A 12-Week Randomized Clinical Trial to Evaluate Metabolic Changes in Drug-Naive, First-Episode Psychosis Patients Treated With Haloperidol, Olanzapine, or Risperidone

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Objective: This study examined the main metabolic side effects induced by antipsychotic treatment in a cohort of first-episode drug-naive subjects.

Method: A randomized, open-label, prospective clinical trial was conducted. Participants were 145 consecutive subjects included in a first-episode psychosis program (PAFIP) from February 2002 to February 2005, experiencing their first episode of psychosis (DSM-IV codes 295, 297, and 298), and never treated with antipsychotic medication. Patients were assigned to haloperidol, olanzapine, or risperidone treatment during 12 weeks. The main outcome measures were changes at 12 weeks in body weight; body mass index; and 12-hours-fasting morning levels of total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, glucose, homeostasis model assessment (HOMA) index, and insulin.

Results: At the endpoint, 128 patients were evaluated (88.3%). The mean doses were haloperidol = 4.2 mg/day, olanzapine = 12.7 mg/day, and risperidone = 3.6 mg/day. A significant weight gain was observed with the 3 antipsychotics: haloperidol = 3.8 (SD = 4.9) kg, olanzapine = 7.5 (SD = 5.1) kg, and risperidone = 5.6 (SD = 4.5) kg. Metabolic parameters showed a worsening lipid profile with the 3 treatments (statistically significant increase in total cholesterol and LDL cholesterol levels). Only the olanzapine group showed significant increases in triglyceride levels. After the 12-week study period, there were no significant changes in parameters involving glucose metabolism for any group.

Conclusions: Drug-naive patients experienced an extraordinary weight gain with first- and second-generation antipsychotics after the first 12 weeks of treatment. Significant increases in total cholesterol and LDL cholesterol levels are associated with the 3 treatments. Weight gain and metabolic disturbances induced by antipsychotics may increase the risk of developing cardiovascular disease.

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In spite of the increasing body of scientific literature focusing on metabolic side effects of antipsychotic therapy, the independent effect of antipsychotics on metabolism has not been well established. These side effects include weight gain, impaired glucose regulation, new-onset diabetes mellitus, and lipid disturbances. Although second-generation antipsychotics have a higher propensity for causing adverse effects on glucose and lipid metabolism,[1,2] first-generation antipsychotics have been linked to obesity[3] and metabolic disturbances as well.[4,5]

Previous studies have reported extensive variations in the magnitude of weight gain experienced with different antipsychotics. The estimated short-term weight gain has ranged from 0.5 kg to 3.5 kg over 12 weeks for haloperidol,[3,6,7] from 4.1 kg to 9.2 kg for olanzapine[3,6,8,9] and from 2.0 kg to 4.6 kg for risperidone.[3,7] The variability of these weight gain estimates could be explained by methodological issues related to nonrandom prescribing patterns, high rates of polypharmacy, study populations with patients at different stages of illness, and limited knowledge of previous exposure to antipsychotic treatments.

Antipsychotic treatment has been associated with a higher risk of hyperglycemia, new-onset diabetes, and dyslipidaemia.[1,2] Olanzapine has been one of the

antipsychotics most frequently implicated in impaired glycemic control[10–12] and lipid abnormalities.[5] For risperidone, the literature suggests that there is an association with glucose dysregulation but the evidence is less strong than with olanzapine therapy.[13–15] Risperidone appears to have little to no effect on lipid profile.[11,16] The published literature is less extensive for haloperidol, but the data available suggest that it has little effect on glycemic and lipid levels.[5,11] Some of these findings should be interpreted with caution because the results are based on uncontrolled studies and retrospective data and have not taken account confounding factors such as body mass index (BMI) or concomitant treatment.

For accurate evaluation of metabolic disturbances induced by antipsychotic exposure and in order to prevent possible confounder factors, we propose to study weight gain and metabolic changes in a cohort of first-episode drug-naive subjects. This was a randomized, open-label, clinical trial of 12-weeks' follow-up examining the main metabolic effects secondary to antipsychotic monotherapy with the most widely prescribed first-generation (haloperidol) and second-generation antipsychotics (olanzapine and risperidone).

METHOD

This 12-week, prospective, open-label, randomized trial was conducted in the outpatient clinic as well as the inpatient psychiatric unit of Marqués de Valdecilla University Hospital, located in the province of Cantabria in the north of Spain. The hospital is a reference center of a catchment area population of 555,000 people. Patients recruited into this trial were drawn from a consecutive sample of 145 patients enrolled in the first-episode psychosis program of Cantabria (PAFIP) from February 2002 to February 2005.

The study protocol was approved by the ethics committee of our hospital. The Mental Health Services of Cantabria provided funding for implementing the first-episode psychosis program, which was established in 2001.

Subjects

Patients were included in the study if they met the following criteria: (1) were aged 15 to 50 years, (2) were living in the catchment area, (3) were experiencing their first episode of psychosis, (4) had never been treated with antipsychotic medication, (5) met DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder, and (6) understood the nature of the study and signed an informed consent document. Patients were excluded for any of the following reasons: (1) met DSM-IV criteria for drug dependence, (2) met DSM-IV criteria for mental retardation, or (3) had a history of neurologic disease or head injury.

The diagnoses were confirmed according to the DSM-IV criteria, using the Structured Clinical Interview for DSM-IV (SCID-I) by an expert psychiatrist after 6 months of the initial contact. All participants were in good general health, and none of them were receiving drugs that potentially can influence their weight, glucose metabolism, or lipid metabolism (e.g., corticoids, statins, hypoglycemic agents).

Study Design

Patients were randomly assigned to receive haloperidol, olanzapine, or risperidone. A computer-generated randomization list was drawn up by a statistician. Treatment dose ranges were 3 to 9 mg/day for haloperidol, 5 to 20 mg/day for olanzapine, and 3 to 6 mg/day for risperidone. Doses could be adjusted as clinically indicated within the prescribed range to target the lowest effective dose. Certain concomitant medications (lormetazepam and clonazepam) were permitted for the management of agitation, general behavior disturbances, and/or insomnia. Only if clinically significant extrapyramidal signs occurred, anticholinergic medication was allowed. Those patients who did not respond after 6 weeks of treatment or who had significant side effects were changed to a different antipsychotic. All patients were informed about potential weight gain, and exercise and dietary recommendations were given. A small group of patients (17.9%), after treatment allocation, were subsequently randomly assigned by computer-generated random blocks to an early behavioral intervention to control weight gain (7 patients in the haloperidol group, 8 patients in the olanzapine group, and 11 patients in the risperidone group). Detailed methods have been described elsewhere.[17]

The study's main outcome measures were changes at 12 weeks in body weight; body mass index; and 12-hours-fasting morning levels of total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, glucose, insulin, and homeostasis model assessment (HOMA) index. For all outcomes, change was computed as the difference from baseline to 12-week observation. The study was powered to detect a difference of 3 kg (with a standard deviation of 4) in mean weight gain between groups using a 2-sided test at the .05 significance level. With these assumptions and 10% lost to follow-up, a sample size of 42 subjects per group was required.

Assessments

Anthropometric measurements. Patients' height was measured at the time of enrollment in the study. Patients' weight was determined at baseline and at 12 weeks. A body mass index (BMI) of 18.5 to 24.9 was considered normal, a BMI of 25.0 to 29.9 was considered overweight, and a BMI of 30 or greater was considered obese.

Table 1. Comparison of Demographic and Clinical Characteristics Between Treatment Groups in a Trial to Evaluate Metabolic Changes in Drug-Naive First-Episode Psychosis Patients

Characteristic	Haloperidol (N = 40), Mean (SD)	Olanzapine (N = 41), Mean (SD)	Risperidone (N = 47), Mean (SD)	F	df	p
Mean dose, mg/d						
During acute treatment (first 6 weeks)	4.8 (1.5)	14.6 (3.5)	3.8 (1.1)			
At 12 weeks	4.2 (1.7)	12.7 (4.6)	3.6 (1.5)			
Age at admission, y	28.6 (8.2)	28.5 (6.5)	26.9 (8.2)	0.689	2,125	.504
Age at illness onset, y	26.8 (6.9)	27.2 (6.6)	25.6 (7.6)	0.610	2,125	.545
Duration of untreated psychosis, mo	21.4 (42.9)	14.5 (33.0)	14.6 (23.9)	0.569	2,125	.567
SANS-SAPS score at intake	19.3 (7.8)	20.1 (7.6)	19.0 (5.3)	0.303	2,125	.739
SANS-SAPS score change at 6 weeks	–10.1 (8.0)	–13.1 (7.0)	–10.9 (6.6)	1.965	2,125	.145
Weight at intake, kg	68.3 (12.2)	66.3 (13.6)	65.5 (12.2)	0.530	2,125	.590
	N (%)	N (%)	N (%)	χ^2	df	p
Sex (male)	25 (62.5)	25 (61.0)	28 (59.6)	0.078	2	.962
Education level (secondary or lower)	17 (42.5)	22 (53.7)	25 (53.2)	1.311	2	.519
Family socioeconomic status[a]	12 (30.0)	10 (25.4)	17 (36.2)	0.487	2	.487
Living in urban area	19 (47.5)	23 (56.1)	26 (55.3)	0.745	2	.689
Unmarried	32 (80.0)	31 (75.6)	43 (91.5)	4.203	2	.122
Living with parents	24 (60.0)	24 (58.5)	33 (70.2)	1.554	2	.460
Living with family	31 (77.5)	34 (82.9)	40 (85.1)	0.881	2	.644
Student	10 (25.0)	3 (7.3)	9 (19.1)	4.649	2	.098
Unemployed	14 (35.0)	20 (48.8)	21 (44.7)	1.658	2	.437
Diagnosis						
Schizophrenia	28 (70.0)	22 (53.7)	25 (53.2)	3.122	2	.210
Other						
Schizophreniform disorder	8 (20.0)	10 (24.4)	10 (21.3)			
Schizoaffective disorder	1 (2.5)	0 (0)	3 (6.4)			
Bipolar disorder	1 (2.5)	1 (2.4)	2 (4.3)			
Psychosis NOS	1 (2.5)	5 (12.5)	5 (10.6)			
Brief psychosis	1 (2.5)	3 (7.3)	2 (4.3)			
Needed hospitalization	27 (67.5)	28 (68.3)	23 (48.9)	4.499	2	.105
Responders (> 40% improvement in BPRS score at 6 weeks)	24 (60.0)	28 (68.3)	24 (51.1)	2.704	2	.259
Concomitant treatments						
Benzodiazepines (0–6 weeks)	21 (52.5)	21 (51.2)	24 (51.1)	0.021	2	.990
Benzodiazepines (12 weeks)	10 (25.0)	6 (14.6)	13 (27.7)	2.303	2	.316
Anticholinergics (0–6 weeks)	30 (75.0)	3 (7.3)	15 (31.9)	40.562	2	< .001
Anticholinergics (12 weeks)	31 (77.5)	2 (4.9)	14 (29.8)	47.491	2	< .001
Hypnotics (0–6 weeks)	8 (20.0)	3 (7.3)	12 (25.5)	5.092	2	.078
Hypnotics (12 weeks)	7 (17.5)	2 (4.9)	3 (6.4)	4.579	2	.101
Antidepressants (0–6 weeks)	1 (2.5)	1 (2.4)	3 (6.4)	1.214	2	.545
Antidepressants (12 weeks)	1 (2.5)	4 (9.8)	4 (8.5)	1.879	2	.391
Mood stabilizers (0–6 weeks)	0 (0)	1 (2.4)	1 (2.1)	0.937	2	.626
Mood stabilizers (12 weeks)	0 (0)	2 (4.9)	1 (2.1)	2.120	2	.346
Drug consumption						
Tobacco	20 (50.0)	25 (61.0)	28 (59.6)	1.191	2	.551
Cannabis	17 (42.5)	19 (46.3)	22 (46.8)	0.188	2	.910
Alcohol	24 (60.0)	20 (50.0)	25 (53.2)	0.845	2	.655

[a]Hollingshead-Redlich Scale.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, NOS = not otherwise specified, SANS-SAPS = Scale for the Assessment of Negative Symptoms and Scale for the Assessment of Positive Symptoms.

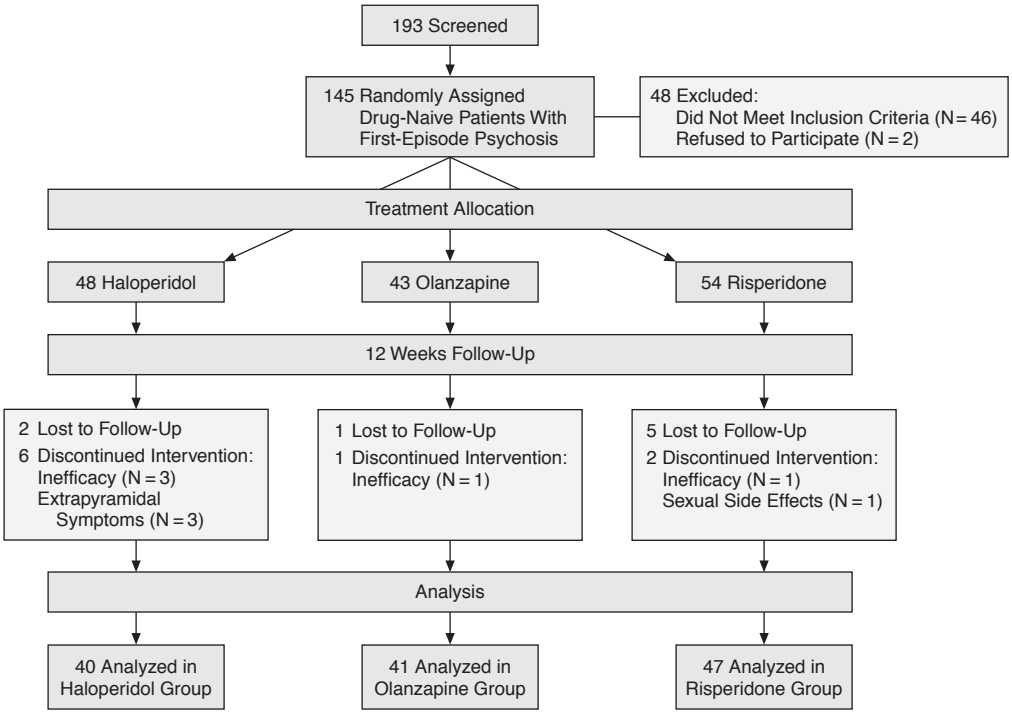
Laboratory Analysis. Biochemical determinations. All determinations were performed in our hospital, including both biochemical and endocrinology analysis. Glucose, total cholesterol, HDL cholesterol, and triglyceride levels were measured by automated methods on a Technicon Dax (Technicon Instruments Corp., Tarrytown, N.Y.), using the reagents supplied by Boehringer-Mannheim (Mannheim, Germany). LDL cholesterol was determined by the Friedewald et al. calculation[18]: LDL = total cholesterol – (HDL + [triglycerides/5]).

HOMA was used to assess insulin resistance (IR). HOMA index was calculated by means of a previously described formula[19]: HOMA = (fasting insulin [μU/mL] × fasting glucose [mmol/L])/22.5.

In addition, a complete blood count and liver function tests based on standard hematological and clinical chemistry values were performed at baseline and 12 weeks (results were within normal limits and data are not shown).

Hormonal levels. Insulin levels were measured by an immunoradiometric assay (IRMA) (Immunotech, Beckman Coulter Company, Prague, Czech Republic) with an average interassay coefficient of variation (CV) of 3.3% and intraassay CV of 2.8%. Sensitivity of

Figure 1. Participant Flow in the Randomized Clinical Trial



method was 0.5 μU/mL. Values for normal weight subjects are 2.1 to 22.0 μU/mL. This assay does not show any cross-reactivity with human proinsulin and C-peptide.

All laboratory measurements were obtained at first visit and at 12 weeks. To diminish variability, in each assay we matched a similar number of samples of the different groups, and the samples of each patient were evaluated in the same assay run.

Statistical Analysis

The analysis has been performed on a "per protocol" or "on-treatment" basis (only participants who fulfill the protocol were included: N = 128 completers) as well as according to the intention-to-treat basis (all patients were included in the treatment group to which they were initially assigned, no matter how long they adhered to the protocol: N = 145). Both showed similar results. We present per protocol analysis because we think it shows less biased results for the following reasons: (1) only 9 patients needed antipsychotic treatment change and none of the changes were related to any of the outcome variables; (2) the exclusion of those 9 patients does not affect the randomization (Table 1); and (3) although the intention-to-treat analysis shows no significant differences from the per protocol analysis, it tends to underestimate the true differences because 6 of 9 patients were changed to the olanzapine group.

To ensure group comparability, baseline sociodemographic and clinical characteristics were tested by 1-way analysis of variance (ANOVA) or χ^2 test for categorical variables. Within-group comparisons were explored by using t tests to examine significant changes between baseline measures and those after 12 weeks of treatment for each medication group. Patients who had incomplete data were excluded analysis by analysis (excluding a case for the analysis in which it has a missing value). The main reason for missing values was an incomplete data collection. Overall, missing data range from 4% to 12% depending on the test.

The relationship between main outcomes and antipsychotic medication was investigated by analysis of covariance (ANCOVA). Change in each parameter between baseline and endpoint was used as the dependent variable, type of medication (treatment group) was used as the independent variable, and parameter level at baseline was used as a covariate. Main potential confounders (sex and age) were added as covariates to the main model. When the analysis revealed significant between-group effects, an additional post hoc analysis (Sidak test) was conducted. The Statistical Package for Social Science (SPSS), version 12.0 (Chicago, Ill.), was used for statistical analyses. All statistical tests were 2-tailed. A cutoff p value of .01 was used to compare changes within-group (paired t test) in order to reduce the number of false positive. For the rest of the analyses, significance was determined at the .05 level.

RESULTS

Enrollment and Characteristics of Study Population

One hundred ninety-three subjects were screened. Of these, 46 were excluded for not meeting the inclusion criteria and 2 refused to participate in the study. This resulted in 145 patients who were included and assigned to treatment (Figure 1): haloperidol (N = 48), olanzapine (N = 43), and risperidone (N = 54). In all, 17 patients (11.7%) did not complete the study. Patient default (N = 8), inefficacy (N = 5), or adverse events (N = 4) were the reasons for discontinuation. We found no statistically significant differences between the percentages of patients who withdrew from each group (p = .193).

Subjects had a mean age of 28.1 years, 62.8% were men, and 82.8% were unmarried. Ninety-six percent were white. Most patients were living with their family (81.3%), and 44.8% were unemployed. Fifty-nine percent had a diagnosis of schizophrenia. The mean duration of psychosis was 16.4 months, with a median duration of 5.5 months. Sixty-four percent needed hospitalization.

For the entire sample, the mean weight at baseline was 66.9 kg (± 7.3 SD) and the mean BMI was 23.1 kg/m^2 (± 3.6 SD). At intake 28.1% had excess weight (23.7% were overweight and 4.4% were obese), and at 12 weeks this number rose to 48.4% (39.8% were overweight and 8.6% were obese). Fifty-seven percent experienced a > 7% increase in their body weight from baseline, and 23.4% had a > 15% increase. The mean weight gain was 5.7 kg in the 12-week period. A substantial weight gain occurred even in the early behavioral intervention group, although to a lesser extent than in the routine care population: 4.8 kg (SD = 4.2) vs. 5.9 kg (SD = 5.6), respectively; t = –0.931, p = .354.

Baseline sociodemographic and clinical data for each group of treatment are listed in Table 1. There were no significant differences between the 3 groups with regard to sex, age, educational level, socioeconomic status, diagnosis, severity of illness, and treatment response. Treatment-emergent extrapyramidal signs and symptoms were more frequent and more severe in the haloperidol-treated group. More detailed results about efficacy and extrapyramidal side effects have been described elsewhere.[20]

Within-Group Comparison

Table 2 shows statistically significant metabolic changes associated with each treatment group. Haloperidol treatment produced significant increases in weight and BMI (t = –4.96, p < .001 and t = –5.34, p < .001, respectively). Total cholesterol levels (t = –3.07, p = .004) and LDL cholesterol levels (t = –3.91, p < .001) significantly increased.

A significant increase from baseline in mean weight (t = –9.0, p < .001) and BMI (t = –9.08, p < .001) was

Table 2. Changes in Weight and Lipid and Glycemic Levels in Drug-Naive First-Episode Psychotic Patients After 12 Weeks of Treatment With Haloperidol, Olanzapine, or Risperidone

	Haloperidol (N = 40)					Olanzapine (N = 41)					Risperidone (N = 47)				
Variable	Baseline, Mean (SD)	12 Weeks, Mean (SD)	N	t	p†	Baseline, Mean (SD)	12 Weeks, Mean (SD)	N	t	p†	Baseline, Mean (SD)	12 Weeks, Mean (SD)	N	t	p†
Anthropometric changes															
Weight (kg)	68.29 (12.19)	72.12 (12.33)	40	–4.955	.000*	66.39 (12.95)	73.86 (13.78)	38	–8.998	.000*	65.26 (12.53)	70.84 (13.02)	43	–8.159	.000*
BMI (kg/m^2)	24.33 (4.24)	25.68 (3.82)	39	–5.338	.000*	22.92 (2.99)	25.53 (3.43)	38	–9.076	.000*	22.20 (3.42)	24.08 (3.29)	43	–8.346	.000*
Lipid profile															
Total cholesterol (mg/dL)	171.10 (34.61)	185.59 (33.42)	39	–3.069	.004*	177.31 (46.95)	200.26 (41.18)	39	–3.974	.000*	178.36 (42.29)	190.36 (37.15)	45	–3.185	.003*
Triglycerides (mg/dL)	82.86 (43.41)	85.28 (40.39)	36	–0.384	.704	94.00 (35.03)	122.06 (64.45)	36	–2.711	.010*	84.29 (47.72)	85.55 (39.92)	42	–0.184	.855
LDL cholesterol (mg/dL)	102.05 (28.14)	118.27 (26.96)	37	–3.905	.000*	110.44 (39.99)	125.75 (35.94)	36	–3.063	.004*	110.14 (33.48)	120.36 (32.99)	42	–3.207	.003*
HDL cholesterol (mg/dL)	52.03 (14.54)	48.51 (12.69)	37	2.252	.031	48.67 (14.29)	48.44 (15.14)	36	0.163	.872	50.50 (14.00)	52.83 (13.13)	42	–1.208	.234
Glycemic parameters															
Glucose (mg/dL)	84.15 (9.25)	85.64 (7.88)	39	–0.982	.333	88.51 (11.87)	88.62 (8.14)	39	–0.046	.963	89.49 (7.60)	87.93 (7.36)	45	1.059	.295
HOMA index	1.50 (1.33)	1.77 (1.21)	36	–0.274	.786	1.95 (2.26)	2.02 (1.55)	37	–1.232	.226	1.76 (1.11)	1.76 (1.19)	39	–0.028	.978
Insulin total (μU/mL)	7.09 (6.40)	8.41 (5.56)	37	–0.561	.578	8.62 (9.86)	9.18 (6.74)	37	–1.238	.224	7.87 (4.7)	8.08 (5.43)	39	–0.202	.841

†Paired samples t test.
*Significant at the .01 level (2-tailed).
Abbreviations: BMI = body mass index, HDL = high-density lipoprotein, HOMA = homeostasis model assessment, LDL = low-density lipoprotein.

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Table 3. Comparison of Changes in Weight, Lipid Parameters, and Glucose Levels From Baseline to 12 Weeks Between Treatment Groups (Haloperidol, Olanzapine, and Risperidone) in Drug-Naive First-Episode Psychosis Patients

				Analysis					
							p‡		
Variable	Haloperidol, Mean (SD)	Olanzapine, Mean (SD)	Risperidone, Mean (SD)	F	df	p†	Haloperidol vs Olanzapine	Haloperidol vs Risperidone	Olanzapine vs Risperidone
Anthropometric changes									
Weight gain (kg)	3.83 (4.89)	7.46 (5.11)	5.58 (4.48)	5.400	2	.006**	.004**	.369	.180
BMI gain (kg/m^2)	1.36 (1.59)	2.62 (1.78)	1.87 (1.47)	5.238	2	.007**	.008**	.844	.051
Lipid profile									
Total cholesterol (mg/dL)	14.49 (29.48)	22.95 (36.06)	12.00 (25.28)	2.122	2	.124	.160	.975	.297
Triglycerides (mg/dL)	2.42 (37.79)	28.06 (62.08)	1.26 (44.47)	6.469	2	.002**	.009**	1.000	.005**
LDL cholesterol (mg/dL)	16.22 (25.26)	15.31 (29.98)	10.21 (20.64)	0.308	2	.735	.950	.989	.822
HDL cholesterol (mg/dL)	–3.51 (9.49)	–0.22 (8.20)	2.33 (12.52)	3.501	2	.034*	.751	.032*	.274
Glycemic parameters									
Glucose (mg/dL)	–1.48 (9.46)	–0.10 (13.83)	1.56 (9.85)	1.147	2	.321	.405	.543	.993
HOMA index	0.28 (1.34)	0.07 (1.60)	0.01 (1.56)	0.277	2	.758	.979	.974	.841
Insulin (μU/mL)	1.32 (6.51)	0.56 (6.03)	0.21 (6.49)	0.353	2	.703	.999	.883	.824

†Analysis of covariance model: parameter change was used as the dependent variable, treatment group was the fixed factor, and baseline parameter level, age, and sex were used as covariates.
‡Pairwise comparisons based on estimated marginal means; Sidak adjustment for multiple comparisons.
*Significant at the .05 level.
**Significant at the .01 level.
Abbreviations: BMI = body mass index, HDL = high-density lipoprotein, HOMA = homeostasis model assessment, LDL = low-density lipoprotein.

observed with olanzapine therapy. The analysis showed that olanzapine treatment induced a worsening of the lipid profile with significantly increasing total serum cholesterol ($t = –3.97$, $p < .001$), triglycerides ($t = –2.71$, $p = .01$), and LDL cholesterol ($t = –3.06$, $p = .004$) levels.

Risperidone treatment resulted in a mean weight gain of 5.6 kg ($t = –8.16$, $p < .001$) in addition to a significant increase in total cholesterol ($t = –3.19$, $p = .003$) and LDL cholesterol ($t = –3.21$, $p = .003$) compared with baseline.

After the 12-week study period, there were no significant changes for any group in parameters involving glucose metabolism (fasting glucose, insulin levels, and HOMA index).

Between-Groups Comparison

As shown in Table 3, differences between groups were observed in weight gain, BMI, and triglyceride levels. Increase in weight gain during the first 12 weeks of antipsychotic treatment was significantly greater for the olanzapine group ($F = 5.40$, $df = 2$, $p = .006$). The median increase in weight was 3.8 kg for the haloperidol group (5.6% of their baseline weight), 7.5 kg for the olanzapine group (11.3% of their baseline weight), and 5.6 kg for the risperidone group (8.6% of their baseline weight). Our study detected statistically significant differences only between the olanzapine and haloperidol groups. Similar results were found comparing BMI changes among groups, with significant differences only between olanzapine and haloperidol groups ($F = 5.238$, $df = 2$, $p = .007$).

Elevations in triglyceride concentrations differed significantly among groups, with subjects treated with olanzapine exhibiting a higher increase compared with subjects treated with haloperidol ($p = .009$) or risperidone ($p = .005$). There were no significant differences comparing total cholesterol ($F = 2.12$, $df = 2$, $p = .124$) or LDL cholesterol ($F = 0.31$, $df = 2$, $p = .735$) levels among groups. Post hoc analysis of HDL levels revealed a significant difference between the haloperidol and risperidone treatment groups ($p = .032$).

There were no significant differences among groups for fasting glucose levels ($F = 1.15$, $df = 2$, $p = .321$), insulin levels ($F = 0.35$, $df = 2$, $p = .703$), and HOMA index ($F = 0.28$, $df = 2$, $p = .758$).

DISCUSSION

This study provides accurate estimates of short-term weight gain and metabolic disturbances associated with antipsychotic treatment. A representative sample of incident cases of first-episode psychosis in our region between 2002 and 2005 has been evaluated, all of them drug naive. Our results reflect notable changes in weight and lipid levels after 12 weeks of treatment. In contrast to most former reports, these findings are not confounded by previous antipsychotic exposure, the use of polypharmacy, or lifestyle changes like diet, smoking habits, or sedentarism due to the illness.

At baseline we have a young and healthy study population. No patient reported personal history of diabetes, hypercholesterolemia, or endocrine dysfunction. The percentage of patients with obesity (BMI > 30: 4.4%), hypercholesterolemia (total cholesterol > 240 mg/dL: 8.6%), and diabetes mellitus (glucose > 126 mg/dL: 0%) was lower than that of the general Spanish population published in a recent meta-analysis by Medrano et al.[21] After

12 weeks of treatment, we observed a marked weight gain (mean = 5.7 kg) leading to 8.6% obesity and 39.8% overweight and a worsening lipid profile.

The temporal relationship between the initiation of treatment and the metabolic changes supports the hypothesis that the higher prevalence of obesity and dyslipidemia in psychiatric patients compared with the general population is mainly attributable to antipsychotic treatment, and psychiatric illness per se probably plays a minor role; that is to say, a schizophrenia diagnosis is not an independent risk factor for developing a metabolic disorder.

The weight gain estimate in this study is higher for all of the 3 treatments than previously reported by most of the preceding surveys.[3,22–26] Only studies including first-episode patients have shown comparable results. Zipursky et al.[6] in a first-episode patient population found a mean weight gain of 9.2 kg after 12 weeks of treatment with olanzapine and 3.7 kg for the haloperidol-treated group, using an observed-cases analysis. Study populations differ in sex and ethnicity but are comparable in age, BMI at baseline, diagnosis, and, more importantly, previous exposure to antipsychotic medication: 100% of our patients had never been exposed to medication, and patients in the Zipursky et al. study had never been exposed (25.9%) or had very limited previous exposure.

Schooler et al.[7] in a double-blind randomized clinical trial described very similar results in weight gain at the third month for haloperidol-treated patients (3.5 kg) and slightly inferior results for the risperidone group (4.6 kg) to the weight gain found in our study. Previous exposure to medication in the study of Schooler et al. was also limited. Lieberman et al.,[15] in a first-episode controlled clinical trial, found a mean weight gain of 7.3 kg for the olanzapine-treated group versus 2.6 kg for the haloperidol group. In this study, the mean weight gain was slightly lower than in previous first-episode psychosis studies, and prior exposure to antipsychotic drugs was higher (74% of patients reported prior treatment, and the mean duration was 5.9 weeks).

Attending to these results we can affirm that the weight gain estimate due to antipsychotic treatment reported in first-episode psychosis studies, with no or very limited previous exposure to medication, is markedly greater than the estimate obtained in study populations with more chronic illness and previously exposed to antipsychotics.[27,28]

High triglyceride levels[16,22,29–31] and, to a lesser extent, high total cholesterol levels[11,22,23] have been reported in patients treated with first- and second-generation antipsychotics. Most of these findings have been reported with olanzapine treatment but not with risperidone or haloperidol. Few studies have examined the changes in other lipid parameters like LDL cholesterol or HDL cholesterol.[23] It is noteworthy that we found a significant increase in LDL cholesterol levels, the main predictor of cardiovascular disease, with the 3 antipsychotics. There were no significant differences between treatments in LDL changes. Similar results were obtained in total cholesterol plasma levels: a significant increase occurred with the 3 antipsychotics without significant differences between them. Although mean values for these lipid parameters remained modestly elevated, patients had a worse lipid profile compared with baseline.

Impaired glucose metabolism has been frequently reported in patients treated with antipsychotic drugs, particularly olanzapine. Data from observational studies,[32,33] retrospective cohort studies,[4,34,35] and controlled clinical trials[11,12,31] have associated antipsychotic treatment with glucose dysregulation. Our data have not shown significant disturbances in glucose metabolism. The lack of positive results in our sample could be explained by the short exposure period and/or the rather low mean doses of antipsychotic used after the first weeks. We did not find hyperinsulinemia, a state that frequently precedes fasting hyperglycemia by months or years, but the hypertriglyceridemia observed in olanzapine group could be interpreted as one of the earliest changes leading to impaired glucose metabolism.[36,37] On the other hand, other factors not related to antipsychotic action, such as a higher mean age, a higher BMI at baseline, and changes in lifestyle, could contribute to positive results in studies involving chronic schizophrenia patients.

Our data differ from the results found in a recent study of 112 drug-naive first-episode psychotic patients. Wu et al.[38] observed a significant increase in insulin levels, C-peptide, and insulin resistance index after 8 weeks of treatment with clozapine, olanzapine, sulpiride, or risperidone. Some peculiarities of this Chinese sample could explain in part the different findings, like the high mean age (34.9 years) or the fact that during the 8 weeks all of them remained hospitalized. Our cohort of first-episode psychotic patients is younger (28.1 years) and we included inpatients (64%) and outpatients (36%). Patients who required hospitalization were discharged as soon as possible (mean = 19.9 days). Therefore, differences in severity of the illness, age, and activity could contribute to the different outcome in glucose disturbances reported in both studies.

In summary, drug-naive first-episode psychosis patients, after a 12-week exposure period, experienced an extraordinary weight gain with the 3 antipsychotics, and the first changes in metabolic parameters were observed. These disturbances do not represent an illness per se, but they increase the long-term risk of the subjects to develop a cardiovascular disease. The complete effect of antipsychotics on weight and metabolism remains unknown, but according to previous studies,[6] weight gain occurs throughout the first year of treatment. Longer follow-up studies in drug-naive patients are warranted to elucidate the entire effect of antipsychotics on metabolism.

Drug names: clonazepam (Klonopin and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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