A Placebo-Controlled, Double-Blind Study of the Efficacy and Safety of Aripiprazole in Patients With Acute Bipolar Mania

Paul E. Keck, Jr., M.D.

Ronald Marcus, M.D.

Stavros Tourkodimitris, Ph.D.

Mirza Ali, Ph.D.

Amy Liebeskind, M.D.

Anutosh Saha, Ph.D.

Gary Ingenito, M.D.

Aripiprazole Study Group

Objective: The authors compared the efficacy and safety of aripiprazole, a novel antipsychotic, to placebo for treatment of patients in an acute manic or mixed episode of bipolar disorder.

Method: This 3-week, multicenter, double-blind study randomly assigned 262 bipolar disorder patients in an acute manic or mixed episode to aripiprazole, 30 mg/day (reduced to 15 mg/day if needed for tolerability), or placebo. Patients remained hospitalized for at least 2 of the weeks. The primary efficacy measure was mean change from baseline in total score on the Young Mania Rating Scale; response was defined as a decrease in score of ≥50%.

Results: Aripiprazole produced statistically significant mean improvements in total score on the Young Mania Rating Scale compared with placebo (–8.2 versus –3.4, respectively) and produced a significantly higher response rate (40% versus 19%). For key efficacy variables (response per Young Mania Rating Scale; Clinical Global Impression—Bipolar Version scores for severity of illness [mania] and change from preceding phase [mania]), aripiprazole separated from placebo by day 4. The completion rate was significantly higher with aripiprazole than with placebo (42% versus 21%). Discontinuations due to adverse events did not differ significantly between the aripiprazole and placebo groups. There were no significant changes in body weight versus placebo, and aripiprazole was not associated with elevated serum prolactin or QTc prolongation.

Conclusions: Aripiprazole had significantly greater efficacy than placebo for the treatment of bipolar disorder patients in acute manic or mixed episodes and was safe and well tolerated in this randomized controlled trial.

For many patients, the effectiveness of current treatments for bipolar disorder is suboptimal. Although lithium, divalproex sodium, and olanzapine—the approved treatments for acute mania—show similar efficacy, clinical trials report nonresponse rates of up to 50% with these agents (1).

Antipsychotics are commonly used for the initial treatment of acute mania, both as monotherapy and as adjuncts to mood stabilizers (1). In acute mania, typical antipsychotics show similar efficacy to lithium (2), but they may have a faster onset of action (3) and they appear more effective in treating psychomotor agitation (4, 5). In addition to olanzapine, more recent clinical studies have demonstrated the efficacy of other atypical antipsychotics in treating acute mania at doses effective for schizophrenia (2). Generally, atypical antipsychotics have a lower risk of neurological side effects compared with typical agents and may be less likely to exacerbate depressive symptoms (6). However, currently available atypical antipsychotics are associated with unwanted side effects, including weight gain (7), hyperprolactinemia (8), QTc prolongation (9), hyperglycemia (10, 11), and dyslipidemia (12).

Aripiprazole is a novel antipsychotic with a pharmacodynamic profile that distinguishes it from other antipsychotics. Aripiprazole is a partial agonist at dopamine D_2 receptors (13, 14), a partial agonist at serotonin 5-HT$_{1A}$ receptors (15), and an antagonist at 5-HT$_{2A}$ receptors (16). In randomized, placebo-controlled studies in patients who experienced an acute relapse of schizophrenia or schizoaffective disorder, aripiprazole improved positive and negative symptoms and demonstrated a favorable safety and tolerability profile, with low liability for extrapyramidal symptoms, weight gain, sedation, hyperprolactinemia, or QTc prolongation (17).

The objective of the current study was to assess the efficacy, safety, and tolerability of aripiprazole for the treatment of patients in a manic or mixed episode of bipolar I disorder.

Method

Patients

This study enrolled male and female patients, age ≥18 years, diagnosed with bipolar I disorder, manic or mixed episode (DSM-IV), who were experiencing an acute relapse that required hospitalization. Female patients of child-bearing potential were

required to agree to use acceptable contraceptive measures and were excluded if they were lactating or pregnant. In addition, patients were required to have a Young Mania Rating Scale (18) score of ≥20 at the time of randomization.

Patients were excluded from the study if they had delirium, dementia, amnestic or other cognitive disorders, schizophrenia, or schizoaffective disorder or if they were experiencing their first manic episode. Other exclusion criteria were duration of current mania >4 weeks; nonresponse to clozapine; probable need for prohibited concomitant therapy (neuroleptic agents, fluoxetine, carbamazepine, divalproex sodium, valproic acid or sodium valproate, lithium, benzodiazepines [except lorazepam], and all other psychotropic drugs) during the study; use of psychoactive substances or a substance use disorder; serum concentrations of lithium >0.6 mmol/liter or divalproex sodium >50 µg/ml (i.e., therapeutic levels) at screening; significant risk of committing suicide or homicide; history of neuroleptic malignant syndrome or seizure disorder; clinically significant abnormal laboratory test results, vital signs, or ECG results; or previous enrollment in an aripiprazole clinical trial.

After complete description of the study to the subjects, written informed consent was obtained from them or from a legally acceptable representative if required by the institutional review board or ethics committee for their study center. The study protocol, procedures, and consent statement were approved by the institutional review boards of each participating site.

Study Design

This was a multicenter, double-blind, randomized, placebo-controlled study. After a 1–7 day screening period to assess patient eligibility and allow elimination of existing psychotropic medications, patients fulfilling study entry criteria were randomly assigned to receive aripiprazole, 30 mg/day, or placebo. During the study, the aripiprazole dose could be reduced to 15 mg/day for tolerability if needed.

The treatment period lasted 3 weeks. Patients were hospitalized for at least the first 2 weeks of treatment. At the end of week 2, patients could be discharged if they had the following scores on the Clinical Global Impression (CGI)—Bipolar Version (19): severity of illness (mania) score ≥3 (mildly ill, minimally ill, or not ill) and a change from preceding phase (mania) score ≥2 (much improved or very much improved). Patients not meeting these criteria stayed in the hospital for the remaining week of treatment. Patients not responding at the end of week 2 (change from preceding phase [mania] score of 4 [no improvement] to 7 [very much worse]) were discontinued from double-blind treatment and offered the option of open-label aripiprazole treatment during week 3.

Efficacy Assessments

Treatment efficacy was assessed at baseline and at days 4, 7, 10, 14, and 21. The primary efficacy measure was mean change in total score (last observation carried forward) on the Young Mania Rating Scale from baseline to the end of study (day 21). The Young Mania Rating Scale consists of 11 items that assess the core symptoms of mania: 1) elevated mood, 2) increased motor activity/energy, 3) sexual interest, 4) sleep, 5) irritability, 6) speech (rate and amount), 7) language/thought disorder, 8) content, 9) disruptive/aggressive behavior, 10) appearance, and 11) insight. The severity of four items (items 5, 6, 8, and 9) is graded from 0 (best) to 8 (worst), while the other seven items are graded from 0 (best) to 4 (worst). The Young Mania Rating Scale total score is the sum of all the items; possible scores range from 0 to 60.

Other efficacy measures included mean change for each of the CGI—Bipolar Version scores for severity of illness and change from preceding phase (i.e., for mania, depression, and overall bipolar illness); discontinuation due to lack of efficacy or entry into open-label aripiprazole treatment; and response (≥50% decrease in Young Mania Rating Scale score from baseline).

Safety and Tolerability Assessments

Reports of adverse events were obtained from patients throughout the study period (including the screening phase). Investigators evaluated reported events for severity and likely relationship to study medication. Patients' vital signs were measured at screening, baseline, and each assessment visit during the study. Twelve-lead ECGs, blood and urine collection, and body weight measurements were performed at screening and the end of the study.

Extrapyramidal symptoms were evaluated by using the Simpson-Angus Rating Scale (20), the Barnes Rating Scale for Drug-Induced Akathisia (21), and the Abnormal Involuntary Movement Scale (AIMS) (22). Evaluations were made at baseline and at each assessment visit for the Simpson-Angus Rating Scale and Barnes Akathisia Scale and at baseline and at the end of the study for the AIMS.

Concomitant Medication

Concomitant medication use was recorded on case report forms. Concomitant use of psychotropic medications (apart from study medication) was prohibited during the study (including the screening phase) except for lorazepam. Lorazepam treatment was allowed only on days 1–4 (≤6 mg/day), 5–7 (≤4 mg/day), and 8–10 (≤2 mg/day).

Anticholinergic treatments for extrapyramidal symptoms were not permitted during screening. Anticholinergic agents were permitted after treatment assignment if deemed necessary by the investigator, but use was limited to 6 mg/day of benztropine (or equivalent) and could not be administered within 12 hours of an efficacy or safety assessment.

Statistical Procedures

Efficacy parameters were analyzed on an intent-to-treat basis from data obtained at each patient's final visit (i.e., last-observation-carried-forward analysis). Efficacy measures were evaluated by analyses of covariance (ANCOVA) that adjusted for baseline score and controlled for study center; rates of discontinuation due to lack of efficacy or entry into open-label aripiprazole treatment, response rates, and change from preceding phase scores were evaluated by the Cochran-Mantel-Haenszel test, which controlled for study center. Data from small centers, defined as no patients in one or more treatment groups, were pooled to form pseudocenters before analysis.

Simpson-Angus Rating Scale, AIMS, and Barnes Rating Scale for Drug-Induced Akathisia scores were analyzed on an intent-to-treat basis from data obtained at each patient's final visit by using ANCOVA after we adjusted for baseline score and controlled for study center.

Results

Patients

The study was conducted at 38 centers in the United States. Overall, 262 patients were randomly assigned to a study treatment condition (130 to aripiprazole, 132 to placebo); this study is one of the largest double-blind, placebo-controlled trials of an antipsychotic as monotherapy for acute mania reported to date. Baseline characteristics for the patients are shown in Table 1.

Of the 262 patients assigned to a treatment condition, eight did not take study medication and thus were excluded from safety and efficacy analyses (aripiprazole: N=

TABLE 1. Demographic and Baseline Clinical Characteristics of Bipolar Disorder Patients in an Acute Manic or Mixed Episode Randomly Assigned to 3 Weeks of Double-Blind Treatment With Aripiprazole or Placebo

Characteristic	Placebo Group (N=132)		Aripiprazole Group (N=130)		Total (N=262)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	40.5	11.8	40.5	12.7	40.5	12.2
Body weight (kg)[a]	86.3	23.4	85.2	20.1	85.8	21.8
	N	%	N	%	N	%
Sex						
Male	55	42	59	45	114	44
Female	77	58	71	55	148	56
History of bipolar disorder						
Not rapid cycling	99	75	102	78	201	77
Rapid cycling	33	25	28	22	61	23
Current episode						
Manic	83	63	93	72	176	67
Mixed	49	37	37	28	86	33

[a] Total N=253 (placebo: N=128; aripiprazole: N=125).

TABLE 2. Study Progression of Bipolar Disorder Patients in an Acute Manic or Mixed Episode Randomly Assigned to 3 Weeks of Double-Blind Treatment With Aripiprazole or Placebo

Outcome	Placebo Group (N=132)		Aripiprazole Group (N=130)		Total (N=262)	
	N	%	N	%	N	%
Completed double-blind treatment	28	21	54	42	82	31
Discontinued double-blind treatment	104	79	76	58	180	69
Entered open-label treatment[a]	37	28	17	13	54	21
Adverse event	13	10	14	11	27	10
Lack of efficacy	16	12	13	10	29	11
Other[b]	38	29	32	25	70	27

[a] Patients not responding at week 2 (scoring ≥4 on the measure of change from preceding phase [mania] from the Clinical Global Impression—Bipolar Version scale) were offered open-label aripiprazole treatment.
[b] Includes those patients who withdrew consent, were lost to follow-up, or were unreliable.

3, placebo: N=5). An additional six patients (aripiprazole: N=2, placebo: N=4) did not have a valid postrandomization efficacy evaluation because of early discontinuation from the study and so were excluded from the efficacy analysis. Hence, valid data from 254 patients and 248 patients were available for the safety analysis and the efficacy analysis, respectively.

Overall, 82 (31%) patients completed the 3-week, double-blind treatment period. The completion rate was significantly higher with aripiprazole treatment than placebo (42% versus 21%) (χ^2=10.90, df=1, p<0.001). Reasons for discontinuation are shown in Table 2. The main difference between the two groups was in the number of patients who did not display an adequate response at week 2 and thus entered open-label treatment with aripiprazole. Discontinuations due to adverse events were similar between the two groups.

The mean dose of aripiprazole at endpoint was 27.9 mg/day for patients in the safety analysis. The majority of patients (86%) receiving aripiprazole during double-blind treatment remained on the 30-mg dose throughout the study. The number of patients requiring lorazepam treatment during the study was comparable in each treatment group (placebo: 108 of 127 [85%]; aripiprazole: 109 of 127 [86%]).

Efficacy

Aripiprazole produced a significant improvement in total scores on the Young Mania Rating Scale from baseline to endpoint compared with placebo (Table 3). The significant difference in mean change between the aripiprazole and placebo group was apparent from day 4 onward (Figure 1).

Response rates were significantly greater with aripiprazole than placebo at all time points from day 4 (14% versus 5%) through endpoint (40% versus 19%) (Figure 2). Aripiprazole produced significantly greater improvements in

severity of illness (mania) scores compared with placebo (Table 3), which were seen at day 4 and all subsequent efficacy assessments (Figure 2). Aripiprazole also produced significantly superior mean scores from day 4 onward compared with placebo for the change from preceding phase (mania) score (Table 3).

In addition to the mania ratings, aripiprazole also produced significantly greater improvements for the CGI—Bipolar Version severity of illness scores for depression and overall bipolar illness and significantly superior change from preceding phase scores for depression and overall bipolar illness than were seen with placebo (Table 3).

Safety

Adverse events. In total, 27 (11%) of the 254 patients available for the safety analysis discontinued from double-blind treatment because of an adverse event, 13 from the placebo group and 14 from the aripiprazole group.

Overall, 11 serious adverse events were experienced by eight patients (3%), four from each treatment group, during double-blind treatment or within 30 days of discontinuation (one patient receiving placebo reported two serious adverse events, and one patient receiving aripiprazole reported three serious adverse events). The reported events in the aripiprazole group were manic reaction (N=3), psychiatric decompensation, overdose of sedatives, and hypertension (one event each). The placebo group reported agitation, accidental injury, chest discomfort, syncope, and urticaria (one event each). The most common, treatment-emergent adverse events are shown in Table 4. Further analysis of somnolence and gastrointestinal events showed that the majority of events occurred during the first week of treatment and resolved within 7 days (Figure 3).

Extrapyramidal symptoms. The most commonly reported extrapyramidal symptom-related adverse events

TABLE 3. Outcome After 3 Weeks for Bipolar Disorder Patients in an Acute Manic or Mixed Episode Randomly Assigned to Double-Blind Treatment With Aripiprazole or Placebo

| Efficacy Assessment	Baseline						3 Weeks				Analysis[a]		
	Placebo			Aripiprazole			Placebo		Ariprazole				
	N	Mean	95% CI	N	Mean	95% CI	Mean Change[b]	95% CI	Mean Change[b]	95% CI	F	df	p
Young Mania Rating Scale[b]	122	29.7	28.7 to 30.7	123	28.2	27.1 to 29.2	−3.4	−5.8 to −0.9	−8.2	−10.6 to −5.7	9.97	1, 210	0.002
Severity of illness[c]	122			124									
Mania		4.7	4.6 to 4.9		4.6	4.4 to 4.7	−0.4	−0.7 to −0.1	−1.0	−1.3 to −0.7	10.66	1, 211	0.001
Depression		2.4	2.1 to 2.6		2.1	1.9 to 2.3	0.1	−0.1 to 0.3	−0.2	−0.5 to 0.0	5.02	1, 211	0.03
Overall bipolar disorder		4.8	4.7 to 4.9		4.6	4.4 to 4.7	−0.4	−0.7 to −0.1	−1.0	−1.3 to −0.7	12.40	1, 211	0.001
							Mean	SD	Mean	SD	χ^2	df	p
Change from preceding phase[c,d]													
Mania							4.1	1.7	3.3	1.7	13.18	1	0.001
Depression							4.0	1.2	3.6	1.3	7.45	1	0.006
Overall bipolar disorder							4.2	1.6	3.4	1.6	13.45	1	0.001
							N	%	N	%	χ^2	df	p
Discontinuation of double-blind treatment[e]							50	41	28	23	10.90	1	0.003

[a] Changes in Young Mania Rating Scale and severity of illness scores were evaluated by analyses of covariance that adjusted for baseline score and controlled for study center. Scores for change from preceding phase and discontinuation rates were evaluated by the Cochran-Mantel-Haenszel test, which controlled for study center.
[b] Last observation carried forward; a negative change indicates improvement.
[c] From the Clinical Global Impression—Bipolar Version scale.
[d] Assessed on a 7-point scale (1=very much improved, 7=very much worse). N=123 for the placebo group, N=124 for the aripiprazole group.
[e] Patient either entered open-label aripiprazole treatment or discontinued because of lack of efficacy. N=123 for the placebo group, N=124 for the aripiprazole group.

FIGURE 1. Mean Change From Baseline in Young Mania Rating Scale Score for Bipolar Disorder Patients in an Acute Manic or Mixed Episode Randomly Assigned to 3 Weeks of Double-Blind Treatment With Aripiprazole or Placebo[a]
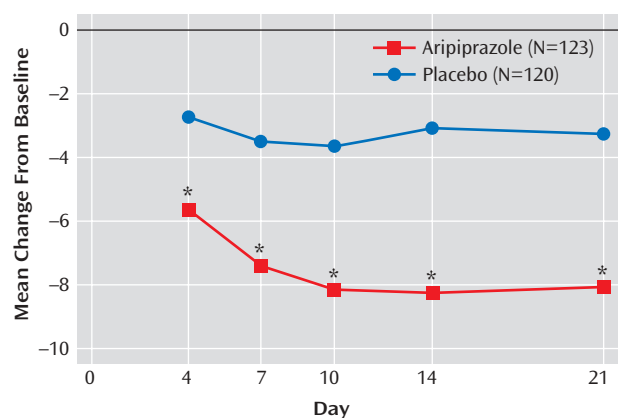
[a] Analysis of covariance that adjusted for baseline score and controlled for study center revealed between-group significant differences (p<0.005) by day 4 that continued to study endpoint.
*p<0.005.

Changes from baseline for Simpson-Angus Rating Scale and Barnes Rating Scale for Drug-Induced Akathisia scores were small but significantly greater in the aripiprazole group compared with the placebo group. Changes from baseline in AIMS score did not differ significantly between the groups (Table 5).

Body weight. Patients in both treatment groups experienced a slight decrease in mean body weight from baseline to endpoint (placebo: –0.8 kg; aripiprazole: –0.3 kg). No statistically significant difference in clinically significant weight gain (≥7% increase from baseline) was detected between the two groups (aripiprazole, N=2; placebo, N=0).

Prolactin

Mean baseline prolactin values were within normal limits for male patients (15.5 ng/ml) and female patients (25.7 ng/ml) in the placebo group and for male patients (18.1 ng/ml) in the aripiprazole group but were above the upper limit of normal for female patients (31.0 ng/ml) in the aripiprazole group. Over the course of the study, mean serum prolactin levels decreased by 12.7 ng/ml (SD=29.0) in the aripiprazole group and 7.2 ng/ml (SD=28.1) in the placebo group (F=6.53, df=1, 175, p≤0.05). Mean endpoint values for both treatment groups, 14.1 ng/ml and 14.8 ng/ml, respectively, were within normal limits.

The percentage of patients with a serum prolactin value above the upper limit of normal during study treatment

were akathisia (11%) and tremor (6%) with aripiprazole and tremor and extrapyramidal syndrome (both 3%) with placebo. Both dose reduction (3%) and discontinuation due to akathisia (1.6%) were infrequent in patients receiving aripiprazole.

FIGURE 2. Response Rates and Improvement Among Bipolar Disorder Patients in an Acute Manic or Mixed Episode Randomly Assigned to 3 Weeks of Double-Blind Treatment With Aripiprazole or Placebo[a]
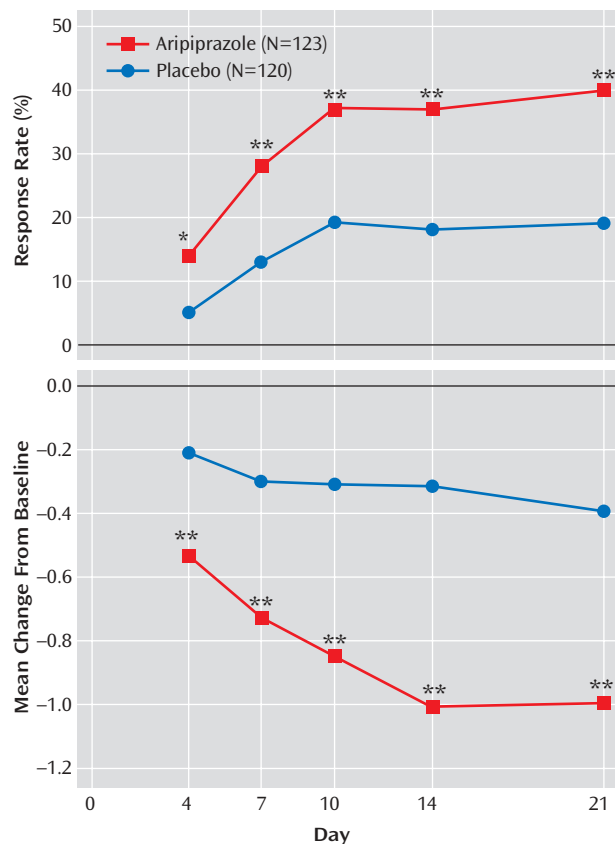
[a] Response was defined as ≥50% decrease in total Young Mania Rating Scale score from baseline, and improvement was measured by change in severity of illness (mania) score from the CGI—Bipolar Version scale. Cochran-Mantel-Haenszel tests that controlled for study center revealed significant between-group differences by day 4 that continued to study endpoint.
* p<0.02.   **p≤0.005.

was higher in the placebo group (17%) than the aripiprazole group (11%). At baseline, 23% of patients in the placebo group and 30% of those in the aripiprazole group had prolactin values above the upper limit of normal.

ECG

One patient who received placebo experienced a clinically significant increase in QTc interval (QTc ≥450 msec and a ≥10% increase from baseline) when Bazett's correction factor was applied. This was normalized when the Food and Drug Administration Neuropharmacological Division correction factor was used. No patients receiving aripiprazole were determined to have a clinically significant increase in QTc interval.

Vital Signs and Laboratory Analyses

There were no clinically significant differences between groups in vital sign changes or laboratory analyses. No patients receiving aripiprazole discontinued from the study

TABLE 4. Treatment-Emergent Adverse Events Among Bipolar Disorder Patients in an Acute Manic or Mixed Episode Randomly Assigned to 3 Weeks of Double-Blind Treatment With Aripiprazole or Placebo

Adverse Event[a]	Placebo Group (N=127)		Aripiprazole Group (N=127)	
	N	%	N	%
Headache	40	31	46	36
Nausea	13	10	29	23
Dyspepsia	13	10	28	22
Somnolence	6	5	26	20
Agitation	24	19	25	20
Anxiety	13	10	23	18
Vomiting	6	5	20	16
Insomnia	11	9	19	15
Lightheadedness	10	8	18	14
Constipation	7	6	17	13
Accidental injury	3	2	15	12
Diarrhea	11	9	15	12
Akathisia	3	2	14	11

[a] Occurring in ≥10% of subjects in either treatment group.

due to vital sign or laboratory abnormalities. The rates of patients with clinically significant levels of fasting serum glucose (≥110 mg/dl) or total cholesterol (≥200 mg/dl) were similar in both groups.

Discussion

The results of the current study suggest that aripiprazole was efficacious, safe, and well tolerated for patients with bipolar I disorder experiencing an acute manic or mixed episode. Aripiprazole produced a statistically significant mean decrease in Young Mania Rating Scale total score by day 4 that was maintained throughout the 3-week study period. Twice as many patients in the aripiprazole group responded to treatment as in the placebo group (40% versus 19%); superior response rates with aripiprazole were evident by day 4.

Other outcome measures provide further support for the efficacy of aripiprazole in treating acute mania. Significantly fewer patients from the aripiprazole group discontinued treatment because of lack of efficacy or entry into open-label aripiprazole treatment than did patients in the placebo group. Aripiprazole significantly improved all CGI—Bipolar Version severity of illness and change from preceding phase scores (i.e., scores for depression and overall bipolar illness as well as scores for mania). The global improvement in depressive symptoms is important in the context of concerns regarding the depressogenic effects of typical antipsychotics in bipolar disorder (6).

Significantly more patients in the aripiprazole group (N=54 [42%]) completed double-blind treatment than in the placebo group (N=28 [21%]). However, forced discontinuation of study drug was a prespecified criterion in patients not responding at week 2 (scoring ≥4 on the measure of change from preceding phase [mania]), and patients were given the option of entering into an open-label aripiprazole treatment group for week 3. Thirteen patients randomly assigned to double-blind treatment with ari-

FIGURE 3. Adverse Events Experienced by Bipolar Disorder Patients in an Acute Manic or Mixed Episode Assigned to 3 Weeks of Aripiprazole Treatment
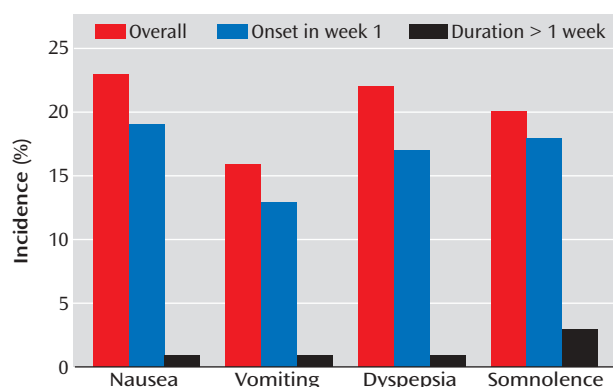
piprazole entered and completed open-label treatment, accounting for an overall completion rate of 67 (52%) in aripiprazole-treated patients. This completion rate is comparable to those seen in two placebo-controlled studies with olanzapine in mania (23, 24).

The primary reason leading to discontinuation in the study was withdrawal of consent, which accounted for 22% of discontinuation in the aripiprazole group and 23% with placebo. The discontinuation rate due to lack of efficacy or adverse events with aripiprazole treatment in the current study (22%) was comparable to the rates of 29% and 31% reported with olanzapine in placebo-controlled studies (23, 24) and to that of a 3-week study with ziprasidone (26%) (25).

Aripiprazole treatment was well tolerated during the study. Adverse events were generally mild to moderate and tended not to be treatment-limiting. The majority of patients (86%) remained on the 30-mg/day dose during the study. The rate of discontinuations due to adverse events was 10% and 11% in placebo and aripiprazole treatment groups, respectively. The incidence of adverse events was similar in both groups, except nausea, dyspepsia, vomiting, constipation, somnolence, accidental injury, and akathisia, which occurred at an incidence of ≥10% in the aripiprazole group and more than twice as frequently than with placebo. Further analysis of somnolence and gastrointestinal side effects revealed that most of these events occurred during the first week of treatment and were of limited duration.

Although aripiprazole was not associated with a significantly different change from baseline AIMS score compared with placebo, there were small but significant changes from baseline in Simpson-Angus Rating Scale and Barnes Rating Scale for Drug-Induced Akathisia scores. The majority of extrapyramidal symptom-related adverse events were mild to moderate in severity. Dose reductions for akathisia (3%) and discontinuation of study medication due to akathisia (1.6%) were both infrequent in the aripiprazole group. Extrapyramidal syndrome and tremor

TABLE 5. Changes in Extrapyramidal Symptoms Among Bipolar Disorder Patients in an Acute Manic or Mixed Episode Randomly Assigned to 3 Weeks of Double-Blind Treatment With Aripiprazole or Placebo

Extrapyramidal Symptom Assessment	Placebo Group (N=120)		Aripiprazole Group (N=123)		Significant Differences[a]		
	Mean	SD	Mean	SD	F	df	p
Simpson-Angus Rating Scale[b]							
Baseline	11.08	1.86	11.32	2.75			
Change at endpoint[c]	–0.10	1.79	0.48	2.62	4.75	1, 208	≤0.05
Barnes Rating Scale for Drug-Induced Akathisia[d]							
Baseline	0.49	0.81	0.56	1.19			
Change at endpoint[c]	–0.11	0.70	0.33	1.17	15.13	1, 208	≤0.01
AIMS total score[e]							
Baseline	0.21	1.07	0.88	2.18			
Change at endpoint[c]	–0.16	1.08	0.01	1.09			

[a] Analyses of covariance that adjusted for baseline score and controlled for study center.
[b] Ten items, each rated from 1 (normal) to 5 (severe). Total score range=10–50.
[c] Last observation carried forward; negative scores indicate improvement.
[d] Rated from 0 (absent) to 5 (severe akathisia).
[e] Ten items rated from 0 (none) to 4 (severe) and two items rated either 0 (no) or 1 (yes). Total score range=0–42. For the placebo group, N=77; for the aripiprazole group, N=99.

were the only other extrapyramidal symptom-related adverse events that led to discontinuation of study treatment (each, 0.8% of aripiprazole patients).

Weight gain is a frequent problem in patients receiving pharmacological treatment for bipolar disorder (23, 24, 26–28). Two recent studies concluded that obesity was more prevalent in patients with bipolar disorder than the general population (29, 30). In the current study, both treatment groups experienced a small decrease in body weight during the study, and there was no significant difference between groups in the incidence of clinically significant weight gain. Mean serum prolactin levels decreased significantly more in the aripiprazole group than with placebo, and none of the patients receiving aripiprazole experienced a clinically meaningful change in QTc interval in random ECGs.

In summary, aripiprazole, 30 mg/day, was effective, safe, and well tolerated in patients with bipolar I disorder experiencing an acute manic or mixed episode. Aripiprazole had a rapid onset of action and provided superior efficacy to placebo that was maintained over the 3-week study period. Treatment with aripiprazole was not associated with weight gain, prolactin elevation, or QTc prolongation, consistent with the findings of earlier studies of patients with schizophrenia. Aripiprazole's favorable safety and tolerability profile may reflect its novel mechanism of action (dopamine-serotonin system stabilizer). Partial agonist activity at dopamine D_2 receptors has been associated with stabilization of the dopamine system (i.e., functional

antagonism in hyperdopaminergic states and functional agonism in hypodopaminergic states) (31–33) and may therefore be linked to a decreased risk for side effects associated with D_2 antagonism (e.g., extrapyramidal side effects and hyperprolactinemia) (34). Longer-term studies in patients with bipolar disorder will be necessary to determine whether the short-term benefits observed in the current study are maintained.

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