

Metabolic Risk with Second-Generation Antipsychotic Treatment: A Double-Blind Randomized 8-Week Trial of Risperidone and Olanzapine

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Background. The second-generation antipsychotics are effective for treating psychotic disorders and incur fewer motor side effects than are commonly experienced with the use of first-generation antipsychotics. However, their use is commonly associated with weight gain and metabolic disturbances. This study examined weight and metabolic changes with two widely used antipsychotics, risperidone and olanzapine; addressing the issue of early monitoring for metabolic side effects.

Methods. This 8-week double blind randomized trial included patients with schizophrenia or schizoaffective disorder ($N = 377$) randomly assigned to risperidone (2–6 mg/day) or olanzapine (5–20 mg/day). Weight, BMI, HbA1C, total cholesterol (TC), LDL-C, HDL-C and triglycerides (TG) were monitored.

Results. Mean BMI increases were higher in the olanzapine group as compared to risperidone (1.3 kg/m^2 (SD = 0.13) vs. 0.7 kg/m^2 (SD = 0.13) ($p < 0.001$). Increases in mean TC (13.5 mg/dl (SD 2.4), LDL-C (11.0 mg/dl (SD 2.2)) and TG (14.8 mg/dl (SD = 7.6)) occurred in the olanzapine group while significant changes in TC (-3.9 mg/dl (SD = 2.5)) and TG (-32.8 mg/dl (SD = 7.8)) were noted in the risperidone group. Men (not women) on olanzapine had higher than expected increases in lipids given the amount of weight gain. Baseline values and prior therapy did not contribute to the significant differences, however BMI increases ($p = 0.0002$) were linked to study discontinuation in both drug groups.

Conclusions. The fact that significant metabolic changes occurred (both positive and negative) in eight weeks is important to clinical care. Monitoring for metabolic changes may be important within the first eight weeks of treatment, as changes can be determined very early in antipsychotic treatment.

Keywords Schizophrenia, Weight, Lipids, Olanzapine, Risperidone, Metabolic

INTRODUCTION

The first-generation antipsychotics were widely used for treatment of psychotic symptoms in the past several decades, however their routine use has been hindered due to extrapyramidal effects and tardive dyskinesia (1). Second-generation antipsychotics (SGA) effectively counter the movement side effects, and produce superior results with respect to affect flattening, alogia, and avolition in many people, albeit from secondary negative symptoms (2). However, some of the SGAs have been associated with excessive weight gain and increased risk of metabolic disorders including diabetes, which is itself a major risk factor for cardiovascular disease (3, 4). The concern over these metabolic effects of SGAs is compounded by the association of mental illness with less healthy lifestyles (5). Even as clinicians are challenged to respond to these adverse effects, it is not clear how seriously they perceive these metabolic consequences of the SGAs (6) or what should be a standard for monitoring people in regard to these problems.

Risperidone and olanzapine, two widely used SGAs, have similar efficacy for the treatment of people with schizophrenia (7–9). Weight gain, however, is reported to be significantly greater with olanzapine than risperidone (7–9), although both drugs are associated with more weight gain than high potency first generation antipsychotics (10). Several large studies utilizing pharmacy and claims data suggest olanzapine also may be associated with a greater risk of Type II diabetes (11–14). The effects of risperidone or olanzapine monotherapy on lipid parameters and glucose regulation and the time course of these effects are less clear. If early monitoring for these effects is possible, clinical management of this serious issue will improve. This report examines weight and metabolic changes in a double blind 8-week study of risperidone and olanzapine in people with schizophrenia and schizoaffective disorder and addresses the issue of early (e.g., within 8 weeks of therapy initiation) monitoring for metabolic side effects.

METHODS

Design

This report used data from a multicenter, randomized, double-blind, comparison of risperidone and olanzapine (9). There was no washout period, however, during the week before random assignment to one of the two treatment groups, all prior oral antipsychotic and anticholinergic medications were discontinued. Depot antipsychotics were discontinued for at least one treatment cycle before a subject was assigned to a study group. The 377 participants were randomly assigned to receive risperidone (2–6 mg/day) or olanzapine (5–20 mg/day) for 8 weeks.

Eligibility Criteria

Inclusion criteria included a DSM-IV diagnosis of schizophrenia or schizoaffective disorder (ages 18–64 years), and a baseline Positive and Negative Syndrome Scale (PANSS) score of 60 to 120 (using a 1–7 scale). Participants could be outpatients or inpatients hospitalized ≤ 4 weeks at the time of screening. Exclusion criteria included another DSM-IV axis I diagnosis, a DSM-IV diagnosis of substance abuse in the 3 months before selection, documented disease of the central nervous system, the use of mood stabilizers or antidepressants, a history of treatment with clozapine for more than 4 consecutive weeks, or being known to be sensitive or unresponsive to risperidone or olanzapine. The Institutional Review Board at each site approved this study and all subjects signed informed consent prior to study entry.

Assessments

A complete description of efficacy and side effect assessments is reported elsewhere. (9) Laboratory measures included total cholesterol (TC), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), triglycerides (TG) and glycosylated hemoglobin (HbA1C). Laboratories were directly measured and drawn prior to the first morning meal and utilized all CDC standardized instruments from one centralized laboratory (Smith Kline Beecham Clinical Laboratories, Mt. Laurel, NJ). TC and TG levels were determined by enzymatic procedures and HDL-C levels were determined after phosphotungstic acid precipitation applying the Olympus AU800 automated chemistry analyzer and using standard Olympus reagents. Glycosylated hemoglobin levels were determined by HPLC using the BioRad Variant automated HPLC analyzer and BioRad HbA1C standard variant analytic test kit. Fasting glucose measurements were not available. LDL-C was calculated using Friedewald's Equation ($TC - (HDL + [TG/5])$). Weights and blood chemistries were measured at baseline and at weeks 2, 4, 6 and 8. Body Mass Index ($BMI = kg/m^2$) was used as a height-adjusted measure of body weight. All laboratories utilized CDC standardized instruments from one centralized laboratory.

Statistical Analysis

Pearson's Chi-Square, Cochran-Mantel-Haenszel (CMH) Chi-Square and Student's *T* tests were used to calculate differences in baseline dichotomous and continuous variables. BMI categories were calculated as normal ($18.5\text{--}24.9\text{ kg/m}^2$), overweight ($25.0\text{--}29.9\text{ kg/m}^2$), Class I obesity ($30.0\text{--}34.9\text{ kg/m}^2$), Class II Obesity ($35.0\text{--}39.9\text{ kg/m}^2$), and Class III Obesity ($> 40\text{ kg/m}^2$). (15) Treatment differences in BMI categories, controlling for baseline, were tested using the CMH chi-square. Categorical analysis examined the number with a clinically significant gain $> 7\%$, (7), (16) and increases $> 10\%$ in TG and $> 5\%$ in LDL-C. (17)

The generalized estimating equation (GEE) method (18) to fit a repeated measures analysis of covariance (ANCOVA) model with terms for the baseline value, time, treatment and time-by-treatment interactions was used. Treatment-by-baseline interactions were assessed to see if baseline values had any effect on treatment outcomes. Least squares means were used to obtain adjusted means by treatment at each visit. An ANCOVA model, adjusting for baseline, was used to examine drug-by-gender-by-race effects among the variables.

ANCOVA, adjusting for the baseline value of each laboratory measure, was conducted to test for treatment differences in week eight (completer) and end-point (last observation carried forward). Because maximal drug exposure and opportunity for toxicity occurred among those completing the trial, 8-week results are the primary reported values. End-point analyses which differed from week eight results are also reported (one instance). Treatment-by-baseline interactions were tested, entering baseline value as a continuous measure and mean changes in strata are presented. A repeated measures logistic model was fitted using the GEE method to test the association of withdrawal with changes in laboratory measures. All statistical tests were two-tailed and performed at an $\alpha = 0.05$.

Regression models estimated changes in laboratory values per unit change in weight in each treatment group during

follow-up. The regression coefficients from these models were compared to regression coefficients from a (cross-sectional) regression of laboratory measures versus weight in the NHANES III (19) survey, a probability sample of the US population that was used as a reference group. These were calculated by comparing $Z = (\text{beta}_{\text{ref}} - \text{beta}_{\text{drug}}) / [\text{se}(\text{ref})^2 + \text{se}(\text{drug})^2]^{1/2}$ to percentiles of the standard normal distribution. Prior treatment in relation to study outcomes was evaluated using the ANCOVA (controlling for baseline value). Post-hoc tests were used to measure specific differences in the groups, controlling for prior therapy.

RESULTS

Participant Characteristics

Three hundred seventy-seven subjects were randomized, 188 to risperidone and 189 to olanzapine (Table 1). The mean doses were 4.7 mg/day (SD = 1.4) of risperidone and 13.1 mg/day (SD = 5.1) of olanzapine. Similar percentages of the participants in the two treatment groups completed the study (71.8% [N = 135] in the risperidone group and 77.2% [N = 146] in the olanzapine group) ($\chi^2 = 1.55$, $df = 1$, $p = 0.21$), as were the

Table 1 Characteristics of Participants Randomized to Risperidone or Olanzapine

Characteristic	Risperidone (N = 188)		Olanzapine (N = 189)		Statistic ^a
	N	(%)	N	(%)	
Sex					
Men	136	(72)	138	(73)	$\chi^2 = 0.041$, $df = 1$, $P = 0.84$
Women	52	(28)	51	(27)	
Race					$\chi^2 = 3.21$, $df = 4$, $P = 0.52$
Caucasian	108	(57)	108	(57)	
Black	57	(30)	65	(34)	
Hispanic	20	(11)	15	(8)	
Oriental	1	(< 1)	0	(0)	
Other	2	(1)	1	(< 1)	
Diagnosis					
Schizophrenia	164	(87)	161	(85)	$\chi^2 = 0.576$, $df = 1$, $P = 0.45$
Schizoaffective Disorder	24	(13)	28	(15)	
Previous Preceding Treatment					$\chi^2 = 1.91$, $df = 3$, $P = 0.59$
Olanzapine	27	(14)	28	(15)	
Risperidone	29	(15)	39	(21)	
Conventional	74	(39)	67	(35)	
Other	58	(31)	55	(29)	
Smoking Status					$\chi^2 = 0.14$, $df = 1$, $P = 0.618$
NonSmoker	65	(35)	70	(37)	
Smoker	123	(65)	119	(63)	
	Mean	(SD)	Mean	(SD)	
Age (years)	41.0	(11.0)	38.9	(10.5)	$F = 4.264$ $df = (1, 344)$ $P = 0.04$
Number of previous hospitalizations	6.4	(10.6)	6.2	(12.0)	$F = 0.01$, $df = 1, 331$, $P = 0.92$
Duration of illness (years)	16.5	(10.5)	15.4	(10.6)	$F = 0.90$ $df = 1, 338$, $p = 0.34$
PANSS Total Score at Baseline	80.7	(12.5)	81.2	(13.5)	$F = 0.0343$ $df = (1, 334)$ $P = 0.85$

^aCochran-Mantel-Haenszel Π^2 or Pearson's Chi-Square test for dichotomous variables and continuous variables were analyzed with analysis of variance.

percentages who discontinued due to an adverse event (11.7% [N = 22] and 9.0% [N = 17]) ($\chi^2 = 0.82$, $df = 1$, $p = 0.37$).

Weight

Mean weight at baseline was 82.70 kg (SD = 19.62) for olanzapine subjects and 83.70 (SD = 20.36) for risperidone subjects ($p = \text{NS}$). Baseline BMIs were 28.15 kg/m² (SD = 6.2) and 28.78 (SD = 7.1), respectively, ($p = \text{NS}$). At week eight, the mean weight gain was 3.8 kg (SD = 0.4) in the olanzapine group versus 2.0 kg (SD = 0.4) in the risperidone group ($F = 11.75$, $df = (1, 259)$, $p < 0.001$). The mean BMI increase was 1.3 kg/m² (SD = 0.13) in the olanzapine group versus 0.7 (SD = 0.13) in the risperidone group ($F = 13$, $df = (1, 259)$, $p < 0.001$). Thirty percent of the olanzapine participants (N = 41 of 137) and 14% of the risperidone participants (N = 18 of 125) had $\geq 7\%$ weight gain ($\chi^2 = 9.0315$, $df = 1$, $p = 0.003$). There were no treatment-by-baseline interactions for weight or BMI. Additionally, there were no race, gender or race-by-gender interactions for weight or BMI for any of the analyses. At baseline 35% of subjects (N = 64) on olanzapine and 31% (N = 55) on risperidone were classified as normal BMI (18.5–24.9 kg/m²). At week eight, 24% of subjects (N = 33) on olanzapine and 29% on risperidone (N = 36) were in the normal BMI range ($\chi^2 = 6.45$ $df = 1$, $p = 0.011$).

Total Cholesterol

Baseline TC was 196.3 (SD = 41.4) and 200.8 (SD = 48.1) mg/dl in the olanzapine and risperidone groups, respectively ($p = \text{NS}$). At week eight, subjects on olanzapine had a significant increase in mean TC of 13.5 mg/dl (SD = 2.4) ($t = 5.511$ $df = 137$ $p < 0.001$), while subjects on risperidone had a decrease in mean TC of -3.9 mg/dl (SD = 2.5) ($F = 24.78$, $df = (1, 266)$ $p < 0.0001$). There was a trend for a treatment-by-baseline interaction ($F = 3.63$, $df = (1, 265)$, $p = 0.058$), indicating that in both groups, subjects in the bottom strata of TC had the greatest increases (see Figure 1).

While no gender-by-treatment interactions were evident, a race-by-gender-by-treatment interaction for cholesterol changes revealed that Black females (14.4 ± 7.7) and White males (17.0 ± 4.3) had the highest increases on olanzapine and greatest decreases on risperidone (Black females— 6.7 ± 7.8 ; White males— 12.0 ± 4.4) ($F = 9$ $df = (1, 230)$ $p = 0.003$). To further characterize the association of weight and TC changes in the drug groups as compared to the general population, comparisons in beta coefficients from a large population based study (NHANES) were used in the regression analysis (19). Men on olanzapine (but not women) had higher than expected increases in TC controlling for the extent of weight gain (NHANES beta 0.83 (0.23), this study beta = 3.93 (1.70) $Z = -1.810$ $p = 0.04$). Among subjects on risperidone, TC changes observed matched those expected given the observed changes in weight.

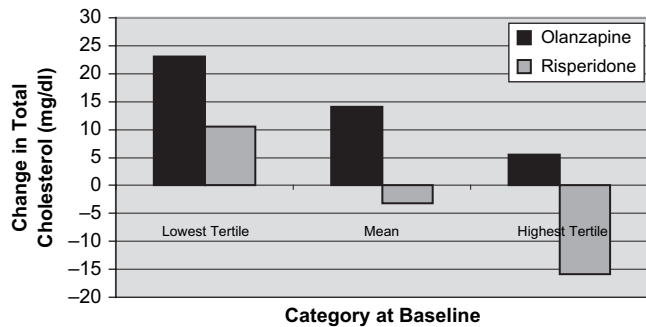


Figure 1 Mean Total Cholesterol Change as a Function of Baseline Value. This graph represents changes in total cholesterol for risperidone and olanzapine treated patients categorized by the baseline total cholesterol values. The categories represented are the lowest (mean 167.0 mg/dl), middle (mean 198.6 mg/dl) and highest tertiles (mean 228.0 mg/dl). Baseline \times treatment interaction $F = 3.63$, $df = 1, 265$, $p = 0.058$. Total cholesterol changes significantly differed between risperidone and olanzapine at all baseline categories (lowest $p = 0.004$, others $p < 0.0001$).

High and Low Density Lipoprotein Cholesterol

At baseline HDL-C was 50.8 (SD = 16.0) and 50.1 (SD = 16.8) mg/dl for olanzapine and risperidone subjects respectively ($p = \text{NS}$). Mean HDL-C changes were minimal (+0.5 olanzapine; +0.08 risperidone: $t = 0.41$ $df = 261$, $p = 0.68$).

Baseline LDL-C was 113.5 mg/dl (SD = 36.9) and 115.7 mg/dl (SD = 37.1) for the olanzapine and risperidone groups, respectively ($p = \text{NS}$). During the study, a significant increase of 11.0 mg/dl (SD = 2.2) occurred for olanzapine-treated subjects ($t = 4.896$, $df = 126$ $p < 0.0001$), while the average increase of 2.9 mg/dl (SD = 2.2) for subjects receiving risperidone was not significant ($p = 0.26$). In addition, a significant between group (treatment-by-drug interaction) difference was noted ($F = 6.86$ $df = (1, 246)$ $p = 0.01$) for the week eight analysis (not significant on endpoint analysis 7.08 mg/dl olanzapine, 2.59 mg/dl risperidone, $p = 0.11$). No significant baseline-by-treatment or gender-by-treatment interactions were observed for LDL-C changes, however a race-by-gender-by-treatment suggested that white males were at greatest risk for LDL-C increases on olanzapine in the end-point data only (end-point data $F = 4.48$ $df = (1, 270)$ $p = 0.04$).

Ninety-four (58%) of those receiving olanzapine and 52 (43%) of subjects receiving risperidone had a $> 5\%$ increase in LDL-C ($\chi^2 = 6.09$, $p = 0.0135$). This did not differ significantly from the finding predicted by NHANES III data.

Triglycerides

While baseline TGs did not differ between the olanzapine (163.2 (SD = 114.6) mg/dl) and risperidone groups (182.9 (SD = 206.8) mg/dl) ($p = 0.25$), significant differences in change were noted at week eight. The mean changes in TG were

14.8 mg/dl (SD = 7.6) for those receiving olanzapine ($t = 2.025$, $df = 137$, $p = 0.04$) vs. -32.8 (SD = 7.8) for those on risperidone ($t = -2.454$, $df = 130$, $p = 0.02$; ($F = 14.44$, $df = (1, 266)$, $p < 0.001$ for treatment difference in mean change). A significant baseline-by-treatment interaction was also noted ($F = 53.47$, $df = (1, 265)$, $p < 0.0001$) (see Figure 2). There were no gender-by-treatment or race-by-sex-by-treatment interactions noted in TG changes.

The number of subjects who had > 10% increases in TG was significantly greater in the olanzapine group ($n = 63$, 46%) than in the risperidone group ($n = 41$, 31%) ($\chi^2 = 5.839$, $p = 0.02$). At eight weeks, TGs increased in the olanzapine subjects even in the absence of weight gain (17.5 mg/dl, $N = 107$ in subjects gaining and 9.6 mg/dl, $N = 28$ in subjects not gaining) ($F = 0.16$, $df = (1, 133)$, $p = 0.69$). Likewise in the risperidone group, reductions in TG occurred similarly in those who did and did not gain weight (-34.6 no weight gain $N = 37$, -38.8 weight gain $N = 87$; $p = \text{NS}$). Compared to the NHANES III sample, men (but not women, $P = \text{NS}$) on olanzapine had significantly greater than expected increases in TG controlling for the extent of weight gain (NHANES beta = 6.84 (1.0), RIS 112 beta = 21.26 (5.41), $Z = -2.622$, $p = 0.004$). For both sexes on risperidone, treatment increases in TG were consistent with those expected from their observed weight.

Glycosylated Hemoglobin

Mean baseline glycosylated hemoglobin (HbA1C) values were 5.76% (SD = 1.12%) and 5.91% (SD = 1.06%) in the olanzapine and risperidone groups. At week eight, there was virtually no change in the mean HbA1C for either group (-0.030% for olanzapine and 0.028 for risperidone) ($P = \text{NS}$). No race or gender interactions were present.

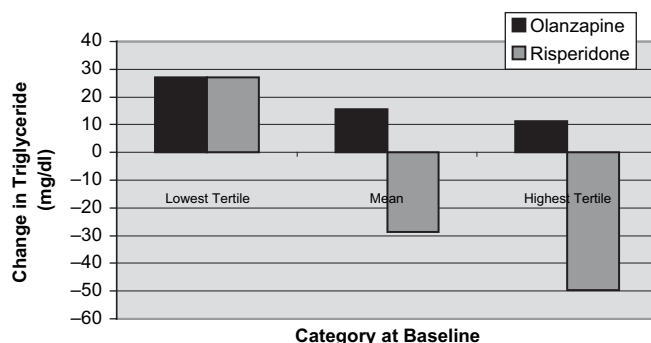


Figure 2 Mean Triglyceride Change as a Function of Baseline Values. This graph represents triglycerides for risperidone and olanzapine treated patients categorized by the baseline total triglyceride values. The categories represented are the lowest (mean 89 mg/dl), middle (mean 173.1 mg/dl) and highest tertiles (mean 205.0 mg/dl). Baseline \times treatment interaction $F = 53.47$, $df = 1, 265$, $p < 0.0001$. Mean triglyceride changes were significantly different between olanzapine and risperidone for the highest ($p < 0.0001$) and middle tertiles ($p < 0.0001$) but not the lowest tertile ($p = 0.74$).

Prior Treatment

Medications prior to study entry are listed in Table 1. Changes in TC, TG, HDL-C and LDL-C were not significantly influenced by prior therapy ($P = \text{NS}$). Weight gain and increases in BMI in the olanzapine group were higher in those previously treated with conventional antipsychotics ($T = -2.30$, $df = 214$, $p = 0.02$ weight; $T = -2.3$, $df = 214$, $p = 0.02$ BMI). Also, those on risperidone ($F = 2.26$, $df = 208$, $p = 0.025$) or conventional antipsychotics ($F = -1.79$, $df = 208$, $p = 0.075$) prior to olanzapine had greater increases in HbA1C values as compared to prior olanzapine treatment.

Early Termination and Weight/Laboratory Changes

A significant association between early termination and change in BMI ($\chi^2 = 13.7034$, $df = 1$, $p = 0.0002$), TC ($\chi^2 = 5.8577$, $df = 1$, $p = 0.016$), and LDL-C ($\chi^2 = 5.5189$, $df = 1$, $p = 0.019$) was observed during the study, but was independent of treatment. The one exception was that increases in TC were associated with early termination on olanzapine ($\chi^2 = 4.2051$, $df = 1$, $p = 0.04$). However, no study discontinuations in either drug group were noted by the patients or clinicians as being directly related to a weight increase.

DISCUSSION

The issue of weight gain with antipsychotic use has become a major focus because of its effects on compliance and the consequences of obesity (i.e., Type II diabetes, coronary artery disease, hypertension) (15). People with schizophrenia already weigh more than the general population and have a higher risk of early death (20). Every effort should be made to educate patients and attempt to minimize weight gain and metabolic sequelae from occurring (21). Our results confirm earlier reports that SGAs are associated with weight gain and that olanzapine associated weight gain occurs to a greater extent than with risperidone.

Although obesity is an established risk factor for both Type II diabetes and coronary artery disease, this study demonstrates the effects of SGAs on metabolic factors beyond just weight. As the number of risk factors increases, the likelihood of cardiovascular disease increases exponentially (22). In order to implement appropriate monitoring and determine the necessity of therapeutic intervention, one must understand the extent to which the SGAs induce metabolic changes, the time course of such changes and the degree to which they occur independently of weight changes.

This study has shed some light on these important questions. After only 8 weeks of treatment (and independent of previous antipsychotic treatment) subjects treated with olanzapine demonstrated significant increases in weight, BMI, TC, TG, and LDL-C. Risperidone patients also experienced weight

gains, however, it was associated with decreases in levels of TG and TC. This is congruent with prior work. A retrospective study also found that in adults, olanzapine was associated with significantly greater increases in metabolic parameters (TG, TC, glucose) as compared to risperidone at one year (23). In a study (N = 19,637) using the UK-based General Practice Research Database, Koro et al. (14) found a four fold increase in the development of hyperlipidemia with olanzapine as compared to no antipsychotic treatment, but did not find a significant risk with risperidone. Others have noted the differential effects of these agents on lipids, (7, 24) however, the short time frame to observe changes as observed in our study is concerning.

A compelling finding in our study is not the association of olanzapine with greater weight gains than risperidone, but that increases in lipid parameters occurring with olanzapine are not solely attributable to weight gain and these changes can be detected in the first few months of therapy. For example, subjects on olanzapine who had no weight gain experienced significant increases in TG of approximately 10 mg/dl. Among those with weight gain in the olanzapine group, the increases in TG were significantly greater than expected ($> 3X$) when compared with data from NHANES III; this was driven primarily by the males. Similarly, increases in TC in males were 4.7 times greater than predicted based on weight gain. Others have also reported that glucose and lipid changes can occur independent of weight gain in patients treated with olanzapine (25). While it is arguable that these changes may not be associated with clinically significant and immediate sequella, these metabolic changes may contribute to the longer-term risk of cardiovascular disease.

Data on the effects of SGAs on LDL-C, the primary target of treatment in the Adult Treatment Panel III Guidelines, (17, 26) are scarce. In this study, LDL-C levels rose significantly in the olanzapine but not the risperidone group. Furthermore, increases in LDL-C levels on olanzapine occurred independently of prior drug exposure. While the LDL-C level is a target for lowering the risk for coronary artery disease, it is noteworthy that it has not been well studied as a monitoring parameter or risk factor in people being treated with SGAs.

Evidence is accumulating that elevated TG levels are an independent risk factor for cardiovascular disease. Recent data suggest that an increase of > 88.6 mg/dl was associated with a 32% increase in disease risk in men and an increase in risk of 76% in women for cardiovascular disease (27). Other investigators have observed decreases in TG when people were switched to risperidone from other antipsychotics, particularly clozapine and olanzapine (24, 28). It is noteworthy, however, that while mean TG increased across all baseline strata for olanzapine, only those in the lowest TG strata at baseline in the risperidone group had increases in mean TG. This suggests that increases in the lowest strata with risperidone may be a regression to the mean. TG changes in the study for both risperidone and olanzapine were independent of prior antipsychotic treatment received.

The association between increases in laboratory parameters and dropouts is of considerable interest given the concern that weight gain may be a risk factor for non-adherence. Obese patients have been found to be significantly more likely to stop medication due to subjective distress (20). In this study, there was a significant association between early termination and change in BMI, TC and LDL-C in both treatment groups. Interestingly however, no subjects dropped from the study specifically for weight gain, thus weight gain may have been perceived by patients indirectly as subjective distress or clinicians may not have elucidated sufficiently from the patient the exact reasons for wanting to discontinue from the study. A recent article has reported that subjective distress associated with weight gain, as opposed to weight gain itself, is a major predictor of nonadherence to antipsychotic medications (29). Another study reported that weight gain was associated with a decrease in perceived life quality and reduced well-being and vitality (30). A literature search found no reports on subjective feelings, distress or symptomatology associated with rapid increases in lipids or other metabolic parameters that would explain a higher rate of discontinuation. Importantly, this finding argues against the claims that weight gain may be associated with clinical improvement (31). Furthermore, this study suggests that subjective distress associated with weight gain not only affects compliance in real-world settings, it also may lead to underestimation of weight gain and abnormal laboratories in clinical trials when subjects drop out. Last-observation-carried-forward models for reporting weight and laboratory parameters may not give a clear indication of the trajectory of change in weight and laboratory parameters, since small changes may lead to early dropouts.

The Mount Sinai Conference on the Pharmacotherapy of Schizophrenia (32) recommended that weight be monitored regularly for the first six months with most SGAs and that glucose, TC, and TG be monitored only if weight gain is $> 7\%$ of body weight. The most recent consensus conference including representatives from the American Psychiatric Association, the American Diabetes Association and others, recommended that lipids and fasting blood glucose levels not be drawn until 12 weeks of therapy (33). Our finding of significant changes in laboratory parameters and weight in eight weeks suggests that these recommendations may need to be adjusted. While 8 week changes may not be clinically significant and immediately associated with sequella, the fact that significant changes are occurring in short time periods is alarming. Therefore, it is crucial in clinical treatment to detect and minimize these effects as early as possible. It is also encouraging that one can detect significant improvements in lipids soon after a change in medications. Additionally, the finding of this study, that there are important changes in metabolic laboratory parameters without weight gain should discourage clinicians from relying upon weight gain as a sentinel indicator of metabolic complications. Further studies aimed at better elucidating both the acute and chronic time course of metabolic abnormalities associated

with SGA treatment should be undertaken as an aid to developing appropriate recommendations for patient monitoring and intervention.

Limitations to the study include the lack of fasting blood glucose values and the use of lipid values not obtained under strictly defined fasting requirements. The protocol recommended that blood draws occur before morning meals, but documentation of adherence was not "evaluated" or available. Due to the post-hoc nature of these metabolic analyses, it is unlikely there were any biases or discrepancies in the way the blood draws were collected, because the treatment groups were randomly assigned and the study was double-blind. Furthermore, all laboratories were performed by the same laboratory using standardized techniques which eliminates across-site differences that may be present. Also, it was not known if the discontinuation of other concomitant medications may have led to the changes in weight and metabolic profiles. However, there is no reason to suspect that the groups at baseline would have greatly differed in the use of other medications which may have contributed to weight changes. Lastly, the measure of HbA1C may not be sensitive enough to detect changes in glucose levels in the short time period of eight weeks. In the normal 90–120-day life span of the red blood cell, glucose molecules join hemoglobin, forming glycosylated hemoglobin. In individuals with poorly controlled diabetes or increasing glucose levels, increases in the quantities of these glycosylated hemoglobins are noted. Thus, measuring HbA1C assesses the effects of long-term serum glucose regulation and the HbA1C level is proportional to average blood glucose concentration over the previous four weeks to three months. However, while evidence suggests that the major proportion (> 50%) of its value is related to a rather short term period of two to four weeks, American Diabetes Association notes it as a measure most reflective of the past 2–3 months. (34, 35) Nevertheless, the 8 week time period may have been insufficient to detect difference in glucose regulation.

There is much more to be understood about the metabolic side effects associated with SGA treatment. Determining individual characteristics that increase the risk of adverse effects and the potential for therapeutic interventions should be major objectives for future research. For example, males in this study receiving olanzapine experienced elevations in TG and TC that were significantly higher than expected given the weight gain that occurred. This population may benefit the most from interventions to lower the risk for developing cardiovascular disease. Current practice recommendations in regard to monitoring weight and metabolic parameters and timing interventions should be reconsidered. Finally, weight gain and metabolic dysfunction are not exclusive to schizophrenia or SGA treatment. In the case of bipolar disorder, these changes may be compounded by mood stabilizer treatment (36). Risperidone and olanzapine each have been prescribed to over 10 million people (37, 38) worldwide for a variety of psychiatric indications. These patients require proactive and thoughtful treatment

in regard to metabolic issues in order improve the long-term outcomes of medication therapy, and improve the health and survival of those with serious mental illness.

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