A 28-Week, Randomized, Double-Blind Study of Olanzapine Versus Aripiprazole in the Treatment of Schizophrenia

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Objective: To evaluate the effectiveness of olanzapine versus aripiprazole in patients with schizophrenia.

Method: Patients aged 18 to 65 years with schizophrenia (diagnosed according to DSM-IV-TR criteria) were randomly assigned to either olanzapine (n = 281) or aripiprazole (n = 285) for 28 weeks of double-blind treatment. The primary outcome was time to all-cause discontinuation. Efficacy was measured by Positive and Negative Syndrome Scale (PANSS) total change from baseline. Time-to-event data were analyzed via the Kaplan-Meier method. The study was conducted from October 2003 to July 2007.

Results: Treatment groups did not differ significantly in time to all-cause discontinuation (p = .067) or all-cause discontinuation rate (olanzapine, 42.7% vs. aripiprazole, 50.2%; p = .053). Olanzapine-treated patients had significantly longer time to efficacy-related discontinuation (p < .001) and a significantly lower efficacy-related discontinuation rate (olanzapine, 8.9% vs. aripiprazole, 16.8%; p = .006). Olanzapine-treated patients had a significantly greater mean decrease (last observation carried forward) in PANSS total score (–30.2) than did aripiprazole-treated patients (–25.9, p = .014). Olanzapine-treated patients had a mean weight change of +3.4 kg (vs. +0.3 kg for aripiprazole-treated patients; p < .001) and a significantly greater incidence of ≥ 7% body weight gain at any time (40.3% vs. 16.4%; p < .001). Fasting mean glucose change was +4.87 mg/dL for olanzapine and +0.90 mg/dL for aripiprazole (p = .045). Incidence of baseline glucose < 100 mg/dL and ≥ 126 mg/dL at any time was 1.7% for olanzapine and 0.6% for aripiprazole (p = .623). Fasting mean total cholesterol change was +4.09 mg/dL for olanzapine and –9.85 mg/dL for aripiprazole (p < .001). Incidence of baseline total cholesterol < 200 mg/dL and ≥ 240 mg/dL at any time was 9.2% for olanzapine and 1.5% for aripiprazole (p = .008). Fasting mean triglycerides change was +25.66 mg/dL for olanzapine and –17.52 mg/dL for aripiprazole (p < .001). Treatment groups did not significantly differ on measures of extrapyramidal symptoms.

Conclusion: Treatment groups did not differ significantly on the primary outcome. Olanzapine-treated patients had significantly greater improvement in symptom efficacy at 28 weeks as well as significantly greater mean increases in weight and glucose and significantly greater worsening on lipids parameters.

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In longer-term clinical trials, duration of remaining on treatment is an important outcome measure that provides a global assessment of both patients' and providers' evaluations of efficacy and tolerability.[1] All-cause treatment discontinuation data are available for olanzapine and other atypical agents from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study[2] and from a more recent integrated analysis[3] of olanzapine clinical trial data. Although aripiprazole was not included in the CATIE study, at 18 months, olanzapine was found to have a significantly longer time to all-cause discontinuation than quetiapine or risperidone, but not ziprasidone.[2] In an integrated analysis[3] of discontinuation data from all published double-blind, randomized clinical trials comparing olanzapine with other antipsychotic agents, olanzapine patients were found to have significantly greater likelihood of remaining on treatment for a longer period of time than patients treated with risperidone, ziprasidone, and quetiapine, but not clozapine.[3]

There have been 2 previous long-term, head-to-head randomized, controlled clinical studies[4,5] of olanzapine and aripiprazole, each with 52 weeks of data available in clinical trial registries. The 2004 study[4] has also been published with 26 weeks of data.[6] In addition to high attrition rates by 52 weeks (87% for aripiprazole and 81% for

olanzapine), the 2004 study reported no treatment group differences on observed case analyses of efficacy measures (e.g., Positive and Negative Syndrome Scale [PANSS] total score and Clinical Global Impressions-Severity of Illness [CGI-S] score).[4] The 2005 study[5] reported statistically significantly higher discontinuation rates with aripiprazole up to week 52 (61% vs. 53% for olanzapine) and statistical differences at endpoint favoring olanzapine on the PANSS total, last observation carried forward (LOCF) at all time points measured beginning at 6 weeks, but only at 6 weeks with the observed-case analysis.[5] In both of these studies,[4,5] significantly greater mean weight gain, incidence of significant (≥ 7%) weight gain, mean increase in total cholesterol, and mean increase in triglycerides were observed for olanzapine-treated patients. An additional 5-day study,[7] comparing olanzapine and aripiprazole in the treatment of agitation in patients with schizophrenia, found no treatment group differences on the PANSS-Excited Component score.

Although there is some evidence that olanzapine has superior efficacy to aripiprazole in treating schizophrenia,[8] randomized, controlled, head-to-head data on therapeutic effectiveness for these 2 antipsychotics are lacking. The primary objective of this study was to determine the long-term effectiveness of olanzapine relative to aripiprazole, as measured by time to all-cause treatment discontinuation in patients with schizophrenia during 28 weeks of double-blind therapy.

METHOD

This randomized, double-blind clinical trial was conducted at 60 study centers in North America, South America, and Australia from October 2003 to July 2007. All procedures were conducted in compliance with the Declaration of Helsinki and the standards established by any applicable institutional review boards. Written informed consent was obtained from all patients after complete description of the study. Female patients who were pregnant or nursing were excluded from the study. Significant medical illness was also an exclusion criterion. Complete exclusion criteria are available upon request. Concomitant medications with primary central nervous system activity were not allowed, with the exception of benzodiazepines as permitted at dosages up to an equivalent of lorazepam 4 mg/day for the first 4 weeks of the study and 2 mg/day afterward.

Patients

Patients were inpatients (16%) or outpatients (84%), 18 to 65 years of age, meeting diagnostic criteria for schizophrenia, according to DSM-IV-TR, with an initial PANSS[9] 30-item total score of ≥ 75, a minimum score of ≥ 4 on one of the PANSS positive items (delusion, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness, or hostility), and a minimum score of 4 on the CGI-S[10] at both visits 1 (screening) and 2 (randomization), with an initial score of ≥ 3 on the Clinical Global Impressions-Improvement (CGI-I)[10] scale at visit 2.

Measures

The primary measure of effectiveness was time to all-cause treatment discontinuation of olanzapine or aripiprazole. Secondary efficacy measures included discontinuation due to lack of efficacy, discontinuation due to efficacy-related reasons (i.e., due to lack of efficacy or due to any of these adverse events: exacerbation of schizophrenia, psychotic disorder, aggression, depression, homicidal ideation, suicide attempt, agitation, anger, anxiety, or delusion), discontinuation due to any adverse event, mean change from baseline to 8 weeks and 28 weeks in PANSS total score (scored on a 1 to 7 scale), PANSS positive and negative subscale scores, CGI-S score, and CGI-I score. PANSS response rate (defined as a ≥ 30% reduction in PANSS total score at endpoint) and PANSS remission rate (defined as an endpoint score of ≤ 3 on all of the following PANSS items: delusions, conceptual disorganization, hallucinatory behavior, excitement, blunted affect, lack of spontaneity and flow of conversation, mannerisms and posturing, and unusual thought content[11]) were also secondary efficacy measures.

Safety monitoring included complete physical and psychiatric examinations, medical history, assessment of adverse events, laboratory analyses, and the following measures of extrapyramidal symptoms: the Simpson-Angus Scale,[12] the Abnormal Involuntary Movement Scale (AIMS),[13] and the Barnes Akathisia Scale.[14]

Efficacy scales were administered at baseline (except for the CGI-I) and at all visits. Adverse events were recorded at each visit. Laboratory measures were generally conducted at baseline, week 12, and week 28. Extrapyramidal symptom measures were conducted at baseline, week 12, and week 28, except for the Barnes Akathisia Scale, which was also measured at weeks 1, 2, 3, 4, 8, and 20. Rater training for the secondary efficacy measures consisted of a brief review of the PANSS and CGI scales. Investigators were selected under the condition that either the investigator or his or her designee was qualified to conduct the PANSS (we required PANSS Certification) and CGI (had to have an M.D. degree). Interrater reliability data were not collected for these secondary outcome measures.

Patient compliance with study medication was assessed at each visit by direct questioning. Any deviation from the prescribed dosage regimen was recorded as noncompliance. Patients who were significantly noncompliant were discontinued from the study. A patient was considered significantly noncompliant if he or she missed more than 5 consecutive days of study medication (full doses), missed

more than 14 cumulative days of study medication (full doses) during the study, or took less than 50% of the prescribed dose within 1 visit interval. Similarly, a patient was considered significantly noncompliant if he or she intentionally or repeatedly took more than the prescribed amount of medication, as judged by the investigator.

Study Design

The study consisted of 2 phases: a 2- to 9-day screening phase and a 28-week double-blind treatment phase. The 2- to 9-day screening phase consisted of screening tests, patient history, and psychiatric and physical examinations. During this phase, patients were tapered off all excluded medications and all criteria for enrollment were verified.

After screening was complete and eligibility was verified, patients began a 28-week double-blind treatment phase, during which they were assigned in random, equal allocation to 1 of 2 treatment groups: olanzapine 15 mg/day or aripiprazole 15 mg/day. Dose increases were allowed at week 2 and at any time thereafter. Dose decreases due to adverse event were allowed at any time by single dose increments. Possible dosages for the treatment groups were as follows: olanzapine 10, 15, 17.5, or 20 mg/day, or aripiprazole 10, 15, 20, or 30 mg/day.

Assuming discontinuation rates of 43.0% for olanzapine and 57.6% for aripiprazole, a sample size of 280 patients per treatment group was calculated to yield 94% power to detect a significant difference in time to discontinuation.

Statistical Analyses

Analyses were done on an intent-to-treat basis. Patients were included in an analysis only if they had a baseline and at least 1 postbaseline measure. Baseline-to-endpoint mean change analyses used LOCF analysis of covariance with therapy and investigator site as fixed effects and baseline as a covariate. Investigators with less than 2 patients per treatment group were pooled within country. All reported mean change scores, unless otherwise specified, reflect least-squares means. We also present results of a mixed-effects model repeated-measures analysis of covariance (MMRM) for the PANSS.[15] PANSS response rates were adjusted[16,17] to correct for a nonzero minimum score on the PANSS (i.e., percent response was calculated as [baseline score – endpoint score]/[baseline score – 30] ×100).

Time-to-event estimates were calculated via the Kaplan-Meier technique, and curves were compared statistically using the log-rank test. Categorical variables (e.g., response and remission rates, frequencies of adverse events) were analyzed using Fisher exact test. All analyses were evaluated for significance with 2-tailed tests at an α level of .05 and performed with Statistical Analysis Systems (SAS) software, version 8 (SAS Institute, Cary, N.C.).

Table 1. Baseline Demographic and Illness Characteristics by Treatment Group

Variable	Olanzapine (N = 281)	Aripiprazole (N = 285)	p Value[a]
Age, y			
Least-squares mean	39.3	38.2	.184
Mean (SD)	38.3 (10.5)	37.3 (10.4)	
Female, n (%)	87 (31.0)	95 (33.3)	.589
Ethnic origin, n (%)			
White	78 (27.8)	90 (31.6)	.821
African descent	87 (31.0)	90 (31.6)	
Hispanic	96 (34.2)	84 (29.5)	
Other[b]	20 (7.1)	19 (6.7)	
Age at first episode, y			
Least-squares mean	22.8	21.9	.193
Mean (SD)	23.1 (7.5)	22.4 (7.8)	
Number of previous episodes			
Least-squares mean	8.4	8.7	.634
Mean (SD)	7.5 (7.6)	8.0 (8.3)	

[a]Tests of mean differences were performed on the least-squares means. Categorical variables were analyzed with Fisher exact test.
[b]Two patients in the aripiprazole treatment group had missing ethnic origin data and are not included here.

RESULTS

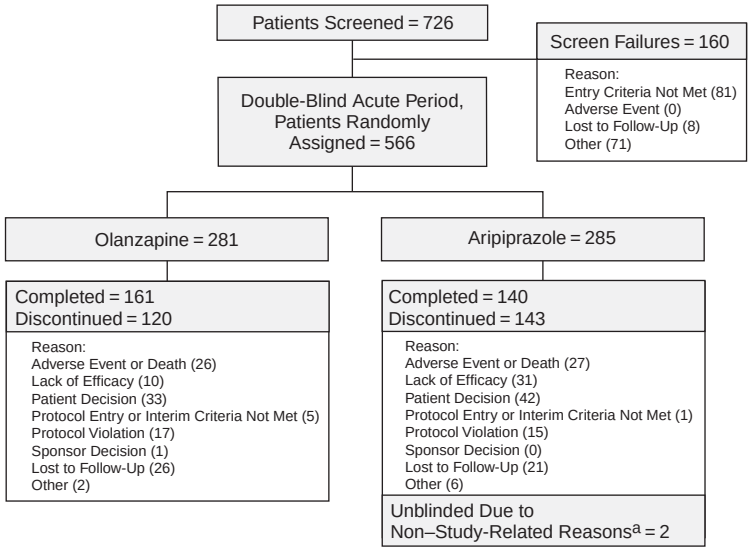
Table 1 shows baseline demographic and illness characteristics for the therapy groups. Most of the patients were male, with a mean age of 38. The mean age at onset of schizophrenia was early 20s, and there was a mean of 8 to 9 previous episodes of exacerbation. The mean baseline PANSS total score of approximately 95 was in the moderate to severe range. The treatment groups did not significantly differ in these baseline characteristics.

Patient Disposition and Dosing Information

Figure 1 is the patient flowchart, showing the movement of patients throughout the study. Approximately 78% of patients who were screened were subsequently randomly assigned to treatment. Thus, 566 patients entered the acute, double-blind treatment phase. A total of 301 patients (53.2%) completed the 28-week acute phase, with the following completion rates by group: olanzapine, 57.3% (161 of 281); aripiprazole, 49.1% (140 of 285); p = .053.

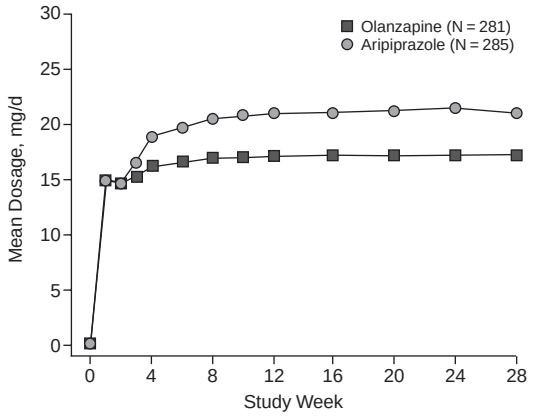
Mean modal dosages were 16.7 mg/day for olanzapine and 19.3 mg/day for aripiprazole. Figure 2 shows visit-wise dosing for the 2 treatment groups. The rates of noncompliance or missing compliance data at any time during the study were not significantly different: olanzapine, 35.2%; aripiprazole, 41.4%; p = .142. One patient (who was randomly assigned to olanzapine) was significantly noncompliant and discontinued from the study. Although the overall rates of benzodiazepine use were not significantly different between the therapies (olanzapine, 47.7%; aripiprazole, 53.0%; p = .239), a post hoc visit-wise analysis showed that the rates of benzodiazepine use were significantly higher for aripiprazole-treated patients at 8 of 12 double-blind visits (week 2, week 3, and weeks

Figure 1. Patient Flow Diagram Showing Reasons for Discontinuation Reported by the Site Investigators



[a]Site was searched by court order for reasons not related to study conduct. These patients were active and unblinded after site closure.

Figure 2. Visitwise Mean Dose Information for the 2 Treatment Groups



8–24; all $p < .05$). Mean benzodiazepine dosage taken (converted to lorazepam equivalents) across all visits (calculated as total dose divided by the days taking benzodiazepines) was not significantly different between treatment groups: olanzapine, 0.58 mg/day; aripiprazole, 0.75 mg/day; $p = .243$. Rates of anticholinergic use were also not significantly different between therapy groups: olanzapine, 21.4%; aripiprazole, 18.6%; $p = .462$.

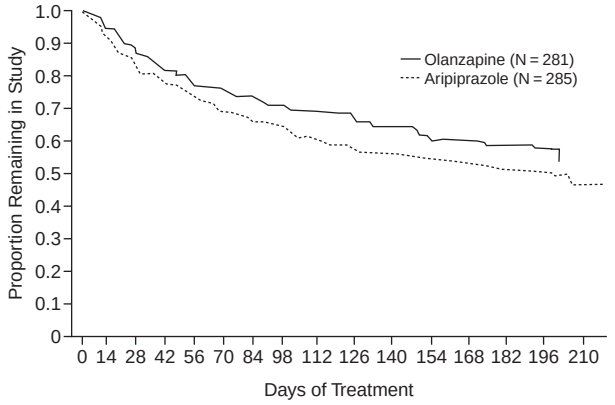
Effectiveness and Efficacy

Figure 3A displays the Kaplan-Meier curves for time to all-cause discontinuation, the primary outcome measure. The overall test of differences (based on log-rank χ^2) between the survival curves was not significant ($p = .067$). The time required for 50% of patients to discontinue for any reason (i.e., "median survival time") was 204 days for the aripiprazole-treated group and could not be calculated for the olanzapine-treated group (i.e., not enough olanzapine patients discontinued to estimate). Overall rates of all-cause discontinuation were 42.7% for olanzapine and 50.2% for aripiprazole ($p = .053$). The olanzapine group had significantly longer time to discontinuation due to lack of efficacy ($p < .001$) and time to discontinuation due to efficacy-related reasons (Figure 3B, $p = .003$). Overall rates of discontinuation due to lack of efficacy were 3.6% for olanzapine and 10.9% for aripiprazole ($p < .001$); rates of discontinuation due to efficacy-related reasons were 8.9% for olanzapine and 16.8% for aripiprazole ($p = .006$). The survival curves for time to discontinuation due to adverse event or death (Figure 3C) were not significantly different ($p = .753$). Rates of discontinuation due to adverse event or death were 9.3% for olanzapine and 9.5% for aripiprazole ($p \approx 1.00$). The treatment groups did not differ significantly in rate of discontinuation due to any specific adverse event.

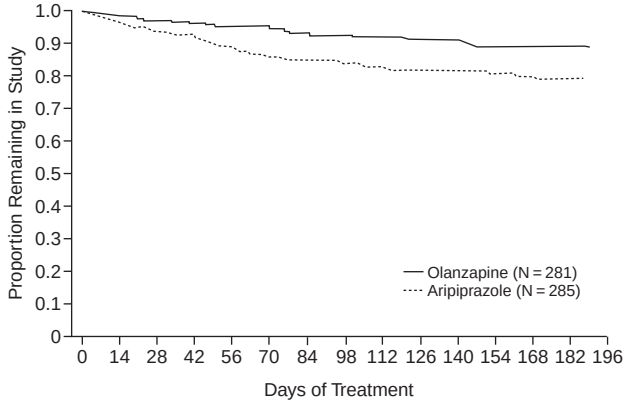
Table 2 provides LOCF mean change from baseline at 8 weeks and 28 weeks for the PANSS total score and other efficacy measures. Olanzapine-treated patients had a significantly greater least-squares mean decrease (LOCF) in the PANSS total and PANSS positive scores than did aripiprazole-treated patients at weeks 8 and 28. The MMRM analysis (least-squares mean change from baseline) revealed that olanzapine patients had a significantly greater PANSS decrease versus aripiprazole at 8 weeks (–29.0 vs. –24.8, respectively; $p = .017$), but at

Figure 3. Kaplan-Meier Survival Curves for Time to Discontinuation by Treatment Group

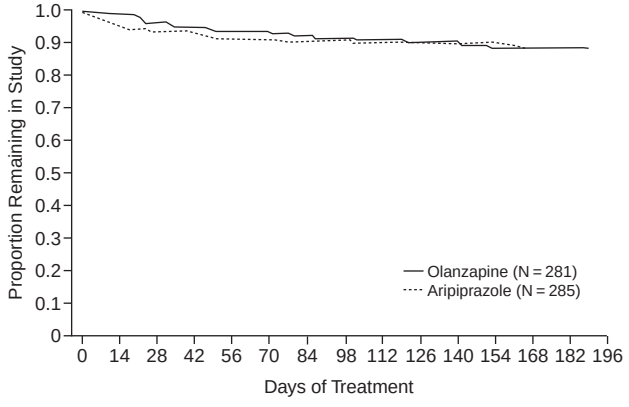
A. Time to All-Cause Discontinuation[a]



B. Time to Discontinuation Due to Efficacy-Related Reasons[b]



C. Time to Discontinuation Due to Adverse Event or Death[c]



[a]Overall log-rank χ^2 p value = .067.
[b]Defined as discontinuation due to lack of efficacy or due to any of the following: exacerbation of schizophrenia, psychotic disorder, aggression, depression, homicidal ideation, suicide attempt, agitation, anger, anxiety, or delusion. Overall log-rank χ^2 p value = .003.
[c]Due to any adverse event, including psychiatric adverse events such as exacerbation of schizophrenia or psychotic disorder. Overall log-rank χ^2 p value = .753.

28 weeks, the decreases were not significantly different (–36.6 vs. –34.4, respectively; p = .261).

Rates of clinical response at various levels (based on percentage improvement in PANSS total score)[17] and rates of remission are shown in Table 3 for weeks 8 and 28. The week 8 response rates using the ≥ 20% and ≥ 30% criteria were significantly higher among olanzapine-treated patients than among aripiprazole-treated patients (p = .003 and p = .023, respectively), as were the ≥ 20% response rates at week 28 (p = .046). Remission rates were not significantly different between groups at week 8 (p = .932) or week 28 (p = .737).

Tolerability and Safety

Forty-six patients (25 olanzapine and 21 aripiprazole) experienced serious adverse events. The treatment groups did not significantly differ in rate of serious adverse events (p = .541). Serious adverse events reported by 2 or more patients within a treatment group were exacerbation of schizophrenia (11 olanzapine and 11 aripiprazole patients), psychotic disorder (4 olanzapine and 3 aripiprazole patients), paranoia (2 olanzapine and 0 aripiprazole patients), pneumonia (2 olanzapine and 0 aripiprazole patients), exacerbation of schizophrenia, paranoid type (2 olanzapine and 2 aripiprazole patients), delusion (0 olanzapine and 2 aripiprazole patients), hallucination (0 olanzapine and 2 aripiprazole patients), and suicidal ideation (0 olanzapine and 2 aripiprazole patients). Serious adverse events leading to discontinuation were exacerbation of schizophrenia; psychotic disorder; exacerbation of schizophrenia, paranoid type; cellulitis; diabetes mellitus; homicidal ideation; acute pancreatitis; parkinsonism; suicide attempt; coronary artery arteriosclerosis; and delusion. Three patients died during the study, 2 in the olanzapine group and 1 in the aripiprazole group. Causes of death included completed suicide in 1 olanzapine patient; acute pancreatitis, pneumonia, and respiratory failure in 1 olanzapine patient; and coronary artery arteriosclerosis, chronic bronchitis, and emphysema in 1 aripiprazole patient. The death due to suicide was considered possibly related to study procedures (i.e., interruption of amitriptyline resulting in exacerbation of the patient's underlying condition) and to noncompliance with study drug, in the opinion of the site investigator. The pancreatitis was considered possibly related to study drug, in the opinion of the site investigator.

Treatment-emergent adverse events occurring in ≥ 5% of olanzapine patients or with statistically significant treatment group differences are presented in Table 4. Of these events, olanzapine patients had significantly higher rates of increased weight, somnolence, increased appetite, sedation, and depression, whereas aripiprazole patients had significantly higher rates of insomnia and upper abdominal pain. As stated earlier, the treatment groups did not significantly differ in rate of discontinuation due to adverse event or death.

Table 2. Baseline-to-Endpoint Mean Changes on Efficacy Measures (LOCF)

	Baseline Score		8-Week Change From Baseline			28-Week Change From Baseline		
Measure	Olanzapine	Aripiprazole	Olanzapine	Aripiprazole	p Value[a]	Olanzapine	Aripiprazole	p Value[a]
PANSS total score								
Least-squares mean	…	…	–25.5	–20.6	.003	–30.2	–25.9	.014
Mean (SD)	95.7 (15.9)	95.0 (15.4)	–26.8 (21.1)	–22.2 (22.3)		–31.5 (24.8)	–27.3 (25.0)	
PANSS positive score								
Least-squares mean	…	…	–5.0	–4.1	.013	–5.9	–5.0	.025
Mean (SD)	16.8 (3.4)	16.8 (3.8)	–5.4 (4.3)	–4.6 (4.8)		–6.2 (4.9)	–5.4 (5.2)	
PANSS negative score								
Least-squares mean	…	…	–7.5	–6.1	.015	–8.8	–7.6	.053
Mean (SD)	30.9 (7.6)	30.0 (7.4)	–7.9 (7.6)	–6.3 (7.9)		–9.3 (9.0)	–7.9 (8.8)	
CGI-S score								
Least-squares mean	…	…	–1.0	–0.9	.226	–1.2	–1.1	.336
Mean (SD)	4.7 (0.7)	4.8 (0.7)	–1.1 (1.1)	–1.1 (1.1)		–1.4 (1.4)	–1.3 (1.3)	
CGI-I score[b]								
Least-squares mean	…	…	2.8	2.9	.273	2.7	2.8	.279
Mean (SD)	4.1 (0.4)	4.1 (0.4)	2.7 (1.2)	2.8 (1.2)		2.6 (1.3)	2.7 (1.4)	

[a]Tests of mean differences were performed on the least-squares means.
[b]CGI-I baseline shown is from visit 2 (randomization); results are observed means rather than mean changes.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.
Symbol: … = not applicable.

Table 3. PANSS Response and Remission Rates by Treatment Group and Level of Improvement

		Response[a]		Remission[b]	
Time	PANSS Improvement Levels	Olanzapine, %	Aripiprazole, %	Olanzapine, %	Aripiprazole, %
Week 8				39.9	40.4
	≥ 20%	73.3	61.4*		
	≥ 30%	60.5	50.9*		
	≥ 40%	49.5	41.4		
	≥ 50%	36.3	33.0		
Week 28				49.5	47.7
	≥ 20%	73.0	64.9*		
	≥ 30%	65.1	58.9		
	≥ 40%	55.2	47.7		
	≥ 50%	47.7	40.7		

[a]Response defined as percentage improvement on PANSS total score. The protocol-specified response criterion was 30%. Response rates were adjusted to correct for a nonzero minimum score on the PANSS (i.e., percent response was calculated as [baseline score – endpoint score]/[baseline score – 30] × 100).
[b]Remission defined as an endpoint score of ≤ 3 on all of the following PANSS items: delusions, conceptual disorganization, hallucinatory behavior, excitement, blunted affect, lack of spontaneity and flow of conversation, mannerisms and posturing, and unusual thought content. Remission rates were not significantly different between groups.
*$p < .05$ between groups.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Table 5 provides mean changes from baseline to 28 weeks in weight, body mass index, fasting glucose, fasting lipids, and prolactin. The olanzapine group had significantly greater mean increases in weight and body mass index than did the aripiprazole group (both $p < .001$), and more olanzapine patients than aripiprazole patients had an increase of ≥ 7% body weight at any time (40.3% vs. 16.4%; $p < .001$). There were also significant differences in mean change between the treatment groups favoring aripiprazole for fasting glucose, fasting total cholesterol, fasting low-density lipoprotein and high-density lipoprotein cholesterol, and fasting triglycerides. There was a significant difference in mean change for prolactin ($p < .001$); however, mean prolactin level actually decreased in both groups. There was a statistically significantly higher percentage of olanzapine patients who had normal or low (< 29 μg/L for female, < 20 μg/L for male) prolactin values at baseline and high (≥ 29 μg/L for female, ≥ 20 μg/L for male) prolactin levels at any time (18.8%) compared with the aripiprazole group (0.6%; $p < .001$). There was a statistically significantly higher percentage of aripiprazole patients who had normal or high (> 2 μg/L) prolactin values at baseline and low (≤ 2 μg/L) prolactin levels at any time (24.2%) compared with the olanzapine group (1.7%; $p < .001$).

Patients with fasting glucose values in ranges of clinical interest[18] at any time were as follows: The percentage of patients with an increase in fasting glucose from < 100

Table 4. Treatment-Emergent Adverse Events Occurring in ≥ 5% of Olanzapine Patients or With Statistically Significant Treatment Group Differences

Adverse Event	Olanzapine (N = 281), n (%)	Aripiprazole (N = 285), n (%)	p Value[a]
Insomnia	47 (16.7)	78 (27.4)	.002
Weight increase	46 (16.4)	20 (7.0)	.001
Somnolence	41 (14.6)	24 (8.4)	.025
Headache	33 (11.7)	50 (17.5)	.057
Increased appetite	33 (11.7)	19 (6.7)	.042
Anxiety	22 (7.8)	31 (10.9)	.249
Fatigue	22 (7.8)	18 (6.3)	.515
Dizziness	19 (6.8)	24 (8.4)	.527
Dry mouth	19 (6.8)	15 (5.3)	.484
Exacerbation of schizophrenia	18 (6.4)	16 (5.6)	.726
Sedation	18 (6.4)	8 (2.8)	.046
Nausea	17 (6.0)	23 (8.1)	.413
Akathisia	15 (5.3)	26 (9.1)	.104
Depression	11 (3.9)	3 (1.1)	.032
Upper abdominal pain	5 (1.8)	15 (5.3)	.038

[a]Rates compared using Fisher exact test.

Table 5. Mean Change from Baseline to 28 Weeks in Weight, Body Mass Index, Fasting Glucose, Fasting Lipids, and Prolactin by Treatment Group (LOCF)

Measure or Test by Group	Baseline, Mean (SD)	Change at 28 Weeks, Least-Squares Mean	95% CI	p Value
Weight, kg				
Olanzapine	80.9 (22.1)	3.4	2.26 to 4.06	< .001
Aripiprazole	80.2 (20.7)	0.3		
Body mass index, kg/m^2				
Olanzapine	27.9 (7.2)	1.25	0.80 to 1.46	< .001
Aripiprazole	27.8 (7.3)	0.11		
Fasting glucose, mg/dL				
Olanzapine	88.6 (16.1)	4.87	0.18 to 7.93	.045
Aripiprazole	88.6 (16.8)	0.90		
Fasting total cholesterol, mg/dL				
Olanzapine	183.6 (39.8)	4.09	8.15 to 19.65	< .001
Aripiprazole	190.4 (44.6)	–9.85		
Fasting LDL cholesterol, mg/dL				
Olanzapine	110.3 (32.1)	1.74	2.86 to 14.09	.003
Aripiprazole	113.1 (37.0)	–6.72		
Fasting HDL cholesterol, mg/dL				
Olanzapine	47.0 (13.2)	–1.70	–5.33 to –0.93	.006
Aripiprazole	51.5 (15.1)	1.43		
Fasting triglycerides, mg/dL				
Olanzapine	150.9 (124.2)	25.66	27.43 to 59.03	< .001
Aripiprazole	146.2 (97.5)	–17.52		
Prolactin, µg/L				
Olanzapine	24.9 (32.4)	–9.63	6.02 to 11.78	< .001
Aripiprazole	26.2 (34.6)	–18.52		

Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, LOCF = last observation carried forward.

mg/dL at baseline (normal) to ≥ 126 mg/dL (high) was not significantly different for the 2 groups: olanzapine, 1.7% (3 of 174); aripiprazole, 0.6% (1 of 168); p = .623. Also, the percentage of patients with an increase in fasting glucose from < 126 mg/dL at baseline (normal/impaired) to ≥ 126 mg/dL (high) was not significantly different for the 2 groups: olanzapine, 1.9% (4 of 210); aripiprazole, 2.9% (6 of 210); p = .751. Finally, the percentage of patients with an increase in fasting glucose from ≥ 100 to < 126 mg/dL at baseline (impaired) to ≥ 126 mg/dL (high) was not significantly different for the 2 groups: olanzapine, 2.8% (1 of 36); aripiprazole, 11.9% (5 of 42); p = .209.

Patients with fasting lipids values in ranges of clinical interest[19] at any time were as follows: The percentage of patients with an increase in fasting cholesterol from < 200 mg/dL at baseline (normal) to ≥ 240 mg/dL (high) was significantly higher for olanzapine (9.2% [14 of 153]) than for aripiprazole (1.5% [2 of 131]; p = .008). The percentage of patients with a decrease in fasting high-density lipoprotein cholesterol from ≥ 40 mg/dL (normal) to < 40 mg/dL (low) was significantly higher for olanzapine (32.3% [31 of 96]) than for aripiprazole (15.7% [17 of 108]; p = .008). (Note that only 36% of the sample [204 of 566] had normal high-density lipoprotein cholesterol at baseline, so most patients were not included in this analysis.) The percentage of patients with an increase in fasting low-density lipoprotein cholesterol from < 100 mg/dL at baseline (normal) to ≥ 160 mg/dL (high) was not significantly different for the 2 groups (0.0% vs. 0.0%). (Note that only 20% of the sample [114 of 566] had normal low-density lipoprotein cholesterol at baseline.) The percentage of patients with an increase in triglycerides from < 150 mg/dL at baseline (normal) to ≥ 200 mg/dL (high) at any time was significantly higher for olanzapine (20.3% [28 of 138]) than for aripiprazole (5.5% [7 of 127]; p < .001).

On scales measuring extrapyramidal symptoms, the groups did not significantly differ in mean change from baseline to 28-week endpoint on the Barnes Akathisia Scale item 4 (from a baseline score of 0.3–0.4, mean change was –0.1 for olanzapine vs. –0.1 for aripiprazole; p = .826) or in the percentage of patients with scale-defined treatment-emergent akathisia (Barnes Akathisia Scale item 4 score of ≥ 2 at any postbaseline visit and a baseline item 4 score < 2): olanzapine, 14.6%; aripiprazole, 15.4%; p = .815. The groups did not significantly differ in mean change on the Simpson-Angus Scale (from a baseline score of 1.8–2.0, mean change was –1.2 for olanzapine vs. –0.9 for aripiprazole; p = .126) or in

the percentage of patients with scale-defined treatment-emergent parkinsonism (total Simpson-Angus Scale score of > 3 at any postbaseline visit and a baseline total score ≤ 3): olanzapine, 4.3%; aripiprazole, 4.2%; p = 1.00. The groups did not significantly differ in mean change on the AIMS (from a baseline score of 0.7–1.1, mean change was –0.5 for olanzapine vs. –0.2 for aripiprazole; p = .184) or in the percentage of patients with scale-defined treatment-emergent dyskinesia (a score of ≥ 3 on any one of the AIMS items 1 through 7 or a score of 2 or greater on any two of the AIMS items 1 through 7 at any postbaseline visit, without either criteria at baseline): olanzapine, 2.1%; aripiprazole, 2.8%; p = .788.

DISCUSSION

The treatment groups did not significantly differ in effectiveness, as measured by time to all-cause discontinuation, in this randomized, double-blind, 28-week study. The effectiveness and efficacy results have been generally consistent among the 3 longer-term head-to-head studies. A prior 2005 study[5] did report significantly higher discontinuation rates for aripiprazole with up to 52 weeks of treatment. The CATIE study,[2] which reported a 64% all-cause discontinuation rate for olanzapine, had the same primary outcome measure as the present study. However, discontinuation rates are not comparable due to different study durations (6 months for our study vs. 18 months for the CATIE study). Time to all-cause discontinuation in the CATIE study was 9.2 months (median survival time) for olanzapine, but the present study did not have enough olanzapine patients who discontinued to calculate a median survival time. Patients in the CATIE study were also less severely ill upon entry (i.e., approximate baseline PANSS total score was 75 vs. 95 in the present study), suggesting important sample differences. However, these study differences suggest the possibility that the duration of the present study may not have been long enough to detect discontinuation differences between olanzapine and aripiprazole. Indeed, the 2005 study,[5] which did detect treatment group differences in discontinuation, was more similar in duration to the CATIE study. Interestingly, a recent 26-week naturalistic study[20] also found no significant differences in time to and rate of all-cause discontinuation between aripiprazole and "standard of care" (i.e., olanzapine, quetiapine, or risperidone).

Upon comparing these results with the other longer-term head-to-head studies,[4,5] dosing appeared comparable and therapeutic, with olanzapine dosages of approximately 16 mg/day and aripiprazole dosages of approximately 19 mg/day. Of note, the starting dosage for the 2005 study was 10 mg/day for olanzapine rather than 15 mg/day.[5] It is perhaps also worthwhile to note that the ethnic origin of the present sample was not typical for a randomized clinical trial, with approximately one third being white, one third being of African descent, and one third being Hispanic.

Both olanzapine and aripiprazole were associated with reductions in the symptoms of schizophrenia in this study. At 28 weeks, the olanzapine group had a significantly greater magnitude of schizophrenic symptom reduction on the basis of the LOCF analysis of PANSS total mean change, but not with the MMRM analysis. Nearly 50% of all patients achieved PANSS remission by the end of the study, which required a score of mild, minimal, or absent on several core items (modified Andreasen et al. criteria).[11] It should be noted that the mean endpoint PANSS total score was approximately 65. Thus, although patients were much improved at the end of treatment, they would still be considered to be in the mild range on the PANSS. Similarly, CGI-S scores moved into the "mildly ill" range by the end of the study.

Regarding safety and tolerability measures, differences in favor of aripiprazole on metabolic parameters, including weight, mean change in glucose, and lipids measures, were consistent with previous studies. Although a previous 52-week study[5] found differences in favor of the olanzapine group on the Simpson-Angus scale and the Barnes Akathisia Scale, the current study results did not identify significant treatment group differences on any extrapyramidal symptom measures. In the current study, the rates of extrapyramidal symptom–related adverse events, such as akathisia and psychomotor hyperactivity, were also not significantly different between the treatment groups, nor was overall concomitant anticholinergic or benzodiazepine use. However, we looked at benzodiazepine use by visit (post hoc), and the majority of the visits did show a significantly higher use of benzodiazepines in the aripiprazole-treated group compared to the olanzapine-treated group. Similarly, in a recent report of a 5-day Eli Lilly–sponsored study[7] of olanzapine and aripiprazole in the treatment of agitation associated with schizophrenia, although the treatment groups did not differ significantly in symptom improvement, a higher proportion of the aripiprazole-treated group received benzodiazepines than did the olanzapine-treated group on the fifth day of treatment.[7] The clinical implications of this finding are not known.

The rate of noncompliance in this study (35.2% for olanzapine and 41.4% for aripiprazole) might seem high; however, it should be noted that noncompliance was defined as any deviation from the prescribed dosing regimen. One of the 566 patients in the study (from the olanzapine group) was significantly noncompliant and therefore discontinued from the study. To explore the effect of compliance on discontinuation, we compared rates of all-cause discontinuation for compliant versus noncompliant patients. Not surprisingly, the noncompliant patients had higher discontinuation rates than compliant patients

(noncompliant patients: olanzapine, 77.8%; aripiprazole, 80.5%; p = .496; compliant patients: olanzapine, 23.1%; aripiprazole, 29.3%; p = .194). The between-treatment comparisons were in the same direction as for all patients. For the compliant patients, the difference between treatments was 6.3% (compared to 7.5% in all patients), and for noncompliant patients, the difference between treatments was numerically smaller (2.7%). Thus, compliance appeared to affect discontinuation but not the comparisons between the 2 treatment groups.[21]

To gain further insight into the relative therapeutic effectiveness of the 2 treatments, we calculated the number needed to treat (NNT) and number needed to harm (NNH) values for certain categorical efficacy and safety parameters in a post hoc analysis. For all-cause discontinuation rates, which were not significantly different between treatment groups, the NNT was 14. This NNT indicates that for every 14 patients treated with olanzapine instead of aripiprazole for 28 weeks, there will be 1 additional patient who does not discontinue treatment. For discontinuation rate due to efficacy-related reasons, the NNT was 13 (95% CI: 8 to 41), indicating that for every 13 patients treated with olanzapine rather than aripiprazole for 28 weeks, 1 additional patient will not discontinue due to lack of efficacy. For discontinuation rate due to adverse events, the NNT was 453. For ≥ 7% body weight gain at any time, the NNH was 5 (95% CI: 4 to 7). The NNH indicates that 1 additional weight gain of ≥ 7% can be expected to occur for every 5 patients treated with olanzapine versus aripiprazole. For total cholesterol normal to high at any time, the NNH was 14 (95% CI: 8 to 39); for HDL cholesterol normal to low at any time, the NNH was 7 (95% CI: 4 to 21); and for triglycerides normal to high at any time, the NNH was 7 (95% CI: 5 to 15).

In summary, the results of this study indicated that olanzapine and aripiprazole were not significantly different in therapeutic effectiveness in patients with schizophrenia over 28 weeks. Although olanzapine patients had significantly greater symptom efficacy, and were less likely to discontinue treatment for efficacy-related reasons, overall discontinuation rates were not different for the 2 therapies. In addition, several metabolic parameters worsened in the olanzapine group compared with the aripiprazole group. The relative benefit and potential risk of antipsychotic medications, weighing both efficacy and tolerability aspects, should be considered when prescribing medications for individual patients, and the potential consequences of weight gain and worsening of other metabolic parameters should be taken into account before starting olanzapine.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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