A Multicenter, Randomized, Double-Blind Study of the Effects of Aripiprazole in Overweight Subjects With Schizophrenia or Schizoaffective Disorder Switched From Olanzapine

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Objective: Major mental disorders are associated with an increased risk for obesity-related cardiovascular mortality, leading to interest in risk-reduction approaches that target weight and risk-related plasma lipids, including use of antipsychotic agents with low metabolic risk. This multicenter, randomized, double-blind study compared the metabolic effects of aripiprazole versus olanzapine in overweight persons with schizophrenia or schizoaffective disorder who were previously on olanzapine treatment.

Method: In total, 173 subjects with DSM-IV-TR–defined schizophrenia or schizoaffective disorder were randomly assigned to receive aripiprazole (N = 88) or olanzapine (N = 85) for 16 weeks in a study conducted from March 30, 2004, to August 8, 2006. Primary and secondary endpoints were mean weight change from baseline and percentage change from baseline in fasting triglyceride levels, respectively.

Results: At week 16, weight decreased significantly with aripiprazole versus olanzapine (–1.8 vs. +1.41 kg; $p < .001$). Significant differences in percentage change in triglyceride levels were observed with aripiprazole (decreases) versus olanzapine (increases) at all timepoints. In addition, significantly more subjects receiving aripiprazole had clinically relevant (≥ 7%) weight loss versus olanzapine (11.1% vs. 2.6%; $p = .038$), and a lower percentage of subjects receiving aripiprazole had clinically relevant weight gain (2.5% vs. 9.1%; $p = .082$). Mean percentage changes in fasting total cholesterol and high-density lipoprotein cholesterol at week 16 were significantly different with aripiprazole versus olanzapine, with no significant effects on glycemic laboratory measures. Mean Clinical Global Impressions-Improvement (CGI-I) scores for both groups were in the range of "no change" to "minimal improvement." CGI-I endpoint scores were statistically significantly better with olanzapine (mean ± SE = 3.09 ± 0.16) versus aripiprazole (mean ± SE = 3.74 ± 0.15; $p < .001$), and more subjects discontinued aripiprazole (N = 32/88; 36%) than olanzapine (N = 22/85; 26%).

Conclusion: Significant improvements in weight and lipids observed during discontinuation of olanzapine and switch to aripiprazole treatment occurred with limited evidence of negative psychiatric effects, relative to uninterrupted continuation of olanzapine treatment. The results suggest that the potential value of therapeutic substitutions involving specific antipsychotic medications should be considered in overall efforts to reduce cardiovascular risk in this population.

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Premature mortality is commonly observed in persons with major mental disorders, primarily related to coronary heart disease (CHD).[1] A recent study analyzing comprehensive inpatient and outpatient data for public mental health clients across multiple U.S. states indicates that persons with major mental disorders lose 25 to 30 years of potential life compared with the general population, with premature CHD as the leading cause of death.[1]

Key modifiable risk factors for CHD include obesity, dyslipidemia, hypertension, hyperglycemia, and smoking. Schizophrenia patients experience an increased prevalence of all these modifiable risk factors compared to the general population,[2] and this high risk status is consistent with observed increases in CHD rates.[3] In particular, persons with schizophrenia have an increased prevalence of a specific constellation of cardiometabolic risk factors related to insulin resistance,[2] termed the *metabolic syndrome*, that increases risk for diabetes mellitus as well as CHD.[4] Fasting triglyceride levels can be used as a predictive biomarker of insulin resistance.[5] The increased prevalence of obesity, impaired glucose tolerance, and type 2 diabetes in patients with psychiatric disorders in comparison to the general population, and the potential contribution of antipsychotic medications to risk,[6] highlight the importance of considering treatment effects in the context of overall efforts to minimize cardiometabolic risk in this population.

Individual atypical antipsychotics can affect CHD risk factors, including weight and lipid profiles, to varying degrees.[7–9] The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), for example, indicated that of the agents tested, olanzapine had the highest risk of weight gain, hemoglobin A_{1c} increase, and dyslipidemia,[10,11] consistent with a number of other studies.[8,9,12,13] In contrast to olanzapine, atypical antipsychotics such as aripiprazole have a relatively low potential for weight gain and no evidence of significant diabetes risk or adverse effects on lipid profiles.[6,9,14] This has led to clinical interest in potential metabolic improvements that might occur during therapeutic substitution of antipsychotics with high liability for weight gain and dyslipidemia to those with a more benign cardiometabolic profile. While a small number of open-label or observational studies have reported the effects of switching antipsychotic medication in patients with metabolic risk factors,[15–18] results from double-blind, randomized trials specifically designed to test the effect of switching antipsychotic drugs on metabolic parameters have not been reported to date.

Aripiprazole is a partial agonist at D_2 dopamine and 5-HT_{1A} serotonin receptors and an antagonist at 5-HT_{2A} and 5-HT_{2C} serotonin receptors.[19–22] While aripiprazole was not approved for use when the CATIE study was initiated, multiple studies have established this agent as a safe and effective treatment for symptoms of schizophrenia, schizoaffective disorder,[23–27] and bipolar mania[28–30] with a low potential for weight gain, diabetes, or adverse effects on lipid profiles.[6,9,19–22] In long-term studies in schizophrenia, aripiprazole treatment has not been associated with a mean increase in body weight from baseline; in some studies, small decreases in mean body weight have been observed.[25,31] To test the metabolic effects of continuing to treat overweight or obese subjects with an agent associated with liability for adverse effects on weight and lipids compared to substitution of an agent with a more benign cardiometabolic profile, this 16-week, multicenter, randomized, double-blind study compared the metabolic effects of aripiprazole and olanzapine in overweight subjects with schizophrenia or schizoaffective disorder who were previously treated with olanzapine.

METHOD

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and consistent with the International Conference on Harmonization, Good Clinical Practice, and applicable regulatory requirements. Written informed consent was obtained from every subject or their legally acceptable representative. The study was conducted from March 30, 2004, to August 8, 2006.

Subjects

To be eligible, male and female subjects aged 18 to 65 years with a *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (DSM-IV-TR) diagnosis of schizophrenia or schizoaffective disorder must have received olanzapine monotherapy at a dose of 10 to 20 mg/day for 1 to 24 months immediately prior to screening and have a body mass index (BMI) ≥ 27 kg/m^2 and a Clinical Global Impressions-Severity of Illness (CGI-S)[32] score ≤ 4. Weight gain during prior olanzapine therapy was verified in the subject history.

The main exclusion criteria were as follows: diagnosis of an Axis I psychiatric disorder other than schizophrenia or schizoaffective disorder; type 1 or type 2 diabetes mellitus; any clinically significant neurologic abnormality, or epilepsy, Parkinson's disease, Alzheimer's disease, multiple sclerosis, residual of stroke, transient cerebral ischemic attacks, or mental retardation; being considered to be at significant risk of committing suicide; an increase in symptoms of schizophrenia/schizoaffective disorder that would require hospitalization or a change in antipsychotic therapy; psychoactive substance or alcohol dependence (DSM-IV-TR) within 3 months before the study, excluding caffeine and nicotine; weight loss > 10% of total body weight within 3 months before screening; and clinically significant vital sign, electrocardiogram (ECG), or laboratory test abnormalities. Subjects were also excluded who had received electroconvulsive therapy within 3 months before enrollment or had received study medication in an aripiprazole clinical study, who participated in a clinical trial with an investigational agent ≤ 4 weeks before the study, or who previously failed to respond to an adequate course (≥ 10 mg/day for ≥ 4 weeks) of aripiprazole for schizophrenia/schizoaffective disorder. Women who were pregnant or breastfeeding or who were of childbearing potential and unwilling/unable to use an acceptable method of contraception for the entire study period

and up to 4 weeks after study completion were also excluded.

Study Design

This was a multicenter, multinational, randomized, double-blind study examining the metabolic effects of aripiprazole and olanzapine in subjects with schizophrenia or schizoaffective disorder previously treated with olanzapine. After a 2-week, open-label observation period during which subjects continued to receive their prior olanzapine therapy, subjects who met entrance criteria at the baseline visit were evenly randomly assigned to either switch to aripiprazole monotherapy or continue olanzapine monotherapy during a 16-week double-blind treatment phase. Study medication was administered orally, once daily. Aripiprazole was titrated to 15 mg/day over 2 weeks (with down-titration of olanzapine), fixed at 15 mg/day for 4 weeks, then flexibly dosed at 10 to 30 mg/day to week 16. For patients in the group continuing on olanzapine treatment, olanzapine was continued at the prior dose for 4 weeks after a mock titration, then flexibly dosed at 10 to 20 mg/day to week 16.

Concomitant Medications

Prohibited antipsychotic medications (those other than study medication) had to be tapered for ≥ 2 months preceding the screening visit, and fluoxetine required a 4-week washout before screening. The following medications were prohibited from 1 week prior to screening to week 16: over-the-counter herbal preparations (including St. John's wort, omega-3 fatty acids, *S*-adenosylmethionine, kava extracts, ephedra-containing supplements, and γ-aminobutyric acid supplements); paroxetine, fluoxetine, quinidine, and carbamazepine; and medications affecting or potentially affecting carbohydrate metabolism. Lipid-lowering treatments could not be initiated at any time during the study; subjects on stable statin doses (≥ 6 weeks prior to study) could continue those doses. Use of antidepressants (except fluoxetine and paroxetine), benzodiazepine/anxiolytics, mood stabilizers and anticonvulsants (except carbamazepine), sleeping agents, and propranolol and other β-adrenergic blockers (for the treatment of extrapyramidal symptoms [EPS]) were permitted. Hydroxyzine and diphenhydramine (for EPS) were allowed only after the primary medical monitor was contacted. Benzodiazepines/sleep agents and anticholinergic agents were prohibited within 6 and 12 hours, respectively, of rating scale assessment.

Efficacy and Safety Assessments

The primary objective was to compare the effects of aripiprazole versus olanzapine on weight change from baseline to week 16 through longitudinal repeated-measures analysis. The secondary objective was to compare the percentage change in fasting triglyceride levels from baseline to week 16 through longitudinal repeated-measures analysis. The tertiary objectives were to compare the safety, tolerability, and efficacy of aripiprazole versus olanzapine, recognizing that only the aripiprazole-treated patients would be changing antipsychotic medication in this study design.

Fasting laboratory measures included changes from baseline in fasting plasma glucose, fasting insulin, fasting C-peptide, fasting lipids (total cholesterol, low- and high-density lipoprotein cholesterol [LDL-C and HDL-C]), and plasma glucose as measured 2 hours postbolus with an oral glucose tolerance test (OGTT). Efficacy measures were Clinical Global Impressions-Improvement (CGI-I)[32] and change from baseline in CGI-S score. CGI-I scores are measured on a scale of 1 (very much improved) to 7 (very much worse); CGI-S scores are measured on a scale of 1 (normal) to 7 (extremely ill). Safety measures included frequency and severity of adverse events (AEs); serious AEs (SAEs); discontinuation due to AEs; vital signs, ECGs; routine laboratory tests; physical examination; EPS-related side effects; change from baseline in rating scale scores for the Simpson-Angus Scale (SAS),[33] Abnormal Involuntary Movement Scale (AIMS)[34] total (sum of items 1–7), and AIMS individual items 8, 9, and 10; use of anticholinergic medications; and waist circumference and BMI.

The mean percentage change from baseline in fasting non-HDL-C was included as an exploratory endpoint.

Efficacy measures, AEs, and concomitant medication use were assessed at baseline (except CGI-I) and every 2 weeks from week 4 to week 16; all other safety assessments were performed at baseline and weeks 4, 8, 12, and 16.

Statistical Analyses

The safety sample included all randomized subjects who received ≥ 1 dose of double-blind study medication. The efficacy sample included all subjects in the safety sample who had ≥ 1 CGI evaluation on, or within 7 days after, the last day of double-blind treatment. With 154 evaluable subjects (based on a 2-tailed test with an α level of .05), the study had 90% power to show a true treatment difference of 3.0 kg in favor of aripiprazole in the change from baseline at week 16 in body weight using longitudinal repeated-measures analysis. Baseline characteristics were summarized as descriptive statistics.

Change from baseline in body weight was analyzed with a longitudinal repeated-measures analysis on the observed case (OC) dataset using the SAS procedure PROC MIXED (SAS Institute Inc.; Cary, N.C.). The model included the fixed categorical effects of treatment, duration of prior olanzapine treatment category (≤ 6 months/> 6 months), treatment-by-week interaction, and duration of prior olanzapine treatment category–by-week interaction, as well as the continuous fixed covariates of baseline

Table 1. Baseline Demographics and Characteristics (randomized sample)

Characteristic	Aripiprazole (N = 88)	Olanzapine (N = 85)	Total (N = 173)
Age, mean ± SD, y	39.7 ± 10.1	38.7 ± 10.1	39.2 ± 10.1
Male/female, N (%)	50/38 (56.8/43.2)	61/24 (71.8/28.2)	111/62 (64.2/35.8)
Race, N (%)			
Caucasian	60 (68.2)	58 (68.2)	118 (68.2)
Black	21 (23.9)	21 (24.7)	42 (24.3)
Asian	1 (1.1)	3 (3.5)	4 (2.3)
Native Hawaiian/Pacific Islander	1 (1.1)	0	1 (0.6)
Other	5 (5.7)	3 (3.5)	8 (4.6)
Current diagnosis, N (%)			
Schizophrenia	68 (77.3)	65 (76.5)	133 (76.9)
Schizoaffective disorder	20 (22.7)	20 (23.5)	40 (23.1)
Age at diagnosis, mean ± SD, y	27.4 ± 9.1	25.4 ± 8.9	26.4 ± 9.0
Duration of illness, mean ± SD, y	12.7 ± 10.5	13.8 ± 9.8	13.3 ± 10.1
CGI-S score, mean ± SD	2.9 ± 0.9	3.0 ± 0.9	3.0 ± 0.9
Duration of prior olanzapine use, mean ± SD, mo	7.8 ± 12.4	6.9 ± 6.8	7.4 ± 10.0
BMI (kg/m^2), mean ± SD[a]	32.5 ± 5.3	32.0 ± 5.0	32.3 ± 5.2
BMI category, N (%)[a]			
< 30 kg/m^2	34 (38.6)	39 (45.9)	73 (42.2)
≥ 30 kg/m^2	54 (61.4)	46 (54.1)	100 (57.8)
Waist circumference, mean ± SD, cm[a]	106.8 ± 12.4	106.7 ± 12.0	106.8 ± 12.2
Waist circumference category, N (%)[a]			
≤ 102 cm (male) or ≤ 88 cm (female)	25 (28.4)	20 (23.5)	45 (26.0)
> 102 cm (male) or > 88 cm (female)	63 (71.6)	65 (76.5)	128 (74.0)

[a]End of baseline measurements.
Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impressions-Severity of Illness scale.

body weight and baseline body weight–by-week interaction. An unstructured matrix for the within-subject error variance–covariance was used.

Percentage change from baseline in fasting triglycerides was compared through a longitudinal repeated-measures analysis. A similar longitudinal model as performed for changes from baseline in weight was applied, but with log transformations.

The CGI-I score and change from baseline in CGI-S score were evaluated using analysis of covariance (ANCOVA) with baseline CGI-S as covariate and treatment and study center as main effects (last-observation-carried-forward [LOCF] dataset). Study center was not included in the analysis of the OC dataset.

Longitudinal analyses for mean changes in body weight and triglyceride levels were also performed according to duration of prior olanzapine therapy (categorized into ≤ 6 months and > 6 months). For CGI-I, a post hoc ANCOVA was performed by duration of prior olanzapine therapy (LOCF).

Changes from baseline in fasting laboratory measures were evaluated using ANCOVA, adjusting for baseline value and with treatment and duration of prior olanzapine treatment category as the main effects (LOCF). Log transformations were applied for analyses of fasting lipid parameters, which for ANCOVA included the log of the relative change (on-treatment values/baseline) as response variable and the log of the baseline value as the covariate, with treatment and duration of prior olanzapine treatment category as main effects.

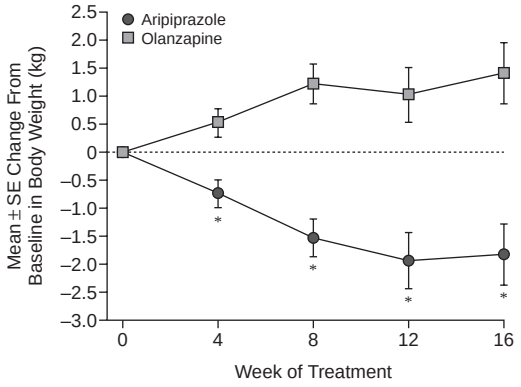
The proportions of subjects who had a ≥ 7% increase or decrease in weight or a ≥ 1 kg/m^2 BMI increase were assessed using the Cochran-Mantel-Haenszel (CMH) General Association test, controlling for baseline BMI. Proportions of subjects with a waist circumference > 102 cm (men) or > 88 cm (women) were evaluated using the CMH General Association test, controlling for baseline waist circumference (LOCF). Changes in safety rating scale scores were evaluated using ANCOVA, adjusting for baseline value and controlling for treatment and study center.

RESULTS

Subject Demographics

Of the 244 enrolled subjects, 173 were randomly assigned to treatment with aripiprazole (N = 88) or olanzapine (N = 85). A total of 119 subjects completed the treatment phase (aripiprazole, N = 56; olanzapine, N = 63), with 54 discontinuations owing to the following: AEs (aripiprazole vs. olanzapine, 7 [8%] vs. 8 [9%]), consent withdrawal (8 [9%] vs. 4 [5%]), loss to follow-up (6 [7%] vs. 6 [7%]), lack of efficacy (7 [8%] vs. 0 [0%]), poor compliance/noncompliance (3 [3%] vs. 3 [4%]), subject no longer meeting criteria (0 [0%] vs. 1 [1%]), or other reasons (1 [1%] vs. 0 [0%]). The safety and efficacy populations comprised 172 and 164 subjects, respectively. Baseline characteristics and demographics are presented in Table 1. At endpoint, the mean daily aripiprazole dose was 16.0 mg/day (range, 5–30 mg/day); the mean daily olanzapine dose was 15.9 mg/day (range, 10–40 mg/day).

Figure 1. Change in Body Weight From Baseline (longitudinal repeated-measures analysis; safety sample)[a]



[a]Mean ± SE baseline body weight: aripiprazole (N = 81), 91.3 ± 2.1 kg; olanzapine (N = 77), 92.7 ± 2.1 kg.
*p < .001, aripiprazole versus olanzapine.

Change in Body Weight (safety sample)

The primary objective was to compare the effects of aripiprazole versus olanzapine on weight change from baseline to week 16 using longitudinal repeated-measures analysis; at week 16, the difference between the weight decrease with aripiprazole (–1.8 kg [N = 56]) versus the increase with olanzapine (+1.41 kg [N = 62]) was statistically significant (p < .001; Figure 1). Significant improvements in body weight were also observed with aripiprazole versus olanzapine at weeks 4, 8, and 12 (p < .001; Figure 1). Changes in body weight stratified according to duration of prior olanzapine treatment (≤/> 6 months) are shown in Table 2, with aripiprazole treatment associated with numerically larger improvements in body weight in the patients previously exposed to longer durations of olanzapine treatment.

At week 16, the proportion of subjects with clinically relevant (≥ 7%) weight gain was numerically lower with aripiprazole versus olanzapine (p = .082; Figure 2). Significantly more subjects had clinically relevant weight loss with aripiprazole versus olanzapine at week 16 (p = .038; Figure 2).

Triglyceride Levels (safety sample)

The secondary objective was to compare the percentage change in fasting triglyceride levels from baseline to week 16 using longitudinal repeated-measures analysis; significant improvements in the mean percentage change from baseline in triglyceride levels were observed with aripiprazole versus olanzapine at week 16 (–14.46% [N = 54] vs. +5.29% [N = 61]; p = .002) and all other timepoints (Figure 3). The significant improvements with aripiprazole versus olanzapine occurred rapidly (observed at the first assessment at week 4) and were sustained for the duration of the study (Figure 3). Percentage changes in triglyceride levels stratified according to duration of prior olanzapine treatment (≤/>6 months) are shown in Table 2, with aripiprazole treatment associated with numerically larger improvements in triglyceride levels in the patients previously exposed to longer durations of olanzapine treatment.

Efficacy Outcomes (efficacy sample)

Overall mean ± standard error (SE) CGI-I scores were significantly better (lower) with olanzapine (3.09 ± 0.16 [N = 80]) versus aripiprazole (3.74 ± 0.15 [N = 84]; p < .001; LOCF) at endpoint and at all timepoints from week 6 to endpoint (p < .05). Endpoint CGI-I scores were also significantly better with olanzapine (2.63 ± 0.14 [N = 61]) versus aripiprazole (3.10 ± 0.14 [N = 56]; p = .020) for subjects who completed the study (OC). The CGI-I scores with both aripiprazole and olanzapine were in the range corresponding to "minimally improved" to "no change" (3–4).

The CGI-I scores at week 16 stratified according to duration of prior olanzapine treatment (≤/> 6 months) are shown in Table 2 (post hoc analysis), with aripiprazole treatment associated with higher CGI-I scores in the patients previously exposed to longer durations of olanzapine treatment.

Mean ± SE CGI-S scores decreased from baseline at week 16 in the olanzapine-treated group (i.e., those continuing their prior medication) (–0.18 ± 0.11 from 3.20 ± 0.08 [N = 80]) and increased slightly in the aripiprazole-treated group (i.e., those changing medication in this study) (+0.11 ± 0.11 from 3.17 ± 0.08 [N = 84]; p = .031 vs. olanzapine; LOCF). For subjects who completed the study, there was no significant difference between endpoint CGI-S scores with olanzapine versus aripiprazole (–0.47 ± 0.08 [N = 61] vs. –0.30 ± 0.08 [N = 56]; p = .150). Mean endpoint CGI-S scores remained in the range corresponding to "mildly ill" to "moderately ill" (3–4).

Safety Outcomes (safety sample)

Significant improvements from baseline in fasting total cholesterol and HDL-C were observed with aripiprazole versus olanzapine at week 16 (Table 3) and all other timepoints (the highest p value at any timepoint was p ≤ .028; LOCF). The percentage decrease in LDL-C was significantly greater with aripiprazole versus olanzapine at week 4 LOCF (p = .016) and week 12 LOCF (p = .017), but not at week 8 LOCF (p = .063) or week 16 LOCF (Table 3; p = .072). There were no significant between-group differences in the increases in fasting plasma glucose, fasting insulin, fasting C-peptide, or plasma glucose (2 hours postbolus OGTT) at week 16 (Table 3) or any other timepoint (LOCF).

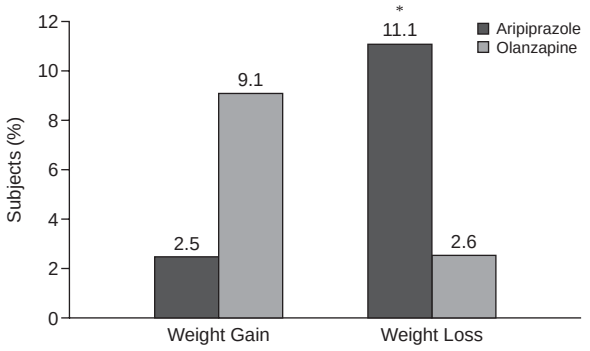
The most common AEs with aripiprazole were insomnia, headache, and nausea, whereas the most common

Table 2. Analysis of Changes From Baseline at Week 16 in Body Weight and Fasting Triglycerides (longitudinal analyses) and CGI-I Scores at Week 16 (post hoc, LOCF analysis) According to Duration of Prior Olanzapine Treatment

	Prior Olanzapine Treatment ≤ 6 Mo				Prior Olanzapine Treatment > 6 Mo			
	Aripiprazole		Olanzapine		Aripiprazole		Olanzapine	
Variable	N	Mean ± SE	N	Mean ± SE	N	Mean ± SE	N	Mean ± SE
Body weight								
Baseline, kg	54	93.3 ± 2.5	47	94.9 ± 2.7	27	89.4 ± 3.4	30	90.3 ± 3.3
Change at week 16, kg	36	–1.6 ± 0.6	35	+1.5 ± 0.7	20	–2.0 ± 1.0	27	+1.5 ± 0.9
Fasting triglycerides								
Baseline, mg/dL	53	175.2 ± 13.5	46	184.2 ± 14.5	27	186.6 ± 24.3	30	217.1 ± 23.1
Percentage change at week 16	35	–11.1 ± 4.6	34	+4.5 ± 5.6	19	–20.0 ± 7.6	27	+6.7 ± 8.9
CGI-I score at week 16	56	3.45 ± 0.16	49	3.10 ± 0.17	28	3.81 ± 0.27	31	2.69 ± 0.26

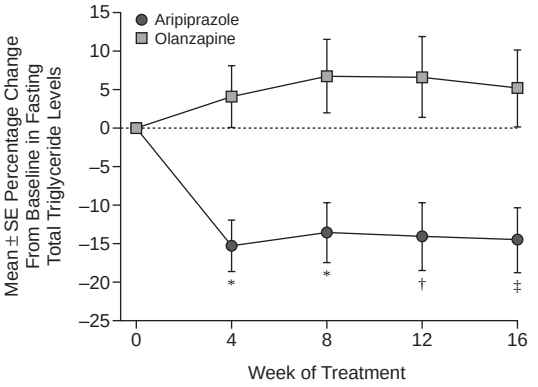
Abbreviations: CGI-I = Clinical Global Impressions-Improvement, LOCF = last observation carried forward, SE = standard error.

Figure 2. Percentage of Subjects With Clinically Relevant (≥ 7%) Weight Change (last observation carried forward; safety sample)



*p = .038, aripiprazole versus olanzapine.

Figure 3. Percentage Change in Fasting Total Triglyceride Levels From Baseline (longitudinal repeated-measures analysis; safety sample)[a]



[a]Mean ± SE baseline fasting total triglyceride levels: aripiprazole (N = 80), 183 ± 13 mg/dL; olanzapine (N = 76), 200 ± 13 mg/dL.
*p < .001, †p = .003, ‡p = .002; aripiprazole versus olanzapine.

AEs with olanzapine were insomnia and weight increase (Table 4).

Six (6.8%) aripiprazole-treated subjects experienced at least 1 SAE. Of these, 3 subjects experienced psychotic disorder (1 event each rated as probably, possibly, or not likely to be treatment-related), 1 of whom also experienced suicidal ideation (rated as not likely to be treatment-related). The other 3 subjects experienced psychomotor hyperactivity (possibly treatment-related), paranoia, or schizophrenia. Nine (10.7%) olanzapine-treated subjects experienced an SAE: 1 event each of Crohn's disease, rectal hemorrhage, disease progression, psychotic disorder, mental disorder, schizoaffective disorder (rated as possibly treatment-related), paranoid-type schizophrenia, suicide attempt, and hypertensive crisis. There were no deaths during the study.

Fifteen subjects discontinued due to AEs: 7 (8.0%) aripiprazole-treated subjects (intentional self-injury, psychotic disorder, and suicidal ideation; nausea; psychotic disorder; psychomotor hyperactivity; schizophrenia; paranoia; insomnia); and 8 (9.5%) olanzapine-treated subjects (depression, hypertension, and suicide attempt; sleepwalking; schizoaffective disorder; disease progression; weight increased; schizophrenia, paranoid type; hepatic enzyme increased; psychotic disorder).

The percentage of subjects with potentially clinically relevant laboratory abnormalities or vital signs was similar with aripiprazole versus olanzapine, with the exception of prolactin, for which 19.3% of aripiprazole-treated subjects and 70.1% of olanzapine-treated subjects had levels greater than the upper limit of normal. The number of subjects with potentially clinically relevant changes in blood pressure was similar with aripiprazole versus olanzapine (3 vs. 5 subjects).

Eight (9.1%) aripiprazole-treated subjects experienced an EPS-related AE versus 5 (6.0%) olanzapine-treated subjects. Akathisia and tremor were seen in 3 subjects each with aripiprazole and 1 subject each with olanzapine. There was 1 episode of dystonia with aripiprazole (1.1%) and no events with olanzapine. Muscle spasm was

Table 3. Glycemic Parameters, Fasting Lipid Parameters, and the Exploratory Outcome Measure (non-HDL-C) at Week 16 (safety sample)[a]

Parameter	Aripiprazole	Olanzapine	p Value
Glycemic parameters			
Fasting plasma glucose, mg/dL			
N	80	76	…
Baseline	95.5 ± 1.4	92.5 ± 1.4	.116
Mean change at week 16	+1.6 ± 1.8	+5.0 ± 1.8	.172
Fasting insulin, μU/mL			
N	78	77	…
Baseline	16.4 ± 2.0	14.4 ± 2.0	.467
Mean change at week 16	+0.3 ± 1.4	+0.6 ± 1.3	.856
C-peptide, ng/mL			
N	77	76	…
Baseline	3.2 ± 0.2	3.1 ± 0.2	.616
Mean change at week 16	+0.4 ± 0.2	+0.04 ± 0.2	.251
Plasma glucose (2 hours postbolus OGTT), mg/dL			
N	79	75	…
Baseline	115.2 ± 4.2	122.9 ± 4.2	.185
Mean change at week 16	+1.4 ± 4.4	+3.4 ± 4.4	.752
Fasting lipid parameters[b]			
Fasting total cholesterol			
Baseline, mg/dL	194.1 ± 4.8	197.7 ± 4.9	.596
Percentage change at week 16	–9.5 ± 1.5	–3.3 ± 1.6	.005
Fasting LDL-C			
Baseline, mg/dL	113.4 ± 4.2	117.4 ± 4.2	.489
Percentage change at week 16	–11.2 ± 2.5	–4.7 ± 2.7	.072
Fasting HDL-C			
Baseline, mg/dL	45.0 ± 1.4	41.7 ± 1.4	.094
Percentage change at week 16	+1.7 ± 1.8	–5.9 ± 1.7	.002
Fasting non-HDL-C*			
Baseline, mg/dL	149.1 ± 5.0	156.0 ± 5.0	.319
Percentage change at week 16	–13.2 ± 2.0	–2.6 ± 2.2	< .001

[a]Values expressed as mean ± SE unless otherwise noted; LOCF analysis.
[b]Aripiprazole, N = 80; olanzapine, N = 76.
Abbreviations: HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, LOCF = last observation carried forward, OGTT = oral glucose tolerance test.

Table 4. Incidence of Treatment-Emergent Adverse Events (patient reported) That Occurred in ≥ 5% of Subjects in Either Treatment Group (safety sample), N (%)

Adverse Event	Aripiprazole (N = 88)	Olanzapine (N = 84)
Any adverse event	56 (63.6)	45 (53.6)
Nausea	6 (6.8)	1 (1.2)
Weight increased	4 (4.5)	5 (6.0)
Headache	8 (9.1)	3 (3.6)
Insomnia	19 (21.6)	9 (10.7)

reported in 1 aripiprazole-treated (1.1%) and 1 olanzapine-treated (1.2%) subject. There was 1 event (1.2%) each of muscle rigidity and oculogyration with olanzapine versus no events with aripiprazole.

At week 16 (LOCF), there was no difference with aripiprazole versus olanzapine in the mean change from baseline in SAS (–0.21 from 11.04 vs. –0.18 from 10.54; p = .822), AIMS total (–0.05 from 0.76 vs. –0.02 from 0.54; p = .914), or AIMS items 8 (+0.01 from 0.19 vs. –0.02 from 0.20; p = .662), 9 (0.00 from 0.02 vs. +0.02 from 0.05; p = .487), or 10 (–0.06 from 0.03 vs. –0.05 from 0.14; p = .758).

Anticholinergic medication for the potential treatment of EPS was used by 5.7% and 7.1% of aripiprazole- and olanzapine-treated subjects, respectively.

The percentage of subjects with high waist circumference did not differ significantly with aripiprazole versus olanzapine at week 16 (68.3% vs. 74.0%; p = .519; LOCF). Significantly fewer subjects experienced clinically relevant BMI increase (≥ 1 kg/m^2) with aripiprazole versus olanzapine (8.6% vs. 32.5%; p < .001; LOCF).

Exploratory Outcome (Safety Sample)

Adjusted mean percentage decreases from baseline in fasting non-HDL-C were significantly greater with aripiprazole versus olanzapine at week 16 (Table 3) and all other timepoints (p < .001; LOCF).

DISCUSSION

This study in overweight subjects with schizophrenia previously treated with olanzapine demonstrated significant improvements in weight and the percentage change in fasting triglyceride levels in subjects who were randomly assigned to switch to aripiprazole versus those who

continued with olanzapine therapy. In addition, significantly more subjects achieved clinically relevant weight loss with aripiprazole versus olanzapine, with both groups maintaining psychiatric symptom stability as measured by mean CGI-I endpoint scores, which stayed in the range of "no change" to "minimally improved," although more subjects overall discontinued aripiprazole (N = 32/88; 36%) than olanzapine (N = 22/85; 26%). To our knowledge, this is the first report of a double-blind, randomized study designed to test whether metabolically at-risk patients can reduce key indicators of metabolic risk via therapeutic substitution of an antipsychotic with higher metabolic risk for an agent with a more benign metabolic profile. The results are relevant to clinical and public health interest in reducing cardiometabolic risk in patients with major mental disorders such as schizophrenia[1] and further confirm that some proportion of overall risk can be modified by individual medication effects.

The results regarding comparative weight changes observed during randomized treatment with the individual agents in this study are consistent with previous evidence of limited adverse effects on adult body weight during aripiprazole treatment[9,23–25,35] and common observations of clinically significant adverse effects on weight during olanzapine treatment.[7,36] A previous meta-analysis of studies concerning weight gain after 10 weeks of antipsychotic treatment at standard doses indicated that olanzapine is associated with a mean weight gain of 4.4 kg.[12] In a previous direct comparison of aripiprazole and olanzapine in a 26-week, double-blind study of patients not selected on the basis of weight status, aripiprazole-treated subjects showed a mean weight loss of 1.37 kg (3.04 lb) compared with a mean increase of 4.23 kg (9.40 lb) with olanzapine treatment ($p < .001$).[37] Similarly, in a long-term (52-week), open-label extension study carried out after 26 weeks of randomized therapy, mean weight gain with aripiprazole was +0.04 kg versus +2.54 kg with olanzapine ($p < .001$).[31] The current results extend these observations specifically to the population of overweight patients taking olanzapine, demonstrating an important proof-of-concept in overweight patients: continued exposure to medications with higher risk of weight gain can lead to further weight increase, whereas substitution of an antipsychotic with lower weight gain risk can contribute to weight loss.

The significant lowering of fasting plasma triglyceride and total cholesterol, and the improvement in HDL-C, seen in this study is consistent with previous evidence of adverse effects of olanzapine on lipid profiles and previous evidence suggesting an absence of such adverse effects or potential improvements in lipid profiles during aripiprazole treatment.[8,13] However, the current report extends these studies and complements a recent related report of nonrandomized antipsychotic switch–related changes in nonfasting weight and lipids, in patients not specifically selected on the basis of weight status.[17] The current double-blind, randomized study extends knowledge to the common therapeutic situation of overweight subjects considering the potential effects of continuing treatment with a higher metabolic risk agent versus substitution of an agent with lower metabolic risk and confirms that improvements in plasma lipids associated with medication substitution are rapid-onset in comparison to changes in weight.

It should be noted that of the lipid fractions measured, fasting plasma triglyceride levels in particular—regulated, in part, by insulin effects on lipolysis—have been used as a predictive marker of insulin resistance,[5] an important early component of cardiometabolic risk. In comparison to insulin resistance and hypertriglyceridemia, hyperglycemia tends to be a later-onset risk predictor, reflecting potentially irreversible reductions in pancreatic β-cell function, which normally maintains glucose homeostasis during insulin resistance via compensatory hypersecretion of insulin.[38] In the current study, subjects were overweight, but nondiabetic, at baseline and would therefore potentially have some insulin-resistance–related reductions in β-cell function, but with enough compensatory capacity remaining to maintain nondiabetic-level plasma glucose concentrations. From this perspective, it is perhaps not surprising that fasting plasma insulin and C-peptide, as well as fasting plasma glucose and 2-hour postload glucose, changed nonsignificantly during the study. One notable limitation of the study is that a greater proportion of subjects had a BMI ≥ 30 at baseline in the aripiprazole group versus the olanzapine group (61.4% vs. 54.1%). This imbalance may have limited the extent to which improvements in metabolic parameters could be compared.

In this study, subjects were randomly assigned to either continue ongoing olanzapine treatment or change antipsychotic medication to aripiprazole, and olanzapine-continuing subjects demonstrated better (lower) mean scores on the CGI-I and CGI-S (LOCF). In addition, more subjects randomly assigned to change to aripiprazole discontinued from the study for any reason (N = 32), compared to discontinuations observed during ongoing olanzapine treatment (N = 22). This result could suggest that treatment with olanzapine is more effective than treatment with aripiprazole, or it could be consistent with a recent supplemental analysis of phase 1 data from the National Institute of Mental Health–funded Clinical Antipsychotic Trials of Intervention Effectiveness study, which indicated that patients continuing current antipsychotic medication treatment tend to continue treatment longer than patients experiencing a change in antipsychotic medication, independent of the specific medications involved.[39] However, our study was not designed to discriminate between these 2 interpretations, similar to other studies of similar design in which one group is randomly assigned to continue their

current antipsychotic medication while a comparison group is assigned to change medications. In studies with this design, the apparent advantage for continuing treatment, compared to switching treatments, may be related to various factors, including the possibility that the population of patients currently taking a particular agent may be enriched for patients who respond particularly well to that particular drug. However, the current study design remains useful for modeling the real-world clinical choice between the risks and benefits of staying on treatment versus the risks and benefits of making a medication switch.

In the current study, the weight and triglyceride improvements associated with switching from olanzapine to aripiprazole were evident in comparison to staying on olanzapine treatment, while the psychiatric tolerability of this switch for all subjects was less certain. For those subjects remaining in the trial, there was a statistically significant CGI-measured advantage in the olanzapine group compared to the group switching to aripiprazole, and more subjects discontinued the trial in the group randomly assigned to discontinue their prior olanzapine treatment and switch to aripiprazole compared to the group staying on olanzapine treatment. Despite the statistically significant differences in CGI-I endpoint scores, both the group of patients switched to aripiprazole and the patients remaining on olanzapine treatment were judged by clinical raters using the CGI-I to be in the range of "no change" to "minimal improvement." In clinical practice, decisions about staying on current treatment versus switching should be informed by a process of shared decision-making incorporating individual patient goals and ability to tolerate risk with respect to either psychiatric or cardiometabolic outcomes.

Patients with modifiable cardiometabolic risk factors, like overweight and obesity or dyslipidemia, can also be considered candidates for adjunctive pharmacotherapies that specifically target those risk factors as a treatment alternative to switching antipsychotic medications. However, the potential benefits of adding medications for this purpose in a patient with schizophrenia must be weighed against potential adverse effects, as well as the evidence that adherence to such medical pharmacotherapies may be even lower than adherence to the primary psychotropic drugs.[40] As clinicians work to minimize untreated, modifiable cardiometabolic risk, there is likely to be a commonly encountered clinical choice between the addition of adjunctive pharmacotherapies for dyslipidemia, obesity, and other metabolic risk factors versus changing the psychotropic regimen to remove potentially contributing agents, with parsimony suggesting the latter approach is preferable. For example, a working principle in the U.S. Public Health Service National Cholesterol Education Program Adult Treatment Panel is to address "secondary" causes of dyslipidemia prior to adding pharmacotherapies for dyslipidemia.[41] However, clinical decision-making in such situations will clearly benefit from more studies like this one that elucidate potential risks and benefits of this approach. The current study results, from psychiatrically stable but overweight or obese outpatients taking a potentially contributory antipsychotic, indicate a generally favorable risk-benefit ratio for therapeutic substitution with an agent having a more benign cardiometabolic risk profile, but additional data characterizing psychiatric and health outcomes beyond the 16 weeks of observation included in this randomized, double-blind study would be useful. The results observed are consistent with recently reported results from an open-label 58-week switch study.[17]

Noted above, data from a supplemental analysis of CATIE data highlight the challenge of switching antipsychotics, in that patients continuing current medication may fare better than those assigned to change medication.[39] To further understand the contribution of this "switch effect" to observed results, subjects were stratified according to duration of prior olanzapine therapy. Results of this post hoc analysis indicate that subjects continuing treatment with olanzapine who were treated with olanzapine for a longer prior duration (> 6 months) had numerically better (lower) CGI-I scores at endpoint than those treated for a shorter duration. Conversely, in the aripiprazole-treated subjects, CGI-I scores were better in the subgroup who were previously treated with olanzapine for ≤ 6 months (post hoc analysis; LOCF), whereas decreases in weight and fasting triglyceride levels were greater in subjects previously treated with olanzapine for > 6 months (longitudinal analyses). The difference in CGI scores between patients continuing on olanzapine treatment and those switching to aripiprazole may thus be attributed in part to the possibility that the sample of patients previously treated for > 6 months on olanzapine could be enriched with drug responders and with patients who, independent of the particular drug, have experienced a maturation and maximization of clinical and functional outcomes that comes with an extended duration of uninterrupted treatment.[39,42] Overall, both agents were well tolerated, with the exception of a small increase in EPS-related symptoms in the subjects who switched to aripiprazole. In the exploratory analyses of change in non-HDL-C, aripiprazole treatment was associated with a significant improvement in non-HDL-C (Table 3), a validated predictor of risk for myocardial infarction.[43–47]

The improvements in weight and lipid profile seen with aripiprazole are relevant to public health goals regarding the reduction of risk of diabetes and cardiovascular disease in this high-risk population. These goals are underlined by results of the CATIE study, in which the 10-year risk for development of CHD was calculated using the Framingham CHD risk function, providing further

evidence of increased risk of CHD events in subjects with schizophrenia entering CATIE, versus matched controls.[3] A consensus statement developed by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity concluded that antipsychotics can affect risk for obesity, diabetes, and dyslipidemia and suggested that this risk should be considered in decisions concerning treatment with these medications.[6] The current results provide experimental support for the consensus statement's recommendation that patients receiving antipsychotic treatment who develop significant weight gain, hyperglycemia, or dyslipidemia should consider switching to a lower risk agent.[6] The recently initiated Comparison of Antipsychotics for Metabolic Problems (CAMP) study will address the effectiveness of different antipsychotics in patients with schizophrenia or schizoaffective disorder for whom a medication change may be indicated based on identified risk for cardiovascular disease despite adequate psychiatric symptom control.[48] That multicenter, rater-blind, randomized study will assess the effects of switching to aripiprazole versus continuing treatment with olanzapine, quetiapine, or risperidone on both metabolic parameters and clinical stability.

In conclusion, overweight patients on olanzapine randomly assigned to continue that treatment or to switch to aripiprazole had significant improvements in the primary outcomes of change in weight and fasting plasma triglyceride induced by the switch to aripiprazole. The results of this study and other ongoing studies (e.g., CAMP) will be important for informing public health efforts to lower the risk for diabetes and cardiovascular disease in this high-risk population.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), diphenhydramine (Benadryl and others), fluoxetine (Prozac and others), hydroxyzine (Vistaril and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), propranolol (Innopran, Inderal, and others), quetiapine (Seroquel), risperidone (Risperdal).

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