Development of an Atherogenic Metabolic Risk Factor Profile Associated With the Use of Atypical Antipsychotics

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Background: It is important to assess cardiovascular risk factors to properly verify the potential consequences of atypical antipsychotic–related weight gain. The objective of the present study was to evaluate whether 2 atypical antipsychotics differ regarding their impact on the cardiovascular disease risk profile compared with a reference group.

Method: We conducted a cross-sectional, multicenter study to assess anthropometric indices of obesity and to obtain a comprehensive fasting metabolic risk profile. Either risperidone or olanzapine had to be prescribed as the first and only antipsychotic for a minimum of 6 months. Patients were compared with a reference group of nondiabetic men. Data were collected from August 1999 to August 2001.

Results: Eighty-seven patients treated with olanzapine (N = 42) or risperidone (N = 45) were evaluated. Olanzapine-treated patients had significantly higher plasma triglyceride concentrations (2.01 ± 1.05 vs. 1.34 ± 0.65 mmol/L, $p \leq .05$), lower high-density lipoprotein (HDL)-cholesterol levels (0.92 ± 0.17 vs. 1.04 ± 0.21 mmol/L, $p \leq .05$), higher cholesterol/HDL-cholesterol ratios (5.62 ± 1.70 vs. 4.50 ± 1.44, $p \leq .05$), higher apolipoprotein B levels (1.07 ± 0.35 vs. 0.92 ± 0.27 g/L, $p \leq .05$), smaller low-density lipoprotein peak particle diameters (252.6 ± 4.1 vs. 255.2 ± 4.3 Å, $p < .01$), and higher fasting insulin concentrations (103.9 ± 67.6 vs. 87.5 ± 56.1 pmol/L, $p \leq .05$) than risperidone-treated patients. Moreover, 33% of olanzapine-treated patients were carriers of 3 atherogenic features of the metabolic syndrome as opposed to a prevalence of only 11% of risperidone-treated patients.

Conclusion: These results suggest that olanzapine-treated patients are characterized by a more deteriorated metabolic risk factor profile compared with risperidone-treated patients. These observations raise concerns about the potential differential long-term deleterious effects of some antipsychotics, such as olanzapine, on cardiovascular health.

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Antipsychotics are the cornerstone of the pharmacologic treatment of schizophrenia. In the last decade, atypical antipsychotics have demonstrated their advantages over typical antipsychotics.[1] Since most atypical agents have similar efficacy, side effect profiles become crucial when considering the optimal treatment.[2] For instance, use of atypical antipsychotics has been associated with significant weight gain.[3–5] Moreover, some authors have reported differential weight gain depending on the atypical used.[6,7] Weight gain is a determinant of patient noncompliance,[8] and this undesirable side effect may also lead to potential long-term health consequences. For instance, it has been reported that weight gain is 1 of 2 main side effects that will cause patients to discontinue treatment, exposing the schizophrenic patient to an increased risk of relapse.[9]

Obesity, particularly when accompanied by excess abdominal fat deposition, is now recognized as a major health hazard. For instance, abdominal obesity has been associated with an increased prevalence of chronic complications, such as type 2 diabetes, dyslipidemia, coronary heart disease, and hypertension.[10–15]

On that basis, weight gain associated with the use of antipsychotic drugs should be a source of concern. Indeed, studies have shown a marked variability of induced weight gain among atypical agents. Estimates range from an average of no change to a weight gain of 4.5 kg (10 lb) after 10 weeks and 12 kg (26 lb) after a year of treatment.[7,16] However, at this stage, there is only limited evidence in the clinical literature on the potentially deleterious metabolic consequences of weight gain associated with antipsychotics. Elevated triglycerides[17–20] and hyperglycemia leading to new cases of type 2 diabetes[21] have been reported. Newcomer et al.[22] reported evidence that new antipsychotic treatments in comparison with typical agents led to a deterioration of plasma glucose homeostasis. Furthermore, they observed that such impact of atypical antipsychotics on plasma glucose regulation appeared to be independent of the variation in the body mass index (BMI). In this regard, a study from Fontaine et al.[23] reported, using the Framingham Heart Study and a population suffering from schizophrenia, that the beneficial effect of new-generation antipsychotics on death related to suicide may essentially be offset by deaths due to a 10-kg (22-lb) weight gain over a 10-year period. Since no extensive prospective metabolic study has been conducted in patients treated with atypical antipsychotics, it was, therefore, important to examine whether or not the increase in body weight reported with the use of some antipsychotic drugs would be associated with a selective accumulation of abdominal fat and with related metabolic alterations considered as markers of cardiovascular disease risk.

The objective of this cross-sectional study was to measure anthropometric indices of obesity and of adipose tissue distribution, as well as to obtain a comprehensive fasting metabolic risk profile in a cohort of patients who were exposed for at least 6 months to 2 antipsychotic drugs, either risperidone or olanzapine. Secondly, we compared the 2 treated groups to a reference group of nondiabetic men selected from the Québec Health Survey.

METHOD

Risperidone- and Olanzapine-Treated Patients

This was an open-label, cross-sectional, multicenter study involving 4 centers in Québec, Canada. Charts at each center were screened for eligible male patients. The ethics review board of each site approved the study, and signed informed consent was obtained from all participating patients. Patients had to be treated for at least 6 months with either risperidone or olanzapine as their first and only atypical treatment with no previous exposure to clozapine, olanzapine, risperidone, or quetiapine. Recent smoking cessation, endocrine diseases, treatment with drugs altering blood pressure, plasma lipids, insulin, and body weight were also considered as exclusion criteria. A total of 87 (olanzapine, N = 42; risperidone, N = 45) adult men (mean ± SD age of 30.2 ± 2.3 years) were recruited over a period of 20 months. Patients were mainly diagnosed by their referring psychiatrist with DSM-IV schizophrenia or other related psychoses (total population: 87%, olanzapine-treated patients: 81%, risperidone-treated patients: 93%).

Psychiatric History

Psychiatric history, including diagnosis, dose of antipsychotic, age at onset of the psychiatric illness, age at the beginning of antipsychotic treatment, duration of illness, and number of prior psychiatric hospitalizations were recorded.

Psychiatric Evaluation

The Clinical Global Impressions (CGI) scale was used to evaluate illness severity.[24]

Anthropometric Measurements

Weight, height, and BMI were determined following the procedures of the Airlie Conference[25] on the standardization of anthropometric measurements, and waist circumference was measured following the recommendations of van der Kooy and Seidell.[26]

Resting Blood Pressure and Pulse Rate

The disappearance of all sounds (Korotkoff phase V) was used to determine diastolic blood pressure.[27] Three supine blood pressure and pulse rate measurements were then taken 3 minutes apart on the nondominant arm with an appropriate cuff size measured after the patient had been resting in the supine position for 5 minutes. The measurements were performed using a mercury sphygmomanometer. Three sitting measurements of blood pressure and pulse rate were also taken following the same procedure.

Plasma Lipoprotein-Lipid Variables

Blood samples were collected from an antecubital vein into vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA) (Miles Pharmaceuticals, Rexdale, Ontario, Canada) after a 12-hour overnight fast for the measurement of plasma lipid and lipoprotein levels. Cholesterol and triglyceride levels were determined in plasma and lipoprotein fractions using a Technicon RA-500 (Bayer, Tarrytown, N.Y.) and enzymatic reagents obtained from Randox (Crumlin, U.K.). Plasma very-low-density lipoproteins (density < 1.006 g/mL) were isolated by ultracentrifugation.[28] The high-density lipoprotein (HDL) fraction was obtained after precipitation of low-density lipoprotein (LDL) in the infranatant (density > 1.006 g/mL) with heparin and $MnCl_2$.[29] The cholesterol and triglyceride concentrations of the infranatant were measured before and after the precipitation step.

Apolipoprotein (apo) B and apo AI concentrations were measured in plasma with a high-sensitive immunoassay performed on the Behring BN-100 nephelometer (Dade Behring, Liederback, Germany). The cholesterol content of HDL_2 and HDL_3 subfractions prepared by the precipitation method was also determined.[30]

Assessment of LDL Size by Gradient Gel Electrophoresis

Nondenaturing 2% to 16% polyacrylamide gel electrophoresis was performed on whole plasma kept at –80°C (–112°F) before use, according to the procedure described by Krauss and Burke[31] and McNamara et al.[32] Gels were cast using acrylamide and bis-acrylamide (30:0.8) obtained from Bio-Rad (Hercules, Calif.). LDL particle size was determined on 8 × 8-cm polyacrylamide gradient gels prepared in batches. A volume of 3 μL of plasma samples was applied on lanes in a final concentration of 20% sucrose and 0.25% bromophenol blue. Electrophoresis was performed in a refrigerated cell (10–15°C [50–59°F]) for a prerun of 15 minutes at 125 V and for the entry of samples into stacking at 70 V for 20 minutes, followed by migration at 150 V for 4 hours. Gels were stained for lipids overnight with Sudan black (Lipostain, Paragon Electrophoresis System, Beckman, Montréal, Canada) in 55% ethanol. Gels were destained in a 45% ethanol solution, and original gel size was restored in a 9% acetic acid and 20% methanol solution. A plasma pool was used as an internal standard. Gels were analyzed by the Imagemaster 1-D Prime computer software (Amersham Pharmacia Biotech, Amersham, England). LDL size was extrapolated from the relative migration of 4 plasma standards of known diameters. The estimated diameter for the major peak in each scan was identified as the LDL peak particle size. Analysis of pooled plasma standards revealed that measurement of LDL peak particle size was highly reproducible, with inter- and intra-assay coefficients of variation of less than 2% and 1.5%, respectively.

Variables of Insulin-Glucose Homeostasis

Blood samples were taken in the morning after an overnight (12-hour) fast and collected in EDTA-containing tubes through a venous catheter placed in an antecubital vein for the determination of plasma glucose and insulin concentrations. Fasting plasma glucose concentrations were determined enzymatically,[33] whereas fasting insulin levels were measured by commercial double-antibody radioimmunoassay (LINCO Research, Inc., St. Louis, Mo.), showing little cross-reactivity (< 0.2%) with proinsulin.[34]

Furthermore, as a crude index of in vivo insulin sensitivity, we used the homeostasis model assessment (HOMA) formula[35] to estimate insulin resistance, as described previously: HOMA index = (fasting insulin [pmol/L] × fasting glucose [mmol/L])/22.5.

Table 1. Characteristics of the Reference Group and Patients Treated With Olanzapine or Risperidone[a]

Variable	Reference N = 708	Olanzapine N = 42	Risperidone N = 45
Medication			
Dose (mg/d)	…	12.4 ± 5.3	2.9 ± 1.7
Duration (mo)	…	20.2 ± 10.8	20.0 ± 12.3
Physical characteristics			
Age (y)	32.8 ± 9.6	31.7 ± 10.4	28.4 ± 9.6[b]
Weight (kg)	75.6 ± 12.7	85.6 ± 16.9[b]	82.7 ± 17.2[b]
Height (cm)	174.0 ± 6.9	175.5 ± 6.3	175.3 ± 6.1
Body mass index (kg/m^2)	24.9 ± 3.8	27.7 ± 4.9[b]	26.8 ± 5.0[b]
Waist circumference (cm)	87.3 ± 10.7	97.2 ± 13.8[b]	93.8 ± 13.9[b]
Psychiatric evaluation			
Illness severity score (CGI)	…	3.8 ± 1.3	3.5 ± 1.3

[a]All values shown as mean ± SD.
[b]Different from reference group, $p \leq .05$.
Abbreviation: CGI = Clinical Global Impressions scale.
Symbol: … = no data available.

Reference Group

A sample of nondiabetic, nonschizophrenic, and nontreated men aged 18 to 59 years was selected from a representative sample of the Québec population as a reference group. Anthropometric measurements (weight, height, BMI, and waist circumference), fasting plasma lipoprotein profile (including total cholesterol, LDL-cholesterol, HDL-cholesterol, total cholesterol/HDL-cholesterol ratio, and plasma triglycerides), fasting glucose, and insulin concentrations were measured in these reference subjects. Blood pressure was not available in the reference group. The reference group was compared with study patients treated with risperidone or olanzapine.

Statistical Analyses

Results are expressed as mean ± SD in tables and as mean ± SEM in figures. Group differences for continuous variables were examined using the general linear model, and the Duncan post hoc test was used in situations where a significant group effect was observed. Pearson correlation coefficients were computed to quantify univariate associations between waist circumference and triglycerides. All analyses were performed with the SAS statistical system (SAS Institute, Cary, N.C.).

RESULTS

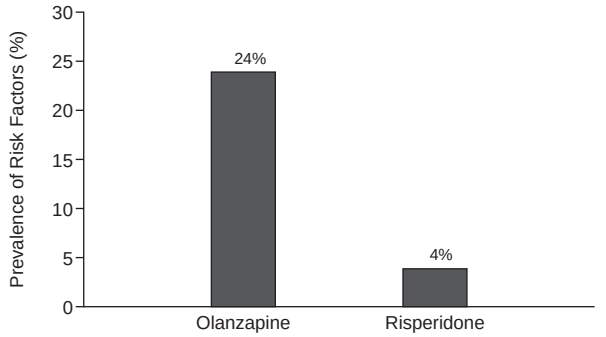
Table 1 shows that study patients treated with risperidone or olanzapine could be, as a group, classified as overweight (weight, 82.7 ± 17.2 vs. 85.6 ± 16.9 kg [182.4 ± 37.9 vs. 188.7 ± 37.3 lb]; BMI, 26.8 ± 5.0 vs. 27.7 ± 4.9 kg/m^2) with a moderately high waist circumference (93.8 ± 13.9 vs. 97.2 ± 13.8 cm) for risperidone and olanzapine, respectively. The reference individuals were leaner (weight, 75.6 ± 12.7 kg [166.7 ± 28.0 lb]; BMI, 24.9 ± 3.8 kg/m^2; waist circumference, 87.3 ± 10.7 cm) than study patients treated with atypical

Table 2. Lipoprotein-Lipid and Metabolic Profiles of the Reference Group and Patients Treated With Olanzapine or Risperidone[a]

Variable	Reference N = 708	Olanzapine N = 42	Risperidone N = 45
Lipoprotein-lipid profile			
Cholesterol (mmol/L)	5.06 ± 1.03	4.99 ± 1.13	4.53 ± 1.14[b,c]
LDL-cholesterol (mmol/L)	3.11 ± 0.90	3.19 ± 1.07	2.82 ± 1.00[b,c]
HDL-cholesterol (mmol/L)	1.21 ± 0.29	0.92 ± 0.17[b]	1.04 ± 0.21[b,c]
HDL_2-cholesterol (mmol/L)	…	0.30 ± 0.12	0.36 ± 0.12[c]
HDL_3-cholesterol (mmol/L)	…	0.62 ± 0.10	0.68 ± 0.15[c]
Cholesterol/ HDL-cholesterol	4.46 ± 1.59	5.62 ± 1.70[b]	4.50 ± 1.44[c]
Triglycerides (mmol/L)	1.69 ± 1.53	2.01 ± 1.05	1.34 ± 0.65[c]
Apolipoprotein B (g/L)	…	1.07 ± 0.35	0.92 ± 0.27[c]
Apolipoprotein A1 (g/L)	…	1.10 ± 0.15	1.16 ± 0.16[c]
LDL peak particle size (Å)	…	252.6 ± 4.1	255.2 ± 4.3[c]
Metabolic profile			
Fasting glucose (mmol/L)	5.22 ± 1.23	5.89 ± 0.72[b]	5.69 ± 0.55[b]
Fasting insulin (pmol/L)	64.6 ± 43.6	103.9 ± 67.6[b]	87.5 ± 56.1[b,c]
HOMA index	15.6 ± 15.2	28.3 ± 20.9[b]	23.7 ± 17.3[b]
Systolic blood pressure (mm Hg)	…	127.7 ± 11.2	121.2 ± 12.7[c]
Diastolic blood pressure (mm Hg)	…	84.4 ± 8.5	80.1 ± 9.9[c]
Heart rate (beats/min)	…	68.3 ± 12.3	65.7 ± 11.3

[a]All values are shown as mean ± SD.
[b]Different from reference group, $p < .05$.
[c]Different from olanzapine group, $p \leq .05$.
Abbreviations: HDL = high-density lipoprotein, HOMA = homeostasis model assessment, LDL = low-density lipoprotein. Symbol: … = no data available.

Figure 1. Prevalence of Carriers of 6 Metabolic Risk Factors Among Olanzapine- Versus Risperidone-Treated Patients[a]



[a]Metabolic risk factors include fasting insulin ≥ 60 pmol/L, apolipoprotein B ≥ 0.96 g/L, LDL peak particle size < 255.5 Å, HDL-cholesterol ≤ 1.0 mmol/L, cholesterol/HDL-cholesterol ratio ≥ 6.0, and triglycerides ≥ 2.0 mmol/L.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

antipsychotics. Table 1 also indicates that no difference was found in illness severity, evaluated with the CGI scale, between the 2 patient groups treated with atypical antipsychotics.

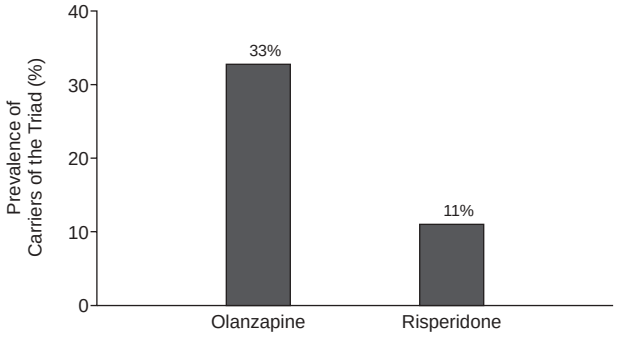
The metabolic risk profile of the study groups and the reference group is shown in Table 2. Olanzapine-treated patients had an overall deterioration in their metabolic risk profile compared with both risperidone-treated patients and reference subjects. Total cholesterol, LDL-cholesterol, and triglyceride levels were significantly higher in olanzapine- than risperidone-treated patients, although not significantly different from the reference group. Risperidone-treated patients had cholesterol and LDL-cholesterol levels lower than the reference group. Despite the fact that both olanzapine- and risperidone-treated patients had lower HDL-cholesterol levels than reference controls, olanzapine-treated patients had the highest cholesterol/HDL-cholesterol ratio. No difference was found between risperidone-treated patients and controls for this variable. Risperidone-treated patients had the lowest plasma triglyceride levels. Furthermore, fasting glycemia, insulinemia, and HOMA-derived level of insulin resistance were significantly higher in both groups of patients treated with atypicals compared with the reference group. However, olanzapine-treated patients were characterized by the highest fasting insulin levels compared with both risperidone-treated patients and reference individuals.

To better evaluate the metabolic risk factor profile among risperidone- and olanzapine-treated patients, atherogenic markers of the metabolic syndrome (fasting hyperinsulinemia, increased apo B concentration, and an increased proportion of small LDL particle size) were assessed. This atherogenic metabolic triad was found to be associated with a 20-fold increase in the risk of developing coronary heart disease in initially asymptomatic middle-aged men followed over a period of 5 years.[36] LDL peak particle size was significantly smaller in the olanzapine group compared with risperidone patients, whereas apo B and insulin levels were highest among olanzapine-treated patients. Finally, both systolic and diastolic blood pressure readings were significantly higher in olanzapine- than in risperidone-treated patients (Table 2).

The simultaneous prevalence of carriers of 6 metabolic risk factors was also quantified among risperidone- versus olanzapine-treated patients. Risk factors were defined as fasting insulin ≥ 60 pmol/L, apo B ≥ 0.96 g/L, LDL peak particle size < 255.5 Å, HDL-cholesterol ≤ 1.0 mmol/L, cholesterol/HDL-cholesterol ratio ≥ 6.0, and triglycerides ≥ 2.0 mmol/L. Figure 1 shows that 24% of the olanzapine-treated patients were characterized by the simultaneous presence of these 6 risk factors compared with a prevalence of only 4% in the risperidone-treated group.

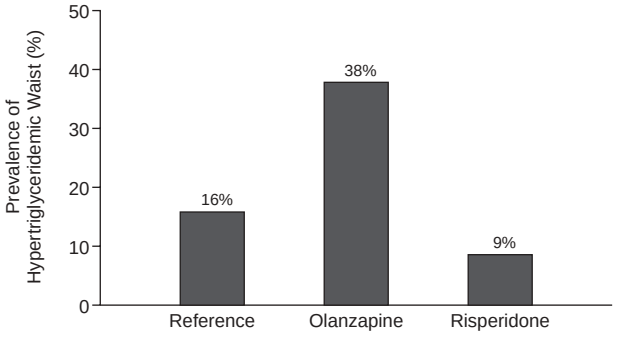
Figure 2 illustrates that one third of olanzapine-treated patients were characterized by 3 critical features of the metabolic syndrome: by the simultaneous presence of insulin ≥ 48.5 pmol/L, apo B ≥ 0.96 g/L, and LDL peak particle < 255.5 Å,[36] as opposed to a prevalence of only 11% among risperidone-treated patients. These metabolic parameters were not measured in the reference group;

Figure 2. Prevalence of Carriers of the Atherogenic Metabolic Triad Phenotype Among Olanzapine- Versus Risperidone-Treated Patients[a]



[a]The atherogenic metabolic triad includes fasting hyperinsulinemia, increased apolipoprotein B concentration, and an increased proportion of small low-density lipoprotein particle size.

Figure 3. Prevalence of Carriers of the "Hypertriglyceridemic Waist" Phenotype Among the Reference Group and Patients Treated With Olanzapine or Risperidone[a]

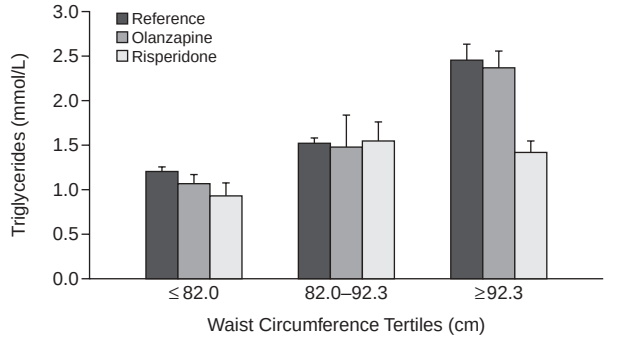


[a]The "hypertriglyceridemic waist" is a waist circumference ≥ 90 cm and combined triglycerides ≥ 2.0 mmol/L.

however, the prevalence of "hypertriglyceridemic waist" (waist circumference ≥ 90 cm, combined triglycerides ≥ 2.0 mmol/L), a simple clinical phenotype which we have recently reported to be predictive of the simultaneous presence of hyperinsulinemia, elevated apo B, and small LDL peak particle size,[37] was assessed across the study groups and the reference group. Figure 3 shows that more than one third of the olanzapine group presented with the high-risk hypertriglyceridemic waist phenotype, whereas its prevalence only reached 9% and 16% in the risperidone and reference groups, respectively.

Finally, Pearson correlation coefficients were performed to evaluate the relationship between triglyceride concentrations and waist circumference in the 3 groups. Whereas significant correlations were found between waist circumference and triglycerides in the olanzapine-treated group ($r = 0.53$, $p \leq .001$) and in the reference group ($r = 0.32$, $p \leq .001$), no association was noted among risperidone-treated patients ($r = 0.21$, not significant). To further explore this difference, subjects were stratified into tertiles of waist circumference (Figure 4). As opposed to controls and to olanzapine-treated patients for whom elevated triglyceride levels were noted in patients in the upper waist tertile (waist circumference ≥ 92.3 cm), no increase in fasting triglyceride levels was found among risperidone-treated patients in the third waist tertile compared with the first waist tertile.

Figure 4. Relationship of Waist Circumference (divided into tertiles) to Fasting Triglyceride Concentration Among the Reference Group and Patients Treated With Olanzapine or Risperidone



DISCUSSION

Atypical antipsychotics offer an increased spectrum of efficacy on positive, negative, cognitive, and affective symptoms and a reduced propensity for extrapyramidal side effects.[1] Despite these undeniable advantages, use of atypical antipsychotics has been associated with significant weight gain.[3–5] Since obesity is a health hazard, it is important to document the consequence of this body weight variation on cardiovascular disease (CVD) risk factors.

The present cross-sectional study compared anthropometric correlates of obesity and CVD risk variables of patients treated with 2 atypical antipsychotics (risperidone vs. olanzapine). Results show that both groups treated with atypicals had similar BMI values and were heavier than the reference group. Moreover, abdominal obesity, as assessed by waist circumference, was not significantly different between the 2 groups, which should have predicted similar deteriorations in the metabolic risk profile. Instead, the olanzapine group had a markedly deteriorated risk profile compared with the reference group and the risperidone-treated patients. One fourth of the olanzapine-treated patients were characterized by a cluster of 6 metabolic risk factors, and each of these factors has been shown to be a significant predictor of CVD events.

Reduced plasma HDL-cholesterol is a major factor responsible for the increase in cholesterol/HDL-cholesterol ratio, which is the best cumulative lipid index to predict the risk of coronary heart disease.[38,39] HDL-cholesterol levels of olanzapine-treated patients were significantly lower than those of risperidone-treated patients. Moreover, our data show that olanzapine-treated patients had a cholesterol/HDL-cholesterol ratio that was increased by more than 1 unit compared with risperidone-treated patients, suggesting a markedly increased CVD risk in the former group.

In the present study, triglyceride levels were higher in the olanzapine group compared with the risperidone and reference groups. Elevated triglyceride concentrations have also been previously observed in olanzapine-treated patients.[40] Furthermore, increased triglyceride concentrations (≥ 2.0 mmol/L) are an important marker of insulin resistance syndrome when accompanied by an increased waist circumference (≥ 90 cm).[37] Our data show that one third of olanzapine-treated patients were carriers of the hypertriglyceridemic waist phenotype (combined triglycerides ≥ 2.0 mmol/L and waist circumference ≥ 90 cm), a form of obesity that we previously reported to be predictive of a high likelihood of having the features of insulin resistance syndrome.[37] Antipsychotic-treated patients displayed normal levels of total cholesterol and LDL-cholesterol, a result that is concordant with the fact that the atherogenic dyslipidemia of the metabolic syndrome profile (low HDL-cholesterol and high triglycerides) is not necessarily associated with marked increases in cholesterol and LDL-cholesterol levels. However, these apparently normal cholesterol and LDL-cholesterol levels should not mislead physicians, since it may mask an increased concentration of small LDL particles, a highly atherogenic condition.[41,42]

In this regard, olanzapine-treated patients were characterized by a greater proportion of small LDL particles than the risperidone group as well as by higher fasting insulin and apo B levels. Previous results from a prospective study of a sample of initially asymptomatic middle-aged men, the Québec Cardiovascular Study, have indicated that the combination of hyperinsulinemia, elevated apo B, and small LDL particles was associated with a 20-fold increase in the risk of having a first ischemic heart disease event over a 5-year follow-up period, which makes this triad of metabolic abnormalities a highly atherogenic condition.[36] The prevalence of this atherogenic metabolic triad reached 33% in olanzapine-treated patients as opposed to 11% among risperidone-treated patients.

A higher incidence of diabetes and of impaired plasma glucose homeostasis has been reported in drug-naïve schizophrenic patients as well as treated patients.[43,44] A recent report by Sernyak and colleagues[45] has highlighted clinically important observations in a large sample (N = 38,632) of patients with schizophrenia, comparing the prevalence of diabetes mellitus in patients treated with both atypical and typical antipsychotics. The authors[45] found that the relative risk of developing diabetes mellitus in young patients (age < 40 years) was almost doubled when treated with atypical instead of typical antipsychotics (odds ratio = 1.63 [95% CI = 1.23 to 2.16]), whereas no difference was found in older patients. In the present study, both groups of patients taking atypicals had higher fasting glucose levels than the reference group. This raised fasting glycemia was accompanied by increased insulinemia and by an increased level of estimated insulin resistance (HOMA index), suggesting a relative state of insulin resistance among patients treated with atypicals. Furthermore, olanzapine-treated patients had plasma insulin levels that were significantly higher than risperidone-treated patients, which may suggest further metabolic deterioration in the former patients. The presence of hyperinsulinemia in fasting subjects has been proposed to be an independent marker of elevated ischemic heart disease risk.[46] Therefore, it may serve as a crude but clinically relevant marker for metabolic disturbances among nondiabetic individuals. Blood pressure was also significantly higher in olanzapine- than in risperidone-treated patients, a finding consistent with the well-documented hyperinsulinemia/insulin resistance–hypertension relationship.[47–49] Further work will be required to confirm with more sophisticated measurements to what extent insulin sensitivity is reduced in these patients and whether elevated blood pressure is indeed the consequence of an induced insulin resistant/hyperinsulinemic state.

Olanzapine-treated patients were characterized by a cluster of metabolic abnormalities that are reminiscent of the features of the metabolic syndrome often resulting from the presence of abdominal obesity.[50] In drug-naïve and drug-free schizophrenic patients, a recent study reported a 3-fold increase in visceral adipose tissue accumulation measured by computed tomography compared with normal age- and sex-matched controls.[51] These results may suggest an increased susceptibility to visceral adipose tissue deposition that may already be present in the schizophrenic population. Although our results showed that olanzapine-treated patients had a more deteriorated metabolic risk profile than risperidone-treated patients, it is possible that olanzapine-treated patients may be more prone to visceral adipose tissue accumulation or that these patients are more susceptible to develop an atherogenic risk profile for any given level of visceral adipose tissue. However, we do not know why risperidone-treated patients had normal triglyceride levels despite a substantially increased waist circumference compared with the reference group. Although further research is needed to validate this finding, it is possible that risperidone may have a specific protective effect

against the hypertriglyceridemia generally associated with weight gain.

On the other hand, whether atypical antipsychotics alter metabolic variables predictive of an increased CVD risk is not well documented. Moreover, schizophrenic patients often present with poor lifestyle habits (smoking, sedentary lifestyles, diets rich in fat and sugar) that predispose them to an increased cardiovascular risk.[52,53] Thus, it remains possible that the physical activity habits of patients taking olanzapine were more altered than in risperidone-treated patients. Energy balance studies are clearly warranted to investigate this possibility. Finally, the present study has the obvious limitations of its cross-sectional design. Thus, without baseline values, it was not possible to evaluate changes in metabolic risk profile in response to atypical antipsychotic therapy, and we cannot exclude with certainty a bias in subjects' selection, although we were very careful to control for this factor. Indeed, our exclusion criteria were very strict in order to limit potential differences between the 2 atypical-treated groups, thereby avoiding potential bias.

These results raise concerns about the potential long-term deleterious effects of antipsychotic compounds on cardiovascular health. Thus, prospective randomized trials are urgently needed to further quantify the magnitude of the impact of these drugs on metabolic risk factors for CVD. Such studies could lead to the development of proper evaluation and treatment algorithm for patients successfully treated for their clinical symptoms of schizophrenia but who are developing the features of the metabolic syndrome, putting them at risk for the development of type 2 diabetes and CVD. Finally, results of the present study provide further evidence that, in order to appropriately assess CVD risk associated with weight gain, one needs to go beyond measuring body weight changes in response to any intervention. Indeed, in the present study, it is clear that body weight would have been a completely inadequate parameter to quantify the differential deleterious effects of the 2 atypical antipsychotics examined on the risk of CVD.

Drug names: clozapine (Clozaril and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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