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Ethnic heterogeneity in glucoregulatory function during treatment with atypical antipsychotics in patients with schizophrenia☆

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Abstract

Objective—Atypical antipsychotics induce weight gain and are linked to increased diabetes risk, but their relative impact on factors that elevate disease risk are unknown.

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Conflict of Interest

We report that potential conflicts of interest of manuscript authors include employment by, or advisors/consultants to, Johnson & Johnson Pharmaceutical Research and Development and/or Ortho-McNeil Janssen Scientific Affairs.

Methods—We performed a 6-month, randomized, double-blind study to evaluate the effects of risperidone and olanzapine in patients with schizophrenia. At baseline and weeks 6 and 24, we quantified: (1) total adiposity by DEXA, (2) visceral adiposity by abdominal CT, and (3) insulin sensitivity (S_I) and (4) pancreatic function (“disposition index”, DI) by intravenous glucose tolerance test.

Results—At baseline, groups (risperidone: $n = 28$; olanzapine: $n = 31$) were overweight or obese by body mass index (risperidone: 28.4 ± 5.4 , olanzapine: 30.6 ± 7.0 kg/m²). Both drugs induced weight gain ($p < 0.004$). Total adiposity was increased by olanzapine at 6 weeks ($p = 0.0006$) and by both treatments at 24 weeks ($p < 0.003$). Visceral adiposity was increased by olanzapine and risperidone by 24 weeks ($p < 0.003$). S_I did not deteriorate appreciably, although a downward trend was observed with risperidone. Given known ethnic differences in adiposity and S_I , we performed secondary analysis in African American and Hispanic subjects. In this subset, olanzapine expanded both total and visceral adiposity ($p < 0.02$); no increase was observed with risperidone. There were modest downward trends for SI with both treatments. By week 24, olanzapine-treated subjects exhibited diminished DI ($p = 0.033$), indicating inadequate pancreatic compensation for insulin resistance.

Conclusions—This is the first prospective study in psychiatric patients that quantified antipsychotic effects on the multiple metabolic processes that increase diabetes risk. Results indicate that ethnic minorities may have greater susceptibility to antipsychotic-induced glucoregulatory complications.

Keywords

Risperidone; Olanzapine; Schizophrenia; Diabetes; Minorities

1. Introduction

Atypical antipsychotics have been associated with weight gain and increased risk of Type 2 diabetes. However, evidence for this relationship has largely been inferred from retrospective analyses (Haddad, 2004; Jin et al., 2002), cross-sectional studies (Henderson et al., 2005), and case reports (Haddad, 2004; Jin et al., 2002; Henderson et al., 2005; Gupta et al., 2001). The pathogenesis of diabetes requires both insulin resistance and diminished pancreatic β -cell secretory compensation for resistance (Porte, 1991), yet few studies have used reliable methods to assess glucoregulatory function in patients receiving antipsychotic treatment. Moreover, few studies have characterized the longitudinal progression of drug effects on the metabolic factors that contribute to the pathogenesis of glucose intolerance and overt diabetes, particularly in ethnic groups with enhanced susceptibility to obesity and diabetes (Fujimoto et al., 1995; Haffner et al., 1996).

Evidence to suggest that atypical antipsychotics may alter glucose metabolism is largely inferential (Bergman and Ader, 2005). Obesity is a powerful risk factor for diabetes, and weight gain is a common side effect of many antipsychotics, although the magnitude varies considerably (Allison et al., 1999; American Diabetes Association, 2004). For two widely prescribed antipsychotics, more substantial weight gain has been reported in olanzapine-treated patients than in those receiving risperidone (Allison et al., 1999; Eli Lilly and Company, 2001). Little is known about the effects of these agents on adiposity *per se*, a potent risk factor in development of insulin resistance, cardiovascular disease, and the metabolic syndrome, and available data are conflicting (Ryan et al., 2004; Graham et al., 2005; Ader et al., 2005; Zhang et al., 2004).

Apparent development of insulin resistance during antipsychotic treatment has been inferred from fasting hyperinsulinemia or fasting-derived indices (Henderson et al., 2005), but such

measurements are unreliable if pancreatic β -cell function is compromised (Kahn and Flier, 2000). Moreover, resistance alone is insufficient to cause diabetes because of the normal compensatory upregulation of insulin secretion that occurs to maintain glucose tolerance (Bergman, 1989; Bergman et al., 2001). Understanding the mechanisms by which antipsychotics may induce diabetes requires that both insulin resistance and pancreatic function are measured in treated subjects, and monitored prospectively during drug therapy.

The present study was undertaken to quantify the effects of the atypical antipsychotics olanzapine and risperidone on glucoregulatory function in a longitudinal design. Longitudinal assessments of body weight and adiposity (total and visceral), insulin sensitivity (S_I), first-phase insulin response, and pancreatic function were performed. Study results have important implications in attempts to identify subjects who may have greater inherent risk for metabolic complications during antipsychotic therapy.

2. Methods

This study was a 6-month, randomized, double-blind, parallel-group comparison of the glucoregulatory and metabolic effects of maintenance therapy with risperidone or olanzapine. The subjects were patients recruited from seven US clinical sites over a 15-month period. Study sites were based in California (VA San Diego Healthcare System; California Neuropsychopharmacology Clinical Research Institute, San Diego; Affiliated Research Institute, San Diego; California Clinical Trials, Beverly Hills), Georgia (Emory University, Atlanta), Texas (University of Texas Health Science Center, San Antonio), and South Carolina (University of South Carolina, Charleston). Sites were chosen for experience in psychiatry and diabetes research (Haffner et al., 1996; Fujimoto et al., 1995; Cossrow and Falkner, 2004). Outpatients (aged 18–65 yrs) with schizophrenia or schizoaffective or schizophreniform disorder using DSM-IV criteria were eligible, and were considered to be psychiatrically stable (CGI-S ≤ 4) and exhibited no exacerbation of symptoms requiring hospitalization for 3 months prior to screening. Subjects with a positive history of diabetes or substance abuse (excluding nicotine and cannabis), significant medical illness, or unstable psychiatric disease were excluded. Subjects with baseline obesity were included to reflect the overall patient population receiving antipsychotics. Subjects may have undergone prior treatment with atypical antipsychotics >30 days prior to baseline examination. Treatment with haloperidol within 30 days of study entry was acceptable. Subjects with a history of clozapine treatment for >4 consecutive weeks continuously within 3 months prior to the screening visit were excluded. The study was approved by Institutional Review Boards of all investigative sites. Written informed consent was obtained from all subjects after complete study description was provided.

2.1. Study design

After screening to determine eligibility, subjects underwent baseline assessment of metabolic status and body composition. In addition to body weight and waist-hip ratio, adiposity was quantified by dual energy X-ray absorptiometry (DEXA) and abdominal computed axial tomography (CT) scan. Indices of glucose homeostasis were assessed by frequently sampled intravenous glucose tolerance test (FSIGT). Subjects were then randomized to risperidone or olanzapine for a 6-month, double-blind treatment phase. Study medication was adjusted over 1 week to reach target dose (risperidone at 6 mg/day and olanzapine at 20 mg/day), while doses of pre-study antipsychotics were reduced and then discontinued. Adiposity and glucose homeostasis were measured at weeks 6 and 24 of treatment.

2.2. Experimental procedures

Anthropometric measurements were made with subjects in lightweight clothing without shoes. Height was measured during screening or at baseline testing and body weight measured weekly from baseline to week 6 and at weeks 8, 12, 16, 20, and 24. Body mass index (BMI) was classified as normal (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), or obese (≥ 30.0 kg/m²) (Pi-Sunyer, 1998). Waist–hip ratio was calculated using minimum waist and broadest hip circumferences. Total body fat mass was assessed by DEXA. Visceral adiposity was calculated from single slice CT scan at the level of the umbilicus. Adiposity was expressed in cm². Procedures for DEXA and abdominal CT scans were standardized across sites.

Insulin-modified FSIGTs were performed on an outpatient basis after an overnight fast. Two basal blood samples were drawn from a catheter inserted in an antecubital vein, and glucose (11.4 g/m²) was injected over 1 min beginning at time 0. Additional samples were drawn at 2, 4, 6, 8, 10, 14, and 19 min, followed by insulin injection (0.03 U/kg) at 20 min and further sampling at 22, 24, 27, 30, 40, 50, 70, 90, 120, 150, 180, 210, and 240 min. Samples were kept on ice until centrifugation, and plasma stored at –20 °C for subsequent assay of glucose and insulin. Glucose was measured by the glucose oxidase method (YSI Model 2700, Yellow Springs, Ohio), with intra-assay coefficient of variation (CV) of <1%. Insulin was assayed by ELISA (Linco, St. Charles, Missouri), with intra- and inter-assay CV of 2 ± 1% and 5 ± 1%, respectively. Both assays were performed in the laboratory of Dr. Richard Bergman at the University of Southern California. Insulin sensitivity (S_I) and glucose effectiveness (S_G) were calculated using MINMOD software (MINMOD Millennium version 6.02) (Boston et al., 2003). First-phase insulin response (AIR_G) was calculated as incremental insulin area from 0 to 10 min and glucose tolerance (K_G) as the negative slope of the natural log of glucose versus time from 10 to 19 min (Lee et al., 1992). To assess the ability of the β -cells to compensate for insulin resistance, we normalized the insulin response to S_I (Bergman et al., 2001), since reductions in S_I should elicit upregulation of β -cell function. Pancreatic β -cell function was defined as the disposition index (DI), calculated as the product of $AIR_G \times S_I$ (Bergman et al., 2001; Bergman, 1989).

2.3. Statistical analysis

All randomized subjects receiving ≥ 1 dose of study medication and ≥ 1 post-baseline FSIGT were used for analysis of the glucoregulatory effects of index antipsychotic therapy. Compliance was verified by measurement of plasma drug levels. Investigative center effect was included in all statistical models. The last-observation-carried-forward rule was applied when subjects discontinued the study before completing the week-6 visit. Similar procedures were applied for subjects discontinuing before week-24 testing.

The primary study endpoint was the change in DI over 24 weeks of treatment. Change from baseline was analyzed using analysis of covariance, with baseline score as covariate, and center and treatment as fixed factors. Wilcoxon signed rank test was used to test for within-group differences from baseline. Data were similarly analyzed for DI changes from baseline to week 6, as well as for all secondary variables (S_I , AIR_G , S_G , K_G , fasting glucose and insulin, and adiposity measures). Given known ethnic differences in S_I , adiposity, and diabetes risk (Haffner et al., 1996; Fujimoto et al., 1995; Cossrow and Falkner, 2004), particularly among African Americans and Hispanics (Cossrow and Falkner, 2004), post hoc analyses of treatment effects were performed on adiposity and FSIGT-derived variables in the African American and Hispanic subjects in each treatment group. All normally distributed data (body weight, adiposity, fasting values) were expressed as mean after adjustment for test site and baseline values. Derived data (S_I , S_G , DI) displayed non-normal distribution, and treatment-associated effects were assessed using non-parametric tests on

median changes. All means and standard errors to follow are adjusted by investigator site and baseline value. Results from initial analyses were corroborated by additional analyses performed independent of study sponsor (Emory University School of Medicine).

3. Results

3.1. Background characteristics (Table 1)

A total of 59 subjects were randomized, and >75% completed the full 24-week treatment period. Study dropout rates were comparable between groups (risperidone, 25.0%; olanzapine, 22.6%) and primarily reflect loss to follow up (57.1% of dropouts in both groups). Two subjects discontinued because of adverse events: weight gain and sedation in an olanzapine subject and a positive pregnancy test in a risperidone subject. Groups were similar for age and ethnicity. Prior use of atypical antipsychotics was also similar between groups ($p = 0.535$).

3.2. Anthropometric variables

At baseline, groups were weight-matched (mean [$\pm$ SE] 186.8 $\pm$ 7.9 lb in the risperidone group and 190.9 $\pm$ 7.0 lb in the olanzapine group; Table 1) and categorized as overweight or obese. The effect of antipsychotic treatment on body weight is illustrated in Fig. 1. Significant weight gain (+3.0 $\pm$ 0.8 lb) was seen within 1 week of starting treatment with risperidone ($p < 0.0001$; Fig. 1), and this was sustained at week 6 (+3.8 $\pm$ 1.2 lb) and week 24 (+4.7 $\pm$ 2.5 lb; $p = 0.0007$ and $p = 0.0006$, respectively). Body weight also increased significantly within 1 week of starting olanzapine treatment (+2.3 $\pm$ 0.7 lb; $p < 0.004$) and increased further at week 6 (+6.4 $\pm$ 1.2 lb; $p < 0.0001$) and week 24 (+9.5 $\pm$ 2.7 lb; $p < 0.0007$; Fig. 1).

Prospective assessment of treatment-induced changes in adiposity is presented in Fig. 2. At baseline, the groups had similar total (risperidone, 22,120 $\pm$ 2109 cm²; olanzapine, 26,964 $\pm$ 2570 cm²) and visceral (92 $\pm$ 16 cm² and 81 $\pm$ 12 cm², respectively, $p > 0.27$) adiposity. Treatment with olanzapine induced a small but significant increase in total adiposity by week 6 (+1436 $\pm$ 458 cm²; $p = 0.0006$) which was sustained to week 24 (+2952 $\pm$ 1265 cm²; $p = 0.0023$ vs. baseline; Fig. 2A). In the risperidone group, total adiposity was not significantly increased until week 24 (+1617 $\pm$ 1141 cm² above baseline; $p = 0.0153$). In contrast, visceral adiposity was increased at week 24 in both the olanzapine- and risperidone-treated groups ($p < 0.0029$ for both, vs. respective baselines; Fig. 2B). No significant within- or between-group changes in waist-hip ratio were observed ($p > 0.57$; data not shown).

3.3. Fasting plasma concentrations

There were minimal effects of antipsychotic treatment on measured plasma values. Fasting glycemia was not affected by either treatment ($p > 0.1$). Of note, two subjects had excursions of fasting glucose into the diabetic range (> 126 mg/dl). One olanzapine-treated subject exhibited fasting hyperglycemia (144 mg/dl) at week 6, which was normalized (101 mg/dl) by week 24, and hyperglycemia (173 mg/dl) developed in a subject receiving risperidone at week 24. In both cases, fasting hyperinsulinemia was also present at these time points (45 and 85 μ U/ml, respectively). Glycosylated hemoglobin remained in the normal range for these and all other subjects (data not shown). Whether these data represent a direct effect of the antipsychotics or an incomplete fasted state is not known.

Fasting insulin levels, which were well-matched in the two groups at baseline (risperidone, 10.3 $\pm$ 1.6 μ U/ml; olanzapine, 8.5 $\pm$ 1.0 μ U/ml; $p = 0.218$), increased during treatment with both olanzapine (week 6, 12.5 $\pm$ 2.0; week 24, 12.0 $\pm$ 1.6 μ U/ml; $p = 0.032$ and $p = 0.013$,

respectively) and risperidone (week 6, 14.1 ± 2.9 ; week 24, 15.5 ± 3.7 $\mu\text{U/ml}$; $p = 0.014$ and $p = 0.045$, respectively).

3.4. FSIGT results (Table 2A)

Normalization of glycemia after glucose injection was unchanged during treatment with risperidone and olanzapine, as reflected in stable K_G that was similar in the two groups ($p > 0.11$). S_I did not change significantly during olanzapine treatment ($p = 0.19$), but there was a downward trend in the risperidone-treated subjects (median, 1.97, 1.37, and 1.01×10^{-4} min^{-1} per $\mu\text{U/ml}$ at baseline, week 6, and week 24; $p = 0.088$ baseline vs. week 24; Table 2A). No significant differences between treatments were observed for SI at any time ($p > 0.88$). AIR_G was similar between groups at baseline, and exhibited a transient 44% increase in the olanzapine-treated subjects at week 6 ($p = 0.0028$); no between-treatment differences were detected during the study ($p > 0.4$). Pancreatic β -cell function, measured by the DI, was unaffected by risperidone ($p > 0.78$) and olanzapine ($p > 0.19$). There were no detectable within-group or between-group changes in S_G ($p > 0.24$; Table 2A).

3.5. Subset analysis: African American and Hispanic subjects

To determine whether antipsychotics exert greater metabolic effects in high-risk subjects, we tested for treatment effects in the combined subset of African American and Hispanic subjects (16 of the 28 subjects of the risperidone group and 17 of the 31 subjects of the olanzapine group; Table 1). This subgroup exhibited no difference in dropout rates between groups (OLZ: 3 of 17 subjects, or 17.7%, RIS: 5 of 16 subjects, 31.3%; $p = 0.44$), with the bulk of the dropouts (three in each group) due to loss to follow-up. In addition, there were no significant differences between treatment groups in baseline body weight (OLZ: 199 ± 10 , RIS: 189 ± 10 lbs; $p = 0.39$), total adiposity ($31,258 \pm 4173$, RIS: $22,998 \pm 2640$ cm; $p = 0.20$), and visceral adiposity (OLZ: 85 ± 22 , RIS: 55 ± 11 cm; $p = 0.09$). There were also no significant differences in baseline FSIGT parameters between groups (Table 2B; $p > 0.19$), although a trend for lower S_G was observed in the OLZ group ($p = 0.08$). The effect of antipsychotics on adiposity in this subset is shown in Fig. 3. Although total fat was unaffected by risperidone treatment at either week 6 (197 ± 685 cm above baseline; $p = 0.29$) or week 24 (586 ± 1831 cm below baseline; $p = 0.17$), a significant increase in the total adipose depot was seen at both time points in the olanzapine group: 2045 ± 643 cm^2 above baseline at week 6 ($p = 0.0062$) and 5049 ± 1303 cm^2 above baseline at week 24; $p = 0.0022$). Changes in total adiposity were significantly greater with olanzapine than risperidone at week 6 ($p = 0.0346$) and week 24 ($p = 0.0160$; Fig. 3A). Visceral adiposity was increased in the olanzapine group by week 6 (baseline, 85 ± 22 cm^2 ; week 6, 104 ± 25 cm^2 ; $p = 0.052$) and was significantly greater at week 24 (130 ± 33 cm; $p = 0.0146$ vs. baseline; Fig. 3B). No significant changes in visceral adiposity were observed in the risperidone-treated subjects ($p > 0.14$). Between-treatment differences in visceral adiposity were not significant ($p = 0.6206$ and $p = 0.3281$ for weeks 6 and 24, respectively).

At baseline, S_I was similar between the African American and Hispanic subgroup (median: 1.93, min/max: 0.33/6.03) and those of non-African American and Hispanic ethnicity (median: 2.20, min/max: 0.48/6.48; $p = 0.63$), but the former exhibited higher AIR_G (median: 689, min/max: 45/4579, vs. median: 344, min/max: 69/1716; $p = 0.005$), as is widely reported (e.g. Haffner et al., 1996). Subjects demonstrated a modest downward trend in S_I (Table 2B), with a small risperidone effect at week 6 (baseline, 2.12; week 6, 1.52×10^{-4} min^{-1} per $\mu\text{U/ml}$; $p = 0.068$), which was compensated by modest increases in AIR_G such that DI was not significantly different from baseline (median change from baseline, -136 ; range, -1727 – 2160 ; $p = 0.54$). During olanzapine treatment, S_I tended to decline by week 24 (baseline, 1.06; week 24, 0.68×10^{-4} min^{-1} per $\mu\text{U/ml}$; $p = 0.060$), but pancreatic function did not adequately compensate, resulting in a significant decrease in DI (median

change from baseline, -387 ; range, -1264 – 455 ; $p = 0.033$), and impaired glucose tolerance (K_G) ($p = 0.0479$ vs. baseline).

4. Discussion

Widespread use of atypical antipsychotics has been complicated by associated weight gain and increased incidence of diabetes. Considerable evidence suggests that the metabolic risk differs between these agents, although results largely emanate from retrospective or cross-sectional studies (Haddad, 2004; Jin et al., 2002; Henderson et al., 2005). In the present study, both olanzapine and risperidone induced significant weight gain, with the effects of olanzapine greater than those of risperidone. Fasting hyperinsulinemia was observed throughout the study period in both treatment groups. Increased adiposity developed with both treatments, although the effects of olanzapine on total adiposity occurred more rapidly than during risperidone treatment. Our data also demonstrate the extensive variability of glucoregulatory measures in this patient population, due in part to inclusion of ethnic minorities prone to insulin resistance and increased adiposity. When analyzed independently, this ethnic subset displayed further differential treatment effects on adiposity and pancreatic function.

Both risperidone and olanzapine increased body weight within 1 week of treatment (Fig. 1), and significant weight gain was sustained in both groups for the entire 24-week treatment period. Weight gain induced by olanzapine exceeded that observed with risperidone at various time points, consistent with published reports (McIntyre et al., 2001). However, unlike results from CATIE and meta-analysis (Lieberman et al., 2005; Allison et al., 1999), we observed no detectable difference in weight gain between treatments at the conclusion of the 24-week study. This result may be due to insufficient statistical power of the present study secondary to small group size, but other factors may also influence observed weight gain. Existence of baseline obesity may contribute to the absence of significant treatment differences in weight gain in our study, since it has been suggested that subjects with low baseline weight tend to exhibit the most pronounced drug-associated increases in body weight (Jones et al., 2001; Lee et al., 2004), although this finding is not universally accepted (Simpson et al., 2001). Finally, the effects of switching from prior antipsychotics on subsequent weight gain have been demonstrated (Weiden et al., in press). Observed weight gain in the risperidone-treated groups may have been underestimated early in the study in those subjects who were switched from antipsychotics associated with greater weight gain, specifically olanzapine ($n = 6$, Table 1). However, it is likely that the confounding influence of switching on observed weight gain would be minimal 24 weeks after the switching occurred.

The mechanisms by which antipsychotics alter energy balance remain under debate (Ota et al., 2002; Ader et al., 2005; Gothelf et al., 2002; Virkkunen et al., 2002; Graham et al., 2005; Basson et al., 2001). Both olanzapine and risperidone reportedly increase caloric consumption in animals (Ota et al., 2002; Ader et al., 2005) and human subjects (Gothelf et al., 2002; Basson et al., 2001). This effect may be mediated by central receptors, including H_1 (Kroeze et al., 2003; Goudie et al., 2003) and $5HT_{2C}$ (Reynolds et al., 2002; Buckland et al., 2005), but peripheral actions have also been proposed. For example, antipsychotics may increase circulating levels of the gut peptide ghrelin, a potent stimulator of appetite and food intake (Nakazato et al., 2001), although results are conflicting (Murashita et al., 2005; Togo et al., 2004). Decreasing energy expenditure may also contribute to drug-associated weight gain (Virkkunen et al., 2002), but such observations are not universally observed (Gothelf et al., 2002; Graham et al., 2005).

Imaging techniques showed increased adiposity in both the olanzapine- and risperidone-treated subjects (Fig. 2), a finding consistent with previous reports (Graham et al., 2005; Ader et al., 2005; Eder et al., 2001; Zhang et al., 2004). However, the present study is the first to examine effects of antipsychotics on adiposity at multiple time points of treatment. This design revealed that olanzapine increased total fat mass more rapidly than risperidone – within 6 weeks of starting treatment. Moreover, both drugs increased adiposity regardless of preexisting overweight or obese status, as evidenced by mean baseline BMI $>25 \text{ kg/m}^2$ in both treatment groups (Fig. 2). This contrasts with data of Thakore and his colleagues, who reported that while drug-naïve subjects with schizophrenia had greater baseline visceral adiposity than healthy controls (Thakore et al., 2002), no further expansion was observed after 6 months of treatment with either olanzapine or risperidone (Ryan et al., 2004). Differences in study demographics may have contributed to this disparity. The prior study (Ryan et al., 2004) examined adiposity in a population of white European subjects. In contrast, the present study included a significant number of African American and Hispanic subjects (Table 1), who have greater susceptibility to increased adiposity than age- and weight-matched non-Hispanic white subjects (Fujimoto et al., 1995). Indeed, the present data support this view *vis à vis* drug-induced adiposity (Fig. 3), especially with olanzapine treatment. Within 6 weeks, African American and Hispanic subjects exhibited significant increases in total adiposity during treatment with olanzapine but not risperidone, and by week 24, olanzapine induced expansion of the visceral adipose compartment. The data suggest that these patients may be particularly vulnerable to the adipogenic effects of some atypical antipsychotics. Finally, although sex differences in adiposity may contribute to observed variability (Zhang et al., 2004), we observed no influence of sex on measured variables in this study.

Treatment effects on glucose metabolism were assessed using minimal model analysis of the FSIGT. Experimental procedures were performed without incident, and all relevant data could be estimated. This approach allowed us to follow the progression of both S_I and pancreatic function (DI) for each subject undergoing treatment. We observed no significant change in S_I with either drug, although a trend toward deterioration was observed (Table 2A). These data are consistent with hyperinsulinemic clamp studies in healthy human subjects, in whom short-term (2-week) treatment with olanzapine or risperidone caused weight gain, but no detectable insulin resistance (Sowell et al., 2003). In contrast, group differences in S_I between antipsychotics (clozapine $<$ olanzapine $<$ risperidone) were reported in a cross-sectional study of subjects with schizophrenia (Henderson et al., 2005), although that study was limited to non-obese volunteers and employed a study design that precluded assessment of treatment effects. In the present study, no such limitation was imposed, and the baseline obesity evident in our study population is more reflective of psychiatric patients undergoing antipsychotic therapy. Consistent with baseline obesity, subjects in the present study were more insulin resistant ($S_I \sim 2 \times 10^{-4} \text{ min}^{-1} \text{ per } \mu\text{U/ml}$) than that reported for lean subjects ($5\text{--}7 \times 10^{-4} \text{ min}^{-1} \text{ per } \mu\text{U/ml}$) (Bergman, 1989). Our inability to detect further decline in S_I with treatment is likely due to both this baseline resistance and to the known non-linearity between obesity and S_I such that the effect of obesity to cause insulin resistance saturates at a level of adiposity evident in our population at baseline (Lillioja and Bogardus, 1988). Finally, it is also possible that antipsychotics may have induced resistance specifically in liver or skeletal muscle (Ader et al., 2005), which would have been detectable only with application of tracer methodology. Indeed, Ader et al. (2005) reported marked hepatic insulin resistance in healthy dogs after 6 weeks' treatment with olanzapine but not with risperidone or placebo.

Insulin resistance alone is insufficient to explain antipsychotic-associated diabetes, since resistance normally prompts a robust compensatory insulin response to maintain glucose tolerance (Bergman et al., 2001). However, there are few clinical studies that rigorously

assess both insulin resistance and pancreatic function to determine whether antipsychotics alter β -cell compensation for resistance (Sowell et al., 2002; Ader et al., 2005; Henderson et al., 2005; Hardy et al., 2007). In a study of healthy subjects, Sowell and Hardy and their colleagues (Sowell et al., 2002; Hardy et al., 2007) report that glucose-stimulated insulin response was unaffected by short-term (2-week) treatment with olanzapine or risperidone. Despite observing weight gain in treated subjects, authors detected no associated insulin resistance, although this may reflect sub-optimal experimental methods for assessment of insulin resistance. Specifically, hyperglycemic clamps used to quantify resistance actually measure glucose metabolism that results from combined effects of elevated glucose and the elevated insulin engendered by that hyperglycemia, and thus does not provide an accurate measure of insulin sensitivity alone. In addition, HOMA-based measures are essentially equivalent to fasting insulin (Bergman et al., 2003) and should be used with restraint in studies in which a β -cell defect may be present, since indices are based on the concept that fasting insulin is elevated in insulin resistant states. In the report of Henderson et al. (2005), authors report unchanged first-phase insulin response in non-obese subjects treated with olanzapine, risperidone, or clozapine, despite measured insulin resistance (olanzapine and clozapine groups), which resulted in non-significant trends towards reduced DI. This study used well-accepted methods for assessment of insulin sensitivity and pancreatic response, but conclusions regarding possible drug effects may be limited by the study's cross-sectional design. While longitudinal assessment to test for possible effects of antipsychotics on insulin sensitivity and secretion are scarce, this issue has been addressed in animals. In a recent study in dogs, olanzapine was found to completely block normal β -cell compensation (as measured by the DI) (Ader et al., 2005). In the absence of a significant decrement in S_I in the present study, we observed no within-group or between-group differences in pancreatic function (DI) in the entire study population (Table 2A). However, in the African American and Hispanic subjects, an effect of olanzapine to reduce DI was observed (Table 2B), and glucose tolerance declined. When analyzed independently, this ethnic subset displayed differential treatment effects on adiposity and pancreatic function, suggesting that some groups may represent an at-risk population for the deleterious metabolic effects of antipsychotics, notably olanzapine.

Limitations of this study include the relatively small group sizes, which constrained our statistical power to detect treatment changes. Little quantitative information was available *a priori* on insulin sensitivity or adiposity in subjects with schizophrenia or on the specific effects of antipsychotics on these parameters. Some of the observed variability in these processes could have been minimized if subject enrollment were restricted to lean subjects or those of single ethnicity. However, the choice to allow obese subjects at baseline was made to best reflect the realities of the psychiatric population undergoing antipsychotic treatment. By using a longitudinal study design in which subjects are tested at multiple time points, we gain information by having each subject serve as his/her own control. In the absence of controls for prior antipsychotic use, our results were also vulnerable to confounding effects of switching between agents of differing metabolic profiles.

In conclusion, this study is the first prospective assessment of the effects of olanzapine and risperidone on adiposity and glucoregulatory function in overweight and obese subjects with schizophrenia. Drug-induced weight gain and increased total and visceral fat mass were observed. Treatment effects on S_I were not detectable, owing to baseline insulin resistance consistent with the subjects' overweight status plus a high degree of variability evident in this study population. Indeed, this study offers the first quantitative evaluation of the biologic heterogeneity of this patient population, which will prove useful in the design of future studies of these agents on glucose homeostasis. Most important, results from the African American and Hispanic subset of subjects indicate that these groups, known to be at increased risk for Type 2 diabetes compared with non-Hispanic white subjects (Cowie et al.,

1993), also demonstrate increased susceptibility to the metabolic effects of antipsychotic medications. Future studies are needed to examine the specific effects of these antipsychotics on minorities and other subjects with preexisting risk factors for diabetes and the metabolic syndrome.

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References

- Ader M, Kim SP, Catalano KJ, Ionut V, Hucking K, Richey JM, et al. Metabolic dysregulation with atypical antipsychotics occurs in the absence of underlying disease: placebo-controlled study of olanzapine and risperidone in dogs. *Diabetes*. 2005; 54:862–871. [PubMed: 15734866]
- Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *American Journal of Psychiatry*. 1999; 156:1686–1696. [PubMed: 10553730]
- American Diabetes Association American Psychiatric Association American Association of Clinical Endocrinologists North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004; 27:596–601. [PubMed: 14747245]
- Basson BR, Kinon BJ, Taylor CC, Szymanski KA, Gilmore JA, Tollefson GD. Factors influencing acute weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. *Journal of Clinical Psychiatry*. 2001; 62:231–238. [PubMed: 11379836]
- Bergman RN. Toward physiological understanding of glucose tolerance: minimal-model approach (Lilly Lecture). *Diabetes*. 1989; 38:1512–1527. [PubMed: 2684710]
- Bergman RN, Ader M. Atypical antipsychotics and glucose homeostasis. *Journal of Clinical Psychiatry*. 2005; 66:504–514. [PubMed: 15816794]
- Bergman RN, Ader M, Huecking K, Van Citters G. Accurate assessment of b-cell function: the hyperbolic correction. *Diabetes*. 2001; 51(suppl 1):S212–S220. [PubMed: 11815482]
- Bergman RN, Zaccaro DJ, Watanabe RM, Haffner SM, Saad MF, Norris JM, et al. Minimal model-based insulin sensitivity has greater heritability and a different genetic basis than homeostasis model assessment or fasting insulin. *Diabetes*. 2003; 52:2168–2174. [PubMed: 12882937]
- Boston RC, Stefanovski D, Moate PJ, Sumner AE, Watanabe RM, Bergman RN. MINMOD millennium: a computer program to calculate glucose effectiveness and insulin sensitivity from the frequently sampled intravenous glucose tolerance test. *Diabetes Technol Therapeut*. 2003; 5:1003–1015.
- Buckland PR, Hoogendoorn B, Guy CA, Smith SK, Coleman SL, O'Donovan MC. Low gene expression conferred by association of an allele of the 5-HT2C receptor gene with antipsychotic-induced weight gain. *American Journal of Psychiatry*. 2005; 162:613–615. [PubMed: 15741483]
- Cossrow N, Falkner B. Race/ethnic issues in obesity and obesity-related comorbidities. *Journal of Clinical Endocrinology and Metabolism*. 2004; 89:2590–2594. [PubMed: 15181028]
- Cowie CC, Harris MI, Silverman RE, Johnson EW, Rust KF. Effect of multiple risk factors on differences between blacks and whites in the prevalence of non-insulin-dependent diabetes mellitus in the United States. *American Journal of Epidemiology*. 1993; 137:719–732. [PubMed: 8484363]
- Eder U, Mangweth B, Ebenbichler C, Weiss E, Hofer A, Hummer M, Kemmler G, et al. Association of olanzapine-induced weight gain with an increase in body fat. *American Journal of Psychiatry*. 2001; 158:1719–1722. [PubMed: 11579009]

- Eli Lilly and Company. Zyprexa (olanzapine): package insert. 2001
- Fujimoto WY, Bergstrom RW, Boyko EJ, Leonetti DL, Newell-Morris LL, Wahl PW. Susceptibility to development of central adiposity among populations. *Obesity Research*. 1995; 3(suppl 2):179S–186S. [PubMed: 8581774]
- Gothelf D, Falk B, Singer P, Kairi M, Phillip M, Zigel L, et al. Weight gain associated with increased food intake and low habitual activity levels in male adolescent schizophrenic inpatients treated with olanzapine. *American Journal of Psychiatry*. 2002; 159:1055–1057. [PubMed: 12042200]
- Goudie AJ, Halford JCG, Dovey TM, Cooper GD, Neill JC. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs (letter to the editor). *Neuropsychopharmacology*. 2003; 28:2209. [PubMed: 12942144]
- Graham KA, Perkins DO, Edwards LJ, Barrier RC Jr, Lieberman JA, Harp JB. Effect of olanzapine on body composition and energy expenditure in adults with first-episode psychosis. *American Journal of Psychiatry*. 2005; 162:118–123. [PubMed: 15625209]
- Gupta S, Lentz B, Lockwood K, Frank B. Atypical antipsychotics and glucose dysregulation a series of 4 cases. *Journal of Clinical Psychiatry (Primary Care Companion)*. 2001; 3:61–65.
- Haddad PM. Antipsychotics and diabetes: review of non-prospective data. *British Journal of Psychiatry*. 2004; 184(suppl 47):s80–s86.
- Haffner SM, D'Agostino RD, Saad MF, Rewers M, Mykkanen L, Selby J, et al. Increased insulin resistance and insulin secretion in non-diabetic African-Americans and Hispanics compared to non-Hispanic Whites: the insulin resistance and atherosclerosis study. *Diabetes*. 1996; 45:742–748. [PubMed: 8635647]
- Hardy TA, Meyers AL, Yu J, Shankar SS, Steinberg HO, Porksens NK. Acute insulin response and β -cell compensation in normal subjects treated with olanzapine or risperidone for 2 weeks. *Diabetes Care*. 2007; 30:157–158. [PubMed: 17192353]
- Henderson DC, Cagliero E, Copeland PM, Borba CP, Evins E, Hayden D, et al. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents. *Archives of General Psychiatry*. 2005; 62:19–28. [PubMed: 15630069]
- Jin H, Meyer JM, Jeste DV. Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: an analysis of 45 published cases. *Annals of Clinical Psychiatry*. 2002; 14:59–64. [PubMed: 12046641]
- Jones B, Basson BR, Walker DJ, Crawford AMK, Kinon BJ. Weight change and atypical antipsychotic treatment in patients with schizophrenia. *Journal of Clinical Psychiatry*. 2001; 62(suppl 2):41–44. [PubMed: 11232752]
- Kahn BB, Flier JS. Obesity and insulin resistance. *Journal of Clinical Investigation*. 2000; 106:473–481. [PubMed: 10953022]
- Kroeze WK, Hufeisen SJ, Popadak BA, Rannock SM, Steinberg S, Ernsberger P, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology*. 2003; 28:519–526. [PubMed: 12629531]
- Lee A, Ader M, Bray GA, Bergman RN. Diurnal variation in glucose tolerance: cyclic suppression of insulin action and insulin secretion in normal weight, but not obese subjects. *Diabetes*. 1992; 41:750–759. [PubMed: 1587401]
- Lee E, Leung CM, Wong E. Atypical antipsychotics and weight gain in Chinese patients: a comparison of olanzapine and risperidone. *Journal of Clinical Psychiatry*. 2004; 65:864–866. [PubMed: 15291666]
- Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. For the clinical antipsychotic trials of intervention effectiveness (CATIE) investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine*. 2005; 353:1209–1223.
- Lillioja S, Bogardus C. Obesity and insulin resistance: lessons learned from the Pima Indians. *Diabetes Metabolism Review*. 1988; 5:517–540.
- McIntyre RS, Mancini DA, Basile VS. Mechanisms of antipsychotic-induced weight gain. *Journal of Clinical Psychiatry*. 2001; 62(suppl 23):23–29. [PubMed: 11603882]

- Murashita M, Kusumi I, Inoue T, Takahashi Y, Hosoda H, Kangawa K. Olanzapine increases plasma ghrelin level in patients with schizophrenia. *Psychoneuroendocrinology*. 2005; 30:106–110. [PubMed: 15358448]
- Nakazato M, Murakami N, Date Y, Kojima K, Matsuo H, Kangawa K, et al. A role for ghrelin in the central regulation of feeding. *Nature*. 2001; 409:194–198. [PubMed: 11196643]
- Ota M, Mori K, Nakashima A, Kaneko YS, Fujiwara K, Itoh M, et al. Peripheral injection of risperidone, an atypical antipsychotic, alters the body weight gain of rats. *Clinical and Experimental Pharmacology and Physiology*. 2002; 29:980–989. [PubMed: 12366389]
- Pi-Sunyer XF. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. National Institutes of Health, National Heart, Lung, and Blood Institute. 1998:1–178.
- Porte D Jr. B-cells in type II diabetes mellitus (Banting Lecture). *Diabetes*. 1991; 40:166–180. [PubMed: 1991568]
- Reynolds GP, Zhang ZJ, Zhang XB. Association of antipsychotic drug-induced weight gain with a 5-HT_{2C} receptor gene polymorphism. *Lancet*. 2002; 359:2086–2087. [PubMed: 12086765]
- Ryan MCM, Flanagan S, Kinsella U, Keeling F, Thakore JH. The effects of atypical antipsychotics on visceral fat distribution in first episode, drug-naïve patients with schizophrenia. *Life Science*. 2004; 74:1999–2008.
- Simpson MM, Goetz RR, Devlin MJ, Goetz SA, Walsh BT. Weight gain and antipsychotic medication: differences between antipsychotic-free and treatment periods. *Journal of Clinical Psychiatry*. 2001; 62:694–700. [PubMed: 11681765]
- Sowell M, Mukhopadhyay N, Cavazzoni P, Carlson C, Mudaliar S, Chinnapongse S, et al. Evaluation of insulin sensitivity in healthy volunteers treated with olanzapine, risperidone or placebo: a prospective, randomized study using the two-step hyperinsulinemic, euglycemic clamp. *Journal of Clinical Endocrinology and Metabolism*. 2003; 88:5875–5880. [PubMed: 14671184]
- Sowell MO, Mukhopadhyay N, Cavazzoni P, Shankar S, Steinberg HO, Breier A, et al. Hyperglycemic clamp assessment of insulin secretory responses in normal subjects treated with olanzapine, risperidone, or placebo. *Journal of Clinical Endocrinology and Metabolism*. 2002; 87:2918–2923. [PubMed: 12050274]
- Thakore JH, Mann JN, Vlahos I, Martin A, Reznick R. Increased visceral fat distribution in drug-naïve and drug-free patients with schizophrenia. *International Journal of Obesity*. 2002; 26:137–141. [PubMed: 11791159]
- Togo T, Hasegawa K, Miura S, Hosojima H, Kojima K, Shoji M, Kase A, et al. Serum ghrelin concentrations in patients receiving olanzapine or risperidone. *Psychopharmacology*. 2004; 172:230–232. [PubMed: 14551671]
- Virkkunen M, Wahlbeck K, Rissanen A, Naukkarinen H, Franssila-Kallunki A. Decrease of energy expenditure causes weight increase in olanzapine treatment: a case study. *Pharmacopsychiatry*. 2002; 35:124–126. [PubMed: 12107860]
- Weiden PJ, Newcomer JW, Loebel AD, Yang R, Lebovitz HE. Long-term changes in weight and plasma lipids during maintenance treatment with ziprasidone. *Neuropsychopharmacology*. in press
- Zhang ZJ, Yao ZJ, Liu Y, Fang Q, Reynolds GP. Effects of antipsychotics on fat deposition and changes in leptin and insulin levels. *British Journal of Psychiatry*. 2004; 184:58–62. [PubMed: 14702228]

Fig. 1.

Comparison of time course of body weight gain between antipsychotic treatment groups (least squares mean $\pm$ SE). Statistics for treatment differences are based on ANCOVA, with center and treatment as the main effects and baseline as covariate. Both treatments were associated with significant weight gain over baseline throughout study period (weeks 1 through 24; $p < 0.004$ for each). There was a significantly greater weight gain with olanzapine compared to risperidone at weeks 5 ($p < 0.05$) and 12 ($p < 0.03$).

Fig. 2. Changes in (A) total adiposity or (B) visceral adiposity during antipsychotic treatment in the entire study population. * $p < 0.02$ vs. baseline. ** $p < 0.003$ vs. baseline. *** $p < 0.0007$ vs. baseline.

Fig. 3. Changes in (A) total adiposity or (B) visceral adiposity during antipsychotic treatment in African American and Hispanic subjects. * $p < 0.02$ vs. baseline. ** $p < 0.007$ vs. baseline. § $p < 0.04$ vs. risperidone.

Table 1

Background characteristics of the subjects

	Risperidone (<i>n</i> = 28)	Olanzapine (<i>n</i> = 31)	Total (<i>N</i> = 59)
Age, mean ($\pm$ SD) years	39.8 $\pm$ 7.6	39.6 $\pm$ 8.3	39.7 $\pm$ 7.9
Sex, <i>n</i> (%) male	22 (78.6)	18 (58.1)	40 (67.8)
Race/ethnicity, <i>n</i> (%)			
African American	14 (50.0)	13 (41.9)	27 (45.8)
Non-Hispanic white	10 (35.7)	11 (35.5)	21 (35.6)
Hispanic	2 (7.1)	4 (12.9)	6 (10.2)
Asian	2 (7.1)	3 (9.7)	5 (8.5)
Body mass index, mean ($\pm$ SD) kg/m ²	28.4 $\pm$ 5.4	30.6 $\pm$ 7.0	29.6 $\pm$ 6.2
Smoking history, <i>n</i> (%) yes	15 (53.6)	20 (64.5)	35 (59.3)
Alcohol use, <i>n</i> (%) yes	4 (14.3)	3 (9.7)	7 (11.9)
Diagnosis, <i>n</i> (%)			
Paranoid schizophrenia	19 (67.9)	21 (67.7)	40 (67.8)
Schizoaffective disorder	7 (25.0)	7 (22.6)	14 (23.7)
Undifferentiated schizophrenia	1 (3.6)	2 (6.5)	3 (5.1)
Disorganized schizophrenia	0 (0.0)	1 (3.2)	1 (1.7)
Schizophrenia NOS	1 (3.6)	0 (0.0)	1 (1.7)
Prior antipsychotic, <i>n</i> (%)			
Olanzapine	6 (21.4)	7 (22.6)	13 (22.0)
Risperidone	4 (14.3)	6 (19.4)	10 (16.9)
Quetiapine	4 (14.3)	2 (6.5)	6 (10.2)

Table 2A
 FSIGT-derived variables of glucose homeostasis in all subjects receiving risperidone (RIS) or olanzapine (OLZ)

	AIR _G (μU/ml)		S _I (× 10 ⁻⁴ min ⁻¹ per μU/ml)		S _g (min ⁻¹)		DI	
	RIS	OLZ	RIS	OLZ	RIS	OLZ	RIS	OLZ
Baseline								
Median	494	533	1.97	2.05	0.022	0.019	932	911
Min/max	45/4579	62/3566	0.33/5.44	0.34/6.77	0.004/0.031	0.006/0.033	15/3949	264/4890
Week 6	567	769	1.37	1.47	0.019	0.018	1015	1101
Median	71/4213	114/3518	0.15/10.87	0.15/11.72	0.003/0.035	0.000/0.033	24/4676	33/5272
Min/max								
	543	612	1.01	1.76	0.020	0.015	933	858
Week 24	100/	67/	0.00/	0.00/	0.009/	0.006/	0/	0/
Median	3870	4669	5.64	6.95	0.032	0.038	4721	3626
Min/max								

FSIGT = frequently sampled intravenous glucose tolerance test.

FSIGT-derived variables of glucose homeostasis in African-American and Hispanic subjects receiving risperidone (RIS) or olanzapine (OLZ)

Table 2B

	AIR _G (μU/ml)		S _I ($\times 10^{-4}$ min ⁻¹ per μU/ml)		S _G (min ⁻¹)		DI	
	RIS	OLZ	RIS	OLZ	RIS	OLZ	RIS	OLZ
Baseline								
Median	607	762	2.12	1.06	0.024	0.017	1893	967
Min/max	45/4579	157/3566	0.33/5.44	0.34/5.80	0.008/0.031	0.006/0.029	15/3949	322/4890
Week 6								
Median	741	1048	1.52	0.88	0.020	0.019	1572	995
Min/max	71/4213	204/3518	0.27/8.89	0.15/5.51	0.013/0.035	0.013/0.033	24/4676	33/5273
Week 24								
Median	901	936	1.08	0.68	0.021	0.015	1023	595 *
Min/max	100/3870	176/4669	0.00/4.90	0.00/5.20	0.009/0.032	0.006/0.026	0/4721	0/3626

FSIGT = frequently sampled intravenous glucose tolerance test.

* $p = 0.033$ vs. baseline.