A Comparison of Weight Change During Treatment With Olanzapine or Aripiprazole: Results From a Randomized, Double-Blind Study

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Background: Weight gain is a side effect of therapy with many atypical antipsychotics and may have important clinical repercussions with respect to long-term health and treatment compliance. The primary objective of this double-blind study was to compare the safety and tolerability of aripiprazole and olanzapine in patients with schizophrenia as evidenced by the percentage of patients exhibiting significant weight gain. ***Method:*** This was a 26-week, multicenter, randomized, double-blind, active-controlled trial in patients with DSM-IV schizophrenia who were in acute relapse and required hospitalization. Significant weight gain was defined as a ≥ 7% increase in body weight from baseline. Body weight, Positive and Negative Syndrome Scale, and Clinical Global Impressions-Improvement scale (CGI-I) assessments were performed at baseline and at regular intervals during the study. The study period was from April 2000 through June 2001. ***Results:*** 317 patients were randomly assigned to aripiprazole (N = 156) or olanzapine (N = 161). Compared with those treated with aripiprazole, a greater proportion of patients treated with olanzapine exhibited clinically significant weight gain during the trial. By week 26, 37% of olanzapine-treated patients had experienced significant weight gain compared with 14% of aripiprazole-treated patients ($p < .001$). Statistically significant differences in mean weight change were observed between treatments beginning at week 1 and sustained throughout the study. At week 26, there was a mean weight loss of 1.37 kg (3.04 lb) with aripiprazole compared with a mean increase of 4.23 kg (9.40 lb) with olanzapine among patients who remained on therapy ($p < .001$). Changes in fasting plasma levels of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were significantly different in the 2 treatment groups, with worsening of the lipid profile among patients treated with olanzapine. There was a consistent and sustained improvement in symptoms in patients who remained on therapy with either olanzapine or aripiprazole as assessed by CGI-I scores and responder rates throughout the study. ***Conclusion:*** Olanzapine had a greater impact on patients' weight than aripiprazole. Significant differences in favor of aripiprazole were also observed in the effects of therapy on plasma lipid profile. Both treatment groups achieved comparable clinically meaningful improvements on efficacy measures. The observed effects on weight and lipids indicate a potentially lower metabolic and cardiovascular risk in patients treated with aripiprazole compared with those treated with olanzapine. *(J Clin Psychiatry 2004;65[suppl 18]:47–56)*

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Weight gain is a side effect of therapy with many atypical antipsychotics and has important clinical repercussions with respect to long-term health and treatment compliance. Additional adverse events such as dyslipidemias, diabetic ketoacidosis, and diabetes mellitus have been documented for various atypical antipsychotics, while other effects of clinical concern include electrocardiographic (ECG) changes, sedation, and risk of breast cancer due to hyperprolactinemia.[1–6] The impact these effects have on patient health and treatment effectiveness has been compared with the extrapyramidal symptoms (EPS) and tardive dyskinesia associated with

first-generation antipsychotics[7] and may significantly influence the treatment choices in the clinic.

The consequences of weight gain alone are clinically significant, as excessive weight gain and obesity are established risk factors for increased morbidity and mortality from cardiovascular disease, hypertension, stroke, and type 2 diabetes[8–11] and may increase the risk for, or exacerbate, diseases such as osteoarthritis, stroke, cancer, asthma, and gallstones.[10,12] Additionally, drug-induced weight gain may affect long-term compliance in patients with mental illness, directly influencing the likelihood of successfully managing the disease.[13,14]

According to the recent consensus statement jointly issued by the American Diabetes Association (ADA) and American Psychiatric Association (APA), the relative risk of inducing weight gain and metabolic abnormalities should be taken into consideration when choosing antipsychotic therapy.[15] The risk of weight gain does not appear to be equal among atypical antipsychotics; the dibenzodiazepine-derived drugs clozapine and olanzapine appear to have the greatest weight gain liability. Little weight gain has been reported with aripiprazole and ziprasidone, while risperidone and quetiapine seem to be associated with weight increases that are somewhat lower than those with olanzapine and clozapine.[16,17] Published comparative studies have confirmed differences in weight gain liability[18] and capacity to precipitate diabetes[19] among some atypical antipsychotics, but comparative data are needed for the newer generation of this drug class.

Aripiprazole, a next-generation atypical antipsychotic, is a novel molecule with a unique mechanism of action that distinguishes it from other antipsychotics. Aripiprazole is a potent partial agonist at D_2 dopamine and 5-HT_{1A} serotonin receptors and an antagonist at 5-HT_{2A} serotonin receptors.[20–23] Aripiprazole improved both the positive and negative symptoms of schizophrenia in controlled trials,[24,25] and recent data suggest a role in treatment of acute bipolar mania.[26] The overall pharmacologic profile of aripiprazole, including low-to-moderate affinity for H_1 histamine receptors, indicates that it should have low likelihood of causing weight gain.[27] A recent 26-week study of 310 patients with chronic schizophrenia found that aripiprazole was not associated with a mean weight increase from baseline, while demonstrating efficacy to prevent relapse of schizophrenia symptoms.[28] In a review of controlled studies involving more than 1500 patients, aripiprazole was associated with a low potential for EPS, weight gain, sedation, hyperprolactinemia, and QTc prolongation.[23] These data indicate that aripiprazole should have lower likelihood of inducing weight gain or metabolic abnormalities than some of the second-generation antipsychotics. In order to confirm this hypothesis, a multicenter, double-blind, randomized 26-week trial comparing the incidence of significant weight gain with aripiprazole and olanzapine in patients with acute relapse of schizophrenia was initiated, and the results from this trial are reported here.

METHOD

Study Design

This randomized, double-blind, parallel-group study was performed at 56 study sites in the United States (N = 41), Canada (N = 5), Argentina (N = 4), Brazil (N = 3), and Mexico (N = 3). The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and received institutional review board (IRB)/ethics committee approval. All patients provided written informed consent and/or consent was obtained from a legally acceptable representative if required by the local IRB.

Patients in acute relapse of schizophrenia requiring hospitalization were enrolled in the study and underwent a minimum 2-day washout of any neuroleptic medication. Following confirmation of eligibility after washout, patients were randomly assigned to treatment with aripiprazole, 15 to 30 mg/day, or olanzapine, 10 to 20 mg/day, in a double-blind fashion. The starting doses were 15 mg/day for aripiprazole and 10 mg/day for olanzapine. The doses of study medications could be increased weekly during the first 2 weeks on the basis of clinical judgment and if the patient's Clinical Global Impressions-Improvement (CGI-I)[29] score was ≥ 3 (minimal improvement or worsening) and thereafter as needed on the basis of efficacy and tolerability. Patients remained hospitalized until day 4, at which time they could be discharged provided they had at least minimal improvement of symptoms (CGI-I score of 1–3). Patients with a CGI-I score of ≥ 4 (no change or worsening) at week 6 were discontinued from the study.

Patient Population

Patients 18 years of age and older with a DSM-IV diagnosis of schizophrenia who were in acute relapse and required inpatient hospitalization were included in the study. Patients could participate if they had had a previous response to a neuroleptic medication other than clozapine and if they had been treated as an outpatient for at least 1 continuous 3-month period during the past 12 months. Women of childbearing potential were required to have a negative pregnancy test at screening and to be using an acceptable method of contraception.

Patients were excluded from the study if they had a DSM-IV diagnosis of schizoaffective disorder or substance use disorder, a positive screen for cocaine or alcohol (blood alcohol concentration ≥ 0.08%), or a clinical history of delirium, dementia, amnesia, or bipolar disorder. Patients could not have been hospitalized for ≥ 14 days immediately prior to screening. Patients who were deemed refractory to neuroleptic medication by the inves-

tigator, who had failed to respond to olanzapine, or who were likely to require concomitant therapy during the study were also excluded. Pregnant or nursing women were not permitted to participate. Other exclusion criteria included known allergy to aripiprazole, quinolinones, or olanzapine; suicidal ideation or suicide attempts; likely requirement for medications that might interfere with the analysis or metabolism of the study drugs; participation in a previous aripiprazole study; use of an investigational drug within 4 weeks of randomization; and clinically significant abnormal laboratory test results at screening.

Patients fulfilling the study entry criteria underwent a washout period for prior neuroleptic medication (2 days minimum or 1 depot cycle after the most recent depot antipsychotic injection). Baseline outcome measurements were then recorded in order to determine eligibility for randomization. Criteria for randomization included a Positive and Negative Syndrome Scale (PANSS)[30] total score of ≥ 60 and a score of ≥ 4 (moderate) on at least 2 of the following PANSS items: delusions, hallucinatory behavior, conceptual disorganization, or suspiciousness.

Concomitant Medications

Most psychotropic medications were not permitted as concomitant therapy during the study, including haloperidol, fluphenazine, carbamazepine, valproate, fluoxetine, and lithium. Patients were not permitted to take drugs for weight control during the study. Beta-blockers for the treatment of akathisia and antihistamines for agitation or anxiety were not permitted. Anticholinergic treatment of EPS was not permitted during screening but could be administered if deemed necessary by the investigators during the study at a dose not exceeding the equivalent of 6 mg/day of benztropine. No anticholinergic agents could be administered within 12 hours of efficacy or safety assessments. Lorazepam, at a dose of up to 4 mg/day, was allowed for the treatment of anxiety but could not be administered within 4 hours of efficacy or safety assessments.

Outcome Evaluations

To ensure standardized weight measures, each site was provided with identical, self-calibrating, self-zeroing weighing scales, and body weight was measured in a standardized fashion (patients were without shoes but otherwise fully clothed).

Body weight, vital signs, PANSS, and CGI-I assessments were performed at baseline (except CGI-I) and at day 4 and weeks 1, 2, 3, 4, 6, 8, 10, 12, 14, 18, 22, and 26. Blood and urine samples were also collected and were analyzed for fasting serum prolactin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride levels at screening and at weeks 3, 6, 12, and 26. Adverse events, including their severity and the likelihood of a relationship to study medication, were also recorded at these assessments.

Other measurements, including 12-lead ECG and clinical laboratory tests, were assessed at regular intervals during the study. Safety was assessed using reports of adverse events, vital sign measurements, and the results of physical examinations and clinical laboratory tests.

Statistical Analysis

The study was powered to detect a difference in the percentage of patients showing significant weight gain from baseline at week 26, assuming 15 percentage points difference between aripiprazole and olanzapine (incidence of 10% with aripiprazole and 25% with olanzapine), using a 2-sided test at the .05 significance level. With these assumptions, a sample size of 280 evaluable patients (140 per group) was required. To allow for an estimated 10% of patients who would be unevaluable for any reason, a minimum of 315 patients needed to be randomized. Significant weight gain was defined as a ≥ 7% increase in body weight.

Other outcome measures included mean change in body weight from baseline to week 26 and clinical improvement such as mean CGI-I score and proportion of clinical responders, defined as those patients who had a CGI-I score of 1 or 2 (very much improved or much improved).

The percentage of patients who showed significant weight gain from baseline was analyzed at week 26 using the last-observation-carried forward (LOCF) data set, excluding patients who did not receive at least 14 days of study medication or who did not have a baseline or an on-treatment weight measurement (primary analysis) and also as incidence over the course of the study using all patients randomly assigned to treatment who received study medication and who had a baseline and on-treatment measurement. Both analyses were performed using the Cochran-Mantel-Haenszel (CMH) test stratified for prior olanzapine use (> 7 consecutive days during the 6 weeks prior to screening) and for body mass index (BMI) at baseline (divided into three groups: < 23 kg/m^2, 23–27 kg/m^2, and > 27 kg/m^2). Other weight outcome measures were determined by analysis of covariance (ANCOVA), which included terms for baseline value, prior olanzapine use, and treatment group. Because of the high number of patients who discontinued the study (72%), results of analyses by time point are described on the observed-case (OC) basis (except for the primary endpoint), as the LOCF analysis would have included a large amount of data carried forward from patients who discontinued the study.

Data on changes in symptoms of schizophrenia were collected in order to ensure adequate response to therapy. ANCOVA was used to evaluate the mean change from baseline to each specified visit in the PANSS total score, including the baseline measure as a covariate and treatment as a main effect. Mean CGI-I score was determined by analysis of variance (ANOVA) for each specified visit.

Table 1. Baseline and Demographic Characteristics of Hospitalized Patients Randomly Assigned to Double-Blind Treatment for Schizophrenia

Variable	Olanzapine (N = 161)	Aripiprazole (N = 156)	Total (N = 317)
Age, y			
Mean	38.2	38.6	38.4
Median	38.0	37.0	38.0
SE	0.87	0.85	0.61
Gender, N (%)			
Male	115 (71)	114 (73)	229 (72)
Female	46 (29)	42 (27)	88 (28)
Weight, kg			
Mean	81.7	81.3	81.5
Median	78.36	78.9	78.6
SE	1.67	1.77	1.21
Body mass index, kg/m^2			
Mean	27.7	27.6	27.7
Median	26.1	26.5	26.4
SE	0.59	0.53	0.40
Prior olanzapine use, N (%)			
Yes	44 (27)	35 (22)	79 (25)
No	117 (73)	121 (78)	238 (75)
Schizophrenia type, N (%)			
Disorganized	10 (6)	7 (4)	17 (5)
Catatonic	0	0	0
Paranoid	138 (86)	133 (85)	271 (85)
Residual	0	3 (2)	3 (1)
Undifferentiated	13 (8)	13 (8)	26 (8)
Age at time of first hospitalization, y			
Mean	24.15	24.86	24.50
Median	22.50	22.00	22.00
SE	0.62	0.64	0.45

Responder rates based on the CGI-I score were analyzed using the CMH General Association test.

RESULTS

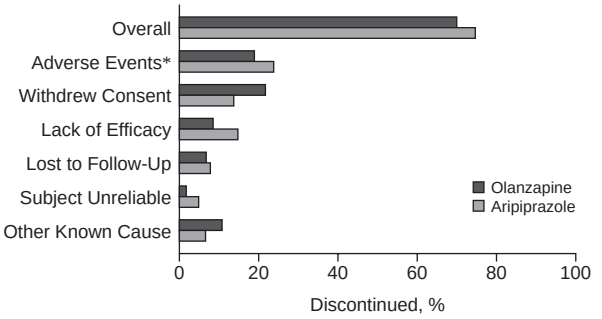
Patients and Disposition

Three hundred seventy-eight patients were enrolled in the study, and 317 were randomly assigned to aripiprazole (N = 156) or olanzapine (N = 161). The treatment groups were comparable with respect to demographic and baseline characteristics (Table 1).

Two hundred twenty-nine patients (72%) discontinued during the study. No significant difference was detected in the overall rate of discontinuation between the 2 groups (Figure 1). The most frequent causes of discontinuation were insufficient response, adverse events, and withdrawal of consent, accounting for 50% of patients in the olanzapine group and 53% of patients in the aripiprazole group. Three patients randomly assigned to treatment were excluded from safety and weight analyses because they did not receive study medication. A further 5 patients were excluded from the weight analysis because they did not have on-treatment weight measurements.

At endpoint, the mean daily doses of study medications were 25.1 mg for aripiprazole and 16.5 mg for olanzapine. Concomitant medication use (including anxiolytics and treatment for EPS) was comparable between the 2 groups.

Figure 1. Rates of and Reasons for Discontinuation in Patients With Schizophrenia Assigned to 1 of 2 Treatment Groups



*Most common adverse events (> 2% of patients) leading to discontinuation in both groups were psychosis and reaction schizophrenic.

Incidence of Weight Gain

A greater proportion of patients treated with olanzapine exhibited significant weight gain (≥ 7%) at any point during the trial compared with those treated with aripiprazole. Of the 155 patients in the olanzapine group, 58 (37%) experienced significant weight gain during the study, compared with 21 (14%) of 154 in the aripiprazole group ($p < .001$). Similar results were obtained when the LOCF data set was used for the analysis of the primary outcome; in this analysis, 33% of patients treated with olanzapine and 13% of those treated with aripiprazole experienced clinically significant weight gain ($p < .001$) at week 26.

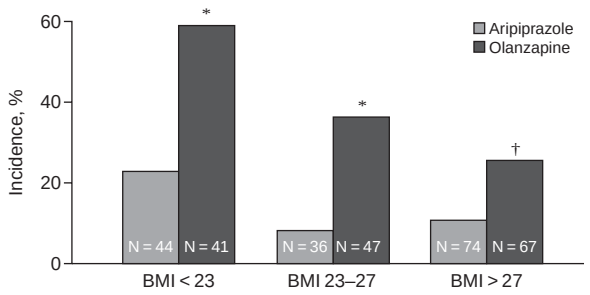
The proportion of patients who exhibited significant weight gain at any point during treatment with olanzapine was significantly greater than the proportion of patients treated with aripiprazole, whether they had previously been treated with olanzapine or not and regardless of the initial BMI (Figure 2).

Other Outcome Measures

Body weight. The mean change in body weight from baseline was significantly different between the treatment groups, with olanzapine-treated patients exhibiting a mean weight gain as opposed to a mean weight loss for patients treated with aripiprazole. At week 26, the mean change in body weight from baseline was +4.23 kg (9.40 lb) for the olanzapine group and –1.37 kg (3.04 lb) for the aripiprazole group ($p < .001$). The difference between treatment groups was statistically significant beginning at week 1 ($p = .002$) and continued at all time points during the study (Figure 3).

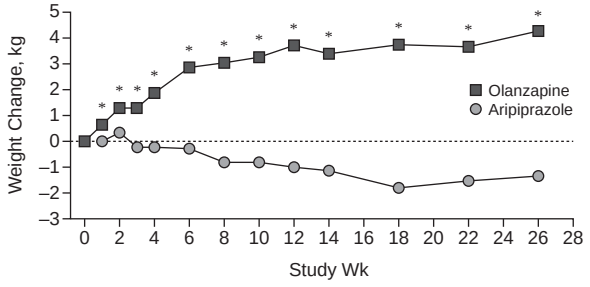
Serum lipids. Differences were observed between treatment groups in the change from baseline to week 26 for serum concentrations of total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol (Figure 4). At week

Figure 2. Incidence of Clinically Significant Weight Gain by Baseline Body Mass Index (BMI) in Patients Treated for Schizophrenia[a]



[a]Clinically significant weight gain defined as ≥ 7% increase from baseline at any time during the study.
*p < .01 vs. aripiprazole.
†p < .05 vs. aripiprazole.

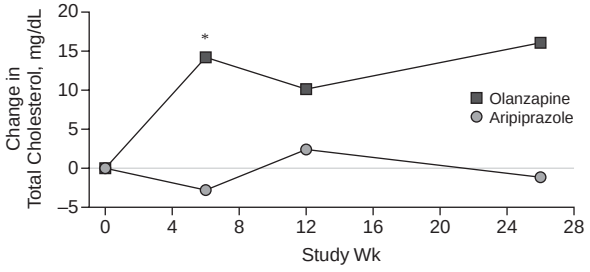
Figure 3. Mean Change From Baseline in Body Weight of Patients Treated for Schizophrenia[a]



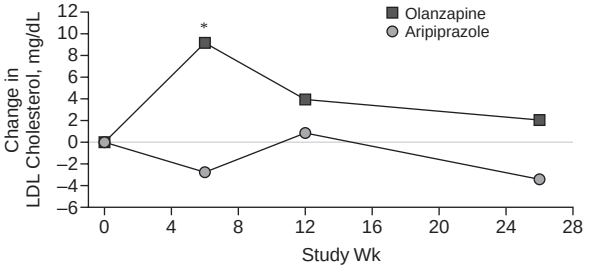
Olanzapine, N =	134	112	101	90	83	80	62	58	54	49
Aripiprazole, N =	130	112	95	76	64	55	49	45	41	41

[a]Analysis based on patients remaining on therapy (observed cases).
*p ≤ .002 vs. aripiprazole.

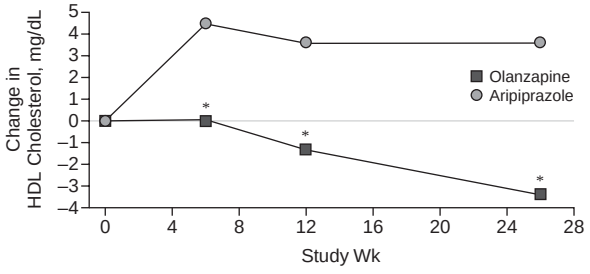
Figure 4. Mean Change From Baseline in Fasting Plasma Lipid Levels of Patients Treated for Schizophrenia



Olanzapine, N =	115	58	47	23
Aripiprazole, N =	108	51	30	22



Olanzapine, N =	114	57	46	22
Aripiprazole, N =	108	51	30	22



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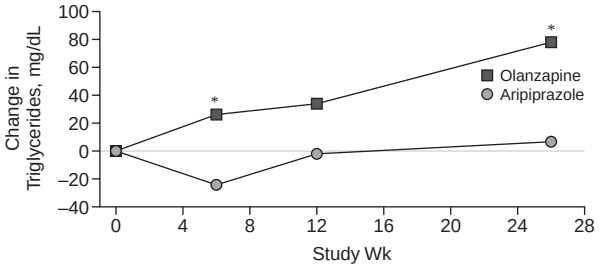
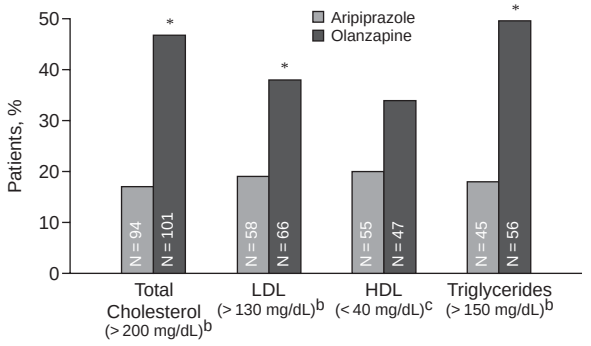


Olanzapine, N =	114	57	46	22
Aripiprazole, N =	108	51	30	22

*p < .05, but small number of patients with fasting lipid measurements makes interpretation of statistical differences difficult.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

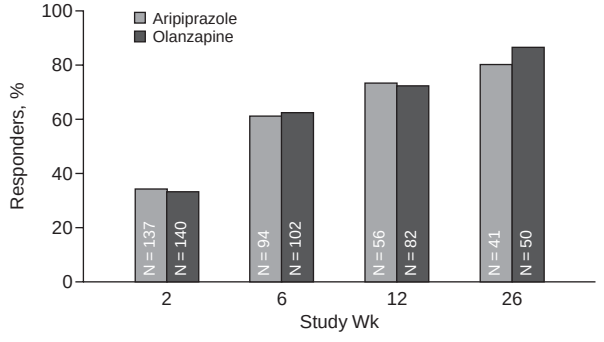
26, the mean changes in fasting triglyceride levels were +79.4 mg/dL with olanzapine and +6.5 mg/dL with aripiprazole (p < .05). The changes in fasting HDL cholesterol levels also favored aripiprazole, with significant differences in changes from baseline to endpoint between the 2 groups (olanzapine, –3.39 mg/dL; aripiprazole, +3.61 mg/dL; p < .05). The differences between changes in fasting total cholesterol levels (+16.3 mg/dL for the olanzapine group and –1.13 mg/dL for the aripiprazole group) and LDL cholesterol (+2.27 mg/dL olanzapine vs. –3.86 mg/dL aripiprazole) showed a similar pattern but did not reach statistical significance. Analysis of the safety data set revealed significant differences in the incidence of new-onset dyslipidemias between the 2 treatment groups (Figure 5). In patients with lipid levels within the normal range at baseline, treatment with olanzapine resulted in significantly more patients exhibiting clinically significant values of total cholesterol (> 200 mg/dL: 47% with olanzapine and 17% with aripiprazole), LDL cholesterol (> 130 mg/dL: 38% with olanzapine and 19% with ari-

Figure 5. Incidence of New Dyslipidemias in Patients Treated for Schizophrenia[a]



[a]Data obtained from fasted plasma samples.
[b]Criterion of ≥ upper limit of normal.
[c]Criterion of ≤ lower limit of normal.
*p < .05 vs. aripiprazole.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Figure 6. Response Rates Among Patients Treated for Schizophrenia Who Remained on Therapy at Specified Time Points[a]

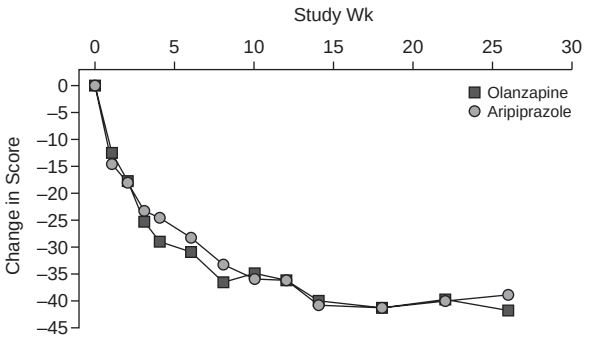


[a]Response defined as Clinical Global Impressions-Improvement scale score of 1 or 2 (very much improved or much improved). No statistically significant differences between treatments were seen at any time point.

piprazole), and triglyceride (> 150 mg/dL: 50% with olanzapine and 18% with aripiprazole) levels.

Reduction in symptoms of schizophrenia. Data on reduction in symptoms of schizophrenia were collected to ensure adequate response during the study and demonstrated robust and clinically meaningful improvements in psychotic symptoms for patients in both treatment groups. For patients remaining on therapy at week 6, mean CGI-I scores were 2.3 in both treatment groups, and the response rates, defined as a CGI-I score of 1 or 2 (very much improved or much improved), were 61% with aripiprazole and 62% with olanzapine. Medically important benefits were maintained throughout the treatment period for patients who remained on therapy, with comparable mean CGI-I scores and responder rates and no clinically meaningful differences between the aripiprazole and olanzapine groups. Eighty percent of patients in the aripiprazole group and 86% in the olanzapine group were classified as responders (p = nonsignificant) at week 26 (Figure 6). Mean change in PANSS score indicated continuous improvement with either olanzapine or aripiprazole (Figure 7).

Figure 7. Mean Change From Baseline in PANSS Total Score for Patients Treated for Schizophrenia Who Remained on Therapy With Olanzapine or Aripiprazole[a]



[a]Baseline PANSS total score: aripiprazole = 94.8, olanzapine = 94.5.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Additional Safety Assessments and Laboratory Measurements

The most common adverse events included headache (32% olanzapine; 23% aripiprazole), insomnia (30% olanzapine; 32% aripiprazole), anxiety (25% olanzapine; 20% aripiprazole), and somnolence (23% olanzapine; 8% aripiprazole). Serious adverse events were reported by 21% of patients. The most common serious adverse events were related to symptoms of the underlying illness (psychosis and schizophrenic reaction), and their incidence was similar in the 2 treatment groups. One patient died by strangulation during the study, which was not considered related to study medication and was classified as a possible homicide or suicide.

The overall incidence of EPS-related adverse events was low (16%) and was comparable for the aripiprazole (17%, N = 26) and olanzapine (16%, N = 25) groups. The pattern of EPS-related adverse events was also similar in the 2 treatment groups: the most common adverse events in this group were parkinsonism events (12% with olanzapine and 11% with aripiprazole) and akathisia (3% with olanzapine and 6% with aripiprazole). The use of concomitant medication for treatment of EPS symptoms reflected the incidence of reported EPS-related adverse events: overall, 15% of patients received these medications during the study, predominantly benztropine.

No clinically significant effects on blood pressure or heart rate were observed with aripiprazole or olanzapine in this study. There were few occurrences of QTc abnor-

malities among study patients using the Bazett's formula[31] (4% olanzapine; 1% aripiprazole). Mean change from baseline to endpoint in QTc interval was similar in the 2 groups (aripiprazole, –3.4 ms; olanzapine, +0.3 ms). A greater percentage of patients treated with olanzapine had clinically significantly raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (6% and 3% of evaluable patients, respectively) compared with those treated with aripiprazole (1% for each measure) at any time point during the study period.

There were no significant differences in the change in mean fasting serum glucose levels from baseline to endpoint between the aripiprazole and olanzapine treatment groups (5 mg/dL and 7 mg/dL, respectively).

Mean decreases in prolactin from elevated baseline levels (mean baseline levels: aripiprazole, 22.6 ng/mL; olanzapine, 29.7 ng/mL) were observed at endpoint in both treatment groups. Among patients who had normal prolactin levels at baseline, 8% in the aripiprazole group and 37% in the olanzapine group experienced increases above the upper limit of normal at some point during the trial.

DISCUSSION

In this 26-week study conducted in patients with acute relapse of schizophrenia, aripiprazole, administered at 15 to 30 mg once daily, had a reduced weight gain liability compared with olanzapine. Over the course of the study, only 14% of patients in the aripiprazole group experienced significant weight gain (i.e., ≥ 7% increase from baseline) compared with 37% of the olanzapine group ($p < .001$). In addition, patients in the aripiprazole group showed a mean decrease in body weight in the course of the study compared with a mean increase for the olanzapine group; this difference was highly statistically significant ($p < .001$).

The changes in body weight were paralleled by changes in plasma lipid profile. Patients treated with olanzapine experienced numerical increases in total and LDL cholesterol levels and statistically significantly increased triglyceride concentrations at week 26 compared with patients treated with aripiprazole. Aripiprazole patients exhibited a small mean improvement in HDL cholesterol levels, which was statistically significantly different from the worsening recorded in the olanzapine group. The incidences of new-onset dyslipidemias with aripiprazole were relatively low and similar to those seen with both placebo and aripiprazole in a previously reported trial (see Casey,[32] this supplement), while patients treated with olanzapine had significantly higher rates for new-onset abnormalities in plasma levels of total and LDL cholesterol and triglyceride.

Clinically robust improvements in symptoms of schizophrenia, as measured by PANSS and CGI-I scores and CGI-I response rate, were observed at week 6, were comparable in the 2 treatment groups, and were generally maintained in patients who remained on therapy.

The data from this trial, which focused on weight change with aripiprazole and olanzapine, are generally in agreement with previously published studies, which reported weight gain as a secondary outcome measure. For example, in a 26-week study comparing aripiprazole with placebo for prevention of relapse in patients with stable schizophrenia, significant weight gain was reported for 6% of patients receiving aripiprazole compared with 4% for placebo.[28] Similarly, the absolute change in body weight reported here (i.e., decrease of 3.04 lb [1.37 kg]) is in line with that in the relapse-prevention study (–2.80 lb [–1.26 kg] compared with –1.93 lb [–0.87 kg] for placebo).[28] In a 52-week trial versus haloperidol, there was a mean increase in weight of 1.05 kg (2.33 lb) for aripiprazole, comparable with the increase of 0.39 kg (0.87 lb) observed with haloperidol.[33] Thus, accumulating data for aripiprazole suggest that this agent has a low liability for weight gain, comparable with that observed with placebo or haloperidol.

The current study is also consistent with the weight gain liability previously reported for olanzapine. In a retrospective analysis of a long-term olanzapine study, 52% of patients who had received olanzapine treatment for more than 39 weeks experienced clinically significant weight gain.[34] Mean weight gain was 6.26 kg (13.91 lb) with olanzapine compared with 0.69 kg (1.53 lb) with haloperidol and remained stable for 1 to 3 years for patients completing 3 years of olanzapine treatment. A similar weight gain (7.9 kg [17.6 lb]) was reported in a retrospective chart review of patients receiving olanzapine for 1 year.[35] A meta-analysis of over 80 studies[16] reported mean increases of 4.15 kg (9.22 lb) with olanzapine after 10 weeks of treatment.

The only previously reported study directly comparing olanzapine and aripiprazole was a 26-week open-label study that examined the effects of aripiprazole and olanzapine on cognition in patients with stable schizophrenia or schizoaffective disorder.[36] In that trial, 6% of patients in the aripiprazole group experienced significant weight gain compared with 25% of the olanzapine-treated patients. The mean change in weight was –0.9 kg (2.0 lb) for aripiprazole versus +3.6 kg (8.0 lb) for olanzapine.[36] These indirect and open-label data from previously completed trials, indicating a differential likelihood of aripiprazole and olanzapine to cause weight gain, were confirmed in the current double-blind study.

The effects on plasma lipid profile that were observed in this study (unfavorable changes with olanzapine and neutral/minimal changes in lipid profile with aripiprazole) were also in agreement with previously published data. In the 26-week study for prevention of relapse, both aripiprazole and placebo were associated with mild favorable changes in fasting plasma lipid profiles.[28] In that study, the incidences of new-onset dyslipidemias were similar

between placebo and aripiprazole and comparable to the rates with aripiprazole reported here.

In contrast, significant increases in serum triglyceride concentrations were associated with olanzapine therapy in small prospective[37] and retrospective reports.[35] An analysis of over 18,000 schizophrenia patients in the United Kingdom found that olanzapine use was associated with a nearly 5-fold greater chance of developing hyperlipidemia compared with no antipsychotic treatment, and a more than 3-fold increase compared with conventional antipsychotic agents.[38] Significant increases in serum triglyceride concentrations were also associated with olanzapine therapy in small prospective[37] and retrospective[35] reports. Finally, the 26-week, open-label cognition study[36] reported that total cholesterol levels showed a median decrease of 8.2 mg/dL from baseline with aripiprazole therapy at week 26, while olanzapine-treated patients showed a median increase of 12.2 mg/dL.

Differences in liability for weight gain between different antipsychotic agents have important clinical implications since excessive weight gain and obesity are established risk factors for increased morbidity and mortality from cardiovascular disease, hypertension, stroke, and type 2 diabetes.[8–10,15] Kannel et al.[11] have recently reported data from the Framingham Study cohort showing that the age-adjusted risk ratio for coronary heart disease is 1.48 times greater in obese men compared with lean men and 2.09 times greater for obese women compared with lean women and that these risk ratios increase to 2.07 (for men) and 10.9 (for women) when 3 or more other risk factors are also present.

This is of particular relevance to patients with schizophrenia, as many have preexisting risk factors for cardiovascular disease, such as obesity and smoking.[39] However, recent evidence suggests that weight gain that leaves individuals within the "normal" weight range also increases the risk of illness and mortality.[40] For example, those who gain 5.0 to 7.9 kg as adults are 1.9 and 1.25 times more likely to develop type 2 diabetes[41] and coronary heart disease,[42] respectively, than those who lose weight or maintain a stable weight.

Estimates of the impact of antipsychotic-induced weight gain on health[43] suggest that a 10-kg increase could result in an additional 416 deaths per 100,000 patients over a 10-year period. The expected effects of weight gain on the risk of developing type 2 diabetes may be further exacerbated, as recent evidence suggests that some antipsychotic agents may directly contribute to increases in blood glucose levels.[44,45]

Differential effects on changes in lipid levels may also have implications for patient health, as dyslipidemias are established risk factors for cardiovascular disease.[46,47] In particular, elevated triglyceride levels are a significant risk factor for coronary artery disease and also appear to precipitate or exacerbate diabetes.[48]

The differences in metabolic response to aripiprazole and olanzapine likely reflect their differing pharmacologic profiles. Although the exact pharmacology of weight gain and metabolic disturbances with antipsychotic therapy is not known, there is a strong correlation between H_1 histamine receptor affinity and weight gain liability of different agents.[49,50] Olanzapine exhibits significant affinity for the H_1 histamine receptor and the M_1 muscarinic cholinergic receptor, both of which are associated with hunger, satiety, and sedation, while aripiprazole has low-to-moderate affinity for these receptors.[27,51] The high rate of somnolence observed in this study is also consistent with this pharmacologic profile.

The high discontinuation rate observed in the current study is typical of many long-term controlled trials of antipsychotic therapy. In a 46-week extension to a 6-week study of olanzapine and haloperidol in patients with schizophrenia, discontinuation rates of 56% to 61% and 74% to 82% were reported after 32 and 46 weeks, respectively, of the extension phase.[52] In 1-year studies of relapse prevention in patients with schizophrenia, discontinuation rates with antipsychotic medication ranged from 44% to 58%.[53,54]

Both aripiprazole and olanzapine were generally well tolerated during the current study, with low potential for EPS and with similar adverse event profiles. Somnolence was, however, 3 times more frequent with olanzapine than with aripiprazole. Somnolence may be an undesirable effect in the long-term treatment of schizophrenia because it affects patients' ability to interact with their environment and impacts their quality of life.[55] In a U.K. surveillance study, somnolence was reported as the most common adverse event reason for discontinuation of treatment with olanzapine.[56]

Both drugs in this study reduced the plasma prolactin levels seen at baseline, which were most likely elevated due to prior antipsychotic treatment. This normalizing effect on prolactin levels with aripiprazole is consistent with other aripiprazole studies[25,57] and is of potential clinical importance because elevated serum prolactin is known to be associated with a variety of clinical sequelae that include sexual dysfunction, gynecomastia, amenorrhea and galactorrhea,[58,59] and increased risk of breast cancer[6] and osteoporosis.[60,61] The rate of new-onset hyperprolactinemia was higher in the olanzapine group compared with the aripiprazole group.

The relative risk of weight gain, dyslipidemias, and diabetes associated with atypical antipsychotics is an issue that is important for the physical and psychological well-being of patients who need this therapy. Establishing a risk-benefit assessment is critical when considering antipsychotic agents. Factors to consider include the nature of the patient's psychiatric condition, past treatment history, patient preference, and comorbidities. Establishing the relative contributions of medications to each condition

can provide clinicians with a context from which they can better tailor treatment to individual patients and monitor side effects. The APA recommends that if a patient gains ≥ 5% of his or her initial weight during antipsychotic therapy, the physician should consider switching to an agent with less metabolic liability.[15] The current study provides direct evidence that aripiprazole exhibits a better safety profile with respect to weight gain and metabolic parameters than olanzapine; these findings indicate that treatment with aripiprazole may help minimize the impact of antipsychotic therapy on cardiovascular risk.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), carbamazepine (Carbatrol, Tegretol, and others), clozapine (Clozaril, Fazaclo, and others), fluoxetine (Prozac and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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