Aripiprazole Added to Overweight and Obese Olanzapine-Treated Schizophrenia Patients

David C. Henderson, MD,† Xiaoduo Fan, MD, MS,*† Paul M. Copeland, MD,† Bikash Sharma, MBBS,* Christina P. Borba, MPH,* Ryan Boxill, PhD,*† Oliver Freudenreich, MD,*† Corinne Cather, PhD,*† A. Eden Evins, MD,*† and Donald C. Goff, MD*†*

Abstract: Olanzapine treatment has been associated with clinically meaningful weight increases, hypertriglyceridemia, insulin resistance, and diabetes mellitus. There are few options for olanzapine responders who fail other antipsychotic agents. Aripiprazole is a potent (high-affinity) partial agonist at D_2 and 5-HT_{1A} receptors and a potent antagonist at 5-HT_{2A} receptor and is associated with less weight gain than olanzapine. We report the results of a 10-week placebo-controlled, double-blind crossover study that examined 15 mg/d aripiprazole's effects on weight, lipids, glucose metabolism, and psychopathology in overweight and obese schizophrenia and schizoaffective disorder subjects treated with a stable dose of olanzapine. During the 4 weeks of aripiprazole treatment, there were significant decreases in weight ($P = 0.003$) and body mass index ($P = 0.004$) compared with placebo. Total serum cholesterol ($P = 0.208$), high-density lipoprotein cholesterol (HDL-C; $P = 0.99$), HDL-2 ($P = 0.08$), HDL-3 ($P = 0.495$), and low-density lipoprotein cholesterol ($P = 0.665$) did not change significantly comparing aripiprazole treatment to placebo treatment. However, total serum triglycerides ($P = 0.001$), total very low-density lipoprotein cholesterol (VLDL-C; $P = 0.01$), and VLDL-1C and VLDL-2C ($P = 0.012$) decreased significantly during the aripiprazole treatment phase. The VLDL-3C tended lower during aripiprazole, but the decrease was not significant ($P = 0.062$). There was a decrease in C-reactive protein comparing aripiprazole treatment to placebo, although it did not reach significance ($P = 0.087$). The addition of aripiprazole to a stable dose of olanzapine was well tolerated and resulted in significant improvements on several outcome measures that predict risk for medical morbidity.

Key Words: aripiprazole, olanzapine, schizophrenia, lipid metabolism, medical morbidity

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In early clinical trials, olanzapine treatment was associated with clinically meaningful weight increases (greater than 7% of baseline weight) in 31.7% of patients who were underweight, 18% of normal weight patients, and 11% of overweight patients.[1] In 4 studies, the mean incidence of weight gain of 7% or greater was 40.5% in patients treated with olanzapine compared with 12.4% of those receiving haloperidol and 3.1% of those receiving placebo.[1] A study of 25 olanzapine-treated inpatients demonstrated a mean weight gain of 12 lb after 12 weeks on a mean olanzapine dose of 13.8 mg.[2] Another study found that 94% of day-treatment patients treated with olanzapine (mean dose, 14.1 mg) experienced weight gain of greater than 7%. The mean weight gain was 22.1 lb over 7 months, although the weight gain correlated with clinical response.[3]

Hypertriglyceridemia has been linked to olanzapine therapy.[4,5] Melkersson and Dahl[6] also assessed 34 schizophrenia patients treated with either clozapine or olanzapine and observed hyperinsulinemia and hyperlipidemia (elevated triglyceride and total cholesterol) in both groups with a positive correlation with clozapine serum levels but not its metabolites. Atmaca et al[7] examined 56 subjects treated with atypical antipsychotic agents and observed a significant increase in weight and triglyceride levels in olanzapine-treated groups. Sheitman et al[8] reported an increase in serum triglyceride from baseline to 16-month reassessment, where triglycerides increased more than 40% whereas cholesterol remained essentially unchanged. Osser et al[2] compared 25 subjects at baseline and 12 weeks after olanzapine initiation; both weight (mean, 12 lb) and fasting triglycerides (mean change, 60 mg/dL) significantly increased. There was a strong association between weight change and triglyceride change. Clozapine and olanzapine treatment have also been most closely associated with insulin resistance in both obese and nonobese patients with schizophrenia.[9–11]

Although switching to a more weight-neutral atypical antipsychotic agent offers promise in halting or reversing weight gain, many patients and their clinicians are reluctant to risk a worsening or return of psychotic symptoms and risk relapse.[12–15] Nonpharmacologic means of weight control have yielded mixed results.[16–18] A number of pharmacologic interventions have also been evaluated, including reboxetine,[19] fluoxetine,[20] sibutramine,[21] amantadine,[22] topiramate,[23] and metformin.[24,25] Aripiprazole is a potent (high-affinity) partial agonist at D_2[26] and 5-HT_{1A} receptors and a potent antagonist at 5-HT_{2A}[27] receptors. In a study of 24 patients with treatment-resistant schizophrenia who had aripiprazole added to decreased doses of clozapine, Karunakaran et al[28] reported an average weight loss of 5.1 kg over 34 weeks. A 6-week open-label trial to examine the effects of adjunctive aripiprazole in 10 clozapine-treated subjects observed a significant decrease in weight (from 219.4 ± 40.0 to 213.7 ± 38.3 lb) and triglycerides (from 274 ± 229 to 176 ± 106 mg/dL).[29]

We now present the results of a 10-week placebo-controlled, double-blind crossover study to examine aripiprazole's effects on weight, lipids, glucose metabolism, and psychopathology in overweight and obese schizophrenia and schizoaffective disorder subjects treated with a stable dose of olanzapine.

MATERIALS AND METHODS

Subjects were recruited from an urban community mental health clinic. The study was approved by the institutional review

From the *Schizophrenia Program, Massachusetts General Hospital; and †Harvard Medical School, Boston, MA.
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Reprints: David C. Henderson, MD, Freedom Trail Clinic, 25 Staniford St, Boston, MA 02114 (e-mail: dchenderson@partners.org).
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board of the Massachusetts Department of Mental Health. Outpatients between the ages of 18 and 65 years with the diagnosis of schizophrenia or schizoaffective disorders were included in the study after providing written informed consent. Patients with active substance abuse, pregnancy, significant medical illness (unstable cardiac disease, malignancy, severe liver, or renal impairment), and unstable psychiatric illness (Clinical Global Impression's severity of illness question of 5 or greater) were excluded from the study. Each patient underwent a diagnostic evaluation by a research psychiatrist (XF), using the *Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.[30] Eligibility was determined by interview, chart review for history and baseline vital signs, and laboratory values. Subjects were eligible for the study if their body mass index (BMI) was 30 kg/m^2 or greater or 27 kg/m^2 or greater with other risk factors (treatment of hypertension of blood pressure [BP] >140/90 mm Hg; lipid abnormalities: total cholesterol ≥200 mg/dL, triglyceride ≥150 mg/dL; or fasting glucose ≥100 mg/dL). Subjects had to be maintained on a stable dose of olanzapine for at least 1 month.

Anthropometric, BP, and Metabolic Assessments

A physical examination and medical history was performed at baseline, and measurements of vital signs, weight, height, BMI, and waist (suprailiac) and hip circumference were performed at each visit. Electrocardiograms were analyzed by the MGH Department of Cardiology at baseline and weeks 4, 6, and 10. Side effects were assessed at baseline and weeks 2, 4, 6, 8, and 10 using the Systematic Assessment for Treatment Emergent Events.[31] Energy expenditure and dietary intake were assessed at baseline and weeks 4, 6, and 10. Subjects were instructed to wear an accelerometer for 4 consecutive days to obtain an objective measure of physical activity. The raw data obtained from a single channel accelerometer (Actigraph model 7164; ActiGraph, Pensacola, Fla) were processed by custom data processing program to estimate energy expenditure.[32,33] During the same 4 days, the subjects maintained a 4-day food record of all food and beverages consumed. Fasting blood samples were assayed for a complete blood count and chemistries at baseline and weeks 4, 6, and 10 using standard laboratory procedures. Lipoprotein subfractionation profile, vertical auto profile (Atherotech Inc, Birmingham, Ala), was performed by Laboratory Corporation of America, (Labcorp, Burlington, NC). Fasting total plasma cholesterol and triglyceride levels were measured enzymatically,[34] with an intraassay coefficient of variation of 1.7% to 2.7% and 0.9% to 1.2%, respectively. Lipoproteins were measured by vertical density-gradient ultracentrifugation followed by measurement of the cholesterol distribution. The major lipoproteins and their subfractions were separated by density gradient centrifugation, and the cholesterol component of each fraction was measured.[35] The vertical auto profile measured low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglycerides, intermediate-density lipoprotein, and lipoprotein (a). The VLDL-C was separated into VLDL-1C and VLDL-2C, which are more buoyant and the main carriers of triglyceride; VLDL-3C are small, dense, atherogenic VLDL remnant particles. The HDL-2C confers the greatest degree of protection against coronary heart disease, and the HDL-3C is less protective. Insulin immunometric assay was performed with an Immulite Analyzer (Diagnostic Product Corporation, Los Angeles, Calif) with an intraassay coefficient of variation of 4.2% to 7.6%. The Homeostasis Model of Assessment of Insulin Resistance (HOMA-IR) was calculated by the following formula: fasting insulin (μU/mL) × fasting glucose (mg/dL)/22.5.[36]

Subjects were assessed with a battery of symptom rating scales at baseline and weeks 4, 6, and 10. The assessment battery was comprised of the Positive and Negative Syndrome Scale (PANSS), the Scale for Assessment of Negative Symptoms, the Hamilton Depression Rating Scale, the Global Assessment Scale, the Fatigue Scale Inventory, the Quality of Life Scale, the Simpson-Angus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale. A single rater performed all assessments throughout the trial.

Randomization

This double-blind, placebo-controlled, crossover study consisted of 2 random-order 4-week treatment arms (aripiprazole 15 mg or placebo) separated by a 2-week adjuvant treatment washout. After baseline, subjects were randomized, double blind, to either aripiprazole or placebo for 4 weeks. After the initial 4 weeks of medication, subjects were reassessed, had a 2-week washout period, and then another complete assessment before receiving the other treatment of another 4 weeks. All assessments were again repeated at week 10.

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences for Windows (version 13.0; SPSS Inc, Chicago, Ill). Descriptive statistics was conducted to characterize the study sample. For the primary outcome variables of interest, analysis of covariance (ANCOVA) was conducted with change scores over 4 weeks of treatment as dependent variables and baseline scores as covariates. Treatment condition (placebo versus aripiprazole) along with treatment order (placebo first vs aripiprazole first) main effects and their interaction term were tested. Because the treatment-order main effect and the interaction term (treatment condition × treatment order) were found nonsignificant for all dependent variables analyzed, ANCOVA models with treatment condition main effect only were reported. This pilot trial included multiple-outcome measures intended to provide an indication of effect size for the purpose of designing future studies. Given the exploratory nature of the study, Bonferroni corrections were not used to control for potential Type I error across multiple comparisons.

RESULTS

Sixteen subjects consented to participate. One subject was found ineligible for the study due to recent changes in medications. Available data from the remaining 15 subjects are included in all analyses. The mean age of subjects was 49 ± 8 years and 10 (67%) were male. Three subjects (20%) were African American and 12 (80%) were white. The mean length of treatment with olanzapine was 71 ± 29 months, and the mean olanzapine dose was 22 ± 11 mg daily. Three subjects (20%) were treated for hyperlipidemia with a lipid-lowering statin, 3 were treated for hypertension (with a β blocker), 1 for hypothyroidism (with thyroid replacement), and 1 for type II diabetes mellitus (with metformin). Six subjects had family histories for obesity, 7 for hypertension, 7 for diabetes mellitus, and 5 for cardiovascular disease.

Fourteen subjects completed the 10-week trial; 1 subject dropped out after the week 4 assessment due to a housing change. During the 4 weeks of aripiprazole treatment, there were significant decreases in weight (P = 0.003) and BMI (P = 0.004) compared with placebo (Table 1). Mean waist circumference tended to decrease during treatment with aripiprazole compared with placebo but was not significant (P = 0.063).

Fasting plasma glucose and fasting insulin concentrations did not change significantly. Insulin resistance, calculated by HOMA-IR analysis, revealed a nonsignificant decrease. Hemoglobin A_{1c} also slightly but not significantly decreased during aripiprazole treatment compared with placebo. There was a decrease in C-reactive protein comparing aripiprazole treatment to placebo, although it did not reach significance ($P = 0.087$).

Lipids

Total serum cholesterol ($P = 0.208$), HDL-C ($P = 0.99$), HDL-2 ($P = 0.08$), HDL-3 ($P = 0.495$), and LDL-C ($P = 0.665$) did not change significantly comparing aripiprazole treatment to placebo treatment. However, total serum triglycerides ($P = 0.001$), total VLDL-C ($P = 0.01$), and VLDL-1C and VLDL-2C ($P = 0.012$) decreased significantly during the aripiprazole treatment phase. The VLDL-3C tended lower during aripiprazole, but the decrease was not significant ($P = 0.062$). The results suggest that a reduction on both the large buoyant VLDL (fractions 1 and 2) and a trend toward reduction in small remnant VLDL (fraction 3) occurred. Four subjects' LDL density pattern improved (from small dense LDL pattern to large buoyant or mixed during aripiprazole treatment compared with 1 subject during placebo treatment; $\chi^2 = 1.9$, $P = 0.166$).

Psychopathology and Side Effects

There was no significant change in total PANSS total or subscores, Barnes Akathisia Scale, Simpson-Angus Scale, Global Assessment Scale, Hamilton Depression Rating Scale, or Quality of Life Scale when comparing each treatment group. There was no significant difference between treatment groups for change in dietary intake or energy expenditure.

Overall, treatment with aripiprazole was well tolerated. Changes in systolic and diastolic BP readings were not statistically significant between the 2 treatment groups. The most common side effects observed were change in appetite (decrease 20%; increase 13%), difficulty falling asleep (27%), and tiredness (27%), none of which were statistically significant.

DISCUSSION

The addition of aripiprazole to a stable dose of olanzapine was well tolerated and resulted in significant improvements on several outcome measures that predict risk for medical morbidity. Of note, subjects experienced significant reductions in weight, BMI, triglycerides, total VLDL-C, and VLDL-1C and VLDL-2C. The small sample size and the short duration of active treatment and washout period may have prevented detection of other metabolic benefits, including possible reductions in fasting insulin and insulin resistance (measured by HOMA-IR). In addition, aripiprazole treatment did not significantly change PANSS scores or other psychiatric measures.

The significant decrease in lipids, particularly triglycerides and VLDL-C, is consistent with previous findings.[29] The triglyceride fluctuation for subjects during placebo treatment is likely related to the food ate the day before and the amount of time they have been fasting. The statistical analysis takes this fluctuation into consideration. The relationship between hyperlipidemia and weight gain remains unclear in antipsychotic agent-treated patients. The dyslipidemia associated with insulin resistance includes hypertriglyceridemia, increase in VLDL secretion from the liver, increase in the atherogenic small dense LDL, and decrease in HDL-C.[37,38] Abnormalities of triglyceride

TABLE 1. Assessment of Metabolic Parameters Over 4 Weeks of Treatment in Olanzapine-Treated Subjects With Schizophrenia (N = 15)

	Placebo			Aripiprazole			ANCOVA		
	Week 0	Week 4	Changes	Week 0	Week 4	Changes	*df*	*F*	*P*
Weight, lb	215.5 ± 37.5	217.7 ± 37.3	2.1 ± 3.3	216.5 ± 37.4	213.5 ± 38.5	−2.9 ± 4.7	1,26	10.5	0.003
Waist circumference, cm	113.5 ± 11.4	114.7 ± 10.8	1.2 ± 3.2	113.6 ± 11.3	112.8 ± 11.2	−0.76 ± 2.3	1,26	3.7	0.063
Waist-hip ratio	0.9 ± 0.0	0.9 ± 0.1	0.0 ± 0.0	0.9 ± 0.1	0.9 ± 0.01	0.0 ± 0.0	1,26	0.1	0.747
Body fat, %	37.9 ± 7.7	39.8 ± 4.8	1.7 ± 6.9	38.1 ± 5.9	37.2 ± 6.3	−0.9 ± 3.9	1,25	2.2	0.149
BMI, kg/m^2	32.9 ± 4.4	33.2 ± 4.5	0.3 ± 0.5	32.9 ± 4.7	32.5 ± 4.7	−0.4 ± 0.7	1,26	10.4	0.003
Fasting glucose, mg/dL	110 ± 53	104 ± 41	−7 ± 20	100 ± 17	98 ± 10	−2 ± 13	1,25	0.1	0.704
Fasting serum insulin, μIU/L	10.8 ± 5.9	12.0 ± 5.4	1.2 ± 3.9	12.5 ± 9.4	10.7 ± 6.4	−1.7 ± 8.6	1,25	1.1	0.297
HOMA-IR	2.9 ± 2.2	3.4 ± 2.7	0.3 ± 1.0	3.2 ± 2.9	2.5 ± 1.5	−0.6 ± 2.6	1,24	1.9	0.171
Hb_{A1c}	5.9 ± 1.2	5.9 ± 1.4	0.04 ± 0.2	5.9 ± 0.9	5.8 ± 0.6	−0.9 ± 0.3	1,24	1.3	0.263
CRP4	4.8 ± 3.2	4.0 ± 2.9	−0.5 ± 1.1	8.5 ± 10.2	4.5 ± 4.5	−4.0 ± 7.0	1,26	3.2	0.087
Triglycerides	173.9 ± 97.0	221.2 ± 134.2	47.6 ± 52.7	199.4 ± 125.2	147.7 ± 61.6	−51.7 ± 78.2	1,25	15.8	0.001
LDL-C	114.2 ± 22.3	117.9 ± 23.7	3.1 ± 15.0	112.7 ± 19.6	112.5 ± 33.5	−0.2 ± 22.2	1,25	0.19	0.665
Lipoprotein (a)	5.8 ± 2.7	6.2 ± 2.5	0.38 ± 1.5	5.9 ± 2.6	5.3 ± 2.5	−0.60 ± 2.7	1,26	1.39	0.25
VLDL-1 and VLDL-2	14.4 ± 7.3	17.3 ± 10.0	2.7 ± 4.6	15.0 ± 9.6	13.1 ± 6.2	−1.9 ± 4.7	1,25	7.38	0.012
VLDL-3	17.5 ± 5.9	19.2 ± 8.6	1.84 ± 6.1	17.6 ± 8.1	16.0 ± 5.4	−1.6 ± 3.2	1,25	3.82	0.062
Total VLDL-C	31.5 ± 12.3	36.6 ± 18.1	5.1 ± 9.3	32.6 ± 17.4	29.1 ± 11.4	−3.4 ± 7.2	1,25	7.76	0.010
HDL-2	10.0 ± 3.5	10.3 ± 2.9	0.46 ± 2.1	10.1 ± 4.2	9.3 ± 2.7	−0.8 ± 2.3	1,25	3.29	0.081
HDL-3	31.3 ± 5.6	31.1 ± 6.6	0.15 ± 2.6	31.4 ± 6.8	32.6 ± 6.0	1.2 ± 5.8	1,25	0.47	0.495
HDL-C	41.3 ± 8.4	41.4 ± 7.9	0.6 ± 3.0	41.5 ± 10.3	41.9 ± 8.4	0.4 ± 7.2	1,25	0.00	0.999
Total cholesterol	187 ± 32	196 ± 37	9 ± 22	187 ± 29	184 ± 41	−3 ± 24	1,25	1.66	0.208

Data are presented as mean ± SD.

HOMA-IR indicates Homeostasis Model of Assessment of Insulin Resistance (fasting serum insulin × fasting plasma glucose/22.5); Hb_{A1c}, glycosylated hemoglobin, 4 C-reactive protein.

and HDL metabolism are the early manifestation of insulin resistance, often detectable even before the development of abnormal postprandial or fasting glucose levels.[39]

Weight loss in the current study could be related to aripiprazole's low histaminergic antagonism or its serotonergic 5-HT_{2C} agonist activity. In an analysis of 17 antipsychotic drugs' receptor affinities, the most robust predictor of a drug's propensity to induce weight gain was antagonism of the H1-histamine receptor.[40] The moderate binding affinity of aripiprazole for this receptor predicts that it would exhibit a minimal propensity to induce weight gain as well as less sedation. However, there was no difference in energy expenditure measured by the Actigraph between placebo and aripiprazole treatment, and the changes cannot be explained by an increase in activity. Although antagonism at the serotonin 5-HT_{2C} receptor cannot fully explain antipsychotic-induced weight gain,[41,42] 5-HT_{2C} receptors have been implicated in the control of appetite.[43,44] Thus, it is possible that 5-HT_{2C} agonist actions of aripiprazole may be partly responsible for the minimal weight gain associated with this compound and for weight loss in the current study.

In conclusion, the addition of aripiprazole in olanzapine-treated subjects with schizophrenia or schizoaffective was well tolerated and did not result in a change of psychiatric symptoms in this small, placebo-controlled crossover study of psychiatrically stable schizophrenia subjects. Improvements were observed on measurements that predict medical morbidity and mortality, including weight, BMI, and triglycerides. However, the combination of olanzapine and aripiprazole cost may be prohibitive, and alternatives approaches such as switching agents may be more suitable. Long-term, placebo-controlled trials are warranted to further assess the efficacy, safety, cost effectiveness, and metabolic benefit of the addition of aripiprazole to olanzapine-treated patients.

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ERRATUM

The authors have noted an error on page 458 (2nd paragraph, 2nd sentence) of the article by Kinon et al entitled "Randomized, double-blind 6-month comparison of olanzapine and quetiapine in patients with schizophrenia or schizoaffective disorder with prominent negative symptoms and poor functioning," which appeared in the October 2006 issue of the Journal (*J Clin Psychopharmacol.* 2006;26:453–461).

The corrected sentence should read:

"Regarding changes in BMI, an increase in BMI of 0.36 ± 1.95 was observed in the OLZ treatment group and an increase of 0.12 ± 1.57 in the QUE treatment group (between-treatment difference, $P = 0.174$)."

Reference

Kinon BJ, Noordsy DL, Liu-Seifert H, et al. Randomized, double-blind 6-month comparison of olanzapine and quetiapine in patients with schizophrenia or schizoaffective disorder with prominent negative symptoms and poor functioning. *J Clin Psychopharmacol.* 2006;26:453–461.