A 12-Month Randomized, Open-Label Study of the Metabolic Effects of Olanzapine and Risperidone in Psychotic Patients: Influence of Valproic Acid Augmentation

Herbert Y. Meltzer, MD; Stefania Bonaccorso, MD, PhD; William V. Bobo, MD, MPH; Yuejin Chen, MD, PhD; and Karuna Jayathilake, MS

ABSTRACT

Objective: Longitudinal data comparing the metabolic effects of olanzapine and risperidone with or without valproic acid supplementation in schizophrenic and bipolar patients are lacking.

Method: This study compares the metabolic effects of olanzapine and risperidone in a prospective, randomized, open-label trial in 160 patients with *DSM-IV-TR* schizophrenia, schizoaffective disorder, or bipolar disorder after 1, 3, 6, and 12 months' treatment. The study was conducted between 2000 and 2006. The primary analysis compared all patients randomized to olanzapine or risperidone; the primary outcome measure was changes in triglycerides (TG), and TG/high density lipoprotein cholesterol (HDL-C) ratio, a risk factor for ischemic cardiovascular disease. Secondary analyses included the effect of concomitant valproic acid.

Results: Significantly greater increases in weight ($F_{4,434}=4.7$), body mass index (BMI) ($F_{4,424}=5.1$), glycosylated hemoglobin (HgbA1c) ($F_{4,427}=4.3$), total cholesterol ($F_{4,429}=4.4$), TG ($F_{4,426}=5.9$), and TG/HDL-C ratio ($F_{4,426}=4.3$) ($P<.005$ for all drug × time interaction effects) were observed at all but the initial time points in the olanzapine- compared to the risperidone patients. Olanzapine/+valproic acid produced significantly greater increases in HgbA1c, BMI, weight, TG, and TG/HDL-C than olanzapine/–valproic acid at 3 and 6 months, while risperidone/+valproic acid produced significantly smaller increases in HgbA1c, BMI, and weight at 1, 3, and 6 months than risperidone/–valproic acid. The olanzapine/+valproic acid group had significantly greater BMI, and weight at 1, 3, and 6 months, and greater HgbA1c at 3 and 6 months, compared with the risperidone/+valproic acid group. There were too few patients treated with mood stabilizers other than valproic acid to analyze effects of any other mood stabilizer separately. Metabolic effects did not differ significantly by diagnostic category (schizophrenia/schizoaffective disorder vs bipolar disorder).

Conclusion: Further study of the metabolic effects of adjunctive valproic acid is indicated, as valproic acid may produce markedly different metabolic effects when combined with various antipsychotic drugs.

Trial Registration: clinicaltrials.gov Identifier: NCT00179062

J Clin Psychiatry 2011;72(12):1602–1610

Submitted: *January 22, 2010; accepted August 3, 2010.*
Online ahead of print: *July 12, 2011 (doi:10.4088/JCP.10m05997).*
Corresponding author: *Herbert Y. Meltzer, MD, 1601 23rd Ave South, Ste 3035, Nashville, TN 37212-8645 (Herbert.meltzer@vanderbilt.edu).*

Atypical antipsychotic drugs are widely used treatments for schizophrenia, schizoaffective disorder, and bipolar disorder. They vary in their propensity to cause adverse metabolic effects.[1–3] Clozapine and olanzapine have the greatest liability in this regard, followed by quetiapine, risperidone, paliperidone, asenapine, iloperidone, aripiprazole, and ziprasidone[1,3–6] according to short-term clinical trials and retrospective chart reviews,[7,8] large automated database studies,[9,10] and the Clinical Antipsychotic Trials of Intervention Effectiveness study.[11–13] A 1-year, open-label study of 235 schizophrenia patients reported significantly more patients randomized to olanzapine had ≥ 7% increases in weight compared to those randomized to risperidone.[14]

The interaction between antipsychotics and mood stabilizers remains largely unexplored.[15,16] This is important, because valproic acid, the mood stabilizer most often used in combination with antipsychotics,[16,17] is known to induce adverse metabolic side effects.[18–21] Valproic acid or lithium augmentation has been associated with increased weight gain[22–24] and topiramate with weight loss.[23] Differences with specific antipsychotic drugs have not been studied. A 4-week study of the combination of valproic acid with olanzapine or risperidone in schizophrenia patients failed to find any differences in weight gain, glucose levels, or cholesterol levels between olanzapine- or risperidone-treated patients, with or without valproic acid.[22]

There is concern about the morbidity and mortality associated with atypical antipsychotic drugs due to their metabolic side effects.[23] Insulin resistance, as measured by the ratio of triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) values (TG/HDL-C), has been proposed as a superior marker of metabolic adversity compared to metabolic syndrome criteria.[24,25] A TG/HDL-C ratio of ≥ 3.5 has been suggested to identify insulin-resistant individuals at higher risk for developing ischemic cardiovascular disease,[26–28] although its predictive power has been challenged.[29]

This 12-month open-label, multicenter, randomized comparison of olanzapine and risperidone on metabolic effects in patients with schizophrenia, schizoaffective disorder, or bipolar disorder was designed to address gaps in current knowledge. We hypothesized that treatment with risperidone would produce significantly less weight gain and adverse metabolic effects than olanzapine, although both drugs would increase them over time. To enhance relevance to clinical practice, the inclusion criteria permitted mood stabilizers at enrollment or subsequent addition. A preliminary report of these results has been provided elsewhere.[30] The effects of drug treatment on psychopathology will be reported separately.

METHOD

A cohort of 204 patients meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision[31] criteria for schizophrenia, schizoaffective disorder, or bipolar disorder from

6 community-based clinical sites in the United States was screened between 2000 and 2006, and 193 patients entered the study. Sample size was determined using data from the Janssen RIS-112 study of risperidone vs olanzapine (Data on file. RIS-USA-112. Janssen Pharmaceutica, Titusville, New Jersey; May 2000). Forty-nine randomized patients per treatment group provided 80% power ($\alpha = .05$) for detecting a difference in weight gain ≥ 7% from baseline (40% rate of weight gain of this magnitude in the olanzapine group vs 15% in the risperidone group). The study protocol was approved by the Institutional Review Boards of Vanderbilt University School of Medicine and individual sites. All subjects provided written informed consent. The protocol was registered on www.clinicaltrials.gov (NCT00179062).

Patient Population

Patients were 18 to 64 years of age. Those who had been treated with olanzapine, risperidone, or clozapine within 1 month of screening or who were antipsychotic naive were excluded. Patients receiving a mood stabilizer, antidepressant, anxiolytic medication, or a combination thereof were permitted to participate. Mood stabilizers were continued during the course of the study. Three of the valproic acid–treated patients were started on valproic acid therapy at the same time they were randomized to study drug. Patients with preexisting, stable type 2 diabetes mellitus were also eligible. Substance abuse but not dependence was permitted. eAppendix 1 at PSYCHIATRIST.COM details specific drugs taken at study entry.

Pharmacotherapy

After completing baseline metabolic and clinical assessments, patients were randomly assigned to oral risperidone (2–6 mg/d) or olanzapine (5–20 mg/d).

Outcome Measures

Body mass index (BMI), weight, blood pressure, total cholesterol, TG, HDL-C, low-density lipoprotein cholesterol (LDL-C), fasting blood glucose, and glycosylated hemoglobin (HgbA1c) levels were assessed at baseline, and at 1, 3, 6, and 12 months following antipsychotic initiation. Blood samples were obtained after a 12–14 hour fast and were analyzed by the Clinical Laboratory of Vanderbilt University Hospital. Clinically significant weight gain was defined as an increase in weight above baseline by ≥ 7%. Patients were weighed in the morning in the fasting state while wearing light clothing.

Baseline metabolic measurements were compared with a control sample of 443 healthy subjects.[32]

Statistical Methods

All statistical analyses were performed using SAS statistical software version 9.1 (SAS institute, Inc, Cary, North Carolina). The distribution of continuous variables was examined using SAS univariate procedures. Categorical variables were analyzed using χ^2 analysis. Treatment effects were analyzed using the SAS PROC MIXED procedure, adjusted for the baseline values of dependent variables included in the analysis. The "repeated" statement was used to model the variation in outcome measures over time across treatment groups, using time as the within-subjects factor and treatment group and valproic acid cotreatment status as between-subjects factors. There were no significant 4-way interactions for sex, treatment, valproic acid cotreatment status, or time for any of the variables of interest. There were no significant effects of race or age for any outcome measure. Within-groups changes in study endpoints included the 12-month follow-up except for valproic acid–cotreated patients in the olanzapine and risperidone groups because of small sample size. Clinically significant weight gain was compared using Fisher exact test. There were too few subjects who received treatment with mood stabilizers other than valproic acid to permit separate analyses of these drugs. All main effects were tested at a 2-tailed α level of .05. Effect size estimates were determined by the method of Cohen.[33] All analyses were adjusted for multiple comparisons using the method of Bonferroni.

RESULTS

Sample Characteristics and Treatment

The primary analyses reported here are those for patients who received olanzapine (n = 82) or risperidone (n = 78) and who had at least 1 follow-up evaluation after baseline assessment (Figure 1). Of those, 29 were receiving non–valproic-acid mood stabilizers at baseline (eAppendix 2).

Secondary analysis focused on olanzapine- (n = 67) or risperidone-treated patients (n = 64) who received either valproic acid or no concomitant mood stabilizer. No interactions between antidepressants and antipsychotic drugs with regard to metabolic measures were found. At baseline, 8 patients in the olanzapine group and 11 in the risperidone group were taking antihyperlipidemic agents, while 8 and 9 patients, respectively, in each group were taking antidiabetic drugs. Analyses of all subjects with follow-up data (n = 160) comparing olanzapine without valproic acid and risperidone without valproic acid with all mood stabilizers combined for each drug are presented in eAppendix 3. Nearly identical results concerning effects of olanzapine or risperidone and concomitant mood stabilizers on weight and metabolic endpoints were observed in this sample and in the 131-member sample that considered only the effects of concomitant valproic acid (discussed below).

The baseline clinical and demographic characteristics of the study sample included in the final analysis are presented in Table 1. There were no significant differences between the study sample and excluded subjects. Body mass index and TG, HDL-C, and LDL-C levels were significantly higher in both patient samples compared with the healthy controls.

There were no significant baseline differences in demographic characteristics or clinical diagnoses between patients randomized to olanzapine and those randomized to risperidone (Tables 1 and 2) or between olanzapine and risperidone patients with and without valproic acid. Patients who received either olanzapine or risperidone with

Figure 1. Disposition of Study Subjects Allocated to Olanzapine or Risperidone With or Without Valproic Acid for Whom There Were Baseline Metabolic Data (N = 160)

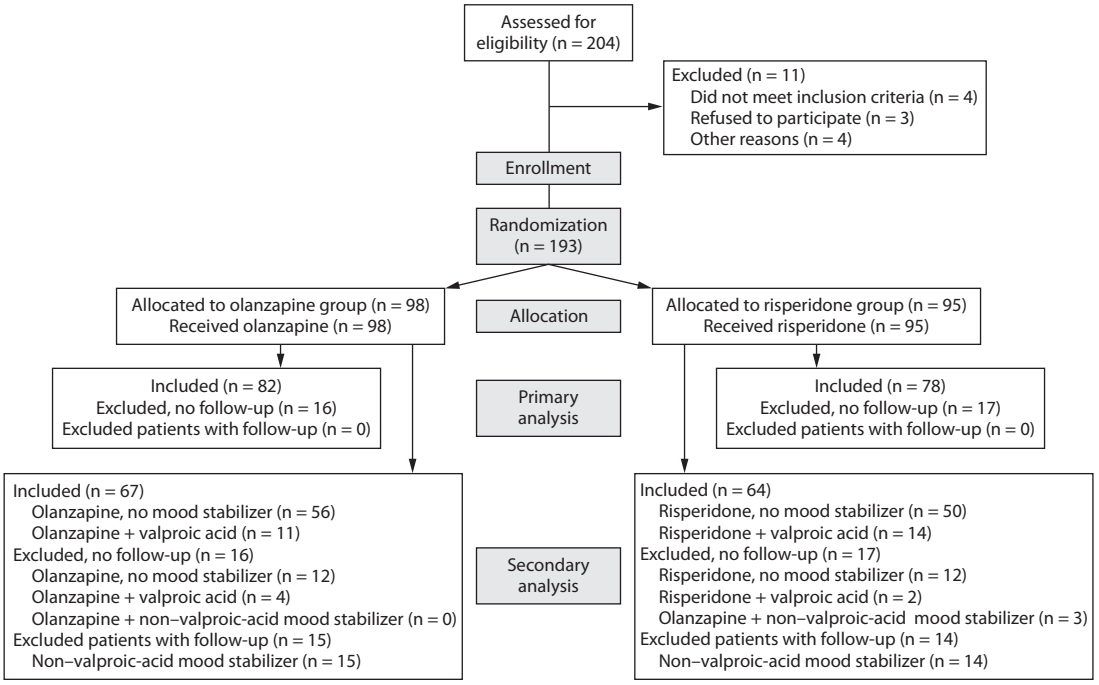


Table 1. Baseline Demographic and Clinical Characteristics of Patients (N = 160) Taking Olanzapine or Risperidone With or Without Valproic Acid[a]

	Total Sample		No Mood Stabilizers[a]		Valproic Acid Added[b]	
Characteristic	Olanzapine (n = 82)	Risperidone (n = 78)	Olanzapine (n = 56)	Risperidone (n = 50)	Olanzapine (n = 11)	Risperidone (n = 14)
Age, y	40.1 (10.8)	39.9 (11.4)	40.0 (11.0)	39.1 (11.7)	41.0 (10.3)	42.6 (10.4)
DSM-IV-TR diagnosis, n (%)						
Schizophrenia/ schizoaffective disorder	37 (45.1)	33 (42.3)	27 (48.2)	22 (44.0)	6 (54.5)	7 (50.0)
Bipolar disorder	45 (54.9)	45 (57.7)	29 (51.8)	28 (56.0)	5 (45.5)	7 (50.0)
Age at illness onset, y	24.3 (9.7)	22.1 (8.6)	24.8 (10.0)	22.7 (9.4)	21.5 (8.3)	20.2 (4.7)
Duration of illness, y	15.7 (11.0)	17.4 (10.4)	14.9 (10.8)	16.0 (10.2)	19.6 (12.0)	22.4 (9.4)
Prior hospitalizations, mean (SD)	3.7 (6.3)	3.9 (5.9)	2.9 (6.2)[b]	2.5 (3.8)[b]	8.2 (5.2)[b]	8.7 (9.0)[b]
Sex, n (%)						
Male	47 (57.3)	38 (48.7)	34 (60.7)	24 (48.0)	7 (63.6)	8 (57.1)
Female	35 (42.7)	40 (51.3)	22 (39.3)	26 (52.0)	4 (36.4)	6 (42.9)
Race, n (%)						
White	53 (64.6)	52 (66.7)	33 (58.9)	33 (66.0)	9 (81.8)	9 (64.3)
African American	25 (30.5)	25 (32.1)	20 (35.7)	16 (32.0)	2 (18.2)	5 (35.7)
Other	4 (4.9)	1 (1.2)	3 (5.4)	1 (2.0)	0	0
Diabetes, n (%)						
Yes	7 (8.5)	5 (6.4)	4 (7.1)	3 (6.0)	2 (18.2)	2 (14.3)
No	75 (91.5)	73 (93.6)	52 (92.9)	47 (94.0)	9 (81.8)	12 (85.7)

[a]Values are mean (SD) unless otherwise specified. [b]Patients who received olanzapine or risperidone with valproic acid cotreatment had significantly more prior hospitalizations than patients who received olanzapine or risperidone with no mood stabilizers ($F = 6.18$, $P = .0006$). No other comparisons were statistically significant.
Abbreviation: *DSM-IV-TR* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision.

valproic acid cotreatment had significantly more prior hospitalizations than those who received no concomitant mood stabilizers ($F = 6.18$, $P = .0006$).

Treatment and Disposition

The schizophrenia/schizoaffective disorder patients received ~25% and 36% higher doses of olanzapine and risperidone, respectively, than did bipolar disorder patients throughout the study (eAppendix 4). There were no significant differences in valproic acid use between patients with bipolar disorder (13.3%) and those with schizophrenia/schizoaffective disorder (18.6%), or between olanzapine- (13.4%) and risperidone-treated patients (17.9%).

Of the 160 patients with baseline and follow-up data, 81.3%, 61.3%, and 45.6% were retained at 3-, 6-, and 12-month follow-up, respectively (eAppendix 5). Dropout rates were independent of treatment group and valproic acid cotreatment status.

Dropouts at 6 months in the olanzapine group had significantly smaller increase in weight and BMI at 3 months compared with those who continued treatment (both comparisons, $P = .02$). There were no significant differences in weight change between early dropouts and patients who continued risperidone treatment.

BMI and Weight

In the primary analysis, there were significant drug, time, and drug × time interactions observed for both BMI

© Copyright 2011 Physicians Postgraduate Press, Inc.

Table 2. Anthropometric and Metabolic Measures for Subjects With Follow-Up Data (N = 160)[a,b]

Outcome Measure	Time Point, mo	Drug Treatment: Olanzapine (n = 82)	Drug Treatment: Risperidone (n = 78)	Between-Group Difference	Source (*F* Statistic, *P* Value, ES): Drug	Time	Drug × Time
Body mass index, kg/m^2	Baseline	28.9 (0.2)	29.0 (0.2)	NS	$F_{1,152}$ = 13.2; *P* = .0004	$F_{4,424}$ = 12.0; *P* = .0001	$F_{4,424}$ = 5.1; *P* = .0005; ES = 0.22
	1	29.7 (0.2)**	29.3 (0.2)	NS			
	3	30.2 (0.2)****	29.5 (0.2)*	.04			
	6	30.8 (0.2)****	29.2 (0.3)	.0001			
	12	30.9 (0.3)****	29.6 (0.3)	.003			
Weight, lb	Baseline	187.2 (1.2)	187.4 (1.3)	NS	$F_{1,157}$ = 12.6; *P* = .0005	$F_{4,434}$ = 13.9; *P* = .0001	$F_{4,434}$ = 4.7; *P* = .0009; ES = 0.21
	1	191.7 (1.2)***	189.6 (1.3)	NS			
	3	195.1 (1.3)****	190.6 (1.4)*	.02			
	6	199.1 (1.5)****	189.2 (1.6)	.0001			
	12	199.5 (1.8)****	192.6 (1.9)*	.009			
Fasting blood glucose level, mg/dL	Baseline	101.4 (2.6)	101.2 (2.6)	NS	$F_{1,157}$ = 3.1; *P* = NS	$F_{4,427}$ = 3.3; *P* = NS	$F_{4,427}$ = 1.9; *P* = NS
	1	104.4 (2.6)	100.4 (2.7)	NS			
	3	106.7 (2.9)	103.2 (3.0)	NS			
	6	115.0 (3.2)****	101.3 (3.4)	.003			
	12	111.2 (3.8)*	108.2 (3.9)	NS			
HgbA1c level, %	Baseline	5.7 (0.1)	5.7 (0.1)	NS	$F_{1,157}$ = 12.7; *P* = .0005	$F_{4,427}$ = 5.3; *P* = .0004	$F_{4,427}$ = 4.3; *P* = .002; ES = 0.20
	1	5.8 (0.1)	5.6 (0.1)	NS			
	3	5.9 (0.1)**	5.5 (0.1)*	.0001			
	6	6.0 (0.1)****	5.7 (0.1)	.0006			
	12	6.0 (0.1)****	5.8 (0.1)	.03			
Total cholesterol level, mg/dL	Baseline	184.8 (2.9)	185.2 (3.0)	NS	$F_{1,157}$ = 25.1; *P* = .0001	$F_{4,429}$ = 2.3; *P* = NS	$F_{4,429}$ = 4.4; *P* = .002; ES = 0.20
	1	201.8 (3.0)****	183.7 (3.0)	.0001			
	3	194.7 (3.3)**	180.9 (3.4)	.004			
	6	198.6 (3.7)***	179.0 (4.0)	.0003			
	12	196.7 (4.6)*	176.1 (4.6)	.002			
HDL-C level, mg/dL	Baseline	47.1 (0.9)	47.5 (0.9)	NS	$F_{1,157}$ = 4.4; *P* = NS	$F_{4,430}$ = 3.1; *P* = NS	$F_{4,430}$ = 1.8; *P* = NS
	1	48.4 (0.9)	46.8 (0.9)	NS			
	3	47.5 (1.0)	45.3 (1.0)	NS			
	6	44.9 (1.1)	44.2 (1.2)**	NS			
	12	48.7 (1.4)	43.7 (1.4)**	.01			
LDL-C level, mg/dL	Baseline	106.9 (2.2)	107.5 (2.3)	NS	$F_{1,150}$ = 6.7; *P* = NS	$F_{4,394}$ = 3.5; *P* = .009	$F_{4,394}$ = 2.4; *P* = NS
	1	120.0 (2.3)	108.6 (2.3)	.0006			
	3	108.3 (2.6)****	106.7 (2.6)	NS	NS		
	6	112.6 (3.0)	104.6 (3.0)	NS			
	12	112.3 (3.6)	105.5 (3.5)	NS			
TG level, mg/dL	Baseline	152.3 (8.8)	152.7 (9.0)	NS	$F_{1,156}$ = 24.3; *P* = .0001	$F_{4,426}$ = 6.7; *P* = .0001	$F_{4,426}$ = 5.9; *P* = .0001; ES = 0.24
	1	174.8 (9.0)*	141.2 (0.1)	.009			
	3	200.1 (9.8)****	146.4 (10.2)	.0002			
	6	235.5 (10.9)****	156.6 (11.7)	.0001			
	12	197.9 (13.4)**	137.3 (13.6)	.002			
Log TG level, mg/dL	Baseline	4.9 (0.04)	4.9 (0.04)	NS	$F_{1,156}$ = 32.4 *P* = .0001	$F_{4,426}$ = 5.9; *P* = .0001	$F_{4,426}$ = 5.7; *P* = .0002; ES = 0.23
	1	5.0 (0.04)**	4.8 (0.04)	.0001			
	3	5.1 (0.04)***	4.8 (0.04)	.0001			
	6	5.2 (0.05)****	4.9 (0.05)	.0001			
	12	5.1 (0.06)****	4.8 (0.06)	.0001			
TG/HDL-C	Baseline	3.7 (0.3)	3.7 (0.3)	NS	$F_{1,156}$ = 16.2; *P* = .0001	$F_{4,426}$ = 6.8; *P* = .0001	$F_{4,426}$ = 4.3; *P* = .002; ES = 0.20
	1	4.2 (0.3)	3.5 (0.3)				
	3	5.2 (0.3)	3.7 (0.3)				
	6	6.2 (0.3)	4.0 (0.4)				
	12	5.0 (0.4)	3.6 (0.4)				

[a]Values are least-squares means (SE) unless otherwise specified. [b]Adjustment of significant *P* values was made using the method of Bonferroni.
****$P \leq .0001$, ***$P \leq .001$, **$P \leq .01$, *$P < .05$, †$P < .08^{(trend)}$ for within-group comparison for each time point against the baseline values.
Abbreviations: ES = effect size, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, log TG = logarithmically transformed values for triglyceride levels, NS = not significant, TG = triglyceride levels.

and body weight after Bonferroni correction (Table 2). There were significant increases in BMI and weight from baseline at all time points in the olanzapine group, but only at 3 (BMI and weight) and 12 months (weight) in the risperidone group. Increases in weight and BMI were significantly greater with olanzapine than with risperidone at 6 and 12 months.

The secondary analysis of concomitant valproic acid showed a significant drug × valproic acid cotreatment × time interaction for both BMI and body weight (Figure 2A; Table 3). Peak increases in BMI occurred at 6 months in both the risperidone without valproic acid and olanzapine without valproic acid groups. An important difference in the effect of valproic acid cotreatment with the 2 antipsychotic

drugs was noted: BMI was significantly greater in the olanzapine patients who received valproic acid (olanzapine plus valproic acid) compared with those who received olanzapine without valproic acid at 3 ($P = .05$, effect size [ES] = 0.23) and 6 months ($P < .0001$, ES = 0.47). In contrast, risperidone without valproic acid was associated with significantly greater weight gain than risperidone plus valproic acid at 1 ($P = .04$, ES = 0.25), 3 ($P < .001$, ES = 0.39), and 6 months ($P = .003$, ES = 0.35). Consequently, olanzapine plus valproic acid was associated with significantly higher BMI than risperidone plus valproic acid at 1 ($P = .01$, ES = 0.30), 3 ($P < .001$, ES = 0.54), and 6 months ($P < .001$, ES = 0.76). Similar results were found for weight (Table 3). Significantly greater proportions of patients with clinically significant weight gain were observed for olanzapine without valproic acid compared with risperidone without valproic acid at 6 months ($\chi^2 = 6.8$, $P = .009$) and 12 months ($\chi^2 = 5.4$, $P = .02$), and for olanzapine plus valproic acid vs risperidone plus valproic acid at 6 ($P = .002$) and 12 months ($P = .007$) (Figure 2B). By 12 months, 63% of all patients who received olanzapine plus valproic acid experienced clinically significant weight gain, producing a near-linear increase in clinically significant weight gain beginning at 1 month. Only 1 subject in the risperidone plus valproic acid group experienced clinically significant weight gain.

Fasting Blood Glucose and Glycosylated Hemoglobin

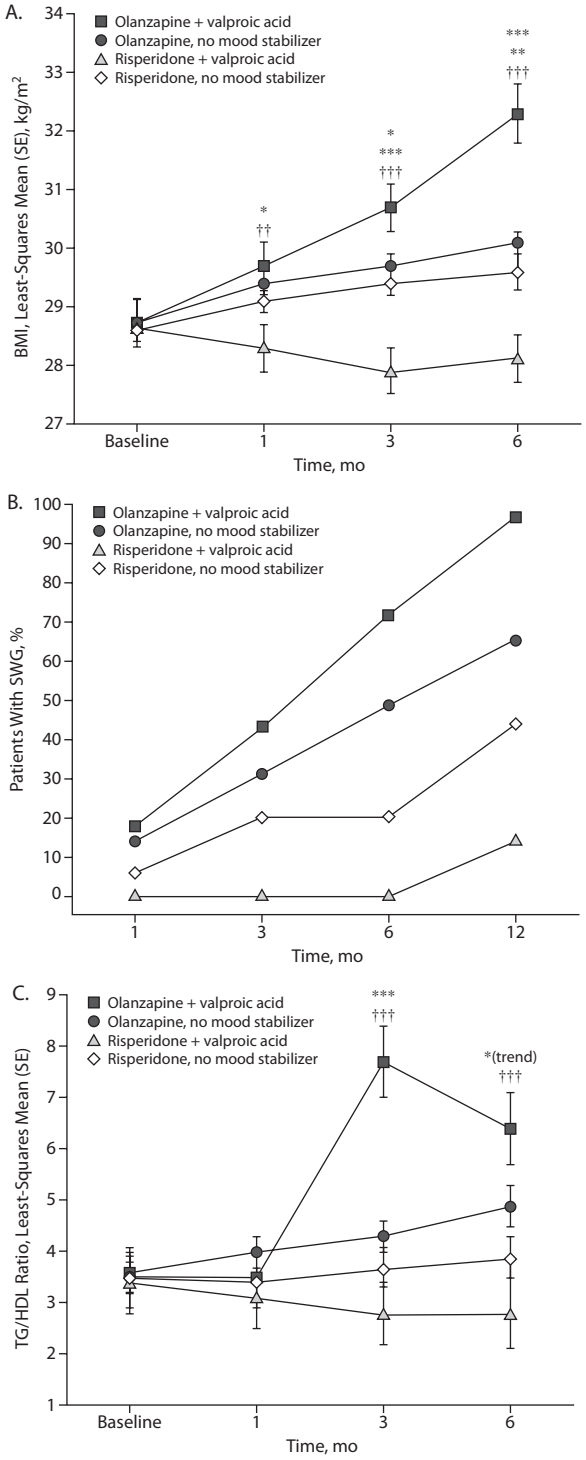
Significant drug, time, and drug × time interactions were found for HgbA1c, but not fasting glucose, comparing all randomized patients (Table 2) after Bonferroni adjustment. Significant increases in HgbA1c from baseline were observed with olanzapine at 3-, 6-, and 12-month follow-up and at 3 months with risperidone. Least-squares mean HgbA1c values were significantly higher for olanzapine at 3 and 6 months. Fasting glucose levels increased significantly only in the olanzapine patients, at 6 and 12 months.

In the secondary analysis of valproic acid effects, there were significant 3-way interaction effects for HgbA1c levels ($F_{3,292} = 5.2$, $P = .002$, ES = 0.27) (Table 3). HgbA1c levels were significantly greater in the olanzapine without valproic acid group vs the risperidone without valproic acid group at 3 ($P = .02$, ES = 0.25) and 6 months ($P = .02$, ES = 0.29). Olanzapine plus valproic acid was associated with significantly higher HgbA1c levels than risperidone plus valproic acid at 3 ($P < .001$, ES = 0.41) and 6 months ($P < .001$, ES = 0.57). Risperidone without valproic acid was associated with significantly higher HgbA1c values at 6 months ($P = .003$, ES = 0.35) than risperidone plus valproic acid.

Fasting Lipids

There were significant drug × time interaction effects for total cholesterol levels, TG levels, logarithmically transformed TG levels, and the TG/HDL-C ratio (Table 2). Each of these measures increased significantly with olanzapine, but not risperidone. No significant changes in HDL-C or LDL-C occurred in either group, except 3-month LDL-C

Figure 2. Changes in (A) Body Mass Index, (B) Proportion of Patients With Clinically Significant Weight Gain,[a] and (C) Triglycerides/High-Density Lipoprotein Cholesterol Ratio[b,c,d,e]



[a]Clinically significant weight gain (SWG) was defined as an increase in weight ≥7% above baseline value. [b]Olanzapine + valproic acid vs olanzapine, no mood stabilizer: $*^{(trend)}P \le .07$; $*P \le .05$, $**P \le .01$, $***P \le .001$. [c]Olanzapine, no mood stabilizer vs risperidone, no mood stabilizer: $\dagger\dagger P \le .01$, $\dagger\dagger\dagger P \le .001$. [d]Risperidone + valproic acid vs risperidone, no mood stabilizer: $*^{(trend)}P \le .07$; $*P \le .05$, $**P \le .01$, $***P \le .001$. [e]Olanzapine + valproic acid vs risperidone + valproic acid: $\dagger\dagger P \le .01$, $\dagger\dagger\dagger P \le .001$.

Abbreviations: BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, TG = triglycerides.

© Copyright 2011 Physicians Postgraduate Press, Inc.

Table 3. Anthropometric and Metabolic Measures for Subjects With Follow-Up Data (n = 131)[a,b]

		Olanzapine		Risperidone		Source (*F* Statistic, *P* Value)			
Outcome Measure	Time Point, mo	No Mood Stabilizer (n = 56)	Valproic Acid (n = 11)	No Mood Stabilizer (n = 50)	Valproic Acid (n = 14)	Time	Drug × Time	Valproic Acid Cotreatment Status × Time	Drug × Valproic Acid Cotreatment Status × Time
Body mass index, kg/m^2	Baseline	28.6 (0.18)	28.7 (0.43)	28.6 (0.19)	28.7 (0.38)	$F_{3,290}$ = 16.0; *P* = .0001	$F_{3,290}$ = 12.5; *P* = .0001	$F_{3,290}$ = 1.1; *P* = NS	$F_{3,290}$ = 7.3; *P* = .0001
	1	29.4 (0.18)****	29.7 (0.43)*	29.1 (0.19)*	28.3 (0.38)				
	3	29.7 (0.20)****	30.7 (0.47)***	29.4 (0.22)**	27.9 (0.39)†				
	6	30.1 (0.23)****	32.3 (0.50)****	29.6 (0.26)***	28.1 (0.42)				
Weight, lb	Baseline	185.5 (1.2)	185.9 (2.7)	185.6 (1.3)	186.1 (2.4)	$F_{3,295}$ = 18.6; *P* < .0001	$F_{3,295}$ = 14.1; *P* < .0001	$F_{3,295}$ = 1.4; *P* = NS	$F_{3,295}$ = 10.1; *P* < .0001
	1	190.4 (1.2)***	192.9 (2.7)*	189.1 (1.3)*	183.5 (2.4)				
	3	192.6 (1.3)****	200.5 (3.1)****	190.9 (1.5)***	180.1 (2.5)*				
	6	195.0 (1.5)****	211.6 (3.2)****	192.5 (1.7)***	182.5 (2.7)				
Fasting glucose level, mg/dL	Baseline	102.8 (3.3)	102.8 (7.4)	102.7 (3.5)	102.7 (6.5)	$F_{3,292}$ = 1.6; *P* = NS	$F_{3,292}$ = 2.0; *P* = NS	$F_{3,292}$ = 0.9; *P* = NS	$F_{3,292}$ = 0.4; *P* = NS
	1	106.5 (3.3)	99.1 (7.4)	101.3 (3.6)	96.3 (6.5)				
	3	107.4 (3.6)	115.5 (9.0)	104.7 (4.0)	101.8 (7.0)				
	6	118.0 (4.1)**	114.3 (8.5)	104.3 (4.6)	92.6 (7.6)				
HgbA1c level, %	Baseline	5.7 (0.1)	5.7 (0.2)	5.7 (0.1)	5.7 (0.1)	$F_{3,292}$ = 2.4; *P* = .07	$F_{3,292}$ = 7.9; *P* = .0001	$F_{3,292}$ = 0.6; *P* = NS	$F_{3,292}$ = 5.2; *P* = .002
	1	5.8 (0.1)	5.8 (0.2)	5.7 (0.1)	5.6 (0.1)				
	3	5.9 (0.1)	6.3 (0.2)**	5.6 (0.1)	5.5 (0.1)				
	6	6.0 (0.1)**	6.5 (0.2)***	5.9 (0.1)	5.3 (0.2)*				
Total cholesterol level, mg/dL	Baseline	185.3 (3.0)	183.7 (6.8)	185.2 (3.2)	185.1 (6.0)	$F_{3,294}$ = 1.8; *P* = NS	$F_{3,294}$ = 3.7; *P* = .01	$F_{3,294}$ = 0.6; *P* = NS	$F_{3,294}$ = 0.7; *P* = NS
	1	200.9 (3.0)****	203.7 (6.8)*	186.1 (3.2)	177.5 (6.0)				
	3	189.2 (3.3)	193.4 (7.9)	178.9 (3.7)	187.5 (6.4)				
	6	193.5 (3.8)†	190.9 (7.9)	180.5 (4.3)	184.9 (7.0)				
HDL-C level, mg/dL	Baseline	47.8 (1.0)	48.9 (2.2)	48.6 (1.0)	47.7 (2.0)	$F_{3,295}$ = 2.6; *P* = .053	$F_{3,295}$ = 1.0; *P* = NS	$F_{3,295}$ = 2.0; *P* = NS	$F_{3,295}$ = 1.5; *P* = NS
	1	48.7 (1.0)	47.2 (2.2)	49.1 (1.1)	42.6 (2.0)*				
	3	48.0 (1.1)	43.6 (2.6)†	46.5 (1.2)	44.7 (2.1)				
	6	45.5 (1.3)	43.9 (2.6)	45.6 (1.4)*	47.1 (2.3)				
LDL-C level, mg/dL	Baseline	107.3 (2.4)	104.4 (5.4)	107.4 (2.5)	106.6 (4.8)	$F_{3,278}$ = 3.6; *P* = .01	$F_{3,278}$ = 2.8; *P* = .04	$F_{3,278}$ = 1.1; *P* = NS	$F_{3,278}$ = 0.7; *P* = NS
	1	119.6 (2.5)***	122.4 (5.4)*	109.1 (2.6)	108.7 (4.8)				
	3	106.0 (2.8)	109.8 (7.3)	103.5 (3.0)	116.8 (5.2)				
	6	114.2 (3.2)†	108.6 (7.3)	104.2 (3.5)	111.0 (5.6)				
Triglycerides level, mg/dL	Baseline	144.1 (8.4)	144.1 (18.9)	144.1 (8.9)	144.0 (16.8)	$F_{3,293}$ = 6.5; *P* = .0003	$F_{3,293}$ = 8.0; *P* = .0001	$F_{3,293}$ = 1.8; *P* = NS	$F_{3,293}$ = 3.6; *P* < .05
	1	166.1 (8.5)*	155.6 (18.9)	141.0 (9.1)	122.2 (16.8)				
	3	170.3 (9.3)*	248.8 (21.9)****	144.9 (10.4)	120.9 (18.0)				
	6	191.3 (10.7)***	247.2 (21.1)****	152.6 (12.0)	127.1 (19.6)				
Log TG level, mg/dL	Baseline	4.8 (0.04)	4.8 (0.09)	4.8 (0.04)	4.9 (0.08)	$F_{3,293}$ = 4.5; *P* = .004	$F_{3,293}$ = 5.2; *P* = .002	$F_{3,293}$ = 0.4; *P* = NS	$F_{3,293}$ = 1.5; *P* = NS
	1	5.0 (0.04)**	4.9 (0.10)	4.7 (0.05)	4.7 (0.08)				
	3	5.0 (0.05)**	5.1 (0.11)*	4.8 (0.05)	4.7 (0.09)				
	6	5.1 (0.05)****	5.2 (0.11)**	4.9 (0.06)	4.8 (1.0)				
TG/HDL-C ratio	Baseline	3.6 (0.28)	3.5 (0.64)	3.5 (0.30)	3.4 (0.57)	$F_{3,293}$ = 7.0; *P* = .0001	$F_{3,293}$ = 8.4; *P* = .0001	$F_{3,293}$ = 2.4; *P* = .06	$F_{3,293}$ = 5.3; *P* = .002
	1	4.0 (0.29)	3.5 (0.64)****	3.4 (0.31)	3.1 (0.57)				
	3	4.3 (0.31)*	7.7 (0.74)***	3.7 (0.35)	2.8 (0.61)				
	6	4.9 (0.36)***	6.4 (0.74)****	3.9 (0.41)	2.8 (0.66)				

[a]Values are least-squares means (SE) unless otherwise specified. [b]There were too few patients cotreated with valproic acid at 12 months to permit valid between-group analyses in which valproic acid cotreatment status was a factor. ****$P \le .0001$, ***$P \le .001$, **$P \le .01$, *$P < .05$, †$P < .08^{(trend)}$ for within group comparison for each time point against the baseline values.

Abbreviations: HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, log TG = logarithmically transformed values for triglyceride levels, NS = not significant, TG = triglycerides.

with olanzapine, and 6- and 12-month HDL-C with risperidone. There were no significant between-groups differences in HDL-C or LDL-C at any time point except for significantly greater LDL-C with olanzapine at 1 month.

In the secondary analysis, there was a significant 3-way interaction effect for TG levels ($F_{3,293}$ = 3.6, *P* = .01, ES = 0.22) (Table 3). Olanzapine without valproic acid was associated with greater TG levels than risperidone without valproic acid at 1 (*P* < .05, ES = 0.23), 3 (*P* = .07, ES = 0.21), and 6 months (*P* = .02, ES = 0.28). Significantly higher TG levels were observed with olanzapine plus valproic acid compared with olanzapine without valproic acid at 3 (*P* = .001, ES = 0.39) and 6 months (*P* = .02, ES = 0.27). Risperidone plus valproic acid and risperidone without valproic acid groups did not differ significantly with respect to TG levels. The olanzapine plus valproic acid group had significantly higher TG values than the risperidone plus valproic acid group at 3 (*P* < .001, ES = 0.53) and 6 months (*P* < .001, ES = 0.48).

The 3-way interaction effect involving valproic acid was also significant for the TG/HDL-C ratio ($F_{3,293}$ = 5.3, *P* < .01, ES = 0.27) (Table 3; Figure 2C). The olanzapine without valproic acid group had a marginally higher TG/HDL-C ratio than the risperidone without valproic acid group at 6 months (*P* = .06) only. The TG/HDL-C ratio in the olanzapine plus valproic acid group was significantly greater than that of subjects treated with olanzapine without valproic acid at 3 months (*P* < .0001, ES = 0.50) and marginally so at 6 months (*P* = .07, ES = 0.21). There were no significant

differences in TG/HDL-C ratio between risperidone without valproic acid and risperidone plus valproic acid groups at any time point. Notably, the olanzapine plus valproic acid group had significantly higher TG/HDL-C levels than the risperidone plus valproic acid group at 3 ($P < .001$, ES = 0.60) and 6 months ($P < .001$, ES = 0.43).

Effects of Treatment by Diagnostic Group

There was a significant 3-way interaction effect for HgbA1c ($F_{4,419} = 3.7$, $P = .006$) due to a large increase in HgbA1c in the bipolar disorder patients who received olanzapine. There were no significant effects by diagnostic group on remaining metabolic endpoints.

DISCUSSION

Olanzapine produced significantly greater increases in weight, BMI, HgbA1c levels, TG levels, and the TG/HDL-C ratio than risperidone, particularly so in patients who received concomitant valproic acid. However, there were clear differences between the effects of the 2 antipsychotic drugs even in those not receiving valproic acid, eg, with regard to significant weight gain and HgbA1c levels. These differences were equally evident in bipolar and schizophrenic patients and men and women. Valproic acid diminished the adverse metabolic effects of risperidone and exacerbated those associated with olanzapine. To our knowledge, this is the first report of antipsychotic/mood stabilizer interaction for metabolic outcomes. Olanzapine and risperidone began to differentiate at 1 month for lipid measures and at 3 months for anthropometric measures, and they widened at later time points. Differences in HgbA1c levels first became significant at 6 months. Olanzapine without valproic acid produced significantly greater frequency of significant weight gain than did risperidone without valproic acid throughout the study.

Mood stabilizers were permitted as part of this protocol because they are commonly combined with antipsychotics,[16,34] and no evidence of metabolic interactions was available at the time the study was planned. An estimated 47.1% of hospitalized psychotic patients receive concomitant mood stabilizer and antipsychotic treatment.[35,36] In our sample, the olanzapine plus valproic acid group experienced the greatest weight gain. In agreement with our results, 1 prior study found that valproic acid did not significantly affect metabolic measures during antipsychotic treatment over 1 month follow-up.[22] Thus, short-term monitoring is inadequate to detect the metabolic effects of antipsychotic/mood stabilizer cotreatment. Casey et al[37] reported significantly greater mean weight gain and decrease in LDL-C levels in patients with schizophrenia who received either olanzapine or risperidone plus divalproex extended-release compared to olanzapine or risperidone monotherapy, respectively, in a 12-week study.

While there were no significant differences in fasting blood glucose levels between antipsychotic treatment groups with or without valproic acid, HgbA1c levels significantly increased in the olanzapine group after 6 months, particularly in patients who received concomitant valproic acid. The greatest increases in HgbA1c levels were observed in the olanzapine plus valproic acid group. Increases in HgbA1c levels of 1% are associated with increase in mortality related to cardiovascular events.[38] HgbA1c levels have also been shown to more strongly predict risk of diabetes, cardiovascular disease, and all-cause mortality than fasting blood glucose levels in nondiabetic adults,[39] and they are now recommended for diabetes diagnosis.[40] The mean increase in HgbA1c levels in olanzapine plus valproic acid patients in this study was 0.8%. Monitoring HgbA1c levels as an index of the longer term metabolic effects of atypical antipsychotic drugs is thus supported.

There is no evidence to suggest that the metabolic effects of olanzapine or risperidone are due to a pharmacokinetic mechanism, as valproic acid did not alter the concentrations of risperidone or 9-hydroxyrisperidone in a pharmacokinetic study.[41] Valproic acid alone is associated with clinically significant weight gain, increases in TG levels, and insulin resistance.[17–20,42,43] The increases in weight, BMI, and other metabolic measures associated with olanzapine plus valproic acid are likely to reflect a pharmacodynamic interaction between these 2 drugs, since the influence of valproic acid on metabolic measures was the opposite in the risperidone patients.

A limitation of this study is the small number of patients treated with valproic acid. Thus, valproic acid interactions reported here could be chance findings. Moreover, we did not randomize patients to valproic acid treatment, and most patients had received valproic acid prior to randomization to olanzapine or risperidone. However, there were no differences in demographic and clinical characteristics between risperidone plus valproic acid and risperidone without valproic acid groups, a fact that provides some buffering against confounding by measurable factors. Clearly, the observed antipsychotic-valproic acid interactions need independent replication. Strengths of this study include randomization to antipsychotic drug treatment, prospective assessment of metabolic effects of drug treatment, assessment of multiple metabolic parameters, and inclusion of schizophrenia, schizoaffective disorder, and bipolar disorder patients in a "real-world" treatment setting. Our results describe the evolution of the effects of olanzapine and risperidone over a 12-month period with the optimal time to detect the longer term effects of olanzapine being 6 months.

The importance of controlling for valproic acid coadministration is a major, if tentative, finding in this study, and it indicates the need for confirmation and study of the influence of valproic acid on other atypical antipsychotic drugs, especially clozapine,[44] which causes weight gain and lipid changes comparable to those of olanzapine.[2]

In conclusion, olanzapine produces significantly greater increases in weight/BMI, HgbA1c, and lipid measures associated with insulin resistance and potential cardiovascular morbidity, compared with risperidone, most notably with valproic acid cotreatment. The drug effects on metabolic

© Copyright 2011 Physicians Postgraduate Press, Inc.

measures were comparable in patients with schizophrenia/schizoaffective disorder and bipolar disorder. These conclusions with regard to valproic acid must be considered tentative because of the small number of valproic acid–treated patients. Additional studies of interactions between mood stabilizers and antipsychotics are warranted.

Drug names: aripiprazole (Abilify), asenapine (Saphris), carbamazepine (Carbatrol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), gabapentin (Neurontin and others), iloperidone (Fanapt), lamotrigine (Lamictal and others), lithium (Lithobid and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal and others), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal and others), topiramate (Topamax and others), valproic acid (Depaken, Stavzor, and others), ziprasidone (Geodon).

Author affiliations: Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, Tennessee (Drs Meltzer, Bobo, and Chen and Mr Jayathilake); and Institute of Psychiatry, King's College, London, United Kingdom (Dr Bonaccorso).

Author contributions: Dr Meltzer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Meltzer and Bonaccorso were responsible for study concept and design and Drs Bonaccorso and Chen for the acquisition of data. Drs Meltzer, Bonaccorso, and Bobo and Mr Jayathilake were responsible for analysis and interpretation of data and Drs Meltzer, Bonaccorso, Bobo, and Chen for the drafting of the manuscript. Drs Meltzer, Bonaccorso, and Bobo were responsible for the critical revision of the manuscript for important intellectual content and Mr Jayathilake for the statistical analysis. Dr Meltzer was responsible for obtaining funding and supervision of the study.

Potential conflicts of interest: **Dr Meltzer** is, or has been, a consultant or grantee to Abbott Laboratories, ACADIA, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, Litmus Molecular Design, Memory, Novartis, Organon, and Pfizer and has been a lecturer for Janssen and Pfizer. **Dr Bobo** has been a grantee of Cephalon and a lecturer for Janssen and Pfizer in the past. **Drs Bonaccorso** and **Chen** and **Mr Jayathilake** report no financial or other relationship relevant to the subject of this article.

Funding/support: This work was supported, in part, by a grant from Janssen Pharmaceuticals, and grants from NARSAD (to S.B. and Y.C.), the Ritter Foundation, and Mr. and Mrs Edward Hintz.

Acknowledgments: This study is dedicated to the memory of Daniel Blevins, medical science liaison of Janssen Pharmaceuticals. Without his assistance, this study could not have been done. The assistance of Kara L. Watts, MA, Vanderbilt University School of Medicine, as chief study coordinator, and Sarah Burnett, RN, Vanderbilt University School of Medicine, as research nurse was invaluable for completion of this study. Finally, we are most grateful to the patients of our study and to Ricardo Sainz-Fuertes, LMS, MSc, MRC Psych, Institute of Psychiatry, King's College, London, for assistance with manuscript revision. Mss Watts and Burnett and Dr Sainz-Fuertes report no financial or other relationship relevant to the subject of this article.

REFERENCES

1. Melkersson K, Dahl ML. Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. *Drugs*. 2004;64(7):701–723.
2. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs*. 2005; 19(suppl 1):1–93.
3. Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. *Mol Psychiatry*. 2008;13(1):27–35.
4. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. *J Clin Psychiatry*. 2004;65(2):267–272.
5. Henderson DC, Cagliero E, Copeland PM, et al. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *Arch Gen Psychiatry*. 2005;62(1):19–28.
6. Meyer JM, Koro CE. The effects of antipsychotic therapy on serum lipids: a comprehensive review. *Schizophr Res*. 2004;70(1):1–17.
7. Gentile S. Long-term treatment with atypical antipsychotics and the risk of weight gain: a literature analysis. *Drug Saf*. 2006;29(4):303–319.
8. Kabinoff GS, Toalson PA, Healey KM, et al. Metabolic issues with atypical antipsychotics in primary care: dispelling the myths. *Prim Care Companion J Clin Psychiatry*. 2003;5(1):6–14.
9. Alméras N, Després JP, Villeneuve J, et al. Development of an atherogenic metabolic risk factor profile associated with the use of atypical antipsychotics. *J Clin Psychiatry*. 2004;65(4):557–564.
10. Smith M, Hopkins D, Peveler RC, et al. First- v second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry*. 2008;192(6):406–411.
11. McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res*. 2005;80(1):19–32.
12. Meyer JM, Davis VG, Goff DC, et al. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: prospective data from phase 1. *Schizophr Res*. 2008;101(1-3):273–286.
13. Meyer JM, Nasrallah HA, McEvoy JP, et al. The Clinical Antipsychotic Trials Of Intervention Effectiveness (CATIE) Schizophrenia Trial: clinical comparison of subgroups with and without the metabolic syndrome. *Schizophr Res*. 2005;80(1):9–18.
14. Alvarez E, Ciudad A, Olivares JM, et al. A randomized, 1-year follow-up study of olanzapine and risperidone in the treatment of negative symptoms in outpatients with schizophrenia. *J Clin Psychopharmacol*. 2006; 26(3):238–249.
15. Stahl SM. Focus on antipsychotic polypharmacy: evidence-based prescribing or prescribing-based evidence? *Int J Neuropsychopharmacol*. 2004;7(2):113–116.
16. Stahl SM, Grady MM. A critical review of atypical antipsychotic utilization: comparing monotherapy with polypharmacy and augmentation. *Curr Med Chem*. 2004;11(3):313–327.
17. Ness-Abramof R, Apovian CM. Drug-induced weight gain. *Timely Top Med Cardiovasc Dis*. 2005;9:E31.
18. Isojärvi JI, Laatikainen TJ, Knip M, et al. Obesity and endocrine disorders in women taking valproate for epilepsy. *Ann Neurol*. 1996;39(5): 579–584.
19. Luef GJ, Lechleitner M, Bauer G, et al. Valproic acid modulates islet cell insulin secretion: a possible mechanism of weight gain in epilepsy patients. *Epilepsy Res*. 2003;55(1–2):53–58.
20. Pylvänen V, Knip M, Pakarinen A, et al. Serum insulin and leptin levels in valproate-associated obesity. *Epilepsia*. 2002;43(5):514–517.
21. Chengappa KN, Chalasani L, Brar JS, et al. Changes in body weight and body mass index among psychiatric patients receiving lithium, valproate, or topiramate: an open-label, nonrandomized chart review. *Clin Ther*. 2002;24(10):1576–1584.
22. Casey DE, Daniel DG, Wassef AA, et al. Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. *Neuropsychopharmacology*. 2003;28(1):182–192.
23. Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res*. 2005;80(1):45–53.
24. Reaven GM. The metabolic syndrome: requiescat in pace. *Clin Chem*. 2005;51(6):931–938.
25. Chapman MJ, Sposito AC. Hypertension and dyslipidaemia in obesity and insulin resistance: pathophysiology, impact on atherosclerotic disease and pharmacotherapy. *Pharmacol Ther*. 2008;117(3):354–373.
26. Jeppesen J, Hein HO, Suadicani P, et al. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. *Circulation*. 1998;97(11):1029–1036.
27. Jeppesen J, Hein HO, Suadicani P, et al. Low triglycerides-high high-density lipoprotein cholesterol and risk of ischemic heart disease. *Arch Intern Med*. 2001;161(3):361–366.
28. McLaughlin T, Reaven G, Abbasi F, et al. Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease? *Am J Cardiol*. 2005;96(3):399–404.
29. St-Pierre AC, Cantin B, Dagenais GR, et al. The triglyceride/high-density lipoprotein cholesterol ratio, the small dense low-density lipoprotein phenotype, and ischemic heart disease risk. *Metab Syndr Relat Disord*. 2004;2(1):57–64.
30. Meltzer HY. Focus on the metabolic consequences of long-term treatment with olanzapine, quetiapine and risperidone: are there differences? *Int J Neuropsychopharmacol*. 2005;8(2):153–156.
31. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Publishing, Inc; 2000.

32. Cheal KL, Abbasi F, Lamendola C, et al. Relationship to insulin resistance of the adult treatment panel III diagnostic criteria for identification of the metabolic syndrome. *Diabetes*. 2004;53(5):1195–1200.
33. Cohen J. *Statistical Power Analysis for the Behavioral Sciences. Revised Edition*. New York, NY: Academic Press; 1977.
34. Lin D, Mok H, Yatham LN. Polytherapy in bipolar disorder. *CNS Drugs*. 2006;20(1):29–42.
35. Citrome L, Levine J, Allingham B. Changes in use of valproate and other mood stabilizers for patients with schizophrenia from 1994 to 1998. *Psychiatr Serv*. 2000;51(5):634–638.
36. Citrome L, Jaffe A, Levine J, et al. Use of mood stabilizers among patients with schizophrenia, 1994–2001. *Psychiatr Serv*. 2002;53(10):1212.
37. Casey DE, Daniel DG, Tamminga C, et al. Divalproex ER combined with olanzapine or risperidone for treatment of acute exacerbations of schizophrenia. *Neuropsychopharmacology*. 2009;34(5):1330–1338.
38. Khaw KT, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk). *BMJ*. 2001;322(7277):15–18.
39. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med*. 2010;362(9):800–811.
40. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2010;33(suppl 1):S62–S69.
41. Spina E, Avenoso A, Facciolà G, et al. Plasma concentrations of risperidone and 9-hydroxyrisperidone: effect of comedication with carbamazepine or valproate. *Ther Drug Monit*. 2000;22(4):481–485.
42. Verrotti A, Greco R, Latini G, et al. Obesity and plasma concentrations of alpha-tocopherol and beta-carotene in epileptic girls treated with valproate. *Neuroendocrinology*. 2004;79(3):157–162.
43. Kim B, Kim SJ, Son JI, et al. Weight change in the acute treatment of bipolar I disorder: a naturalistic observational study of psychiatric inpatients. *J Affect Disord*. 2008;105(1–3):45–52.
44. Facciolà G, Avenoso A, Scordo MG, et al. Small effects of valproic acid on the plasma concentrations of clozapine and its major metabolites in patients with schizophrenic or affective disorders. *Ther Drug Monit*. 1999;21(3):341–345.

eAppendixes are available at PSYCHIATRIST.COM

eAppendix 1. Pretrial Medications by Diagnostic Group (N = 160)[a]

	Diagnostic Group	
Medication	Schizophrenia/ Schizoaffective Disorder (n = 70)	Bipolar Disorder (n = 90)
No previous antipsychotic drug, n[b]	34	67
Previous antipsychotic drug, n	36	23
Quetiapine	16	10
Ziprasidone	4	3
Aripiprazole	0	2
Typical neuroleptics	16	8
No previous valproic acid, n	59	80
Previous valproic acid, n	11	10

[a]Eligible patients who were treated with antipsychotics and/or valproic acid prior to study entry may have received treatment with multiple drugs listed in Table 1. As such, the pretrial drug treatment categories are not mutually exclusive.
[b]These patients were not taking an antipsychotic drug at the screening visit.

eAppendix 2. Adjunctive Non–Valproic-Acid Mood Stabilizers/Anticonvulsants Taken by Subjects Among All Patients With Schizophrenia/Schizoaffective Disorder or Bipolar Disorder Randomized to Receive Olanzapine or Risperidone (n = 193)[a,b]

	Treatment Group	
Mood Stabilizer/Anticonvulsant, n	Olanzapine (n = 98)	Risperidone (n = 95)
Carbamazepine	4	3
Gabapentin[c]	3	4
Oxcarbazepine	2	4
Lithium[c]	3	3
Lamotrigine	3	1
Topiramate[c]	4	4

[a]All values are numbers of patients who were taking individual mood stabilizers or anticonvulsants other than valproic acid at baseline. [b]A total of 29 patients were taking non–valproic-acid mood stabilizers/ anticonvulsants at the time of randomization and were continued on these medications during follow-up when deemed clinically appropriate by the study clinicians. Some patients took a combination of these, which is reflected in the numbers presented in this appendix. [c]On visual inspection of the limited data from this group, lithium appeared to be associated with increased weight, BMI, and TG/HDL-C ratio in the olanzapine group but not the risperidone group. Lithium was associated with a modest reduction in glycosylated hemoglobin observed in both the olanzapine- and risperidone-treated groups. Gabapentin was also associated with increases in weight and BMI in the olanzapine group but not the risperidone group. Topiramate was associated with a modest weight reduction in the olanzapine group and a reduction in BMI in both the olanzapine and risperidone groups. Note that these observations are based on only 3–4 patients per combination at 1–3 months and even fewer at 6 months.
Abbreviations: BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, TG = triglycerides.

doi:10.4088/JCP.10m05997
© Copyright 2011 Physicians Postgraduate Press, Inc.

eAppendix 3. Anthropometric and Metabolic Measures for All Subjects With Follow-Up Data (N = 160)[a]

Outcome Measure	Time Point, mo	Risperidone: No Mood Stabilizer (N = 50)	Risperidone: Any Mood Stabilizer[b] (N = 28)	Olanzapine: No Mood Stabilizer (N = 56)	Olanzapine: Any Mood Stabilizer[b] (N = 26)	Source (*F* Statistic, *P* Value): Time	Drug × Time	Mood Stabilizer[b] × Time	Drug × Mood Stabilizer[b] × Time
BMI, kg/m^2	Baseline	187.1 (1.6)	187.6 (2.1)	187.1 (1.5)	187.4 (2.2)	$F_{4,416} = 10.0$; $P = .0001$	$F_{4,416} = 6.5$; $P = .0001$	$F_{4,416} = 0.8$; P = NS	$F_{4,416} = 3.3$; $P = .01$
	1	190.7 (1.6)†	187.6 (2.1)	192.1 (1.5)**	191.0 (2.2)				
	3	192.6 (1.8)**	187.8 (2.2)	194.2 (1.6)****	197.1 (2.4)***				
	6	194.1 (2.5)**	181.9 (2.6)*	196.7 (1.8)****	203.7 (2.6)****				
	12	194.6 (2.5)**	189.8 (2.9)	199.9 (2.1)****	198.4 (3.3)***				
Weight, lb	Baseline	29.0 (0.2)	29.0 (0.3)	28.9 (0.2)	29.0 (0.3)	$F_{4,426} = 12.4$; $P = .0001$	$F_{4,426} = 6.5$; $P = .0001$	$F_{4,426} = 0.6$; P = NS	$F_{4,426} = 4.1$; $P = .003$
	1	29.5 (0.2)†	29.1 (0.3)	29.7 (0.2)**	29.5 (0.3)				
	3	29.7 (0.3)*	29.2 (0.4)	30.1 (0.3)****	30.4 (0.4)***				
	6	29.9 (0.3)**	28.1 (0.4)*	30.5 (0.3)****	31.4 (0.4)****				
	12	29.9 (0.4)*	29.2 (0.5)	31.0 (0.3)****	30.6 (0.5)***				
Fasting blood glucose level, mg/dL	Baseline	101.3 (3.3)	101.1 (4.4)	101.5 (3.1)	101.1 (4.6)	$F_{4,419} = 2.9$; $P = .02$	$F_{4,419} = 1.6$; P = NS	$F_{4,419} = 0.3$; P = NS	$F_{4,419} = 0.2$; P = NS
	1	99.9 (3.4)	101.0 (4.4)	105.2 (3.1)	102.6 (4.7)				
	3	103.3 (3.8)	102.9 (4.8)	106.0 (3.5)	108.5 (5.2)				
	6	103.1 (4.4)	98.6 (5.5)	116.7 (3.9)***	111.9 (5.4)†				
	12	109.9 (5.0)	105.7 (6.3)	110.5 (4.7)†	112.9 (6.9)				
HgbA1c level, %	Baseline	5.7 (0.1)	5.7 (0.1)	5.7 (0.1)	5.7 (0.1)	$F_{4,419} = 5.0$; $P = .0002$	$F_{4,419} = 5.7$; $P = .0002$	$F_{4,419} = 0.9$; P = NS	$F_{4,419} = 3.0$; $P = .02$
	1	5.6 (0.1)	5.6 (0.1)	5.8 (0.1)	5.7 (0.1)				
	3	5.6 (0.1)	5.5 (0.1)	5.8 (0.1)†	6.0 (0.1)**				
	6	5.8 (0.1)	5.5 (0.1)	5.9 (0.1)**	6.2 (0.1)****				
	12	5.9 (0.1)	5.6 (0.1)	6.0 (0.1)**	6.0 (0.1)*				
Total cholesterol level, mg/dL	Baseline	185.2 (3.7)	185.4 (5.0)	185.2 (3.5)	183.9 (5.2)	$F_{4,421} = 2.3$; $P = .06$	$F_{4,421} = 4.9$; $P = .0008$	$F_{4,421} = 1.9$; P = NS	$F_{4,421} = 0.8$; P = NS
	1	185.9 (3.8)	180.0 (5.0)	200.9 (3.6)***	204.0 (5.3)**				
	3	178.9 (4.4)	184.1 (5.5)	189.2 (3.9)	207.2 (5.9)***				
	6	180.6 (5.1)	176.6 (6.3)	193.4 (4.5)	208.7 (6.2)****				
	12	178.6 (5.9)	172.0 (7.4)	198.1 (5.5)*	193.8 (8.1)				
HDL-C level, mg/dL	Baseline	47.9 (1.1)	47.0 (1.5)	47.1 (1.1)	47.2 (1.6)	$F_{4,422} = 2.8$; $P = .03$	$F_{4,422} = 1.6$; P = NS	$F_{4,422} = 0.2$; P = NS	$F_{4,422} = 0.7$; P = NS
	1	48.5 (1.1)	44.0 (1.5)	48.0 (1.1)	49.3 (1.6)				
	3	45.9 (1.3)	44.2 (1.6)	47.3 (1.2)	48.0 (1.8)				
	6	45.0 (1.5)	43.0 (1.9)†	44.8 (1.4)	45.3 (1.8)				
	12	44.4 (1.8)†	42.5 (2.2)†	49.3 (1.6)	47.3 (2.4)				
LDL-C level, mg/dL	Baseline	107.6 (2.8)	107.3 (4.1)	107.6 (2.7)	105.6 (4.0)	$F_{4,386} = 3.0$; $P = .02$	$F_{4,386} = 2.1$; $P = .08$	$F_{4,386} = 1.6$; P = NS	$F_{4,386} = 0.3$; P = NS
	1	109.1 (2.9)	107.6 (4.1)	119.6 (2.8)***	120.7 (4.1)**				
	3	103.7 (3.3)	111.6 (4.3)	106.3 (3.0)	114.8 (5.3)				
	6	104.5 (3.9)	104.5 (4.9)	114.2 (3.6)	109.2 (5.5)				
	12	106.0 (4.5)	104.6 (5.6)	115.3 (4.3)	104.7 (6.9)				
TG level, mg/dL	Baseline	150.1 (11.1)	157.1 (14.9)	152.0 (10.4)	153.0 (15.6)	$F_{4,418} = 9.4$; $P = .0001$	$F_{4,418} = 8.6$; $P = .0001$	$F_{4,418} = 2.9$; $P = .02$	$F_{4,418} = 3.6$; $P = .007$
	1	146.9 (11.3)	131.4 (14.9)	174.4 (10.6)†	176.2 (15.8)				
	3	150.8 (12.8)	139.3 (16.2)	178.1 (11.4)†	252.9 (17.6)****				
	6	159.0 (14.8)	152.8 (18.4)	199.4 (13.2)**	304.3 (18.0)****				
	12	144.8 (17.0)	125.2 (21.5)	181.9 (15.8)†	231.9 (23.4)**				
Log TG level, mg/dL	Baseline	4.8 (0.05)	4.8 (0.1)	4.9 (0.05)	4.9 (0.1)	$F_{4,418} = 6.5$; $P = .0001$	$F_{4,418} = 6.4$; $P = .0001$	$F_{4,418} = 0.9$; P = NS	$F_{4,418} = 1.7$; P = NS
	1	4.8 (0.1)	4.8 (0.1)	5.0 (0.05)**	5.0 (0.1)				
	3	4.8 (0.1)	4.9 (0.1)	5.0 (0.1)**	5.2 (0.1)**				
	6	4.9 (0.1)	4.9 (0.1)	5.1 (0.1)***	5.4 (0.1)****				
	12	4.8 (0.1)	4.7 (0.1)*	5.1 (0.1)**	5.1 (0.1)*				
TG/HDL-C ratio	Baseline	3.7 (0.4)	3.8 (0.5)	3.7 (0.3)	3.7 (0.5)	$F_{4,418} = 9.2$; $P = .0001$	$F_{4,418} = 6.7$; $P = .0001$	$F_{4,418} = 2.4$; $P = .05$	$F_{4,418} = 3.3$; $P = .01$
	1	3.6 (0.4)	3.3 (0.5)	4.2 (0.3)	4.2 (0.5)				
	3	3.8 (0.4)	3.4 (0.5)	4.5 (0.4)†	6.7 (0.6)****				
	6	4.1 (0.5)	3.9 (0.6)	5.1 (0.4)**	8.2 (0.6)****				
	12	3.7 (0.5)	3.4 (0.7)	4.4 (0.5)	6.3 (0.7)**				

[a]Values are least-squares means (SE) unless otherwise specified. [b]Mood stabilizer cotreatment (including valproic acid and any drug listed in eAppendix 1).

****$P \leq .0001$, ***$P \leq .001$, **$P \leq .01$, *$P < .05$, †$P < .08$ (trend) for within-group comparison for each time point against the baseline values.

Abbreviations: BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, log TG = logarithmically transformed values for triglyceride levels, TG = triglycerides.

doi:10.4088/JCP.10m05997
© Copyright 2011 Physicians Postgraduate Press, Inc.

eAppendix 4. Dosages of Olanzapine, Risperidone, and Valproic Acid Used During Follow-Up[a,b]

	Schizophrenia/Schizoaffective Disorder Daily Dosage, Mean (SD), mg/d			Bipolar Disorder Daily Dosage, Mean (SD), mg/d		
Time Point, mo	Olanzapine	Risperidone	Valproic Acid	Olanzapine	Risperidone	Valproic Acid
1	13.6 (5.0)**	4.4 (1.3)***	1,187.5 (555.2)	10.1 (4.7)	3.2 (1.5)	977.3 (596.4)
3	15.1 (4.6)**	4.8 (1.3)***	1,225.0 (606.1)	10.9 (5.3)	3.2 (1.6)	916.7 (530.3)
6	15.0 (5.2)*	5.1 (1.4)***	1,194.4 (704.6)	11.2 (5.4)	2.7 (1.4)	708.3 (245.8)
12	14.3 (5.1)	4.7 (1.0)***	1,125.0 (737.4)	11.2 (2.5)	2.7 (1.3)	625.0 (322.7)

[a]Mean (SD) daily doses are provided (mg/d) for patients in each group who received concomitant valproic acid.
[b]*t* Test was used to compare mean doses of study drugs in patients with schizophrenia or schizoaffective disorder vs those with bipolar disorder: $*P < .05$, $**P \leq .01$, $***P \leq .001$.

eAppendix 5. Subject Retention During Follow-Up[a]

				Sample by Valproic Acid Cotreatment Status (n = 131)			
	Total Sample (N = 160)			No Concomitant Valproic Acid (n = 106)		Valproic Acid Added (n = 25)	
Time Point, mo	All Subjects n = 160	Olanzapine n = 82	Risperidone n = 78	Olanzapine n = 56	Risperidone n = 50	Olanzapine n = 11	Risperidone n = 14
3	130 (81.3)	68 (82.9)	62 (79.5)	47 (83.9)	36 (72.0)	8 (72.7)	13 (92.9)
6	98 (61.3)	52 (63.4)	46 (59.0)	34 (60.7)	26 (52.0)	7 (63.6)	10 (71.4)
12	73 (45.6)	40 (48.8)	33 (42.3)	24 (42.9)	18 (36.0)	4 (36.4)	7 (50.0)

[a]All values are n (%).

doi:10.4088/JCP.10m05997