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Aripiprazole plus divalproex for recently manic or mixed patients with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind maintenance trial

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Objectives The goal of this study was to investigate the safety and efficacy in preventing relapse of a mood episode in recently manic or mixed episode patients with bipolar I disorder stabilized with aripiprazole and divalproex combination.
Methods This randomized, 24-week, double-blind, placebo-controlled multicenter study enrolled patients from 23 centers in Korea. Patients with bipolar I disorder who had manic or mixed episode entered a 6-week open-label stabilization phase. After meeting stabilization criteria, 83 patients were randomly assigned to placebo + divalproex or aripiprazole + divalproex treatment group for the 24-week, double-blind maintenance phase.
Results During the 6-month double-blind treatment, the time to relapse of any mood episode in the aripiprazole group was longer than the placebo group, but the difference did not reach statistical significance ($p = 0.098$). After controlling for mean divalproex level, the time to depressive episode relapse in the aripiprazole group was longer than those in the placebo group ($p = 0.029$). Weight gain ($\geq$7% increase) occurred in 22.5% aripiprazole group and 18.6% placebo group ($p = 0.787$).
Conclusions In this study, relapse of mood episode occurred fewer and later for aripiprazole with divalproex treatment than divalproex monotherapy, but the differences were not statistically significant.

KEY WORDS—aripiprazole; divalproex; bipolar disorder; maintenance; relapse prevention

INTRODUCTION

During the past decade, several treatments including antipsychotics, anticonvulsants, lithium, or electroconvulsive therapy have been reported to be efficacious and successful in the acute phase of bipolar disorder. However, there are unmet needs in the maintenance treatment for bipolar disorder. Lithium and valproate have been used as first-line therapy for patients with acute phase and maintenance treatment of patients with bipolar I disorder, although the need for more effective pharmacotherapy during the maintenance phase of treatment is critically important because outcomes after an acute manic episode have been generally reported as poor. Several longitudinal studies after hospitalization have shown that many of these patients fail to experience full recovery (Tohen *et al*., 1990; Gitlin *et al*., 1995; Goldberg *et al*., 1995; Strakowsky *et al*., 1998), and for those who recover, over half can expect to experience a relapse within 1 year of treatment (Solomon *et al*., 1995). These limitations have prompted the assessment of other potential maintenance treatments including second-generation antipsychotics and other mood stabilizers.

Aripiprazole is a novel antipsychotic with a unique pattern of receptor pharmacology that distinguishes it from other antipsychotics. Aripiprazole is a partial agonist at

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dopamine D2 receptors, a partial agonist at serotonin 5-HT1A receptors, and an antagonist at 5-HT2A receptors (Inoue *et al*., 1996; Burris *et al*., 2002; Jordan *et al*., 2002; McQuade *et al*., 2002). In randomized, placebo-controlled studies on patients with bipolar manic or mixed episodes, aripiprazole monotherapy was shown to produce rapid, sustained improvements in manic and psychotic symptoms relative to the baseline and placebo at study end point and delay the time to relapse of mood episodes (Keck *et al*., 2003; Keck *et al*., 2006). However, pharmacotherapy increasingly has involved combination therapy, typically consisting of a combination of mood stabilizers or mood stabilizer and another psychotropic agent such as an antipsychotic. Hence, we performed this study to evaluate the long-term efficacy and safety of aripiprazole given in combination with divalproex in the prevention of mood episodes in patients with bipolar I disorder. The study tested the hypothesis that the combination of aripiprazole and divalproex would be better than divalproex monotherapy for preventing relapse of mood episodes.

PATIENTS AND METHODS

Subjects

Patients with bipolar disorder with manic or mixed episodes who fulfilled the inclusion and exclusion criteria were eligible for participation in the acute phase trial. The inclusion criteria included a current DSM-IV (American Psychiatric Association, 1994) diagnosis of bipolar disorder with a current manic or mixed episode and a requirement for antipsychotic treatment on the basis of clinical experience or investigator preference. Patients at entry had to have a score of $\geq$20 on the Young Mania Rating Scale (YMRS) (Young *et al*., 1978). Eligible patients were ages 18–65 years old at the time they enrolled in the study. The exclusion criteria were as follows: patients with the following clinical symptoms diagnosed using DSM-IV: delirium, dementia, or amnestic or other cognitive disorders; schizophrenia or schizoaffective disorder; patients who do not respond to clozapine; patients diagnosed with substance abuse-related disorders according to DSM-IV within the past 3 months (abuse, intoxication, dependency, and/or withdrawal symptoms); patients known to have allergy or hypersensitivity reaction to aripiprazole or other quinolinones; patients at high risk of suicide attempt or with the history of murder or mental status test; patients with the history of neuroleptic malignant syndrome; patients with a past history that may cause serious adverse events (SAEs) that can affect the safety or efficacy evaluation during the clinical trial period; patients with clinically significant abnormality in laboratory test, vital signs, or ECG; pregnant women or child-bearing women who do not or cannot use appropriate contraception; patients given psychotropic medications (except benzodiazepines) 1 day before baseline visit; and patients treated with fluoxetine for the last 4 weeks.

Study design

The design was a multicenter, randomized, parallel-group, double-blind study comparing aripiprazole plus divalproex and placebo plus divalproex in the maintenance treatment of adult patients with bipolar I disorder for up to 36 weeks. Acute phase for 6 weeks included an open-label aripiprazole and divalproex combination treatment period during which patients had to achieve clinical stability for 2 weeks to enter the randomized maintenance phase for 24 weeks.

The study was conducted at 23 centers in Republic of Korea between October 2007 and January 2010. The study protocol was compliant with the current amendment of the Declaration of Helsinki and International Conference on Harmonization/Good Clinical Practice guidelines. A written informed consent form approved by the relevant institutional review boards was signed by all patients.

Acute phase. All of the participants who met the enrolment criteria received open-label aripiprazole and divalproex combination treatment for 6 weeks. Aripiprazole 20 mg as initial dose was given once daily for 7 days. After the 7 days, the dosage could be adjusted to 10–30 mg according to the judgment of the investigator. Divalproex doses could be maintained or changed within the usual therapeutic dose range. Investigators were instructed to adjust the doses of the divalproex to obtain serum concentrations in the usual therapeutic range (50–120 μg/mL). Antipsychotics other than aripiprazole and mood stabilizers other than divalproex were not allowed during the trial.

Maintenance phase. Patients were eligible for inclusion regardless of whether their index episode was manic or mixed. To qualify for the randomized treatment phase, patients had to have received treatment with aripiprazole and divalproex for 6 weeks during the acute phase and to have reached clinical stability, defined as total scores of $\leq$12 on the YMRS (Young *et al*., 1978) and total scores of $\leq$13 on the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979), assessed on at least two consecutive visits spanning at least 6 weeks in the open-label acute phase.

At randomization, patients received aripiprazole plus divalproex or placebo plus divalproex in a flexible,

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double-blind manner. The dose of aripiprazole and divalproex could be adjusted as clinically indicated within the dosage range of 10–30 mg/day of aripiprazole and within the target concentrations of divalproex. Zolpidem or other hypnotics including triazolam, zopiclone, flurazepam for insomnia, lorazepam up to 4 mg/day or other benzodiazepines up to equivalent dose of lorazepam 4 mg/day for anxiety, and anticholinergic medications for extrapyramidal symptoms were permitted throughout the study.

Efficacy assessments. The primary efficacy endpoint was the time from randomization to relapse of any mood episode during the maintenance phase. Relapse of mood episode is defined as any of the following: initiation of any medication to treat mixed, manic, or depressive symptoms, including an antipsychotic, antidepressant, or mood stabilizer other than divalproex; psychiatric hospitalization; YMRS total score of $\geq$15 or MADRS total scores of $\geq$16. YMRS and MADRS scores were recorded at each visit. Visits were conducted at baseline, weeks 1, 2, 3, and 6 of the acute phase and baseline, weeks 1, 2, 4, 6, 8, 12, 16, 20, and 24 of maintenance phase. The overall level of patient acceptance of aripiprazole compared with placebo was assessed by examining the time to all-cause treatment discontinuation. Other secondary efficacy endpoint included severity of manic, depressive, and psychotic symptoms, as quantified by scores on the YMRS, the MADRS, the Clinical Global Impression scale modified for bipolar disorder (CGI-BP) (Spearing *et al*., 1997), and the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962).

Safety assessments. The occurrence of adverse events (overall and drug-related) and withdrawals due to adverse events were recorded at each assessment. Extrapyramidal symptoms were assessed with the Simpson–Angus Scale (SAS) (Simpson and Angus, 1970), the Barnes Akathisia Rating Scale (BARS) (Barnes, 1989), and the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976). Additional safety endpoints including laboratory test results, vital signs, weight, body mass index, and electrocardiography and physical examination results were monitored throughout the trial.

Statistical analysis

An intent-to-treat (ITT) population was used for all efficacy analyses in each phase. ITT population consisted of the subjects who had investigational product at least once and had evaluable efficacy data after baseline. The primary analysis was based on the Kaplan–Meier method, and *p*-values were obtained from the log-rank test for equality of the survival curves for the two treatment groups. Time to discontinuation for any reason during study period was also analyzed using the Kaplan–Meier method and log-rank test. Scores on the YMRS, MADRS, CGI-BP, and BPRS were analyzed using a mixed-model repeated measures analysis of all assessments from randomization up to the endpoint. Endpoint was defined as the day of mood episode or the day of censoring (completion or discontinuation). The treatment group was included as fixed-effect term. Repeated measures analysis of covariance (RM-ANCOVA) models and paired *t*-test were used to analyze continuous variables measured at each visit and on treatment. RM-ANCOVA models included the baseline measures as covariate and the treatment group as main effect.

The safety populations comprised all subjects who received one or more dose of investigational products during randomized treatment period. Descriptive statistics were used to summarize changes from baseline in laboratory test results, weight, vital signs, ECG results, and scores on the SAS, BARS, and AIMS.

RESULTS

Baseline characteristics of patients

A total of 175 subjects were enrolled to the acute phase; of these, 125 patients (71.4%) completed the acute phase. Sixty-eight patients were male (38.9%), and mean age was 38.3 ± 11.4 years. One hundred sixty-six (94.9%) patients were diagnosed as manic episode (Table 1). The baseline mean YMRS total score was 30.3 ± 8.4. Of the 125 patients who completed acute phase, 94 patients were screened for double-blind randomized maintenance phase. Eighty-three patients were randomly assigned to aripiprazole ($n = 40$) and placebo ($n = 43$) (Figure 1). The demographics of the subjects randomized are summarized in Table 1.

Medication

During the acute phase, the mean dose was 21.9 ± 4.7 mg/day for aripiprazole and 985.1 ± 290.6 mg/day for divalproex. During the maintenance phase, the mean daily dose of aripiprazole was 17.9 ± 7.1 mg in the aripiprazole group. The mean divalproex dose was 1119.7 ± 395.7 mg/day in the placebo group and 893.0 ± 281.8 mg/day in the aripiprazole group ($p = 0.004$). Mean serum divalproex concentration was 79.1 ± 27.0 μg/mL at week 1 of the acute phase and 70.1 ± 32.8 μg/mL at the endpoint of the acute phase. At the baseline of the maintenance phase, the mean serum divalproex concentrations were 67.6 ± 29.7 μg/mL in the aripiprazole group and 69.1 ± 31.9 μg/mL in the placebo group ($p = 0.821$). At the endpoint of the maintenance

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Table 1. Clinical and demographic characteristics of the study sample

	Acute phase	Maintenance phase		
Characteristics	ARI + VAL ($N = 175$)	Total ($N = 83$)	PBO + VAL ($N = 43$)	ARI + VAL ($N = 40$)
Age (years), mean (SD)	38.3 (11.4)	38.3 (11.9)	38.3 (11.0)	38.3 (13.0)
Male, *n* (%)	68 (38.9)	32 (38.6)	19 (44.2)	13 (32.5)
Weight, mean (SD)	64.5 (12.2)	66.4 (11.5)	66.5 (10.8)	65.2 (11.6)
BMI category, *n* (%)				
BMI <23	68 (38.9)	28 (33.7)	15 (34.9)	13 (32.5)
BMI 23–27	82 (46.9)	35 (42.2)	17 (39.5)	18 (45.0)
BMI >27	25 (14.3)	20 (24.1)	11 (25.0)	9 (22.5)
YMRS, mean (SD)	30.3 (8.4)	3.6 (3.4)	3.2 (3.5)	4.1 (3.2)
MADRS, mean (SD)	9.4 (7.8)	3.9 (3.1)	3.6 (2.9)	4.3 (3.4)
BPRS, mean (SD)	23.5 (14.6)	4.0 (3.8)	4.0 (4.0)	3.9 (3.6)
CGI-BP-S-overall, mean (SD)	4.8 (1.1)	1.8 (0.7)	1.8 (0.8)	1.8 (0.7)
Current/recent episode, *n* (%)				
Manic	166 (94.9)	80 (96.4)	41 (95.3)	39 (97.5)
Mixed	9 (5.1)	3 (3.6)	2 (4.7)	1 (2.5)

ARI, aripiprazole; VAL, divalproex; PBO, placebo; SD, standard deviation; BMI, body mass index; YMRS, Young Mania Rating Scale; MADRS, Montgomery–Åsberg Rating Scale; BPRS, Brief Psychiatric Rating Scale; CGI-BP-S, Clinical Global Impression-Bipolar version-Severity.

phase, the mean serum divalproex concentrations were 49.2 ± 31.9 μg/mL in the aripiprazole group and 78.4 ± 26.7 μg/mL in the placebo group ($p < 0.001$). The percentage of patients receiving divalproex treatment within the therapeutic dose range (50–125 μg/mL) at week 1 and week 6 of the acute phase were 83.3% and 72.2%, respectively. At the baseline of the maintenance phase, the serum concentrations of the 75.0% of aripiprazole group and the 69.8% of placebo group were within the therapeutic dose range ($p = 0.595$). The percentage of patients whose serum concentration was within therapeutic dose range at the endpoint of maintenance phase were

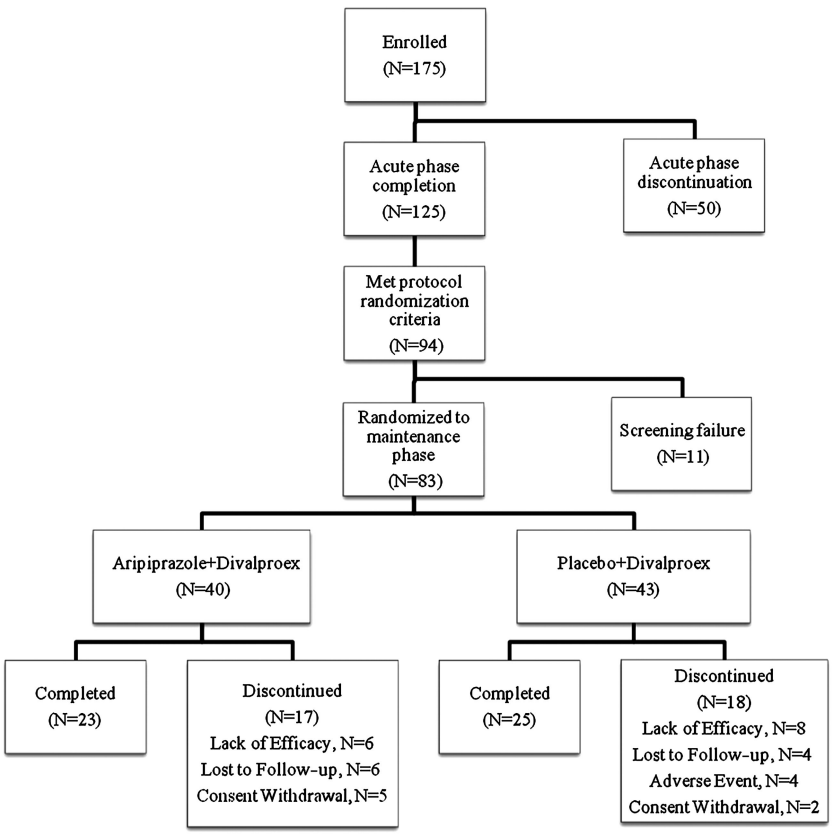

Figure 1. Disposition of patients by study phase

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50.0% in the aripiprazole group and 83.3% of the placebo group ($p = 0.007$).

During the acute phase, concomitant psychotropic medications were used in 165 patients (94.3%), most commonly anxiolytics (90.2%), hypnotics (61.1%), and anti-Parkinsonian drug (34.2%). During the maintenance phase, 28 (65.1%) of patients in the placebo group and 30 (75.0%) patients in the aripiprazole group received at least one concomitant medication.

Efficacy

Acute phase. Data from 171 patients were analyzed according to the ITT principle. There were significant difference from baseline to endpoint in YMRS (paired *t*-test: $p < 0.0001$), MADRS (paired *t*-test: $p < 0.0001$), CGI-BP-S mania and overall score (paired *t*-test: $p < 0.0001$), and BPRS (paired *t*-test: $p < 0.0001$), but not in CGI-BP-S depression score (paired *t*-test: $p = 0.2553$) (Table 2). The changes in the mean YMRS, MADRS, CGI-BP-S mania/overall, and BPRS scores were significant from baseline, starting as early as week 1. Response and remission rates based on the YMRS total score were 74.9% and 72.5% at week 6, respectively (Figure 2).

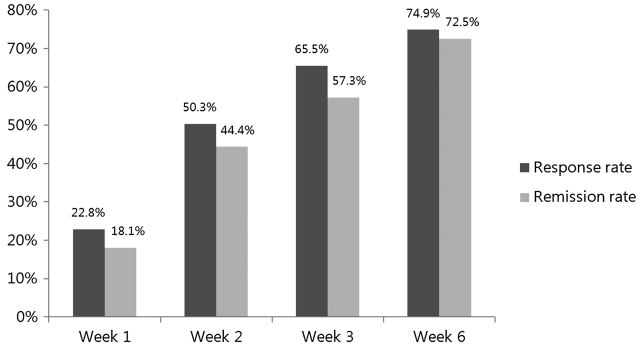

Figure 2. Response and remission rate by Young Mania Rating Scale during the acute phase

Maintenance phase

Time in study. The median of treatment days for the aripiprazole group was 165.5 days, and the median of treatment days for the placebo group was 165.0 days. Overall, 57.8% (48/83) of patients reached the end of the study at 24 weeks of treatment; 57.5% (23/40) of the aripiprazole group and 58.1% (25/43) of the placebo group.

Time to relapse of a mood episode. During the 6-month double-blind treatment, the log-rank test showed that the time to relapse of any mood episode in the aripiprazole group was longer than the placebo group (Figure 3(A)), but the difference did not reach statistical significance ($p = 0.098$). Fewer patients in the aripiprazole group experienced mood episodes (15.0%) than placebo group (32.6%), which was not statistically significant ($p = 0.076$).

Secondary efficacy variables. Time to relapse of depression episode (Figure 3(C)) was longer in the aripiprazole treatment group than in the placebo group, but the difference was not statistically significant ($p = 0.066$). No significant differences were observed in time to manic relapse (Figure 3(B), $p = 0.769$) and time to all-cause treatment discontinuation (Figure 3(D), $p = 0.853$) in both groups.

Additionally, fewer patients in the aripiprazole group experienced depressive episodes (7.5%) than in the placebo group (23.3%), which was not statistically significant ($p = 0.070$). No significant difference was observed in relapse rate of manic episode (7.5% in the aripiprazole group, 9.3% in the placebo group; $p = 1.000$) and rate of all-cause treatment discontinuation (42.5% in the aripiprazole group, 41.9% in the placebo group; $p = 1.000$).

Aripiprazole combination treatment was associated with a lower severity of interepisode mania and depression symptoms during the period of remission than

Table 2. Mean changes in YMRS, MADRS, BPRS, and CGI-BP-S scores from baseline during acute phase

			Day 7		Day 14		Day 21		Day 42	
		Baseline	Mean change	*p*-value[a]	Mean change	*p*-value[a]	Mean change	*p*-value	Mean change	*p*-value[a]
YMRS		30.3 ± 8.4	−9.3 ± 7.2	<0.0001	−14.9 ± 8.9	<0.0001	−17.8 ± 10.1	<0.0001	−20.5 ± 11.5	<0.0001
MADRS		9.4 ± 7.8	−1.7 ± 4.5	<0.0001	−2.7 ± 5.9	<0.0001	−3.6 ± 6.6	<0.0001	−3.2 ± 8.1	<0.0001
BPRS		23.5 ± 14.6	−6.5 ± 8.1	<0.0001	−10.4 ± 10.3	<0.0001	−12.6 ± 11.7	<0.0001	−13.8 ± 13.3	<0.0001
CGI-BP-S	Overall	4.8 ± 1.1	−0.8 ± 0.8	<0.0001	−1.5 ± 1.1	<0.0001	−1.9 ± 1.3	<0.0001	−2.3 ± 1.5	<0.0001
	Manic	4.9 ± 1.0	−0.9 ± 0.9	<0.0001	−1.6 ± 1.1	<0.0001	−2.0 ± 1.3	<0.0001	−2.5 ± 1.5	<0.0001
	Depression	1.5 ± 1.0	−0.1 ± 0.5	0.1409	−0.1 ± 0.8	0.3236	−0.1 ± 0.8	0.3462	0.1 ± 1.0	0.2553

[a]Paired t-test. YMRS: Young Mania Rating Scale, MADRS: Montgomery-Asberg Depression Rating Scale, BPRS: Brief Psychiatric Rating Scale, CGI-BP-S: Clinical Global Impression-Bipolar version-Severity.

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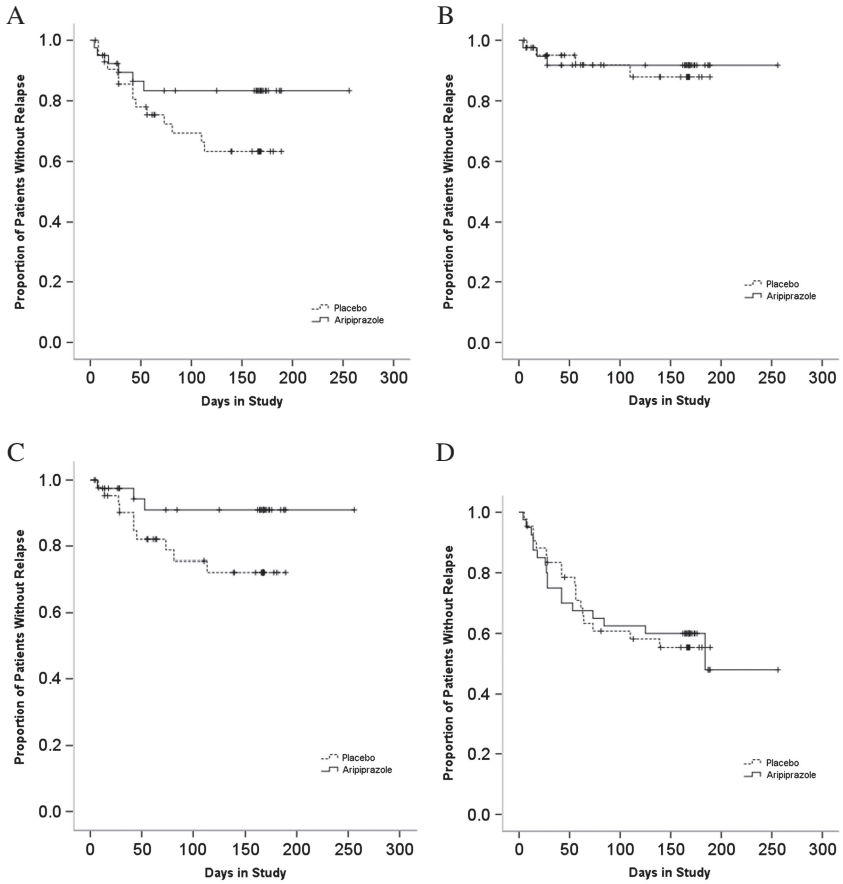

Figure 3. Kaplan–Meier curves for time from randomization to relapse of a mood episode and discontinuation from the study. (A) Any mood episode, (B) manic episode, (C) depressive episode, and (D) all-cause discontinuation

placebo combination treatment, as measured by YMRS, MADRS, and CGI-BP-S (Table 3). In the analyses using RM-ANCOVA, YMRS ($p = 0.008$), CGI-BP-S overall ($p = 0.013$), and CGI-BP-S depression ($p = 0.046$) scores showed significant group effect. MADRS ($p = 0.057$) and BPRS ($p = 0.078$) scores showed a trend that favored aripiprazole over placebo. However, CGI-BP-S mania ($p = 0.124$) scores did not show significant group effect.

Relation of valproate serum concentration to outcome. Additional analysis was carried out to clarify the impact of the difference in divalproex level to mood episode relapse. We used the Cox proportional hazards model, including treatment and mean serum divalproex level as factors to analyze the time to any mood episode by estimating the hazard ratio (HR) of relapse between the two treatment groups. HRs and corresponding 95% confidence intervals (CIs) were determined for aripiprazole group versus placebo group.

After controlling for mean divalproex level, the time to relapse of any mood episode in the aripiprazole group was numerically longer than the placebo group during the maintenance phase (Figure 4(A)). For aripiprazole group versus placebo group, the HR for the time to relapse of a mood episode was 0.40 (95% CI, 0.15–1.07; $p = 0.069$), corresponding to a risk reduction of 60%. When time to depressive episode relapse was examined (Figure 4(C)), Cox regression showed that those in the aripiprazole group had a longer time to relapse than those in the placebo group (HR = 0.23; 95% CI, 0.06–0.86; $p = 0.029$). No significant differences were observed in time to manic relapse (Figure 4(B), $p = 0.963$) and time to all-cause treatment discontinuation ($p = 0.795$, Figure 4(D)) in both groups.

Safety

Acute phase. The aripiprazole and divalproex combination was well tolerated throughout the 6-week study period. One hundred four patients (59.4%) reported 332 adverse events. Among these, 48 patients (27.4%) and 102 adverse events were judged by the investigator to be treatment related. Almost all adverse events were mild to moderate. Two cases of SAEs were reported:

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Table 3. Secondary efficacy measure outcomes during maintenance phase

	PBO + VAL		ARI + VAL		Analysis[a]	
Outcome	Mean	SD	Mean	SD	*F*-value	*p*-value
YMRS						
Baseline score	3.2	3.5	4.1	3.2		
Endpoint score	4.7	10.0	3.2	7.2	1.108	0.296
MADRS						
Baseline score	3.6	2.9	4.3	3.4		
Endpoint score	6.0	9.2	5.7	8.5	1.880	0.174
BPRS						
Baseline score	4.0	4.0	3.9	3.6		
Endpoint score	7.0	10.2	4.6	8.6	3.215	0.077
CGI-BP-S (overall)						
Baseline score	1.8	0.8	1.8	0.7		
Endpoint score	2.2	1.6	1.9	1.3	2.802	0.098
CGI-BP-S (mania)						
Baseline score	1.8	0.8	1.7	0.7		
Endpoint score	1.7	1.3	1.6	1.2	0.226	0.636
CGI-BP-S (depression)						
Baseline score	1.3	0.7	1.4	0.7		
Endpoint score	1.9	1.3	1.7	1.1	4.497	0.037

ARI, aripiprazole; VAL, divalproex; PBO, placebo; SD, standard deviation; YMRS, Young Mania Rating Scale; MADRS, Montgomery–Åsberg Rating Scale; BPRS, Brief Psychiatric Rating Scale; CGI-BP-S, Clinical Global Impression-Bipolar version-Severity.
[a]Repeated measures analysis of covariance model with treatment group as factor and baseline value as covariate. For those patients who did not complete 24 weeks of treatment, their last observation was carried forward.

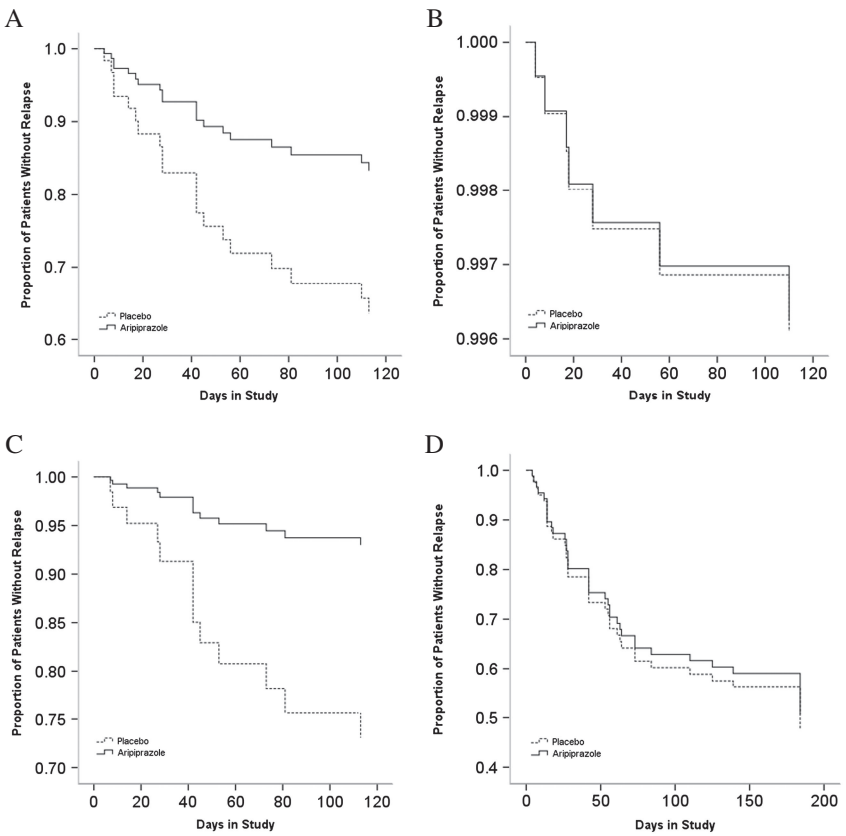

Figure 4. Time from randomization to relapse of mood episode and discontinuation from the study after controlling mean divalproex level. (A) Any mood episode, (B) manic episode, (C) depressive episode, and (D) all-cause discontinuation

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self-harm in one patient and aggravated manic symptom in another patient. Discontinuation due to adverse events occurred in nine patients (5.1%) overall: sedation and akathisia ($n=1$, 0.6%), rash and fatigue ($n=1$, 0.6%), insomnia ($n=1$, 0.6%), skin rash ($n=1$, 0.6%), akathisia ($n=1$, 0.6%), agitation ($n=1$, 0.6%), manic symptom ($n=1$, 0.6%), blurred vision ($n=1$, 0.6%), and asymptomatic ECG abnormality ($n=1$, 0.6%). Most common adverse events (≥5%) were headache (14.9%), constipation (13.7%), akathisia (13.1%), diarrhea (8.0%), dyspepsia (8.0%), insomnia (8.0%), extrapyramidal symptom (5.7%), and back pain (5.1%). Extrapyramidal symptom-related adverse events including akathisia, extrapyramidal symptom, and tremor were reported in 38 patients (21.7%). The majority (70%) of new onset events of extrapyramidal symptom-related adverse events occurred before week 3. AIMS score was not significantly changed during the study period, but SAS (0.2 ± 1.1, $p=0.0130$) and BARS (0.1 ± 0.7, $p=0.0492$) scores showed statistically significant increase from baseline to endpoint. SAS and BARS scores were significantly higher at week 1 and were numerically higher through week 3. However, this magnitude of change was not clinically meaningful.

The mean weight significantly increased by 1.5 ± 3.0 kg ($p<0.0001$). However, a small number of patients ($n=26$, 14.9%) showed clinically significant weight increase (≥7%). The mean increase of fasting serum triglyceride was also significant from 107.5 ± 74.2 mg/dL at baseline to 164.9 ± 233.7 mg/dL at week 6 ($p=0.0013$). There were five patients with clinically significant levels (≥150 mg/dL) of fasting serum triglyceride at week 6. Other laboratory tests, ECG, and vital signs did not show clinically significant change.

Maintenance phase

During the maintenance phase, a similar proportion of patients in both groups reported any adverse events (55.8%, 24/43, in the placebo group and 50.0%, 20/40, in the aripiprazole group). Adverse events occurring at a ≥3% incidence in either group are presented in Table 4. In the aripiprazole group, adverse events reported at an incidence of ≥3% and at least twice that of the placebo group were insomnia (10.0%), alopecia (10.0%), and tremor (5.0%). The incidence of SAEs was greater in the placebo group (11.6%) than in the aripiprazole group (5.0%). The incidence of adverse events related to EPS in aripiprazole group was not different from that in the placebo group (10.0% vs 11.6%, respectively; $p=1.000$). None of patients discontinued because of EPS. The analyses of changes from baseline to endpoint in AIMS ($p=0.287$), BARS ($p=0.377$), and SAS ($p=0.906$) total scores using RM-ANCOVA showed no significant group effect. The SAEs reported in the placebo group were suicide (one case), poor impulse control (one case), depression (one case), mania (one case), irritability (one case), and back pain (one case). The SAEs reported in the aripiprazole group were impulsive behavior (one case), irritability (one case), and metatarsalgia (one case). More patients in the placebo group than in the aripiprazole group (9.3% vs 0%, respectively) discontinued the maintenance phase because of adverse events.

Table 4. Most common (≥3%) adverse events during the maintenance phase

Event	PBO + VAL ($N=43$)	ARI + VAL ($N=40$)
Constipation	6 (14.0)	1 (2.5)
Headache	5 (11.6)	1 (2.5)
Extrapyramidal symptom	5 (11.6)	4 (10.0)
Anxiety	3 (7.0)	0 (0.0)
Insomnia	2 (4.7)	4 (10.0)
Depression	2 (4.7)	1 (2.5)
Upper respiratory tract infection	2 (4.7)	1 (2.5)
Alopecia	2 (4.7)	4 (10.0)
Tremor	1 (2.3)	2 (5.0)
Dyspepsia	1 (2.3)	2 (5.0)

Data are presented as number (%).
ARI, aripiprazole; VAL, divalproex; PBO, placebo.

During the maintenance phase, patients in the placebo group had a mean weight gain of 1.0 ± 3.8 kg ($p=0.106$), and those in the aripiprazole had a group gain of 1.2 ± 5.4 kg ($p=0.175$). The proportion of patients experiencing ≥7% weight gain were 18.6% ($N=8$) in the placebo group and 22.5% ($N=9$) in the aripiprazole group ($p=0.660$). Significant (≥7%) weight loss was observed in 4.7% of patients in placebo group and 2.5% in the aripiprazole group ($p=1.000$).

Changes in glucose and lipid parameters recorded over the course of the study are presented in Table 5. In the placebo group, mean level changes from randomization to endpoint serum AST ($+7.7 \pm 12.7$ IU/L) and ALT ($+7.6 \pm 17.1$ IU/L) were significant. Aripiprazole group experienced a mean increase in serum ALT ($+5.1 \pm 13.2$ IU/L) and triglyceride ($+41.0 \pm 90.9$ mg/dL) from randomization to endpoint. However, no patients experienced clinically significant hypertriglyceridemia during the maintenance phase.

DISCUSSION

We found that the time to relapse of any mood episode and depressive episode were longer in patients who were treated with aripiprazole, adjunctive to divalproex than patients who were treated with divalproex monotherapy,

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Table 5. Mean baseline to end point changes in safety measures during the maintenance phase

Outcome	Treatment	Baseline	Baseline to endpoint change	*p*-value[a]
Weight	PBO + VAL	66.8 ± 10.9	1.0 ± 3.8	0.106
	ARI + VAL	65.9 ± 12.2	1.2 ± 5.4	0.175
BMI	PBO + VAL	24.6 ± 2.7	0.4 ± 1.4	0.069
	ARI + VAL	24.7 ± 3.7	0.5 ± 2.0	0.145
Laboratory analyses				
AST (IU/L)	PBO + VAL	19.4 ± 9.6	7.7 ± 12.7	0.002
	ARI + VAL	18.9 ± 6.5	3.2 ± 9.2	0.064
ALT (IU/L)	PBO + VAL	17.5 ± 13.3	7.6 ± 17.1	0.019
	ARI + VAL	16.6 ± 8.9	5.1 ± 13.2	0.039
HDL-cholesterol (mg/dL)	PBO + VAL	48.3 ± 11.3	−0.5 ± 8.5	0.732
	ARI + VAL	49.3 ± 10.7	−2.0 ± 8.9	0.235
LDL-cholesterol (mg/dL)	PBO + VAL	97.0 ± 28.7	5.8 ± 26.6	0.247
	ARI + VAL	103.4 ± 31.2	9.0 ± 34.4	0.176
Triglyceride (mg/dL)	PBO + VAL	148.4 ± 92.7	1.4 ± 125.6	0.951
	ARI + VAL	117.9 ± 68.0	41.0 ± 90.9	0.024
Total cholesterol (mg/dL)	PBO + VAL	170.1 ± 29.8	6.4 ± 34.5	0.309
	ARI + VAL	173.8 ± 34.4	12.7 ± 36.3	0.066
Fasting glucose (mg/dL)	PBO + VAL	88.6 ± 21.7	4.0 ± 26.1	0.403
	ARI + VAL	107.0 ± 47.8	−4.9 ± 34.6	0.449
Prolactin (ng/mL)	PBO + VAL	7.2 ± 7.1	3.6 ± 16.1	0.248
	ARI + VAL	6.2 ± 6.3	0.0 ± 4.3	0.976

ARI, aripiprazole; VAL, divalproex; PBO, placebo.
[a]Paired *t*-test.

and that the advantage of adjunct aripiprazole fell short of statistical significance. The results of the present study are similar to previous studies in which adjunctive aripiprazole was added to lithium or to valproate in patients with inadequate response to lithium or valproate monotherapy (Marcus *et al*., 2011) and in which ziprasidone plus mood stabilizer was compared with placebo plus a mood stabilizer (Bowden *et al*., 2010). Moreover, in the present study, time to relapse of depressive episode reached statistical significance after controlling mean divalproex level, with longer time to relapse in the adjunctive aripiprazole-treated patients. However, adjunctive aripiprazole did not delay the time to relapse for mania. The delayed time to relapse of depression observed in aripiprazole-treated patients was also supported by the group effect that favored aripiprazole over placebo in MADRS and CGI-BP-S depression scores. Moreover, the observed improvement in the symptoms of mania suggests that maintenance treatment with aripiprazole adjunctive to divalproex can result in long-term symptom stability, consistent with the aripiprazole monotherapy data (Keck *et al*., 2006). However, some results are inconsistent with the results of previous studies (Keck *et al*., 2006; Bowden *et al*., 2010; Marcus *et al*., 2011). In the previous 26-week placebo-controlled study that investigated the efficacy and tolerability of aripiprazole monotherapy in the prevention of a relapse of a mood episode in patients with bipolar I disorder (Keck *et al*., 2006), the time to relapse was significantly longer in those who received aripiprazole compared with those who received placebo. In the previous study, aripiprazole was better than placebo in terms of the time to manic relapse, but not the time to depressive relapse. One of the main differences of the present study and the previous study is the definition of relapse. In the previous study, relapse was defined as 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 the study drug for manic and/or depressive symptoms. The definition of relapse in this study was broader than that used by Keck *et al*. (2006). In this study, exceeding total scores of manic or depressive symptom scale (YMRS total score $\geq$15 or MADRS total scores $\geq$16) was included in the definition of relapse. Lower mean aripiprazole dose during the maintenance phase could affect the results as well. In previous relapse prevention studies with aripiprazole, daily dose of aripiprazole were 23.6–25.2 mg/day (Keck *et al*., 2006; Keck *et al*., 2007). The adjunct aripiprazole with mean daily dose of 17.9 ± 7.1 mg may not be sufficient to show satisfactory effect of preventing relapse into mania. Low daily dose of aripiprazole in this study could have an effect on the relatively low incidence of adverse events reported during the maintenance phase (50.0%) despite the combination treatment with divalproex. In the previous study, 74% of patients who were treated with aripiprazole monotherapy reported adverse events. In addition, the results from Marcus *et al*. (2011) found that the time to a relapse for mood episodes favored adjunctive aripiprazole to lithium; there was no significant difference in the outcomes between treatment

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with aripiprazole plus valproate and placebo plus valproate. However, the previous study was not designed to determine whether one mood stabilizer combination was superior to the other, and the study was not adequately powered to detect statistical differences between mood stabilizer groups. Moreover, patients were not randomized to lithium or valproate group (Marcus *et al*., 2011). The results from the present study showed that valproate treatment combined with aripiprazole was beneficial in maintenance treatment and were consistent with the results from maintenance studies that reported the effectiveness of valproate monotherapy (Macritchie *et al*., 2001).

Tolerability is of particular concern in the long-term administration of medication, especially when several medications are combined. The findings of this study are consistent with the known tolerability profile of aripiprazole, as well as divalproex in patients with bipolar disorder (Keck *et al*., 2007; Torrent *et al*., 2008; Suppes *et al*., 2009). The effects of aripiprazole on weight and metabolic profiles are of particular interest in bipolar maintenance treatment. In the current long-term study, the overall effect of mean weight change in patients treated with aripiprazole is consistent with the weight effects seen in 26-week studies in patients with aripiprazole monotherapy (Keck *et al*., 2006). Aripiprazole adjunct to divalproex did not increase the incidence of clinically significant weight gain compared with divalproex monotherapy. The proportion of patients experiencing significant weight gain during the maintenance phase was not different in the aripiprazole group when compared with that of the placebo group.

In terms of metabolic and laboratory profile, at the 6-week endpoint of acute phase, there were five patients with clinically significant levels of fasting serum triglyceride. During the maintenance phase, the aripiprazole group experienced mean increase in serum ALT and triglyceride from randomization to endpoint. Because mean serum AST and ALT levels were significantly increased in the placebo group, the increase of hepatic enzymes could be contributed to divalproex. Although the incidence of the clinically significant increase was low, fasting serum triglyceride was increased significantly from baseline to endpoint. It has been reported that aripiprazole has minimal effects on body weight, glycemic control, or serum lipid profile. However, McQuade *et al*. (2004) reported that abnormal total cholesterol (>200 mg/dL) and/or fasting triglycerides (>150 mg/dL) were observed in 17% of aripiprazole-treated patients whose lipids were normal at baseline. Tolliver *et al*. (2008) also reported three cases of hypertriglyceridemia who were treated with aripiprazole monotherapy or add-on therapy. Although the cases of elevation of triglycerides with aripiprazole treatment could be mild and reversible (McQuade *et al*., 2004), these result suggests that some patients are susceptible to dyslipidemia and monitoring for lipid abnormalities in patients treated with aripiprazole may be warranted.

In the results of the current study with respect to EPS, the incidence of adverse events related to EPS in aripiprazole group was not different from that in the placebo group. The analysis of scores on the AIMS, BARS, and SAS yielded minimal differences between the aripiprazole group and the placebo group. Thus, these results suggest that the EPS-related adverse events in patients with bipolar I disorder are similar between the aripiprazole group and the placebo group.

One of the strengths of the present study is the high completion rate in the maintenance phase (57.8%). This is higher than those of previous placebo-controlled adjunctive trials (21–57.5%) in bipolar maintenance (Tohen *et al*., 2009; Vieta *et al*., 2008; Suppes *et al*., 2009; Bowden *et al*., 2010). Moreover, because the present study did not use an enriched patient population for aripiprazole monotherapy, the potential bias especially problematic in studies with active comparator treatments could be avoided.

The present study had a number of limitations. First, the statistical power of the study was based on the assumption that 146 patients receiving maintenance treatment during the preceding acute phase would have met remission criteria. However, only 83 patients were available for the randomization. This reduced sample size might have prevented the primary outcome variable from being statistically significant. Second, the definition of stability during the acute phase was too short (two consecutive weeks). Some maintenance studies required at least four to six consecutive weeks of remission state (Bowden *et al*., 2003; Keck *et al*., 2006). The stabilization phase might be longer than two consecutive weeks prior to randomization to circumvent early relapse. However, long periods of stabilization could increase the rate of patient discontinuation. Another maintenance study included patients whose manic or depression score below the cutoff for 2 weeks (Tohen *et al*., 2009). Third, although plasma concentrations of divalproex should be maintained within the therapeutic range, the mean divalproex levels nevertheless went lower than the therapeutic range in the aripiprazole group. Antimanic response is generally associated with levels greater than 45–50 μg/mL (Bowden *et al*., 1996); low dose of divalproex in the aripiprazole group may be associated with lack of preventive effect for manic relapse. Although recommended therapeutic range of divalproex is widely used in many bipolar maintenance trials, there have only been a few studies

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on the relation of serum concentration of divalproex to relapse prevention for the maintenance phase of bipolar disorder treatment. Most clinical trials studying the relationship between divalproex concentration and antimanic effect have involved acute mania patients only. Forth, only patients with manic or mixed episodes were enrolled. Therefore, it is not possible to infer the benefits of adjunctive aripiprazole in depressed bipolar patients in the acute phase and maintenance phase after depressive episode. Additionally, the maintenance phase was relatively short.

In summary, our results indicate that long-term use of the combination of aripiprazole plus divalproex may prolong the time in symptomatic remission compared with divalproex monotherapy in patients who have achieved remission with the combination treatment. Despite the many limitations, this study suggests that the aripiprazole plus divalproex combination could be a valuable option for the acute treatment for manic episode and maintenance treatment after manic episode of bipolar I disorder.

CONFLICT OF INTEREST

No conflict of interest declared.

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