Aripiprazole Monotherapy for Maintenance Therapy in Bipolar I Disorder: A 100-Week, Double-Blind Study Versus Placebo

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Objective: A 26-week, double-blind, placebo-controlled relapse prevention study of aripiprazole was designed a priori with a prospective, 74-week, double-blind, placebo-controlled extension phase. Efficacy and tolerability of aripiprazole for relapse prevention in bipolar I disorder was, therefore, evaluated for 100 weeks.

Method: Patients with DSM-IV bipolar I disorder, recent manic or mixed episode, received open-label aripiprazole 15 or 30 mg/day (started at 30 mg/day) for 6 to 18 weeks. Patients achieving stabilization (Young Mania Rating Scale score ≤ 10 and Montgomery-Asberg Depression Rating Scale score ≤ 13 for 6 consecutive weeks) entered the double-blind phase, at which point they were randomly assigned to double-blind treatment with aripiprazole or placebo for 26 weeks. The primary endpoint was time to relapse for any mood episode. Patients who completed the 26-week stabilization continued in a double-blind fashion with aripiprazole or placebo for an additional 74 weeks and were monitored for relapse, efficacy, and tolerability. The study was conducted from March 2000 to June 2003.

Results: In total, 161 patients met the stabilization criteria and were randomly assigned to aripiprazole (N = 78) or placebo (N = 83). At 100 weeks, time to relapse was significantly longer with aripiprazole (N = 7) than placebo (N = 5; hazard ratio = 0.53 [p = .011; 95% CI = 0.32 to 0.87]); however, a further 24 patients had discontinued due to study closure. Aripiprazole was superior to placebo in delaying time to manic relapse (p = .005; hazard ratio = 0.35 [95% CI = 0.16 to 0.75]); however, no significant differences were observed in time to depressive relapse (p = .602; hazard ratio = 0.81 [95% CI = 0.36 to 1.81]). The adverse events reported during 100 weeks of treatment with aripiprazole versus placebo (≥ 5% incidence and twice placebo rate) were tremor, akathisia, dry mouth, hypertension, weight gain, vaginitis, abnormal thinking, pharyngitis, and flu syndrome. Mean weight change from baseline to 100 weeks (last observation carried forward) was +0.4 ± 0.8 kg with aripiprazole and –1.9 ± 0.8 kg with placebo.

Conclusions: Over a 100-week treatment period, aripiprazole monotherapy was effective for relapse prevention in patients who were initially stabilized on aripiprazole for 6 consecutive weeks, and it maintained a good safety and tolerability profile.

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The persistent, episodic nature of bipolar disorder means that the majority of patients can expect a lifelong course of recurrent acute episodes, in addition to residual symptoms in the intervening periods. Recurrence rates can reach up to 49% within 2 years of recovery from an initial episode,[1] and polarity of the index episode tends to predict the polarity of relapse, with increasing episodes escalating the risk for recurrence.[2] The fluctuating course

of bipolar disorder has a significant negative impact on annual income, job status, social interactions, and recreational activities.[3,4] Thus, effective maintenance therapy is essential, and acute management must anticipate the longitudinal course of the illness.

Treatment selection should consider the available clinical data from large, well-designed studies, and clinical recommendations exist based on such an evidence-based approach.[5] The longest study conducted to date was a 2-year study showing that lithium monotherapy was significantly more effective than placebo for the prevention of relapse.[6] In addition, two 18-month studies showed that both lithium and lamotrigine monotherapies were more effective than placebo at delaying the time to relapse of a mood episode.[7–9]

Of the available atypical agents, aripiprazole and olanzapine are U.S. Food and Drug Administration (FDA)–approved for maintaining efficacy in bipolar I disorder in previously stabilized patients. To date, there are limited extended long-term (> 1 year) clinical data. Several 1-year studies have examined the efficacy of olanzapine monotherapy,[10–12] and an 18-month study was conducted in combination with lithium or valproate.[13] Olanzapine was associated with significant improvements in both time to relapse and rate of relapse.[10,11,13] These studies used a similar design to the study presented herein: a stabilization phase, followed by a double-blind, maintenance phase, and the low completion rates in these studies illustrate how difficult it can be to keep patients on treatment for such long periods.

Aripiprazole is pharmacologically distinct from other atypical antipsychotics, as the efficacy of this agent is mediated through its dopamine partial agonist activity at D_2 and D_3 receptors,[14,15] 5-HT_{2A} antagonist activity,[16] and 5-HT_{1A} partial agonist activity.[17] The safety and efficacy of aripiprazole have been evaluated in both short- and longer-term studies in patients with bipolar I mania. In 2 randomized, double-blind, placebo-controlled, 3-week studies,[18,19] aripiprazole showed significantly greater symptom improvement and response rates than placebo. In a 12-week, double-blind study[20] of aripiprazole versus haloperidol, aripiprazole demonstrated a similar improvement of symptoms to haloperidol, with a significantly greater response rate and a higher completion rate than haloperidol. In these bipolar studies, aripiprazole displayed a safety and tolerability profile similar to that observed in the short-term studies of patients with schizophrenia and schizoaffective disorder.[21,22] Aripiprazole has also been studied in a relapse prevention double-blind, placebo-controlled, 26-week study,[23] which showed that aripiprazole was superior to placebo in delaying the time to relapse. Additionally, aripiprazole-treated patients had significantly fewer relapses than placebo-treated patients.

The safety and efficacy of aripiprazole for the prevention of relapse in patients with bipolar I disorder with a manic or mixed episode were evaluated beyond the initial 26-week study.[23] This same study was designed a priori to continue monitoring patients in a double-blind, placebo-controlled fashion for an additional 74 weeks, for a total of 100 weeks of double-blind treatment. This study is the first long-term (> 18 months) randomized, controlled study to examine the efficacy and safety of an atypical antipsychotic, aripiprazole, as monotherapy compared with placebo for the prevention of relapse in patients with bipolar I disorder who have been stabilized for 6 consecutive weeks following a recent manic or mixed episode.

METHOD

Design

Details of the study methods have been described previously.[23] Briefly, this was a randomized, double-blind, parallel-group, placebo-controlled study. Following stabilization (Young Mania Rating Scale [YMRS][24] total score ≤ 10 and a Montgomery-Asberg Depression Rating Scale [MADRS][25] total score ≤ 13 during 4 consecutive visits over a minimum of 6 weeks) with open-label aripiprazole (15 or 30 mg/day), patients were eligible for entry to the double-blind phase of this study. The double-blind period was designed a priori to consist of an initial, 26-week phase, followed by a prospective, 74-week extension phase. Patients were randomly assigned to receive either aripiprazole or placebo in a 1:1 ratio for an initial 26 weeks, the results of which have been reported elsewhere.[23] Patients who completed the initial 26-week period without a relapse were offered to continue a further 74 weeks of double-blind treatment under the same treatment regimen to allow them a total of 100 weeks of double-blind treatment. A predetermined number of relapses (N = 45) was defined for the primary outcome measure at the 26-week timepoint. Entrance into the 74-week double-blind, extension phase ended when 45 patients had relapsed. All patients continued in a double-blind, placebo-controlled fashion in the study until the last randomized patient completed the 26-week phase. At that time, the study was terminated, and any patient remaining in the 74-week phase was discontinued, regardless of what timepoint they had reached. Thus, the double-blind design was maintained throughout. All study sites had received prior institutional review board/institutional ethics committee approval before initiating the study. The study was conducted from March 2000 to June 2003.

Patients

Participants met the criteria for bipolar I disorder according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV).[26] Patients were eligible for entry into the stabilization phase of the

study if they had recently completed a 3-week, placebo-controlled acute mania study of aripiprazole, if they met eligibility criteria for an acute mania study but had declined participation, or if they had experienced a manic or mixed episode requiring hospitalization and treatment within the previous 3 months. All psychotropic medications, except lorazepam and anticholinergic agents, were discontinued prior to enrollment. Further details of the inclusion and exclusion criteria are available in the publication of the first 26-week double-blind phase.[23]

Assessments

During the initial screening, patients who had not been previously enrolled in an aripiprazole acute mania study provided medical, psychiatric, and medication histories. Diagnoses were performed using the Structured Clinical Interview for DSM-IV (SCID)[27] or the Mini-International Neuropsychiatric Interview (MINI).[28] Physical examinations, 12-lead electrocardiograms (ECGs), clinical laboratory tests, pregnancy tests (when applicable), and drug screens were performed, and vital signs were recorded. Assessments for treatment safety and symptom stability were made every 2 weeks during the stabilization phase. Study visits took place at randomization (day 1 of the double-blind phase), weekly from weeks 1 to 4, biweekly from week 6 to week 28, monthly from week 28 to week 52, and bimonthly from week 52 to week 100. Patients were also contacted by telephone at regular intervals between the scheduled visits to monitor compliance with the study medication and to ensure their well-being.

Dosing Schedule

Study medication was administered orally, once daily, at approximately the same time each day. Patients first received open-label treatment with aripiprazole, initially 30 mg/day during the stabilization phase. The dose could be decreased to 15 mg/day at any time, depending on tolerability. Following entry to the double-blind phase of the study, patients were assigned, in a double-blind manner, to continue the dose of aripiprazole that they were taking at the end of the stabilization phase or to receive placebo. Based on the investigator's assessment of therapeutic effect and tolerability, the dose of aripiprazole could be increased or decreased to either 30 mg/day or 15 mg/day at any time during the study.

Concomitant Medications

During the double-blind phase of the study, lorazepam could be given at a dose of up to 2 mg/day during the first month, 1 mg/day during the second month, and 1 mg/day up to 4 times per week for the next 18 weeks. Only anticholinergic agents (maximum dose not exceeding the equivalent of benztropine 6 mg/day) were also permitted during the double-blind phase of the study.

Efficacy Measures

The primary efficacy endpoint was the time to relapse for a mood episode, whether manic, depressive, or mixed, during the double-blind initial 26-week period of the study. A discontinuation of the study due to lack of efficacy was defined as a relapse (indicated by hospital admission due to a mood episode and/or addition to or increase in psychotropic medication other than study drug, for manic and/or depressive symptoms). Time to a manic relapse and time to a depressive relapse during the double-blind phase were regarded as key secondary endpoints. The same endpoints were also evaluated at the end of the 100-week, double-blind treatment.

Additional efficacy measures included the mean change from double-blind randomization to endpoint in the YMRS total score,[24] MADRS total score,[25] and Clinical Global Impressions-Bipolar Version (CGI-BP) Severity of Illness scores (mania, depression, overall),[29] which were conducted at each study visit, as well as the Positive and Negative Syndrome Scale (PANSS) total score,[30] cognitive subscale score, and hostility subscale score, which were evaluated at weeks 40, 52, 68, and 100 during the 74-week double-blind extension phase. The efficacy scales were administered by experienced raters, and every effort was made to ensure that the same rater administered the scales for individual patients.

Safety Measures

Treatment-emergent adverse events (AEs; using COSTART terminology) were collected from the commencement of the study. Patients were asked about AEs and were observed by the investigator during each assessment for signs indicative of AEs. The Simpson-Angus Scale (SAS),[31] Abnormal Involuntary Movement Scale (AIMS),[32] and Barnes Akathisia Rating Scale (BARS)[33] were also evaluated at weeks 40, 52, 68, 84, and 100 during the double-blind extension phase. Vital sign measurements, alterations in body weight, waist circumference, and 12-lead ECG results were also used to assess the safety of the treatment regimen. Clinical laboratory tests included fasting and nonfasting measurements of triglyceride, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, total cholesterol, and glucose levels. Ideally, all measurements would be made in fasting patients; however, this was not always possible.

Data Analysis

The primary efficacy measure, time to relapse, was evaluated by statistical methods that were designed for the time-to-event data. Kaplan-Meier survival curves were generated for the time-to-relapse data, and differences between treatment groups were tested using log-rank tests at an α level of .05 to indicate statistical significance. Patients who did not relapse, including those

who discontinued participation early for reasons other than relapse, were censored on the date of their last efficacy evaluation or the last dose of study medication. The key secondary efficacy measures were time to either manic or depressive relapse. The log-rank test was used to compare the time to event distributions of the 2 treatment groups, and estimated Kaplan-Meier survival curves for each treatment were obtained using Kaplan-Meier methodology. For the analysis of time to manic or depressive relapse, relapses other than manic (for the manic relapse analysis) or depressive (for the depressive relapse analysis) were considered censored. Analysis of covariance (ANCOVA) modeling was used to analyze continuous variables measured at baseline and following treatment. For all efficacy and safety analyses, ANCOVA models included the baseline measure as covariate and treatment group as main effect. Primary presentations of results from ANCOVA and analysis of variance were the model-based estimates and the 95% confidence intervals (CIs) for treatment differences (aripiprazole minus placebo). Changes from baseline were derived by subtracting the baseline score from that of each follow-up visit. Efficacy and safety analyses were performed on last-observation-carried-forward (LOCF) data for the combined 26-week and 74-week double-blind, extension phases. LOCF values at week 26 for those patients who did not enter the 74-week double-blind, extension phase were carried forward to week 100.

Sample Size Considerations

There was no preplanned sample size or power considerations for the extended double-blind phase, as the number of patients who continued was dependent on the number that completed the first 26-week period of double-blind treatment. All safety and efficacy analyses were performed using SAS statistical software, version 6.12 or higher (SAS Institute Inc.; Cary, N.C.). For the comparison of aripiprazole with placebo, 2-tailed tests were used to determine statistical significance, and $p \leq .05$ was considered to be statistically significant.

RESULTS

Disposition of Patients

A detailed breakdown of patient disposition during stabilization and the initial 26-week double-blind phase of the study is provided in Keck et al.[23] Of the 206 patients who completed the stabilization phase, 161 entered the double-blind phase and were randomly assigned to placebo (N = 83) or aripiprazole (either 15 or 30 mg) (N = 78). In total, 67 patients completed the initial 26-week, double-blind period, and 66 entered the 74-week double-blind, extension phase of the study. Study completion rates and the reasons for discontinuation from the 74-week, double-blind, extension phase are reported in Figure 1. During the 74-week extension, there were more discontinuations due to lack of efficacy from the placebo group (26%) than the aripiprazole group (13%), and discontinuations due to AEs were low in both groups (placebo, 0%; aripiprazole, 3%). During the 74-week, double-blind, extension phase, most of the discontinuations due to "other reasons" occurred because the study was closed by the sponsor when the prespecified number of relapses had been attained (N = 10 for placebo and N = 14 for aripiprazole). An additional 1 aripiprazole-treated patient became pregnant during this phase and was also discontinued from the study. A total of 12 patients completed the full 100-week, double-blind period of study. There was no difference between treatment groups in the completion rate of the 74-week, double-blind extension phase (placebo, 19% [5/27]; aripiprazole, 18% [7/39]). Overall, a total of 12 patients completed the full 100-week, double-blind period of study (placebo, 6% [5/83]; aripiprazole, 9% [7/78]).

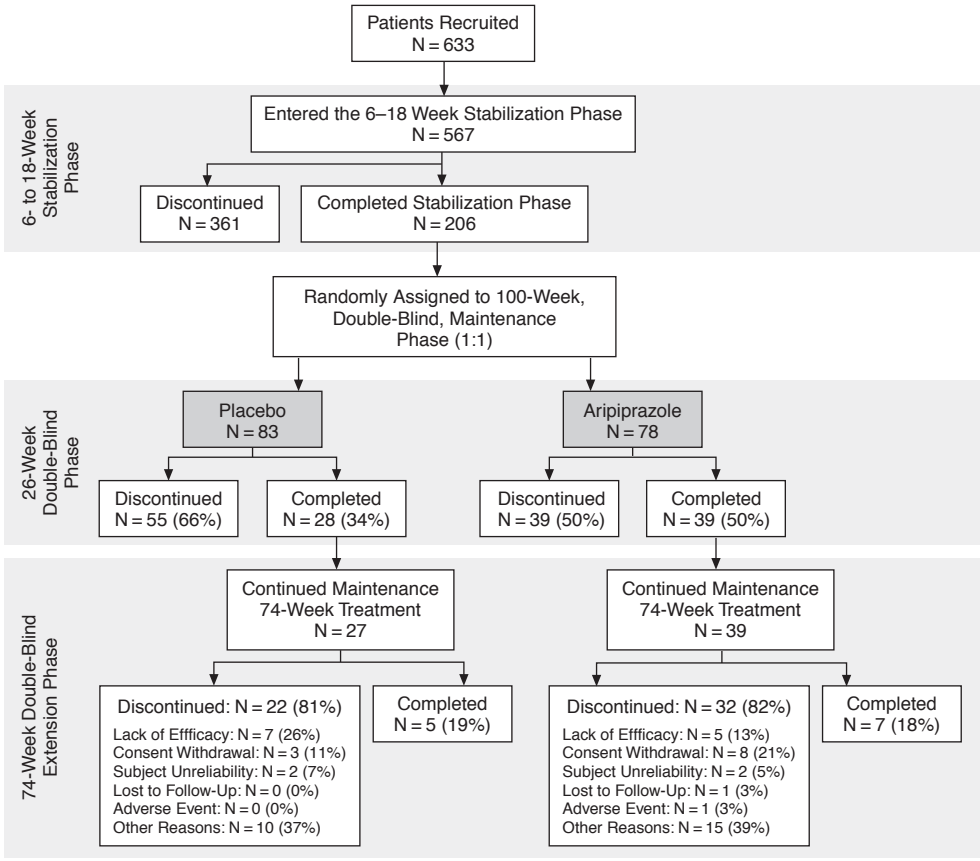
Patient Characteristics

The baseline characteristics of those 161 patients who were originally randomly assigned to double-blind treatment with placebo or aripiprazole have been previously presented.[23] The mean age of patients randomly assigned to each arm was similar (placebo, 40.3 ± 1.2 years; aripiprazole, 39.0 ± 1.5 years). The proportion of men was higher in the aripiprazole than the placebo group (38% vs. 28%). A similar proportion of patients in each group had rapid-cycling bipolar disorder (placebo, 17%; aripiprazole, 18%). The proportion of patients with a current episode of mixed-type mania was higher in the aripiprazole group (placebo, 22%; aripiprazole, 38%; p = .024, Fisher exact test).

Medications

At the start of the 74-week double-blind period, patients were receiving a mean aripiprazole dose of 23.8 mg/day. This is similar to the mean dose received by patients who completed the entire 100-week study on aripiprazole (23.6 mg/day, N = 7). The mean aripiprazole dose during the last 7 days of treatment—at whatever timepoint that occurred during the combined 26-week and 74-week double-blind phases—was 24.1 mg/day (range, 12.9–30.0 mg/day, N = 77). At the end of the 100-week period, 38% of patients were receiving a modal dose of aripiprazole 15 mg/day and 62% of patients were receiving a modal dose of 30 mg/day during their last 7 days on the medication, regardless of when their medication was terminated, even if that occurred in the first 26 weeks. During the 74-week, double-blind extension phase of this study, 21 (78%) of the 27 patients in the placebo group and 24 (62%) of the 39 patients in the aripiprazole group received at least 1 concomitant central nervous system medication. The 3 most commonly used medication

Figure 1. Disposition of Patients by Study Phase[a]



[a]During the 74-week, double-blind, extension phase, all but 1 of the discontinuations due to "other reasons" (N = 10 for placebo and N = 14 for aripiprazole) occurred because the study was closed by the sponsor when the prespecified number of relapses had been attained. One additional aripiprazole-treated patient became pregnant during the 74-week, double-blind, extension phase and was also discontinued from the study.

classes in the 74-week, double-blind, extension phase were other analgesics and antipyretics (N = 13; 48%), anxiolytics (N = 11; 41%), and anticholinergics (N = 8; 30%) in the placebo group and anticholinergics (N = 18; 46%), anxiolytics (N = 12; 31%), and other analgesics and antipyretics (N = 12; 31%) in the aripiprazole group.

Efficacy

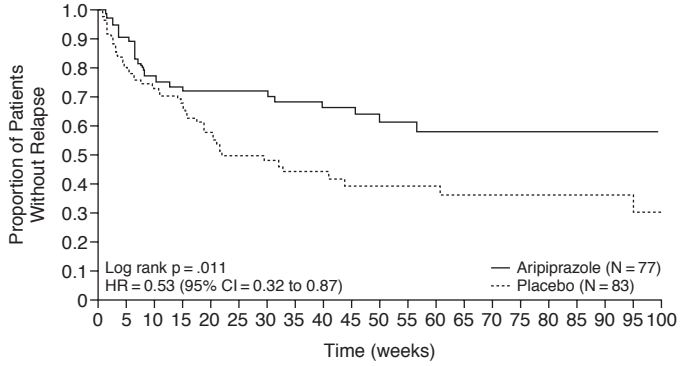
Primary efficacy data. Time to relapse into any mood episode during double-blind treatment was significantly longer for patients who received aripiprazole than placebo (p = .011; hazard ratio, 0.53 [95% CI = 0.32 to 0.87]; Figure 2).

Secondary efficacy data. Time to manic relapse was significantly longer for aripiprazole-treated than placebo-treated patients (p = .005; hazard ratio, 0.35 [95% CI = 0.16 to 0.75]; Figure 3A). No difference was noted in time to depressive relapse between groups (p = .602; hazard ratio, 0.81 [95% CI = 0.36 to 1.81]; Figure 3B). In addition, the proportion of patients experiencing relapse by week 100 was 52% (43 of 83 patients) for the placebo group, whereas it was 33% (25 of 77 patients) for the aripiprazole group (relative risk = 0.64 [95% CI = 0.44 to 0.94], p = .02).

The percentage of patients who experienced a relapse of manic, depressive, mixed, or unknown type is shown in Figure 4. Notably, aripiprazole treatment resulted in significantly fewer manic relapses than placebo (12% vs. 28%, p < .05).

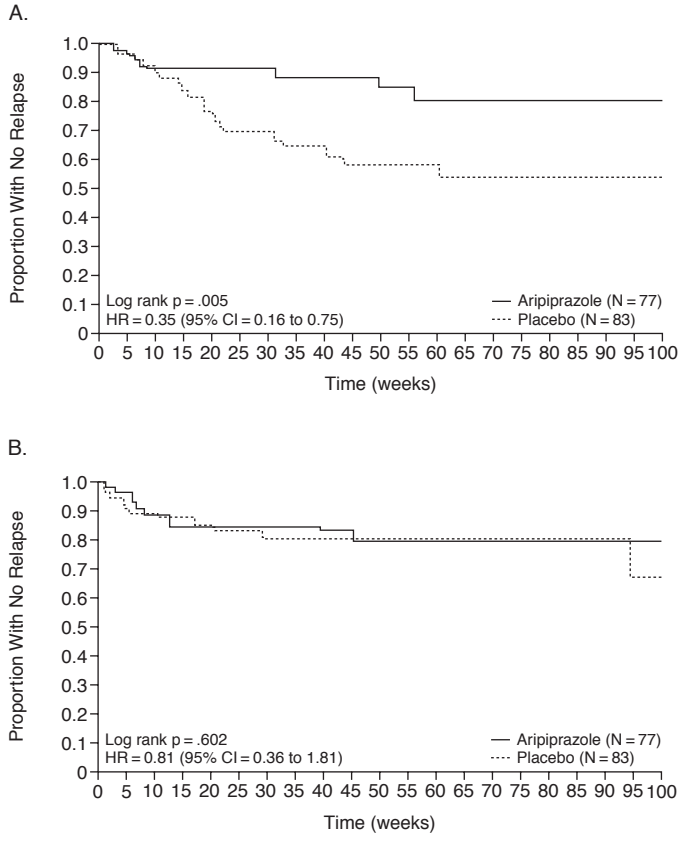
The mean (± SE) change in YMRS total score (LOCF) from baseline of the double-blind phase to week 100 increased (worsened) more in the placebo group than in the aripiprazole group (9.4 ± 1.2 vs. 4.9 ± 1.2; p = .01) (Table 1). On the MADRS score, the change from baseline of the double-blind phase to week 100 (LOCF) was not significantly different between aripiprazole and placebo (Table 1). At week 100, the mean change from baseline of the double-blind phase to endpoint in both PANSS cognitive subscale score and PANSS hostility subscale score favored aripiprazole (Table 1). At the end of the

Figure 2. Time From Randomization to Relapse for Any Reason (Kaplan-Meier survival curves)



Abbreviation: HR = hazard ratio.

Figure 3. Time From Randomization to (A) Manic Relapse and (B) Depressive Relapse (Kaplan-Meier survival curves)



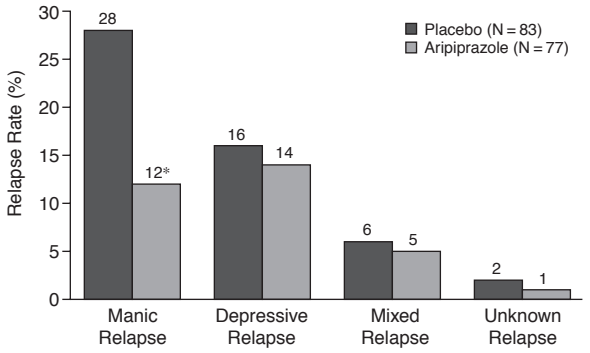
Abbreviation: HR = hazard ratio.

study, the mean change from baseline of the double-blind phase to week 100 in the CGI-BP Severity of Illness (overall) score was in favor of aripiprazole (placebo, 1.6 ± 0.2; aripiprazole, 1.0 ± 0.2; p = .01), as was the mean change from baseline of the double-blind phase to week 100 in the CGI-BP Severity of Illness (mania) score (placebo, 1.1 ± 0.2; aripiprazole, 0.6 ± 0.2; p = .02). Clinical Global Impressions-Bipolar Version Severity of Illness (depression) scores were not significantly different between groups.

Safety

Adverse events. Across the entire double-blind, 100-week period, 60 (72%) patients in the placebo group and

Figure 4. Relapse Rate by Type



*Relative risk = 0.42 (95% CI = 0.21 to 0.85), p < .05.

Table 1. Change in Secondary Efficacy Endpoints From Baseline of the 100-Week Double-Blind Maintenance Phase to Study Endpoint (week 100; LOCF)[a]

Rating Scale	Placebo (N = 81)	Aripiprazole (N = 77)	p Value
YMRS total score			
Baseline	2.1 ± 2.3	2.5 ± 2.8	
Change to week 100	9.4 ± 1.2	4.9 ± 1.2	.01
MADRS total score			
Baseline	4.5 ± 4.2	3.9 ± 3.5	
Change to week 100	7.9 ± 1.2	6.2 ± 1.3	.31
PANSS			
Total score[b]			
Baseline	36.4 ± 6.7	35.8 ± 6.1	
Change to week 100	11.8 ± 1.6	7.9 ± 1.7	.10
Cognitive subscale score[b]			
Baseline	8.6 ± 2.2	8.6 ± 2.0	
Change to week 100	3.3 ± 0.5	1.5 ± 0.5	.01
Hostility subscale score[b]			
Baseline	4.4 ± 0.9	4.4 ± 0.9	
Change to week 100	2.3 ± 0.4	1.2 ± 0.4	.03
CGI-BP Severity of Illness			
Overall score			
Baseline	1.4 ± 0.7	1.4 ± 0.7	
Change to week 100	1.6 ± 0.2	1.0 ± 0.2	.01
Mania score			
Baseline	1.3 ± 0.6	1.3 ± 0.7	
Change to week 100	1.1 ± 0.2	0.6 ± 0.2	.02
Depression score			
Baseline	1.5 ± 0.8	1.3 ± 0.6	
Change to week 100	0.8 ± 0.2	0.8 ± 0.2	.90

[a]Baseline values are expressed as mean ± SD; change from baseline is expressed as mean ± SE.
[b]Aripiprazole, N = 74; placebo, N = 75.
Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar Version, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, YMRS = Young Mania Rating Scale.

60 (78%) patients receiving aripiprazole reported at least 1 AE. The AEs reported at an incidence of ≥ 5% and at least twice that of the placebo group with aripiprazole treatment are shown in Table 2. Serious AEs (SAEs) occurred more frequently in the placebo group than in the aripiprazole group (23% vs. 12%). The most common SAEs (≥ 3%) reported by placebo- or aripiprazole-treated patients were manic reaction (12% vs. 8%) and depression (5% vs. 0%).

Table 2. Incidence of Adverse Events That Occurred in the Aripiprazole Treatment Group at an Incidence of ≥ 5% and Twice the Rate of the Placebo Group

Body System	Placebo (N = 83), N (%)	Aripiprazole (N = 77), N (%)
Any adverse event	60 (72.3)	60 (77.9)
Nervous system		
Tremor	1 (1.2)	7 (9.1)
Akathisia	1 (1.2)	6 (7.8)
Abnormal thinking	2 (2.4)	4 (5.2)
Cardiovascular system		
Hypertension	3 (3.6)	6 (7.8)
Digestive system		
Dry mouth	1 (1.2)	6 (7.8)
Metabolic/nutritional system		
Weight gain	0	5 (6.5)
Urogenital infection		
Vaginitis[a]	0	3 (6.4)
Respiratory system		
Pharyngitis	2 (2.4)	4 (5.2)
Body as a whole		
Flu syndrome	0	4 (5.2)

[a]Incidence adjusted for gender (women): placebo, N = 60; aripiprazole, N = 47.

The rates of discontinuation due to AE were higher in the placebo group than in the aripiprazole group (28% vs. 16%). The most common (≥ 3%) of these AEs were manic reaction (11%), depression (10%), insomnia (5%), and anxiety (4%) in placebo-treated patients and manic reaction (7%) in aripiprazole-treated patients.

Adverse events related to extrapyramidal symptoms (EPS) occurred more frequently with aripiprazole than with placebo (placebo, 15%; aripiprazole, 22%). The most common (≥ 3%) of these were tremor (placebo, 1%; aripiprazole, 9%), akathisia (placebo, 1%; aripiprazole, 8%), and hypertonia (placebo, 2%; aripiprazole, 4%). Resolution of these AEs was reported in the majority of patients prior to the end of the study, with only 2 patients discontinuing because of akathisia and none discontinuing because of tremor or hypertonia. During the double-blind phase, mean changes from baseline of the double-blind phase to week 100 on the SAS (placebo, –0.2 ± 0.2; aripiprazole, 0.3 ± 0.2), AIMS (placebo, 0.05 ± 0.1; aripiprazole, 0.3 ± 0.1), and BARS global akathisia score (placebo, –0.2 ± 0.1; aripiprazole, 0.02 ± 0.1) were minimal in both the placebo and aripiprazole groups and were not significantly different between groups.

Clinical laboratory results. Mean serum prolactin levels (± SD) at the time of randomization to the double-blind phase were 10.1 ± 6.6 for placebo (N = 63) and 11.3 ± 9.0 for aripiprazole (N = 66). At week 100, placebo-treated patients showed a mean increase (± SE) in prolactin levels compared with aripiprazole-treated patients (placebo, 6.2 ± 1.8; aripiprazole, –0.7 ± 1.8; p = .007, LOCF).

Table 3. Baseline Combined Fasting and Nonfasting Lipid Levels in Placebo- and Aripiprazole-Treated Patients and Change Following the 100-Week Treatment Period[a]

Laboratory Parameter	Placebo (N = 71)	Aripiprazole (N = 70)	p Value
Total cholesterol[b]			
Baseline	192 ± 43	184 ± 35	
Change to week 100	1.8 ± 3.4	3.7 ± 3.5	NS
LDL			
Baseline	110 ± 34	104 ± 30	
Change to week 100	4.4 ± 2.8	4.5 ± 2.8	NS
HDL			
Baseline	51 ± 19	47 ± 14	
Change to week 100	0.3 ± 1.0	1.6 ± 1.0	NS
Triglycerides			
Baseline	168 ± 135	167 ± 110	
Change to week 100	–16.9 ± 8.9	–23.8 ± 9.0	NS
Glucose[b]			
Baseline	97 ± 32	93 ± 27	
Change to week 100	1.0 ± 2.7	1.6 ± 2.8	NS

[a]Values shown in mg/dL. Baseline values are expressed as mean ± SD, change from baseline is expressed as mean ± SE. Median days on treatment: aripiprazole, 224 (223 days for total cholesterol and glucose); placebo, 127.
[b]Aripiprazole, N = 71; placebo, N = 73.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, NS = nonsignificant.

Table 4. Incidence of Abnormal Pooled Fasting and Nonfasting Lipid Levels at Endpoint (%)[a]

Laboratory Parameter	Placebo (N = 71)	Aripiprazole (N = 73)	p Value
Total cholesterol[b]	8.2	10.8	NS
LDL	8.4	9.6	NS
HDL	23.9	27.4	NS
Triglycerides	14.1	17.8	NS
Glucose[b]	16.4	20.3	NS

[a]The thresholds for abnormal lipid and glucose values were defined as follows: total cholesterol ≥ 240 mg/dL, LDL cholesterol ≥ 160 mg/dL, HDL cholesterol < 40 mg/dL, triglycerides ≥ 200 mg/dL, glucose ≥ 110 mg/dL. Median days on treatment: aripiprazole, 215 (212 days for total cholesterol and glucose); placebo, 127.
[b]Aripiprazole, N = 74; placebo, N = 73.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, NS = nonsignificant.

At week 100, there were no statistically significant differences between placebo- and aripiprazole-treated patients in the change from double-blind baseline in combined fasting and nonfasting glucose, HDL cholesterol, LDL cholesterol, triglycerides, or total cholesterol levels (Table 3). Furthermore, the incidence of abnormal glucose or lipid levels was similar between placebo and aripiprazole over the 100-week treatment period (Table 4).

Vital signs. No clinically concerning findings were noted with regard to physical examinations or vital signs during the double-blind phase.

Weight gain and blood lipids. The mean weight change in patients treated with placebo was –1.9 ± 0.8 kg (–4.3 lb) and +0.4 ± 0.8 kg (+0.9 lb) with aripiprazole ($p = .052$, LOCF). Analysis of mean weight change (LOCF) by body mass index (BMI) at baseline of the double-blind phase showed no significant difference ($p > .05$) in weight change between placebo and aripiprazole for patients with baseline BMI values < 23 kg/m^2 (–1.9 ± 1.3 kg [N = 8] vs. 1.8 ± 1.6 kg [N = 6]) (–4.2 lb vs. 4.1 lb) and > 27 kg/m^2 (–1.8 ± 1.3 kg [N = 34] vs. –0.8 ± 1.3 kg [N = 37]) (–4.0 vs. –1.7 lb). Patients with baseline BMI values of 23 to 27 kg/m^2 showed a significant difference in weight change with placebo versus aripiprazole (–2.6 ± 1.5 kg [N = 14] vs. 3.0 ± 1.7 kg [N = 11] [–5.7 vs. 6.7 lb]; $p = .0250$). Overall, clinically significant weight increase (≥ 7%) occurred in 3/61 (5%) placebo-treated and 12/60 (20%) aripiprazole-treated patients ($p = .01$). Numbers of patients demonstrating clinically significant weight gain were as follows across BMI groups: < 23 kg/m^2: placebo, 0; aripiprazole, 2; 23 to 27 kg/m^2: placebo, 1, aripiprazole, 4; > 27 kg/m^2: placebo, 2; aripiprazole, 6. Although completion rates were too low to draw firm conclusions regarding an observed cases analysis, the findings were similar to those seen using LOCF analysis.

DISCUSSION

This study is the longest double-blind, placebo-controlled study to date to investigate the efficacy, tolerability, and safety of any agent other than lithium for the prevention of relapse in the treatment of bipolar I disorder. Overall, aripiprazole monotherapy (15 or 30 mg/day) was superior to placebo in both preventing relapse and delaying the time to relapse over a 100-week, double-blind period. This significant difference in risk of relapse translates to a number needed to treat (NNT) of 6, meaning that we need to treat 6 patients with aripiprazole to prevent a relapse. Given that the index episode is a predictor of the symptom pole into which patients are likely to relapse, it is important that aripiprazole delayed time to manic relapse. Although aripiprazole did not delay time to depressive relapse, it did not increase the likelihood of depressive relapse. In addition, the rates of relapse into depression were relatively low for both placebo and aripiprazole, seeming to confirm the observation that patients are more likely to relapse into the same episode as the index episode.

Aripiprazole was well tolerated over 100 weeks, and there was no notable difference in the AE profile compared with the 26-week double-blind phase. Placebo treatment was associated with higher rates of SAEs (23% vs. 12%) and discontinuation due to AEs (28% vs. 16%) than aripiprazole, mainly attributed to worsening of manic and depressive symptoms, which emphasizes the therapeutic benefits of continuing aripiprazole treatment past 26 weeks. Compared with the previous 26-week double-blind phase, notable changes in rates of permitted concomitant medication use with aripiprazole during the

74-week extension were an increase of anticholinergic (30% vs. 46%) and EPS concomitant medication (48% vs. 49%) and a decrease of anxiolytic (41% vs. 31%) use. The high rate of anticholinergic use in the 74-week extension phase was accompanied by a low rate of akathisia (N = 2 [5.1%]) and no events of extrapyramidal syndrome (0%), suggesting that these agents may have been used prophylactically, which is not consistent with the protocol.

This study has a number of notable strengths. First, this 100-week study is the longest double-blind, placebo-controlled study for any atypical antipsychotic. Second, the stabilization phase and required period of maintaining clinical stability (6–18 weeks and 6 consecutive weeks, respectively) in this study were longer than those used in the olanzapine studies (6–12 weeks and 2 consecutive weeks, respectively). In addition, the stringency of the stabilization criteria—YMRS score ≤ 10 and MADRS score ≤ 13—that were maintained for 6 consecutive weeks had a positive impact on relapse rates, as these remained low, even with placebo.

Some limitations must also be considered in the interpretation of these findings. All patients were stabilized for at least 6 weeks on aripiprazole treatment prior to randomization. Thus, it is an enriched population who continue into the double-blind treatment, and the results are applicable only to those patients who respond and are stabilized on aripiprazole treatment following a manic or mixed episode. Moreover, entry to the 74-week, double-blind, extension phase of the study was dependent on completion of the initial 26-week, double-blind treatment period without a relapse. Thus, it was an enriched population who entered the 74-week period. However, patients who did not enter the a priori–defined 74-week period were included in efficacy and safety analyses (analyses were performed, as prespecified, on LOCF data for the combined 26-week and 74-week extension phases). A post hoc analysis (data not shown) showed no major difference in demographic characteristics between those patients who completed the first 26 weeks and continued treatment and the demographics of those patients who did not continue. Only 27 placebo-treated patients and 39 aripiprazole-treated patients entered the final 74-week period, and only 12 patients completed the study. This high attrition rate is not uncommon in long-term trials,[8,12] but it makes it difficult to generalize the study results to the wider population of patients with bipolar mania. However, it should be noted that the study was stopped once the predefined number of relapses occurred; therefore, some patients who may have completed did not have the opportunity to do so. If we account for the patients who did not have the opportunity to complete (N = 10 for placebo and N = 14 for aripiprazole), the completion rate for the 74-week, double-blind, extension phase increases from 19% to 29% with placebo and from 18% to 28% with aripiprazole. Although these rates are still less than 30%, this is not unusual for studies of this nature. For example, an 18-month study with lamotrigine showed low completion rates (placebo 0%, lithium 2%, and lamotrigine 5%).[8] A shorter, 48-week study with olanzapine showed completion rates of 7% with placebo and 21% with olanzapine.[12] It is also notable that median time to relapse could not be assessed in this study, as the median value was never achieved in the aripiprazole arm over the 100-week period, making comparison with shorter studies that use this endpoint difficult.

Although there are weaknesses of study designs such as that used here to show maintenance of efficacy in bipolar disorder, they should not detract from the evidence for efficacy of the approved agents over other agents not approved for maintaining efficacy in bipolar disorder. Although agents such as divalproex and typical antipsychotics are used in this indication, there is a paucity of data to support this use. For example, a 52-week, randomized, double-blind study involving 372 patients with bipolar mania showed that divalproex did not differ significantly from placebo in time to any mood episode.[34] Of the antipsychotics, the older typical agents, such as perphenazine, are suboptimal for use in bipolar maintenance therapy due to AEs such as tardive dyskinesia, EPS, and prolactin elevation,[35,36] in addition to the potential to precipitate switching to depression. Of the available atypical agents, aripiprazole and olanzapine are the only ones that are FDA-approved for maintaining efficacy in bipolar I disorder in stabilized patients.

The results of this study compare favorably with those of other relapse prevention studies for approved treatments. Relapse rates over 100 weeks (placebo 52% vs. aripiprazole 33%) were similar to those seen in a previous olanzapine versus lithium study that was much shorter—52 weeks (olanzapine, 30.0%; lithium, 38.8%).[11] Relapse rates in a placebo-controlled, long-term (52-week) olanzapine study showed that 47% of patients relapsed with olanzapine compared with 80% of those receiving placebo.[12] Similarly, an olanzapine versus divalproex comparative study showed relapse rates of 42% and 57%, respectively, over 47 weeks.[10] In the 2-year study showing the efficacy of lithium in relapse prevention, the rate of relapse with placebo was 80%, compared with 43% with lithium.[6] This is higher than the relapse rate with aripiprazole seen in the study presented herein (33%). Similar relapse rates were seen in the 18-month study comparing placebo and lamotrigine monotherapy (70% vs. 47%).[8]

Additionally, the metabolic profile of long-term therapy in bipolar disorder is of particular relevance. There is growing evidence to suggest that obesity and metabolic disorders in bipolar disorder have been correlated with poorer clinical and functional outcome measures[37–39] and increased risk of other medical comorbidities.[40,41] In this study, there was no significant difference in mean weight gain between treatment groups, and

changes were low over the 100-week period (placebo, –1.9 ± 0.8 kg; aripiprazole, +0.4 ± 0.8 kg; p = .052, LOCF), although more patients treated with aripiprazole (N = 12, 20%) demonstrated clinically significant weight gain (≥ 7% change from baseline) compared with placebo (N = 3, 5%). With aripiprazole, these findings are consistent with other long-term studies in schizophrenia.[21,42] Furthermore, in a shorter-term study (47 weeks) with other bipolar medications, 24% of olanzapine-treated patients and 18% of divalproex-treated patients had clinically significant weight gain. Over a 12-month study,[10] clinically significant weight gain was observed in 30% of olanzapine-treated patients versus 10% of lithium-treated patients.[11]

The implications of weight gain and how it translates to other metabolic complications are of growing interest and concern in the treatment of bipolar disorder. As hyperlipidemia is a major risk factor for life-threatening cardiovascular events, clinicians should consider additional metabolic measures when selecting an antipsychotic medication to treat patients with bipolar I disorder.[43] Although some patients presented with clinically significant weight gain in this study, no differences were found between placebo and aripiprazole in the change from baseline of the double-blind phase to week 100 in changes from baseline in glucose and lipid levels. Nevertheless, weight gain and other metabolic correlates should be regularly monitored for clinically significant changes in this population as they can be precursors to further poorer overall outcomes.

In conclusion, these are the first 2-year data in bipolar disorder since the lithium studies of the 1970s, and this study is the longest double-blind, placebo-controlled study of an atypical agent in the treatment of bipolar disorder. This study showed that over the course of a 100-week treatment period, aripiprazole monotherapy continued to be effective in relapse prevention in patients initially stabilized with aripiprazole for 6 consecutive weeks. In addition, aripiprazole treatment maintained a safety and tolerability profile during the 100 weeks that was similar to that during the first 26 weeks. These data support the initial efficacy and safety assessment at the 26-week timepoint, and additionally provide evidence for the use of aripiprazole as a maintenance therapy for bipolar I disorder.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), divalproex (Depakote), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), valproate (Depacon and others).

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