A Randomized, Double-Blind, Placebo-Controlled 26-Week Trial of Aripiprazole in Recently Manic Patients With Bipolar I Disorder

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Objective: To investigate the safety and efficacy of aripiprazole in preventing relapse of a mood episode in recently manic- or mixed-episode patients with bipolar I disorder stabilized on aripiprazole.

Method: This randomized, double-blind, parallel-group, placebo-controlled, multicenter study enrolled patients from 76 centers in 3 countries (Argentina, Mexico, United States) from March 2000 to June 2003. Bipolar I disorder (DSM-IV) patients who had recently been hospitalized and treated for a manic or mixed episode entered an open-label stabilization phase (aripiprazole monotherapy: 15 or 30 mg/day, 6–18 weeks). After meeting stabilization criteria (Young Mania Rating Scale score of ≤ 10 and Montgomery-Asberg Depression Rating Scale score of ≤ 13 for 6 consecutive weeks), 161 patients were randomly assigned to aripiprazole or placebo for the 26-week, double-blind phase. The primary endpoint was time to relapse for a manic, mixed, or depressive episode (defined by discontinuation caused by lack of efficacy).

Results: Aripiprazole was superior to placebo in delaying the time to relapse ($p = .020$). Aripiprazole-treated patients had significantly fewer relapses (25%) than placebo patients (43%; $p = .013$). Aripiprazole was superior to placebo in delaying the time to manic relapse ($p = .01$); however, no significant differences were observed in time to depressive relapse ($p = .68$). Weight gain (≥ 7% increase) occurred in 7 (13%) aripiprazole-treated and 0 placebo-treated patients. Adverse events (≥ 5% incidence and twice that of placebo) reported by aripiprazole-treated patients were akathisia, pain in the extremities, tremor, and vaginitis.

Conclusions: Aripiprazole, 15 or 30 mg/day, was superior to placebo in maintaining efficacy in patients with bipolar I disorder with a recent manic or mixed episode who were stabilized and maintained on aripiprazole treatment for 6 weeks, as shown by a longer time to relapse.

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Bipolar I disorder is a lifelong episodic illness characterized by recurrent manic, depressive, or mixed symptoms and episodes.[1] Without adequate long-term treatment, bipolar disorder is associated with high rates of morbidity.[2] Thus, the goals of treatment of bipolar disorder include prevention of recurrent mood symptoms and episodes to allow optimal functioning and quality of life.[3]

Although effective treatment of acute mood episodes in bipolar disorder is important, preventing or delaying subsequent mood episodes is a primary treatment objective.[4–7] Up to 40% of patients who respond to initial treatment have relapses within 1 year.[8] Patients most frequently relapse into a mood episode similar to the index episode.[9] Thus, an initial episode of mania predicts subsequent relapse into manic or mixed episodes, and each additional episode increases the risk for recurrence.[10]

Lithium and valproate have been used extensively and successfully as first-line therapy for acute and maintenance treatment of patients with bipolar I disorder, although their adverse event profiles[5,6] have prompted the assessment of other potential treatments including second-generation antipsychotics and lamotrigine. In the United States, aripiprazole, olanzapine, risperidone, quetiapine, and ziprasidone are currently indicated for the

treatment of acute mania. Aripiprazole and olanzapine are the only atypical antipsychotic, U.S. Food and Drug Administration (FDA)–approved medications indicated for maintenance therapy in bipolar I disorder.[11–14] It is important to note that the FDA requires a placebo-controlled study design before it will grant approval of an indication for treating acute mania or for longer-term treatment. Furthermore, the Depression and Bipolar Support Alliance has provided a consensus on the use of placebo in mood disorder studies that reflects the current need for placebo-controlled trials in a population of patients who nonetheless have inherently high placebo response rates.[15]

Aripiprazole is a novel antipsychotic with a unique pharmacologic profile. It is a partial agonist at dopamine D_2 receptors[16,17] and serotonin 5-hydroxytryptamine 1A ($5\text{-}HT_{1A}$) receptors[18] and an antagonist at $5\text{-}HT_{2A}$ receptors.[19]

The safety and efficacy of aripiprazole have been evaluated in inpatients with bipolar I disorder who were experiencing acute manic or mixed episodes. In 2 double-blind, placebo-controlled, 3-week studies,[20,21] aripiprazole was associated with significantly greater symptom improvement and response rates than placebo. In a third, 3-week, placebo-controlled, randomized trial (data on file, Otsuka America Pharmaceutical, Inc., Rockville, Md., April 2003), a fixed-dose design was used to investigate treatment with aripiprazole for acute mania. Aripiprazole-treated patients demonstrated symptom improvement comparable to that in the other 2 acute trials[20,21]; however, the placebo response rate was considerably higher than in the flexible-dose studies. Thus, the primary outcome measurement in the aripiprazole-treated group was not different from that in the placebo group (data on file, Otsuka America Pharmaceutical, Inc., Rockville, Md., April 2003). In a 12-week, double-blind, comparative study of aripiprazole and haloperidol in inpatients and outpatients,[22] aripiprazole exhibited a significantly greater rate of response (defined as a ≥ 50% decrease in Young Mania Rating Scale [YMRS] scores and continuation of therapy) and a higher completion rate than haloperidol. In these studies, aripiprazole displayed a favorable safety and tolerability profile similar to that observed in the short-term studies of patients with schizophrenia and schizoaffective disorder.[23]

The present study is the first randomized, controlled trial to examine the safety and efficacy of aripiprazole compared with placebo in preventing relapse of bipolar I disorder in patients recently stabilized after experiencing a manic or mixed episode.

PATIENTS AND METHOD

Patients

This randomized, double-blind, parallel-group, placebo-controlled, multicenter study enrolled patients from 76 centers in 3 countries (Argentina, Mexico, United States) from March 2000 to June 2003. All study sites received institutional review board (IRB)/institutional ethics committee (IEC) approval before initiation of the trial. All study participants met criteria for bipolar I disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV). Patients could enter the stabilization phase if they recently completed a 3-week, placebo-controlled, acute mania study of aripiprazole; if they met eligibility criteria for an acute mania study but declined participation; or if they experienced a manic or mixed episode requiring hospitalization and treatment within the previous 3 months. All psychotropic medications, except those permitted by the study protocol, were discontinued before randomization.

Patients included men and women aged 18 years and older who could understand and comply with protocol requirements and who could provide written informed consent as required by the IRB/IEC. Women of childbearing potential were required to have negative results on urine or serum pregnancy tests within 72 hours of starting study medication and to use acceptable methods of contraception; they were excluded if they were pregnant or lactating.

Patients were excluded if they had history or symptoms of a cognitive disorder, schizophrenia, or a schizoaffective disorder or if they had psychotic symptoms better explained by another medical condition or attributed to substance abuse. Also excluded were patients considered unresponsive to clozapine, those who met DSM-IV criteria for any significant psychoactive or substance use disorder, and those with positive results on urine toxicology screening for cocaine.

Other reasons for exclusion included known allergy or hypersensitivity to aripiprazole or other quinolinones, history of neuroleptic malignant syndrome, and seizure disorder. Patients were also excluded if they participated in a clinical trial with another investigational agent within the past month or if they underwent electroconvulsive therapy within the past 2 months.

Additionally, patients were excluded from the double-blind phase if they had been noncompliant with study medication or were in significant violation of the protocol during the stabilization phase; had been in the stabilization phase for more than 18 weeks; or had positive screening results for lithium, divalproex, or drugs of abuse.

Study Design

During the stabilization phase, patients received open-label treatment with aripiprazole (15 or 30 mg/day) for a minimum of 6 weeks to a maximum of 18 weeks. Patients remained in this phase until their symptoms were stable, as defined by the following criteria: a YMRS[24] total score of ≤ 10 and a Montgomery-Asberg Depression Rating

Scale (MADRS)[25] total score of ≤ 13 during 4 consecutive visits over a minimum of 6 weeks.

Patients meeting study criteria for stability during the 6- to 18-week stabilization phase were eligible to enter the double-blind phase. At the start of the double-blind phase, patients were randomly assigned to receive aripiprazole or placebo in a 1:1 ratio in a double-blind fashion for up to 26 weeks. Aripiprazole was not tapered in patients randomly assigned to placebo. However, because of its long elimination half-life, aripiprazole blood levels were expected to gradually diminish over the first 2 weeks of randomized treatment.

Assessments

During the screening period, patients not previously enrolled in an aripiprazole acute mania study provided medical, psychiatric, and medication histories and were diagnosed using the Structured Clinical Interview for DSM-IV (SCID)[26] or the Mini-International Neuropsychiatric Interview (MINI).[27] Physical examinations, 12-lead electrocardiography (ECG), clinical laboratory tests, pregnancy tests (when applicable), and drug screens were performed and vital signs were recorded.

Patients were assessed for treatment safety and symptom stability every 2 weeks during the stabilization phase. During the double-blind phase, each patient had a study visit at randomization (day 1), weekly visits from weeks 1 to 4, and biweekly visits from weeks 6 to 26. Throughout the study, patients were also contacted by telephone at scheduled intervals between scheduled visits so that compliance with the study medication could be monitored and to ensure their well-being.

Dosing Schedule

Study medication was administered orally, once a day, at approximately the same time each day. During the stabilization phase, patients received open-label treatment with aripiprazole at a starting dose of 30 mg/day. The dose could be decreased to 15 mg/day at any time for tolerability. Subsequently, patients were assigned in a double-blind fashion to the aripiprazole dose that they were taking at the end of the stabilization phase or placebo. At any time during the double-blind phase, the dose of aripiprazole or placebo could be increased or decreased to 30 mg or 15 mg, respectively, based on the investigator's assessment of therapeutic effect and tolerability.

Concomitant Medications

During the open-label stabilization and the double-blind randomization phases, all psychotropic medications except lorazepam and anticholinergic agents were specified to be excluded. During screening and the first 4 weeks of the stabilization phase, concomitant use of lorazepam up to a dose of 6 mg/day was allowed. The maximum permitted dose during the stabilization phase was decreased to 3 mg/day for the fifth week and to 2 mg/day thereafter. During the double-blind phase, maximum permitted lorazepam doses were 2 mg/day during the first month, 1 mg/day during the second month, and 1 mg/day up to 4 times per week during the remaining 18 weeks.

Patients requiring treatment for extrapyramidal symptoms (EPS) during the study could be administered benztropine or a similar anticholinergic agent at a dose not exceeding the equivalent of benztropine 6 mg/day. No anticholinergic agents were to be taken in the 12 hours before rating scale assessments for efficacy or safety. Anticholinergic treatment for EPS was not permitted on the day before the baseline visit. Patients were instructed to refrain from drinking alcoholic beverages or using illicit drugs.

Efficacy Measures

The primary efficacy endpoint was the time to relapse for a mood episode, whether manic, depressive, or mixed, during the double-blind phase. Relapse was defined by a discontinuation of the study attributed to lack of efficacy (indicated by hospital admission because of a mood episode or addition to or increase in psychotropic medication other than study drug for manic and/or depressive symptoms). Key secondary endpoints included time to manic relapse and time to depressive relapse during the double-blind phase.

Additional efficacy measures included mean change from randomization to endpoint in the YMRS total score,[24] MADRS total score,[25] Positive and Negative Syndrome Scale (PANSS) total score,[28] PANSS cognitive subscale score, PANSS hostility subscale score, and Clinical Global Impressions-Bipolar Version (CGI-BP) Severity of Illness scores (mania, depression, overall).[29]

Experienced raters administered the efficacy scales, and every effort was made to ensure that the same rater administered all scales for a given patient.

Safety Measures

Data collection of treatment-emergent adverse events began at study initiation. Patients were asked about adverse events and were observed by the investigator during each assessment for signs indicative of adverse events, which were defined as any new medical problem or any exacerbation of an existing problem experienced by a patient while enrolled in the study (using COSTART [Coding Symbols for a Thesaurus of Adverse Reaction Terms] terminology).

The Simpson-Angus Scale (SAS),[30] Abnormal Involuntary Movement Scale (AIMS),[31] and Barnes Akathisia Rating Scale (BARS)[32] were used to assess EPS, abnormal involuntary movements, and akathisia.

Clinical laboratory examination included hematologic evaluations, serum chemistry profiles (fasting), urinalysis, urine screens for drugs of abuse, serum concentrations of

lithium and valproic acid, and urine or serum pregnancy tests (for women of childbearing potential). Safety was also assessed by measuring vital signs, body weight, and waist circumference and by 12-lead ECG results.

Statistical Analysis

Data analysis. The primary efficacy measure (time to mood relapse) was evaluated using survival analysis. The efficacy population comprised all patients randomly assigned to treatment during the double-blind phase who received at least 1 dose of study medication and who provided at least 1 postbaseline primary outcome assessment. Kaplan-Meier survival curves were generated for the time-to-event data, and differences among treatment groups were tested using log-rank tests at an alpha of .05 level of significance. Patients who did not have relapses, including those who discontinued participation early for reasons other than relapse, were censored on the date of the last efficacy evaluation or the last dose of study medication, whichever was later. No adjustments were made for the number of investigator sites that randomly assigned at least 1 patient because the number was so large (50 sites).

The key secondary efficacy measures, time to mania and time to depression relapse, were analyzed using a hierarchical testing procedure so that the overall probability of a type 1 error was .05. If aripiprazole was significantly superior to placebo in the primary efficacy analysis, time to manic relapse was tested. If aripiprazole was significantly superior to placebo for that analysis, then time to depressive relapse was tested. The last-observation-carried-forward (LOCF) data set included data recorded at a given visit or, if no observation was recorded at that visit, data carried forward from the previous visit.

Analysis of covariance (ANCOVA) models were used to analyze continuous variables measured at baseline and on treatment. ANCOVA models included the baseline measure as covariate and the treatment group as main effect. Primary presentations of results from ANCOVAs and analyses of variance were the model-based estimates and the 95% confidence interval (CI) for treatment differences (aripiprazole minus placebo). Change scores were derived by subtracting the baseline score from the score at each follow-up visit. Because the study consisted of multiple phases and not all evaluations were performed at the same visit, the definition of baseline could vary from analysis to analysis.

The Cochran-Mantel-Haenszel (CMH) General Association Test was used to analyze the percentage of patients who discontinued participation for any reason. The CMH Row Means Test was used to evaluate variables on an ordinal or an integer scale.

Sample size considerations. It was expected that the 6-month placebo relapse rate would be 45% and that the aripiprazole relapse rate would be 20%. Forty-five events would be required to yield 87% power to detect a 25% difference in the percentage of patients in both groups who had relapses, assuming these relapse rates, a dropout rate of 18% for reasons other than relapse, and a 2-sided test at the .05 level. Based on these assumptions, it was expected that 152 patients would have to be randomly assigned to obtain 150 evaluable patients (75 per treatment group) to yield 45 events (number of patients who had relapses).

The stabilization safety sample comprised all patients in the stabilization phase who took at least 1 dose of open-label study medication. The stabilization efficacy sample comprised all patients who were in this stabilization safety sample and had at least 1 efficacy evaluation after entry into the open-label phase. The double-blind safety sample comprised all patients in the randomized sample who took at least 1 dose of study medication in the double-blind phase. The double-blind efficacy sample comprised all patients in the double-blind safety sample who underwent at least 1 postrandomization efficacy evaluation.

All safety and efficacy analyses were performed using SAS statistical software, version 6.12 or higher (SAS Institute Inc., Cary, N.C.). In comparing aripiprazole with placebo, probability values were derived from 2-tailed tests of significance and were rounded to 3 decimal points; $p \leq .05$ was considered statistically significant.

RESULTS

Disposition of Patients

A total of 633 patients were enrolled in the study; 567 entered the stabilization phase, including 333 who had participated in earlier studies of aripiprazole for acute mania.[20,21,33] Of the 567 participants, 206 (36%) completed the stabilization phase and 361 (64%) discontinued, mainly because of adverse events (22%), lack of efficacy (12%), or withdrawal of consent (12%). A total of 161 patients (28%) who completed the stabilization phase entered the double-blind phase and were randomly assigned to receive either aripiprazole or placebo. Of these 161 patients, 67 (42%) did not have relapses and completed the double-blind phase and 94 (58%) discontinued, mainly because of lack of efficacy (placebo, 43%; aripiprazole, 24%) (Figure 1). Of the patients who entered the stabilization phase (N = 567), only 12% completed the study. A Kaplan-Meier plot for time to discontinuation for any reason is presented by treatment group in Figure 2.

Patient Characteristics

Table 1 summarizes the characteristics of patients in the randomized sample. Demographic characteristics of the treatment groups were similar except that more men were randomly assigned to the aripiprazole group (38%)

Figure 1. Disposition of Patients by Study Phase

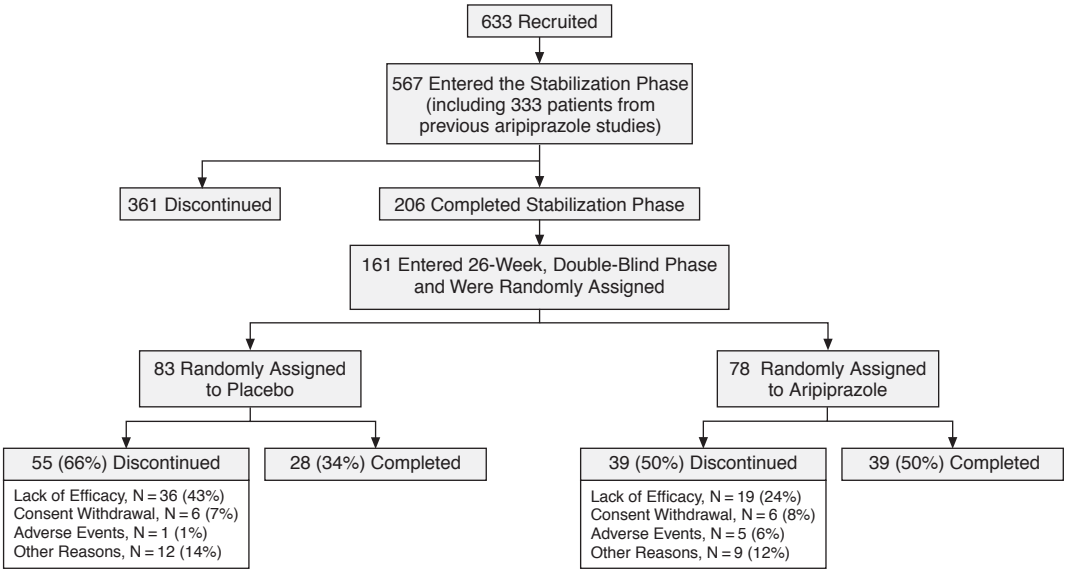
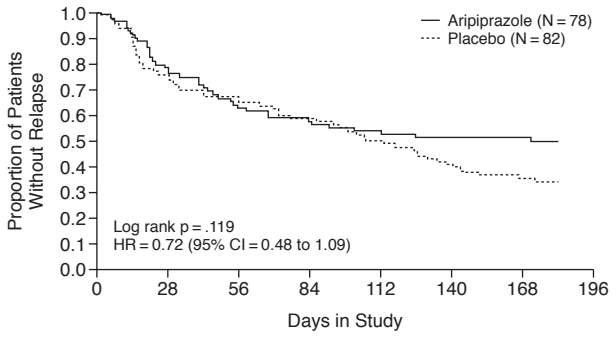


Figure 2. Time From Randomization to Discontinuation for any Reason



Abbreviations: CI = confidence interval, HR = hazard ratio.

Table 1. Characteristics of Patients With Bipolar I Disorder in the Randomized Sample

Variable	Placebo (N = 83)	Aripiprazole (N = 78)	Total (N = 161)
Age, mean ± SE, y	40.3 ± 1.2	39.0 ± 1.5	39.6 ± 0.9
Sex, N (%)			
Male	23 (28)	30 (38)	53 (33)
Female	60 (72)	48 (62)	108 (67)
Race, N (%)			
White	56 (67)	48 (62)	104 (65)
Hispanic/Latino	17 (20)	20 (26)	37 (23)
Black	5 (6)	5 (6)	10 (6)
Asian/Pacific Islander	4 (5)	2 (3)	6 (4)
American/Alaskan Native	0	1 (1)	1 (1)
Other	1 (1)	2 (3)	3 (2)
Rapid cycling, N (%)			
Yes	14 (17)	14 (18)	28 (17)
No	69 (83)	64 (82)	133 (83)
Current episode, N (%)			
Mania	65 (78)	48 (62)	113 (70)
Mixed	18 (22)	30 (38)	48 (30)

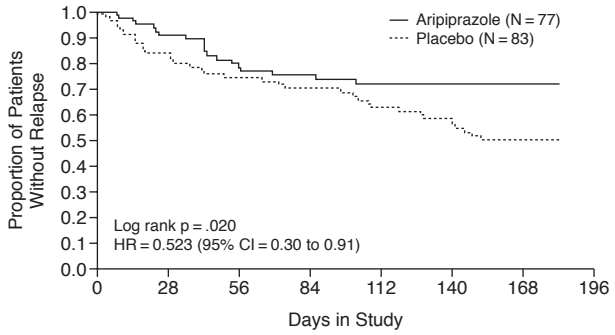
than to the placebo group (28%). More patients with a current episode of mania were randomly assigned to treatment with placebo (78%) than to treatment with aripiprazole (62%), and fewer patients with a mixed-type current episode were randomly assigned to treatment with placebo (22%) than to treatment with aripiprazole (38%). These differences were not expected to have a significant impact on the interpretation of the results.

Patients who were randomly assigned to the double-blind phase had been stabilized (evidenced by YMRS score of ≤ 10 and MADRS score of ≤ 13 during 4 consecutive visits) for a mean duration of 88.8 days (median = 85 days; range, 37–264). At the start of the double-blind phase, mean baseline YMRS scores (± SE) were 2.1 ± 0.3 for the placebo group (N = 82) and 2.6 ± 0.3 for the aripiprazole group (N = 76). Mean baseline MADRS scores (± SE) were 4.5 ± 0.4 and 3.9 ± 0.4, respectively.

Medications

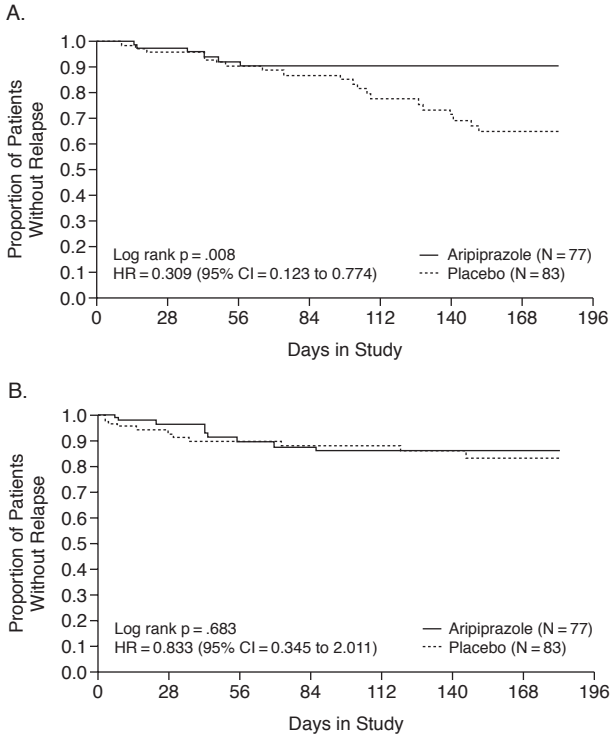
The mean aripiprazole dose was 25.2 mg/day (N = 541) at the stabilization phase endpoint, 24.4 mg/day for patients randomly assigned to the double-blind phase (N = 161), and 24.3 mg/day at the double-blind phase endpoint (N = 77). During the double-blind phase, 59 (71.1%) of 83 patients in the placebo group and 55 (71.4%) of 77 patients in the aripiprazole group received at least 1 concomitant medication. The 3 most commonly used medication classes in the double-blind phase were

Figure 3. Time From Randomization to Relapse



Abbreviations: CI = confidence interval, HR = hazard ratio.

Figure 4. Time From Randomization to (A) Manic Relapse and (B) Depressive Relapse



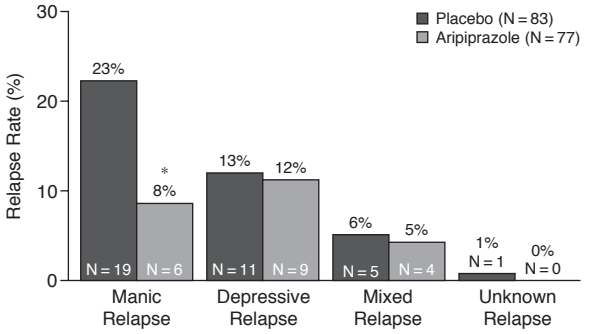
Abbreviations: CI = confidence interval, HR = hazard ratio.

anxiolytics such as lorazepam (N = 38, 45.8%), other analgesics and antipyretics (N = 30, 36.1%), and anticholinergics (N = 26, 31.3%) in the placebo group and anticholinergics and anxiolytics (N = 30, 39% for each) followed by other analgesics and antipyretics (N = 26, 33.8%) in the aripiprazole group.

Efficacy

Primary efficacy data. Time to relapse was significantly longer for aripiprazole-treated than for placebo-treated patients (p = .020) (Figure 3). The hazard ratio (HR) for aripiprazole/placebo was 0.52 (95% CI = 0.30 to 0.91). In addition, the proportion of patients not experiencing relapse by week 26 was 49% for placebo-treated patients, whereas it was 72% for aripiprazole-treated patients.

Figure 5. Distribution of Relapses by Type in the Placebo Group and the Aripiprazole Group During the Double-Blind Phase



*p = .009; time to manic relapse significantly different.

Secondary efficacy data. With regard to the key secondary efficacy endpoints, aripiprazole was superior to placebo in delaying the time to manic relapse (p = .01; HR = 0.31 [95% CI = 0.12 to 0.77]; Figure 4A); however, no significant differences were observed in time to depressive relapse (p = .68; HR = 0.83 [95% CI = 0.35 to 2.01]; Figure 4B).

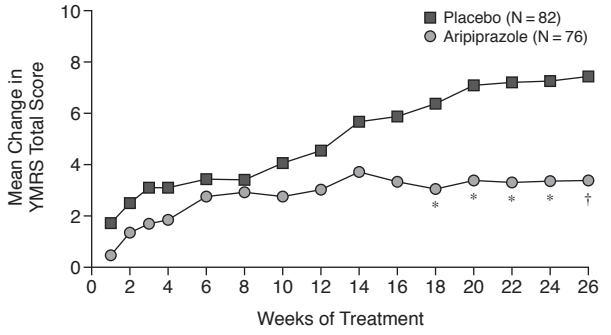
Additionally, aripiprazole-treated patients had significantly fewer relapses than placebo-treated patients (placebo, 36/83 [43%]; aripiprazole, 19/77 [25%]; p = .013). The distribution of relapses by type between the treatment groups is shown in Figure 5. Aripiprazole therapy resulted in significantly fewer relapse episodes of mania than placebo (8% vs. 23%, respectively; p = .009).

The mean change from baseline to endpoint in the YMRS total score was significantly in favor of aripiprazole during weeks 18 through 26 in the double-blind phase (Figure 6). On the MADRS, however, a significant difference between the treatment groups was not evident at endpoint in the double-blind phase (Figure 7).

For the PANSS total score, a numerical trend favored aripiprazole over placebo at any time point. Mean (± SE) changes in PANSS total scores at week 26 were 5.2 ± 1.6 for aripiprazole and 9.1 ± 1.5 for placebo (p = .077). At week 26, both the PANSS cognitive subscale score (mean change from baseline: aripiprazole, 0.8 ± 0.5; placebo, 2.5 ± 0.5; p = .014) and the PANSS hostility subscale score (mean change from baseline: aripiprazole, 0.8 ± 0.3; placebo, 1.8 ± 0.3; p = .032) showed a significant difference in favor of aripiprazole.

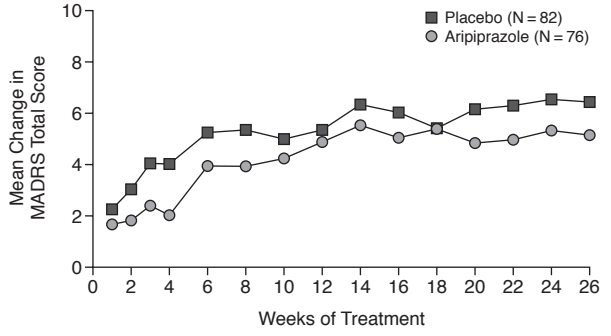
At week 26, the mean change from baseline in the CGI-BP Severity of Illness (overall) score was significantly in favor of aripiprazole compared with placebo

Figure 6. Mean Change From Last Stabilization Phase Visit in the YMRS Total Score[a]



[a]Baseline YMRS scores, mean (SE): aripiprazole, 2.55 (0.3); placebo, 2.06 (0.3).
*.01 ≤ p ≤ .05 versus placebo (last observation carried forward).
†p ≤ .01 versus placebo (last observation carried forward).
Abbreviation: YMRS = Young Mania Rating Scale.

Figure 7. Mean Change From Last Stabilization Phase Visit in the MADRS Total Score[a,b]



[a]Last-observation-carried-forward data.
[b]Baseline MADRS scores, mean (SE): aripiprazole, 3.9 (0.4); placebo, 4.5 (0.4).
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

(aripiprazole, 0.7 ± 0.2; placebo, 1.3 ± 0.2; p = .02). Similarly, the mean change from baseline in the CGI-BP Severity of Illness (mania) score was significantly in favor of aripiprazole (aripiprazole, 0.4 ± 0.1; placebo, 0.9 ± 0.1; p = .013) at week 26. For CGI-BP Severity of Illness (depression), there were no statistically significant differences in scores between the aripiprazole and placebo groups.

Safety

Adverse events. During the double-blind phase, 58 (69.9%) of 83 patients receiving placebo and 57 (74.0%) of 77 patients receiving aripiprazole reported at least 1 adverse event. Adverse events occurring at a ≥ 5% incidence in either treatment group are presented in Table 2. In the aripiprazole group, adverse events reported at an incidence of ≥ 5% and at least twice that of placebo were tremor (9.1%), akathisia (6.5%), vaginitis (6.4%), and pain in the extremities (5.2%). The incidence of serious adverse events (SAEs) was greater in the placebo group than in the aripiprazole group (13.3% vs. 7.8%, respectively). The most common (≥ 3%) SAEs reported by placebo-treated patients were manic reaction (6.0%) and depression (3.6%); the most common (≥ 3%) SAE reported by aripiprazole-treated patients was manic reaction (5.2%). One patient in the placebo group attempted suicide during the double-blind phase. There were no suicides in either group.

Table 2. Incidence of Adverse Events That Occurred at a Rate of ≥ 5% in the Placebo and Aripiprazole Groups During the Double-Blind Phase of the Study

Adverse Events by Body System	Placebo (N = 83), N (%)	Aripiprazole (N = 77), N (%)
Any adverse event	58 (69.9)	57 (74.0)
Body as a whole		
Asthenia	7 (8.4)	6 (7.8)
Headache	14 (16.9)	6 (7.8)
Pain in the extremities	1 (1.2)	4 (5.2)
Pain in the back	5 (6.0)	3 (3.9)
Cardiovascular system		
Hypertension	3 (3.6)	4 (5.2)
Digestive system		
Nausea	4 (4.8)	7 (9.1)
Nervous system		
Anxiety	12 (14.5)	13 (16.9)
Insomnia	16 (19.3)	12 (15.6)
Depression	12 (14.5)	9 (11.7)
Nervousness	5 (6.0)	8 (10.4)
Tremor	1 (1.2)	7 (9.1)
Agitation	9 (10.8)	6 (7.8)
Akathisia	1 (1.2)	5 (6.5)
Manic reaction	11 (13.3)	5 (6.5)
Somnolence	6 (7.2)	4 (5.2)
Depersonalization	8 (9.6)	3 (3.9)
Respiratory system		
Upper respiratory infection	8 (9.6)	7 (9.1)
Urogenital system		
Vaginitis[a]	0	3 (6.4)
Urinary tract infection	3 (3.6)	4 (5.2)

[a]Incidence adjusted for sex: placebo, N = 60; aripiprazole, N = 47.

More patients in the placebo group than in the aripiprazole group (19.3% vs. 10.4%, respectively) discontinued the study because of treatment-emergent adverse events. The most common (≥ 3%) of these adverse events were depression (7.2%), manic reaction (6.0%), and insomnia (4.8%) in placebo-treated patients and manic reaction (3.9%) in aripiprazole-treated patients.

Adverse events related to EPS occurred more frequently in the aripiprazole group than in the placebo group. The most common (≥ 3%) of these were akathisia (placebo, 1.2%; aripiprazole, 6.5%), tremor (placebo, 1.2%; aripiprazole, 9.1%), and hypertonia (placebo, 1.2%; aripiprazole, 3.9%). Most patients reported resolution of these adverse events before the end of the study; only 1 patient discontinued because of akathisia, and none discontinued because of tremor or hypertonia.

Table 3. Analysis of SAS, AIMS, and BARS Scores for the Double-Blind Phase

Variable	SAS			AIMS			BARS		
	Aripiprazole (N = 76)	Placebo (N = 81)	Treatment Difference (95% CI)	Aripiprazole (N = 73)	Placebo (N = 79)	Treatment Difference (95% CI)	Aripiprazole (N = 76)	Placebo (N = 81)	Treatment Difference (95% CI)
Score at last stabilization visit, mean (SE)[a]	10.59 (0.18)	10.79 (0.18)	–0.20 (–0.71 to 0.31)	0.14 (0.10)	0.25 (0.10)	–0.12 (–0.40 to 0.17)	0.37 (0.08)	0.28 (0.07)	0.08 (–0.12 to 0.29)
Change from last stabilization visit[a] at double-blind phase endpoint LOCF, mean (SE)[b]	0.19 (0.18)	–0.14 (0.17)	0.32 (–0.17 to 0.81)	0.09 (0.10)	0.06 (0.10)	0.03 (–0.24 to 0.31)	–0.05 (0.07)	–0.14 (0.06)	0.09 (–0.09 to 0.28)

[a]Not all evaluations were performed at the same visit; thus the definition of *baseline* varies by analysis.
[b]Negative change score signifies improvement.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, CI = confidence interval, LOCF = last observation carried forward, SAS = Simpson-Angus Scale.

During the double-blind phase, mean baseline to endpoint changes on the SAS, AIMS, and BARS were minimal in the placebo and the aripiprazole groups (Table 3). In addition, at any time during the double-blind phase, 6 (7.4%) of 81 placebo patients and 7 (9.2%) of 76 aripiprazole patients had SAS total scores of ≥ 15 (moderate severity) (relative risk [RR] = 1.24; 95% CI = 0.44 to 3.53), and 2 (2.5%) of 81 placebo patients and 4 (5.3%) of 76 aripiprazole patients had a Barnes Global Clinical Assessment of Akathisia item score of ≥ 3 (moderate to severe) (RR = 2.13; 95% CI = 0.40 to 11.30).

Clinical laboratory results. Mean serum prolactin levels (± SE) were similar in both treatment arms at the start of the double-blind phase (placebo, 10.4 ± 1.1 ng/mL; aripiprazole, 11.4 ± 1.0 ng/mL). Placebo-treated patients experienced a mean increase in serum prolactin levels from randomization to endpoint (4.2 ± 1.6 ng/mL; LOCF data set). In contrast, aripiprazole-treated patients experienced mean decreases in serum prolactin concentrations from randomization to endpoint LOCF (–0.4 ± 1.6 ng/mL). The endpoint LOCF treatment difference was –4.6 (95% CI = –9.1 to –0.1).

During the double-blind phase, 3 (4.1%) of 73 patients in the placebo group and 5 (6.8%) of 74 patients in the aripiprazole group had potentially clinically significant elevations in creatine phosphokinase concentration (≥ 3 times the upper limit of normal, i.e., ≥ 2.0 mg/dL), but none had associated symptoms consistent with neuroleptic malignant syndrome.

Vital signs. No clinically important changes were noted with regard to vital sign measurements and physical examinations. A review of adverse events with potential cardiovascular etiology showed no clinically important findings, especially regarding QTc interval increases.

Weight gain. At the start of the double-blind phase (randomization), the mean (± SE) weight was similar in both groups: 85.3 ± 3.0 kg in the placebo group (N = 60) and 86.1 ± 3.1 kg in the aripiprazole group (N = 56). Weight change from randomization to endpoint (LOCF) in the placebo group showed a mean weight loss of 1.7 ± 0.8 kg, whereas patients in the aripiprazole group showed a mean weight gain of 0.5 ± 0.8 kg. The endpoint LOCF treatment difference was 2.19 (95% CI = –0.06 to 4.43).

At the end of the double-blind phase, significant weight gain (≥ 7% increase from randomization) was seen for 13% (7/56) of the aripiprazole-treated patients but for none (0/60) of the placebo patients. Since the denominator of the Mantel-Haenszel relative risk estimator for aripiprazole/placebo is zero, relative risk and 95% confidence intervals cannot be computed. Of the 7 aripiprazole-treated patients with clinically significant weight gain, 1 had a body mass index (BMI) of < 23 (low-normal), 2 had a BMI of 23 to 27 (normal-overweight), and 4 had a BMI of > 27 (overweight-obese). Significant

Table 4. Median Metabolic Parameters During Double-Blind Phase

Metabolic Parameter	Placebo	Aripiprazole
Fasting glucose, median, mg/dL		
Baseline	86.0	85.5
Change from baseline[a]	6	4
Fasting HDL cholesterol, median, mg/dL		
Baseline	45.0	45.0
Change from baseline[b]	2	3
Fasting LDL cholesterol, median, mg/dL		
Baseline	106.0	113.0
Change from baseline[b]	15	16

[a]Median days on treatment were 151.0 for placebo and 181.5 for aripiprazole.
[b]Median days on treatment were 159.0 for placebo and 181.0 for aripiprazole.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

weight loss (≥ 7% decrease from randomization) was seen for 2% of aripiprazole patients and 17% of placebo patients (RR = 0.11; 95% CI = 0.01 to 0.81). No patients discontinued because of weight gain.

Other metabolic parameters measured during the double-blind phase included change from baseline in fasting glucose and fasting total cholesterol (Table 4). No differences were observed between the aripiprazole- and placebo-treated groups for any of these parameters.

DISCUSSION

This 26-week, multicenter, randomized, double-blind, placebo-controlled trial was designed to investigate the safety and efficacy of aripiprazole as monotherapy to prevent the relapse of mood episode in patients who had recently experienced a manic or mixed episode and who had subsequently been stabilized on aripiprazole treatment before being randomly assigned to double-blind therapy. Aripiprazole, 15 or 30 mg/day, was superior to placebo in delaying time to relapse of a mood episode.

Other recent long-term studies have used similar trial designs by using a responder population established in the open-label stabilization phase before studying the medication in the double-blind phase in a placebo-controlled fashion.[4,34,35] One of the main differences among these trials is in the criteria used to define stability in the open-label stabilization phase. For example, in a recent study of lamotrigine and lithium monotherapy in bipolar disorder,[4] patients were eligible for randomization after reaching a CGI-Severity score of ≤ 3 for at least 4 continuous weeks. A study of olanzapine required a YMRS score of ≤ 12 and a Hamilton Rating Scale for Depression (HAM-D) score of ≤ 8 for 2 consecutive weeks.[34] The proportion of rapid cyclers and the relapse rate in earlier studies were higher than seen in our study. In addition, relapse rates were highest in the studies with the shortest duration of stabilization criteria. The present study is the first to use the most stringent criteria to date to define stability: YMRS score of ≤ 10 and MADRS score of ≤ 13 maintained for at least 6 consecutive weeks. Because of the enrichment design of this trial, the data discussed are considered generalizable to those patients who respond acutely to aripiprazole for manic or mixed episodes.

Criteria used for relapse in the present study (discontinuation because of lack of efficacy as determined by hospitalization for a mood episode or addition to or increase in psychotropic medication other than the study drug for manic and/or depressive symptoms) were designed to identify prodromal indicators of relapse before the occurrence of a full relapse. These criteria were established to minimize the exposure of placebo-treated patients to full relapse and to provide representative criteria of real-world clinical practice. It should be noted that, although the exposure of a stabilized patient to placebo should be kept to a minimum, registrational trials, such as this one, require placebo control; the study design was approved by the FDA for providing data to acquire an approval for use in the patient population studied. To minimize the long-term exposure to placebo, length of the double-blind phase was taken into consideration (e.g., 26 weeks vs. 52 weeks) as were the criteria to assess relapse (e.g., syndromal vs. prodromal criteria). Until non-inferiority-designed studies can be considered a scientifically valid substitute for a placebo design, when investigating a new medication in a population with a potential for a high placebo response, placebo-controlled study designs, even in a long-term setting, may still be warranted.

Based on the primary efficacy endpoint, time from randomization to relapse in the double-blind phase, aripiprazole was effective in maintaining the stability of patients with bipolar I disorder whose most recent episode was manic or mixed type. The probability of precluding a relapse was higher for aripiprazole-treated patients (Figure 3; HR = 0.52) than for placebo-treated patients, which means that aripiprazole reduced the risk for relapse by approximately 48%. Overall, aripiprazole-treated patients experienced significantly fewer relapses than placebo-treated patients. In particular, aripiprazole significantly decreased the incidence of manic relapse, the index episode for this cohort.

Regarding the key secondary efficacy endpoints, time to relapse for mania and time to relapse for depression during the double-blind phase, aripiprazole was statistically superior to placebo in delaying the time to relapse for mania. The delayed time to relapse of mania observed in aripiprazole-treated patients was also supported by the significantly lower mean YMRS total scores seen in aripiprazole-treated patients. No significant differences were observed between aripiprazole-treated and placebo-treated patients with regard to delay of time to relapse for depression. This finding may reflect that the study was

not powered to detect differences in rates of relapse of depression, and the study participants enrolled in the present trial were those who had experienced an index episode of manic (70%) or mixed (30%) symptoms. In this study, coadministration of analgesics and antipyretics or permitted anxiolytics and anticholinergics were unlikely to confound interpretation of the efficacy of aripiprazole compared with placebo.

Calabrese and colleagues and other researchers have shown, in recent studies of long-term treatment of bipolar disorder, that the index mood episode before enrollment is strongly predictive of the type and frequency of relapse.[4,9,35,36] Patients presenting with depression were found to experience relapses into depression rather than mania at a ratio of 2.4:1, whereas initial episodes of mania were followed by relapses into mania rather than depression at a 1.3:1 ratio.[4,9,35,36] The data presented here suggest that, compared with placebo, aripiprazole did not increase the liability to relapse into depressive or mixed episodes. To fully evaluate whether aripiprazole precludes depressive relapses, patients presenting with an episode of bipolar depression would have to be studied.

In this study, as in the 3-week placebo-controlled studies,[20,21] all patients entered the stabilization phase at an aripiprazole starting dose of 30 mg/day, with a decrease to 15 mg/day allowed, if necessary, for tolerability. The intent of this trial, however, was not to evaluate a specific dose for long-term therapy but to investigate the efficacy of the range of 15 to 30 mg/day. Among patients who met stabilization criteria and subsequently were randomly assigned, 37% received 15 mg/day, and 63% received 30 mg/day. At the double-blind phase endpoint, 41% of patients were taking aripiprazole 15 mg/day, and 59% were taking 30 mg/day. Hence, aripiprazole doses of 15 mg/day and 30 mg/day may both be efficacious in maintaining stability in patients with bipolar I disorder.

In trials of this nature, comparing adverse event rates among patients receiving active agents and placebo permits a qualitative assessment of whether certain events are more likely to be associated with a given drug. In the present study, however, comparing the effects of aripiprazole and placebo may be confounded by the fact that all patients received open-label aripiprazole during the stabilization phase and entered the double-blind phase of the trial based on stabilization criteria while continuing to tolerate the medication (15 mg/day or 30 mg/day). Nevertheless, treatment-emergent adverse events reported in the double-blind phase were generally consistent with those reported in earlier 3-week, placebo-controlled, acute mania studies[20,21,33] and in the 12-week haloperidol-controlled study in acute bipolar mania.[22] The higher incidence of adverse events that led to study discontinuation and of SAEs observed in the placebo group may be attributed to the higher incidences of manic reaction and depression in these patients.

In the aripiprazole group, adverse events reported at an incidence of ≥ 5% and at least twice that of placebo were tremor, akathisia, vaginitis, and pain in the extremities. However, none of these adverse events were seen at an incidence of ≥ 10%. This suggests that aripiprazole-treated patients who were stabilized and entered the double-blind phase continued to tolerate the medication over the course of the 26-week trial.

Results of this study with respect to EPS, prolactin levels, and QTc interval prolongation were consistent with findings of earlier bipolar mania studies[20–22,33] and of a 26-week schizophrenia study.[37] The incidences of akathisia and tremor were higher for aripiprazole-treated patients; however, most aripiprazole-treated patients who reported tremor or akathisia during the double-blind phase experienced resolution. Furthermore, during the double-blind phase, there were no discontinuations because of tremor, and only 1 aripiprazole-treated patient discontinued because of akathisia. Analysis of scores on the SAS, AIMS, and BARS yielded minimal differences among patients receiving aripiprazole or placebo. Thus, these results suggest that, although the frequency of EPS-related events was higher for aripiprazole-treated patients, the severity of EPS-related events in patients with bipolar I disorder was similar between aripiprazole- and placebo-treated patients. In addition, there was no report of tardive dyskinesia in aripiprazole-treated patients.

Hyperprolactinemia is of interest because it may lead to galactorrhea, amenorrhea, reduced bone density, and sexual dysfunction.[38] The incidence of potentially clinically significant elevated prolactin levels was similarly low for the aripiprazole and placebo groups.

Review of adverse events of potential cardiovascular etiology, specifically with regard to QTc interval changes, revealed no clinically important findings during the double-blind phase, and no patient discontinued the study because of an ECG abnormality. In addition, there were no significant changes in vital signs.

The effects of aripiprazole on weight gain are of particular interest because obesity is more prevalent in persons with bipolar I disorder than in the general population[39,40] and because obesity is correlated with poor outcome in this disorder.[41] Furthermore, weight gain has been a frequent problem in patients receiving short-term[42,43] and long-term[44,45] treatment with atypical antipsychotics for bipolar disorder.

In the current long-term study, the overall effect of mean weight change in patients with bipolar I disorder is consistent with the weight effects seen in 26-week studies with aripiprazole in patients with chronic schizophrenia.[37,46] The incidence of significant weight gain in aripiprazole-treated patients is also in line with that reported in the long-term aripiprazole trials[37,46]; however, the incidence of clinically significant weight gain in placebo-treated patients in the current trial is not consis-

tent with that of the other long-term trial.[37] The cause for this finding is unclear. Nonetheless, some patients experienced clinically significant weight gain with aripiprazole during the double-blind phase, indicating that some patients are susceptible to excessive weight gain and should be monitored when receiving psychotropic medications.

The American Psychiatric Association (APA) practice guidelines recommend maintenance treatment for all patients with bipolar I disorder and suggest lithium and valproate as first-line therapies.[47] With regard to antipsychotics, the practice guidelines advocate the use of these agents for "persistent psychosis or prophylaxis against recurrence."[47] The assumption underlying APA maintenance therapy recommendations is that antipsychotics are more poorly tolerated than lithium or valproate in long-term use.[47] Although this may be true for antipsychotics with significant metabolic, extrapyramidal, or endocrinologic side effects, newer atypical antipsychotics, such as aripiprazole, may provide options for long-term therapy for bipolar I disorder. Furthermore, the recent publication of the TIMA (Texas Implementation of Medication Algorithms) guidelines for bipolar I disorder recommend aripiprazole as a level II option after level I options—lithium, valproate, lamotrigine, olanzapine—fail as maintenance treatment in patients with a recent hypomanic/manic/mixed episode.[48]

CONCLUSIONS

This long-term study conducted in patients with bipolar I disorder evaluated time to relapse to a mood episode in patients stabilized and maintained on aripiprazole using the most stringent criteria for stabilization to date (YMRS score of ≤ 10 and MADRS score of ≤ 13 for 6 consecutive weeks). Aripiprazole, the first dopamine partial agonist to be approved for the treatment of acute mania associated with bipolar I disorder, was superior to placebo in maintaining efficacy in patients with bipolar I disorder with a recent manic or mixed episode. Aripiprazole exhibited no unusual or unexpected adverse events during the conduct of this trial and maintained a tolerability profile consistent with that found in other short- and long-term placebo-controlled studies with aripiprazole.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakene and others), ziprasidone (Geodon).

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