diabetes Care.* 2002;25:517–523.
43. Durbin RJ. Thiazolidinedione therapy in the prevention/delay of type 2 diabetes in patients with impaired glucose tolerance and insulin resistance. *Diabetes Obes Metab.* 2004;6(4):280–285.
44. Wu RR, Zhao JP, Guo XF, et al. Metformin addition attenuates olanzapine-induced weight gain in drug-naive first-episode schizophrenia patients: a double-blind, placebo-controlled study. *Am J Psychiatry.* 2008;165(3):352–358.