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Efficacy and Safety of Low- and High-Dose Cariprazine in Acute and Mixed Mania Associated With Bipolar I Disorder: A Double-Blind, Placebo-Controlled Study

Joseph R. Calabrese, MD; Paul E. Keck, Jr, MD; Anju Starace, BSc, MBA; Kaifeng Lu, PhD; Adam Ruth, PhD; István Laszlovszky, PharmD; György Németh, MD, PhD; and Suresh Durgam, MD

ABSTRACT

Objective: This phase 3 trial evaluated the efficacy, safety, and tolerability of low- and high-dose cariprazine in patients meeting *DSM-IV-TR* criteria for acute manic or mixed episodes associated with bipolar I disorder.

Method: This multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed/flexible-dose study was conducted from February 2010 to December 2011. Patients were randomly assigned to placebo, cariprazine 3–6 mg/d, or cariprazine 6–12 mg/d for 3 weeks of double-blind treatment. Primary and secondary efficacy parameters were change from baseline to week 3 in Young Mania Rating Scale (YMRS) total score and Clinical Global Impressions-Severity of Illness (CGI-S) score, respectively. Post hoc analysis examined change from baseline to week 3 in YMRS single items.

Results: A total of 497 patients were randomized; 74% completed the study. The least squares mean difference (LSMD) for change from baseline to week 3 in YMRS total score was statistically significant in favor of both cariprazine groups versus placebo (LSMD [95% CI]: 3–6 mg/d, −6.1 [−8.4 to −3.8]; 6–12 mg/d, −5.9 [−8.2, −3.6]; $P < .001$ [both]). Both cariprazine treatment groups showed statistically significant superiority to placebo on all 11 YMRS single items (all comparisons, $P < .05$). Change from baseline in CGI-S scores was statistically significantly greater in both cariprazine groups compared with placebo (LSMD [95% CI]: 3–6 mg/d, −0.6 [−0.9 to −0.4]; 6–12 mg/d, −0.6 [−0.9 to −0.3]; $P < .001$ [both]). The most common (≥ 5% and twice the rate of placebo) treatment-related adverse events for cariprazine were akathisia (both groups) and nausea, constipation, and tremor (6–12 mg/d only).

Conclusions: Results of this study demonstrated that both low- and high-dose cariprazine were more effective than placebo in the treatment of acute manic or mixed episodes associated with bipolar I disorder. Cariprazine was generally well tolerated, although the incidence of akathisia was greater with cariprazine than with placebo.

Trial Registration: ClinicalTrials.gov identifier: NCT01058668

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Corresponding author: *Joseph R. Calabrese, MD, 10524 Euclid Ave, Room 12-135, Cleveland, OH 44106 (joseph.calabrese@uhhospitals.org).*

The classic description of bipolar disorder emphasizes a cyclical nature of illness with full-blown episodes of mania and depression interspersed with periods of relative euthymia. However, more recent clinical evidence suggests that bipolar disorder may have a more chronic course characterized by mood lability, residual symptoms, sleep disturbance, cognitive impairment, and increased risk of medical and psychiatric comorbidity between major mood episodes.[1]

Bipolar disorder conceptualized as a chronic rather than cyclical condition necessitates an inclusive treatment paradigm defining wellness as acute remission of emergent mood episodes and amelioration of a broad range of symptoms.[1] Comprehensive treatment of all aspects of bipolar disorder may result in better patient outcomes. Psychotropic medications for bipolar mania include atypical antipsychotics and mood stabilizers as first-line treatment options.[2]

Cariprazine, an atypical antipsychotic candidate, is an orally active and potent dopamine D_3 and D_2 receptor partial agonist with preferential binding to D_3 receptors. The D_2 receptor is known to play a fundamental role in mediating the antimanic properties of atypical antipsychotic agents.[3] The D_3 receptor is also thought to be involved in the modulation of mood and may present a novel target for the treatment of the broad mood symptoms associated with bipolar disorder.[4–6] The high and balanced occupancy of cariprazine at both D_2 and D_3 receptors, which is unique to cariprazine,[7] may provide distinct benefits in treating acute and mixed mania.

In a previous 3-week, phase 2 clinical trial in patients with manic or mixed episodes associated with bipolar I disorder, cariprazine 3–12 mg/d demonstrated statistically significant improvements versus placebo in improving mania symptoms and was generally well tolerated.[8] The current phase 3 trial evaluated the efficacy, safety, and tolerability of low- and high-dose cariprazine in patients with acute manic or mixed episodes associated with bipolar I disorder.

METHOD

This randomized, double-blind, placebo-controlled, parallel-group, fixed/flexible-dose study in adult patients with bipolar I disorder (NCT01058668) was conducted at 65 centers in the United States, Romania, Russia, Ukraine, Croatia, and Serbia. The study was conducted from February 2010 to December 2011. Each study center received approval from appropriate ethics committees, institutional review boards, or government agencies. The study was conducted in compliance with ICH-E6 Good Clinical Practice guidelines and the Declaration of Helsinki. Participants provided written informed consent.

Clinical Points

- Cariprazine 3–6 and 6–12 mg/d demonstrated significant advantage over placebo on the primary and secondary outcome measures.
- Cariprazine was generally well tolerated; the most frequent adverse event was akathisia.
- These results suggest that cariprazine, a D_3 and D_2 receptor partial agonist with preference for D_3 receptors, may provide an effective new treatment option for patients with manic or mixed episodes associated with bipolar I disorder.

Patients

Male or female patients (age, 18–65 years) with bipolar I disorder, manic or mixed type, with or without psychotic symptoms based on *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (*DSM-IV-TR*)[9] criteria were eligible to enter the study. Patients had baseline Young Mania Rating Scale (YMRS)[10] total score ≥ 20, score ≥ 4 on at least 2 of 4 YMRS items (irritability, speech, content, disruptive/aggressive behavior), and Montgomery-Asberg Depression Rating Scale (MADRS)[11] total score < 18. Patients experiencing a first manic episode or meeting criteria for rapid cycling were excluded. Additional exclusion criteria included principal Axis I disorders other than bipolar I, cognitive/psychotic disorders, severe Axis II disorders, alcohol/substance abuse/dependence (prior 3 months), risk of suicide (ie, suicide attempt in past year, score ≥ 5 on MADRS item 10 [suicidal thoughts], significant suicide risk based on investigator judgment, or Columbia-Suicide Severity Rating Scale [C-SSRS][12] report), pregnancy/breastfeeding, or significant medical illness.

Treatment-related exclusions included electroconvulsive therapy or treatment with depot neuroleptics ≤ 3 months before study. Patients requiring treatment with prohibited medication including psychotropic drugs were excluded. Notable exceptions included lorazepam, diazepam, or oxazepam for agitation or eszopiclone, zolpidem, zolpidem extended release, chloral hydrate, or zaleplon for sleep; rescue medications for extrapyramidal symptoms (EPS) were permitted.

Study Design

The 6-week study comprised a no-drug washout period of up to 7 days, 3 weeks of double-blind treatment, and a 2-week safety follow-up. Patients were randomly assigned (1:1:1) to placebo, cariprazine 3–6 mg/d (low dose), or cariprazine 6–12 mg/d (high dose). Patients randomly assigned to cariprazine 3–6 mg/d received 1.5 mg on day 0 and 3 mg on days 1 and 2; starting on day 3, the dose could be increased in 1.5-mg increments to 6 mg/d by day 5 based on response and tolerability. Patients randomly assigned to cariprazine 6–12 mg/d received 1.5 mg on day 0, 3 mg on day 1, and 6 mg on day 2; starting on day 3, the dose could be increased in 3-mg increments to 12 mg/d by day 5. Decrease to the previous dose was allowed if there were tolerability issues. No dose increase or decrease was allowed after day 14 except for a drug holiday for up to 3 days.

All patients were hospitalized during screening and for a minimum of 2 weeks during double-blind treatment. Patients could be discharged starting on day 14 if they had a Clinical Global Impressions-Severity of Illness (CGI-S)[13] score ≤ 3 (mildly ill), had no significant risk of violent/suicidal behavior, and were ready for discharge based on investigator judgment.

Efficacy Evaluations

Efficacy evaluations included the YMRS and CGI-S (screening, baseline [day 0], and days 3, 5, 7, 10, 14, and 21), CGI-Improvement (CGI-I) scale[13] (days 3, 5, 7, 10, 14, and 21), MADRS (screening and days 0, 7, 14, and 21), and Positive and Negative Syndrome Scale (PANSS)[14] (days 0, 7, 14, and 21). Safety was assessed via treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, vital signs, electrocardiograms, EPS scales (Barnes Akathisia Rating Scale [BARS],[15] Simpson-Angus Scale [SAS],[16] and Abnormal Involuntary Movement Scale [AIMS]),[17] and C-SSRS.

Statistical Analyses

All efficacy analyses were based on the ITT population, defined as all patients who received study drug and had ≥ 1 postbaseline assessment of the YMRS total score.

The primary and secondary efficacy parameters were mean change from baseline to week 3 in YMRS total score and CGI-S score, respectively. Comparison of cariprazine 3–6 mg/d and 6–12 mg/d versus placebo was performed using a mixed-effects model for repeated measures (MMRM) with treatment group, study center, visit, and treatment group–by-visit interaction as fixed effects and the baseline value and baseline-by-visit interaction as the covariates; an unstructured covariance matrix was used to model the covariance of within-patient scores. Sensitivity analyses for the primary efficacy parameter used a pattern-mixture model (PMM) based on nonfuture-dependent missing value restrictions[18] and analysis of covariance model with treatment group and study center as factors and baseline YMRS total score as the covariate with missing values imputed using the last-observation-carried-forward (LOCF) approach. YMRS effect sizes (Cohen *d*) were calculated post hoc for MMRM and LOCF models. Additionally, post hoc analysis was conducted to evaluate change from baseline to week 3 for all YMRS single items using an MMRM model.

Additional efficacy parameters (MADRS and PANSS total score change from baseline to week 3, CGI-I score at week 3) were analyzed using an MMRM model similar to the primary and secondary analyses. YMRS response (≥ 50% total score improvement) and remission (total score ≤ 12) rates at week 3 were analyzed using a logistic regression model with treatment group and corresponding baseline score as explanatory variables with missing values imputed using the LOCF approach; number needed to treat (NNT)

Table 1. Patient Disposition, Demographics, and Disease Characteristics at Baseline

		Cariprazine	
	Placebo	3–6 mg/d	6–12 mg/d
Patient disposition[a]			
Randomized, n	161	167	169
Safety population, n	161	167	169
ITT population, n	160	165	167
Completed study, n (%)	122 (75.8)	129 (77.2)	119 (70.4)
Entered safety follow-up, n (%)	144 (89.4)	146 (87.4)	148 (87.6)
Reason for premature discontinuation, n (%) (safety population)			
Adverse event	8 (5.0)	15 (9.0)	25 (14.8)**
Insufficient therapeutic response	15 (9.3)	2 (1.2)**	5 (3.0)*
Other	16 (9.9)	21 (12.6)	20 (11.8)
Patient demographics (safety population)			
Age, mean (SD), y	41.5 (11.4)	43.1 (12.2)	41.2 (11.3)
Men, n (%)	89 (55.3)	90 (53.9)	85 (50.3)
White, n (%)	114 (70.8)	117 (70.1)	114 (67.5)
Weight, mean (SD), kg	81.7 (16.0)	82.4 (16.2)	81.5 (16.8)
BMI, mean (SD), kg/m^2	28.0 (5.2)	28.2 (5.3)	28.0 (4.9)
Disorder characteristics (safety population)			
Duration of bipolar I disorder, mean (SD), y	13.5 (8.8)	15.2 (10.5)	14.2 (9.7)
Age at onset, mean (SD), y	28.0 (10.4)	27.9 (11.3)	27.2 (10.2)
Duration of current manic episode, n (%)			
≤ 7 d	18 (11.2)	20 (12.0)	22 (13.0)
> 7 ≤ 14 d	72 (44.7)	68 (40.7)	72 (42.6)
> 14 ≤ 21 d	24 (14.9)	25 (15.0)	28 (16.6)
> 21 d	47 (29.2)	54 (32.3)	47 (27.8)

[a]Good Clinical Practice violations were identified at 1 study center; the 9 patients from this center were excluded from analyses.
*P < .05 vs placebo (Fisher exact test).
**P < .01 vs placebo (Fisher exact test).
Abbreviations: BMI = body mass index, ITT = intent-to-treat.

estimates for YMRS response and remission were calculated post hoc. Post hoc analyses evaluated remission rates using a more stringent criterion (YMRS total score < 8).

Tests for statistical significance were performed at the 2-sided 5% significance level; confidence intervals (CIs) were 2-sided 95% CIs. To control for multiple comparisons for the primary and secondary efficacy parameters, a matched parallel gatekeeping procedure[19] was used. Significance of the secondary endpoint for each dose would not be claimed unless the corresponding primary outcome was significant. Additional and by-visit efficacy analyses were not controlled for multiple comparisons. Comparisons between cariprazine groups and placebo for mean change from baseline in the individual YMRS items were controlled for multiple comparisons using the Hochberg procedure.[20] For all efficacy parameters, statistical significance was defined as P values < .05.

All safety measures were based on the safety population, defined as all patients who received at least 1 dose of study medication. TEAEs were analyzed using descriptive statistics (n [%]). Post hoc statistical testing was performed for mean changes from baseline in clinical laboratory parameters, vital signs, and extrapyramidal symptom scales; P values were based on a 2-sample t test. Treatment-emergent EPS (parkinsonism) was defined as SAS score ≤ 3 at baseline and > 3 at any postbaseline visit; treatment-emergent akathisia was defined as BARS score ≤ 2 at baseline and > 2 at any postbaseline visit; P values were based on χ^2 testing.

RESULTS

The majority of patients were enrolled at study centers in the United States (54%). Patient disposition and demographics are summarized in Table 1. Rates of premature discontinuation were similar between groups. Significantly more cariprazine 6–12 mg/d patients than placebo patients discontinued due to adverse events. Significantly more placebo patients than cariprazine patients discontinued due to insufficient therapeutic response.

Baseline characteristics and bipolar history were similar among groups (Table 1). Mean YMRS, CGI-S, and PANSS scores at baseline indicated moderate to severe illness[10,13,21]; MADRS scores indicated low levels of depression at baseline (Table 2).

Efficacy

YMRS total score change from baseline to week 3 was statistically significantly greater for both cariprazine groups compared with placebo (Figure 1A, Table 2). Primary results were supported by PMM and LOCF sensitivity analyses (P < .001 for both cariprazine groups vs placebo for all PMM location shifts and week 3 LOCF; data not shown). Statistically significant separation from placebo on YMRS total score was observed at every visit from day 5 through day 21 (Figure 1A) for both cariprazine groups. CGI-S total score mean change from baseline was statistically significantly greater for both cariprazine groups versus placebo (Table 2).

Table 2. Efficacy Outcomes (MMRM, ITT population)

	Placebo (n = 160)	Cariprazine 3–6 mg/d (n = 165)	Cariprazine 6–12 mg/d (n = 167)
Primary efficacy measure: YMRS total score			
Baseline, mean (SD)	32.6 (5.8)	33.2 (5.6)	32.9 (4.7)
LS mean (SE) change at week 3	−12.5 (0.8)	−18.6 (0.8)	−18.5 (0.8)
LSMD[a] (95% CI)		−6.1 (−8.4 to −3.8)	−5.9 (−8.2 to −3.6)
P value[b]		< .001	< .001
Secondary efficacy measure: CGI-S			
Baseline, mean (SD)	4.8 (0.7)	4.8 (0.6)	4.8 (0.6)
LS mean (SE) change at week 3	−1.3 (0.1)	−1.9 (0.1)	−1.9 (0.1)
LSMD[a] (95% CI)		−0.6 (−0.9 to −0.4)	−0.6 (−0.9 to −0.3)
P value[b]		< .001	< .001
Additional efficacy measures			
CGI-I			
LS mean (SE) score at week 3	2.9 (0.1)	2.2 (0.1)	2.2 (0.1)
LSMD[a] (95% CI)		−0.7 (−0.9 to −0.4)	−0.7 (−0.9 to −0.4)
P value		< .001	< .001
MADRS total score			
Baseline, mean (SD)	9.5 (3.6)	9.5 (3.7)	9.8 (3.6)
LS mean (SE) change at week 3	−2.4 (0.4)	−4.0 (0.4)	−3.6 (0.4)
LSMD[a] (95% CI)		−1.5 (−2.5 to −0.6)	−1.2 (−2.1 to −0.2)
P value		.002	.023
PANSS total score			
Baseline, mean (SD)	61.6 (15.1)	62.8 (14.9)	62.1 (15.3)
LS mean (SE) change at week 3	−6.9 (0.9)	−14.3 (0.8)	−13.6 (0.9)
LSMD[a] (95% CI)		−7.4 (−9.7 to −5.0)	−6.7 (−9.0 to −4.3)
P value		< .001	< .001
YMRS responders			
≥ 50% reduction from baseline at week 3, n (%)	60 (37.5)	100 (60.6)	99 (59.3)
P value		< .001	< .001
YMRS remitters			
YMRS total score ≤ 12 at week 3, n (%)	47 (29.4)	74 (44.8)	74 (44.3)
P value		.003	.005

[a]LSMD from placebo.
[b]*P* values for primary and secondary efficacy analyses were adjusted for multiple comparisons.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, ITT = intent-to-treat, LS = least squares, LSMD = LS mean difference, MADRS = Montgomery-Asberg Depression Rating Scale, MMRM = mixed-effect model for repeated measures, PANSS = Positive and Negative Syndrome Scale, SE = standard error of the mean, YMRS = Young Mania Rating Scale.

Post hoc analysis of primary results yielded effect sizes of 0.62 and 0.60 for cariprazine 3–6 mg/d and 6–12 mg/d, respectively, using the MMRM approach. LOCF effect sizes were 0.58 and 0.53 for the cariprazine 3–6 and 6–12 mg/d groups, respectively. Post hoc analyses of YMRS single items showed statistically significant superiority of both cariprazine groups versus placebo following multiplicity adjustment on all 11 items (Figure 1B).

Statistically significant differences between both cariprazine doses versus placebo were also seen on all other efficacy parameters at week 3 (Table 2). A greater percentage of patients in the low- and high-dose cariprazine groups compared with placebo met YMRS response and remission criteria at week 3 (Table 2). For the cariprazine 3–6 mg/d group, the NNT estimates for response and remission were 5 (95% CI, 3 to 8) and 7 (95% CI, 4 to 20), respectively. Similar results were observed in the cariprazine 6–12 mg/d group, with NNT estimates of 5 (95% CI, 4 to 9) for response and 7 (95% CI, 4 to 22) for remission. Using the more stringent cutoff for remission (YMRS score < 8), a significantly greater percentage of patients achieved remission in the 6–12 mg/d group (25%) than placebo (16%) at week 3 ($P = .039$); remission rates in the cariprazine 3–6 mg/d group (22%) were also greater than placebo (16%), but the difference did not achieve statistical significance.

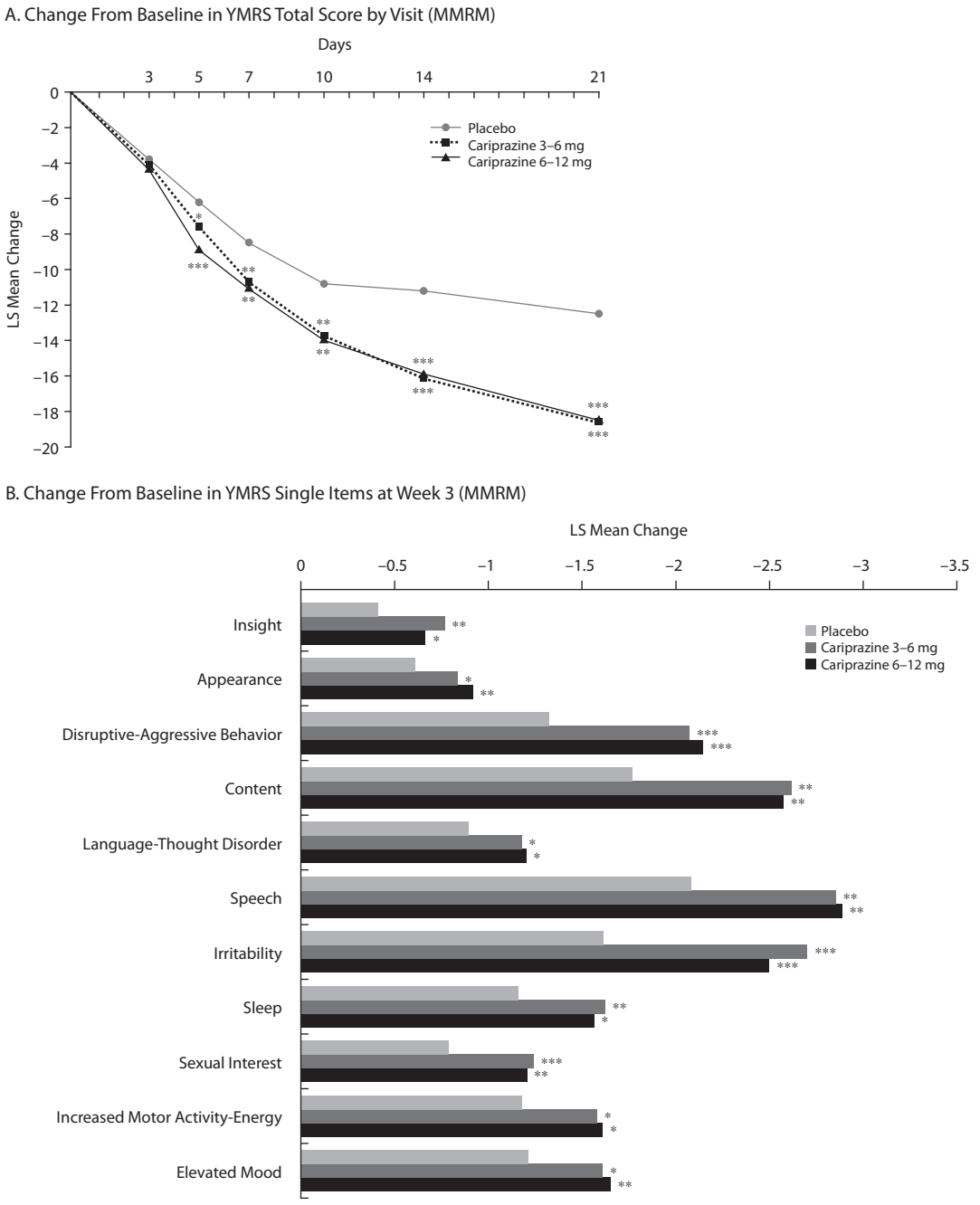
Safety

The final mean daily doses for the cariprazine 3–6 mg/d and 6–12 mg/d groups were 4.8 mg and 9.1 mg, respectively. In the cariprazine 3–6 mg/d and 6–12 mg/d groups, 74% of patients received 6 mg/d and 70% of patients received 12 mg/d at the final visit, respectively.

Adverse events. An overall summary of AEs is presented in Table 3. Common cariprazine TEAEs (≥ 5% in either cariprazine group and twice placebo) were akathisia (both cariprazine doses) and nausea, constipation, and tremor (cariprazine 6–12 mg/d only). The majority of TEAEs were considered by the investigator to be mild or moderate in intensity.

The most common AEs leading to discontinuation were mania (3 [2%] placebo, 3 [2%] cariprazine 3–6 mg/d, and 2 [1%] cariprazine 6–12 mg/d patients) and akathisia (0 placebo,

Figure 1. Improvement in YMRS Total Scores and Single Items



*$P < .05$, **$P < .01$, ***$P < .001$. P values adjusted for multiple comparisons in Figure 1B.
Abbreviations: LS = least squares, MMRM = mixed-effects model for repeated measures, YMRS = Young Mania Rating Scale.

3 [2%] cariprazine 3–6 mg/d, and 5 [3%] cariprazine 6–12 mg/d patients). All 3 serious adverse events in the placebo group (mania, bipolar disorder, and bipolar I disorder) and 4 of 7 in the cariprazine 3–6 mg/d group (mania [2], bipolar disorder, aggression) were associated with worsening of mania or bipolar disorder. There were no SAEs in the cariprazine 6–12 mg/d group. SAEs led to premature discontinuation in 0 placebo patients and 4 cariprazine 3–6 mg/d patients (2%; mania [2 patients], aggression, and bipolar disorder). One death from pulmonary embolism occurred in a female patient with a history of mild hypertension; she received double-blind cariprazine 3–6 mg/d for 8 days before study discontinuation due to insufficient therapeutic response. The death occurred 9 days after discontinuation of study drug and was not considered related to treatment.

Benzodiazepine use to control agitation was similar between cariprazine groups (3–6 mg/d, 64%; 6–12 mg/d, 63%) and placebo (58%).

Laboratory parameters. There were no statistically significant differences between cariprazine and placebo for mean change from baseline in metabolic parameters, liver enzymes, or prolactin (Table 4), with the exception of

Table 3. Overall Summary of Adverse Events During Double-Blind Treatment (safety population)[a]

	Placebo (n = 161)	Cariprazine 3–6 mg/d (n = 167)	Cariprazine 6–12 mg/d (n = 169)
Patient discontinuations due to AE	8 (5.0)	15 (9.0)	25 (14.8)**
Deaths	0 (0)	1 (0.6)	0 (0)
Patients with ≥ 1 SAE	3 (1.9)	7 (4.2)	0 (0)
Patients with ≥ 1 TEAE	98 (60.9)	131 (78.4)	127 (75.1)
Most frequent TEAEs (≥ 5% in any group)			
Akathisia	6 (3.7)	29 (17.4)	37 (21.9)
Headache	15 (9.3)	18 (10.8)	19 (11.2)
Nausea	9 (5.6)	16 (9.6)	19 (11.2)
Constipation	4 (2.5)	8 (4.8)	18 (10.7)
Insomnia	15 (9.3)	15 (9.0)	17 (10.1)
Vomiting	8 (5.0)	14 (8.4)	13 (7.7)
Extrapyramidal disorder	8 (5.0)	16 (9.6)	11 (6.5)
Restlessness	8 (5.0)	14 (8.4)	10 (5.9)
Tremor	3 (1.9)	4 (2.4)	9 (5.3)
Diarrhea	11 (6.8)	4 (2.4)	9 (5.3)

[a]Values expressed as n (%).
**$P < .01$ vs placebo.
Abbreviations: AE = adverse event, SAE = serious adverse event, TEAE = treatment-emergent adverse event.

Table 4. Change From Baseline in Clinical Laboratory Values and Safety Parameters (safety population)

	Placebo		Cariprazine 3–6 mg/d		Cariprazine 6–12 mg/d	
Parameter	n	Mean Change (SD)	n	Mean Change (SD)	n	Mean Change (SD)
Liver function						
Alanine aminotransferase, U/L	156	1.4 (16.3)	161	5.0 (24.0)	164	4.3 (19.7)
Aspartate aminotransferase, U/L	156	−0.4 (10.6)	161	1.1 (11.8)	164	0.1 (9.7)
Alkaline phosphatase, U/L	156	−0.6 (12.4)	161	0.1 (14.8)	164	1.1 (13.5)
Total bilirubin, mg/dL	154	0.0 (0.2)	161	0.1 (0.2)	164	0.0 (0.2)
γ-Glutamyl transferase, U/L	156	−1.6 (20.0)	161	3.4 (30.1)	164	−0.3 (25.6)
Metabolic parameters						
Total cholesterol, mg/dL	156	−2.2 (31.9)	161	0.9 (39.1)	164	−1.2 (36.1)
LDL cholesterol, mg/dL	156	1.9 (26.5)	161	0.1 (32.1)	164	1.4 (31.6)
HDL cholesterol, mg/dL	156	−2.6 (11.2)	161	−1.8 (12.5)	164	−1.6 (10.2)
Triglycerides, mg/dL	156	−7.3 (82.5)	161	14.3 (75.4)*	164	−6.2 (69.9)
Fasting glucose, mg/dL	140	3.6 (23.5)	148	8.1 (26.5)	149	6.4 (21.0)
Prolactin, ng/mL	147	−7.8 (29.0)	152	−5.8 (26.0)	154	−8.7 (24.2)
Vital signs[a]						
Systolic blood pressure, mm Hg	161	−0.8 (9.2)	165	0.3 (9.6)	167	1.1 (10.1)
Diastolic blood pressure, mm Hg	161	0.9 (7.7)	165	1.5 (7.9)	167	2.5 (8.3)
Pulse, bpm	161	−0.5 (9.7)	165	1.7 (11.6)	167	1.2 (10.9)
Body weight, kg	161	0.3 (2.3)	165	0.6 (2.2)	167	0.6 (2.1)
Waist circumference, cm	155	0.8 (5.5)	155	0.4 (3.3)	163	0.7 (3.0)
Extrapyramidal symptoms						
AIMS total score	160	0.0 (0.4)	165	0.0 (0.9)	167	0.0 (0.8)
BARS total score	160	−0.1 (0.9)	165	0.4 (1.5)*	167	0.4 (1.7)*
SAS total score	160	−0.1 (1.0)	165	0.5 (2.1)*	167	0.7 (2.6)*

[a]Blood pressure and pulse based on supine values.
*$P < .05$ vs placebo.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, HDL = high-density lipoprotein, LDL = low-density lipoprotein, SAS = Simpson-Angus Scale.

increased triglycerides in the 3–6 mg/d group (mean [SD] change: 3–6 mg/d, 14.3 mg/dL [75.4]; placebo, −7.3 mg/dL [82.5]; $P = .015$); mean (SD) change in triglyceride levels in the cariprazine 6–12 mg/d (−6.2 mg/dL [69.9]) was similar to placebo ($P = .889$). No patient met Hy's Law criteria (ALT or aspartate aminotransferase [AST] ≥ 3 × upper limit of normal [ULN], total bilirubin ≥ 2 × ULN, and alkaline phosphatase < 2 × ULN).[22]

Vital signs and cardiac safety. Mean changes in vital signs were similar across groups (Table 4). No cariprazine-treated patient had a potentially clinically significant increase in systolic blood pressure (≥ 180 mm Hg and increase ≥ 20 mm Hg) or pulse rate (≥ 120 bpm and increase ≥ 15 bpm). Potentially clinically significant increases in diastolic blood pressure (≥ 105 mm Hg and increase ≥ 15 mm Hg) occurred in only 1 placebo patient (0.6%) and 1

cariprazine 3–6 mg/d patient (0.6%). The percentage of potentially clinically significant changes in body weight (> 7% increase or decrease) was generally small and similar between groups (placebo, 2%; 3–6 mg/d, 1%; 6–12 mg/d, 2%). The incidence of orthostatic hypotension was similar between groups (placebo, 12%; 3–6 mg/d, 12%; 6–12 mg/d, 9%). No patient in any treatment group had a Fridericia QTc interval of > 500 msec; 1 patient each in the placebo and cariprazine 6–12 mg/d groups had a Bazett QTc interval of > 500 msec.

Extrapyramidal symptoms. Mean changes in AIMS total score were similar between groups; mean change in BARS and SAS total scores was significantly higher in both cariprazine groups relative to placebo (Table 4). Significantly more patients in the cariprazine groups relative to placebo met criteria for treatment-emergent EPS (parkinsonism) (placebo, 1%; 3–6 mg/d, 11% [$P < .001$]; 6–12 mg/d, 14% [$P < .001$]) and akathisia (placebo, 4%; 3–6 mg/d, 20% [$P < .001$]; 6–12 mg/d, 23% [$P < .001$]).

Discontinuations due to EPS-related AEs including akathisia/restlessness occurred in 11 patients (3 [2%] cariprazine 3–6 mg/d and 8 [5%] cariprazine 6–12 mg/d); none of the AEs were classified as SAEs. Most EPS-related TEAEs were mild or moderate in intensity (placebo, 96%; 3–6 mg/d, 93%; 6–12 mg/d, 93%). Use of antiparkinson medication was higher in the cariprazine treatment groups (both groups, 17%) than in placebo (7%); use of β-blocking agents was also higher in the cariprazine groups (3–6 mg/d, 4%; 6–12 mg/d, 5%) versus the placebo group (1%).

Suicidal ideation and behavior. Based on C-SSRS assessments, no suicidal behavior was noted; suicidal ideation was recorded for 1.9% of placebo-treated patients and 1.2% and 2.4% of cariprazine 3–6 mg/d and 6–12 mg/d patients, respectively. Suicidal ideation AEs were reported in 1 placebo patient and 0 cariprazine patients.

DISCUSSION

In this phase 3 study, both low (3–6 mg/d) and high (6–12 mg/d) doses of cariprazine demonstrated efficacy and were generally well tolerated in adult patients with acute manic or mixed mania associated with bipolar disorder. Both cariprazine groups showed significant superiority over placebo on the primary efficacy parameter, mean change from baseline to week 3 on YMRS scores. Statistical superiority occurred early and was maintained through the end of treatment in both cariprazine groups.

Improvement on the CGI-S, CGI-I, PANSS, and MADRS was also statistically greater for both cariprazine doses versus placebo. These results suggest that cariprazine-treated patients improved in global disease severity and did not show worsening or exacerbation of depressive or psychotic symptoms.

Treatment effect sizes for YMRS improvement were similar for the low-dose (0.62, MMRM; 0.58, LOCF) and high-dose (0.60, MMRM; 0.53, LOCF) cariprazine groups. There was no active comparator in this trial, so no direct comparisons to other antipsychotics could be made. Indirect comparison was possible, based on a meta-analysis of 29 trials (N = 7,295) in mania. This analysis found an overall effect size of 0.40 (95% CI, 0.32 to 0.47; $P < .0001$) for atypical antipsychotics as a group versus placebo.[23] Cariprazine data from the previous phase 2 study in acute or mixed mania[8] were included in this meta-analysis; the largest effect sizes for atypical antipsychotics versus placebo in this study were risperidone and cariprazine (effect size: 0.66 [3 trials] and 0.51 [1 trial], respectively), with at least moderate effect sizes observed for the other atypical agents (range, 0.26–0.46). The current phase 3 results support the efficacy of cariprazine seen in the meta-analyses.

Treatment response as opposed to disease remission is highly correlated with the occurrence of residual symptoms, rapid relapse, and more chronic illness,[24,25] and therefore remission is considered the treatment goal in bipolar mania. Although no standardized definition for remission exists, a virtual lack of symptoms is most commonly operationalized as a YMRS cutoff score ≤ 12.[24] Using this definition of remission, statistically significantly greater percentages of cariprazine patients in both the low- and high-dose groups (45% and 44%) versus placebo (29%) achieved remission at week 3; the NNT was 7 for both groups. Cariprazine compared favorably to pooled data that reported remission rates of 40%–50% for risperidone,[26] quetiapine,[27] and olanzapine[28]; a recent meta-analysis determined that the NNT for remission for atypical antipsychotics as a group was 8.[29] While a YMRS cutoff of ≤ 12 is the most commonly used definition of remission in clinical trials, more stringent definitions may better identify patients that are truly asymptomatic.[24] In a recent publication, the International Society for Bipolar Disorders recommended a YMRS score < 8 for measuring remission in bipolar mania, as this cutoff may be more representative of minimal symptomatology and a patient's ability to function.[30] Using the more stringent YMRS score < 8 criterion, greater rates of remission were observed in the cariprazine 6–12 mg/d group (25%) compared with placebo (16%).

Post hoc investigation of YMRS single items revealed significant improvements in both low- and high-dose cariprazine groups versus placebo on all 11 YMRS items. Statistical significance versus placebo was maintained on all YMRS items for both cariprazine dose groups following adjustment for multiple comparisons. These results confirmed findings from a previous phase 2 cariprazine study, which showed significant effects with cariprazine 3–12 mg/d versus placebo across the entire spectrum of YMRS-measured mania symptoms.[8] As unresolved symptoms are common following antipsychotic treatment, the remission data and broad efficacy seen across mania symptoms following cariprazine treatment are particularly encouraging.

Cariprazine was generally well tolerated. Discontinuations due to adverse events and incidences of akathisia were more frequent in the cariprazine 6–12 mg/d group relative to the 3–6 mg/d group. The tolerability profile was generally similar between dose groups on other safety parameters.

The most common AEs leading to discontinuation were mania and akathisia. The incidence of SAEs was low in all 3 groups (2% placebo, 4% low-dose cariprazine, and 0% high-dose cariprazine); most SAEs were related to the worsening of mania or bipolar disorder.

Similar to some atypical antipsychotics, cariprazine was associated with higher incidence of EPS relative to placebo. The only EPS-related TEAEs occurring at an incidence of ≥ 5% and twice the rate of placebo were akathisia and tremor. Akathisia was reported in approximately 17% and 22% of patients in the cariprazine 3–6 and 6–12 mg/d groups, respectively, compared with 4% of patients in the placebo group. Akathisia resulted in premature discontinuation of treatment in approximately 2% and 3% of patients in the cariprazine 3–6 and 6–12 mg/d groups, respectively. No other EPS-related AE resulted in discontinuation of ≥ 2% of patients in any treatment group. Incidences of treatment-emergent EPS (parkinsonism) and akathisia per the SAS and BARS, respectively, were also more common in the cariprazine groups versus the placebo group. EPS-related TEAEs were generally classified as mild or moderate (approximately 93% in each cariprazine group) in intensity.

Cardiovascular disease is responsible for the largest total number of excess deaths in bipolar disorder, with risk factors almost twice as prevalent in bipolar patients versus the general population.[31] The risk for cardiovascular disease in bipolar disorder can exist independently of the treatment used to manage it, although medications may exacerbate some risks.[32] In this study, mean changes from baseline in metabolic parameters (eg, cholesterol, triglycerides, fasting glucose) were similar among groups, with the exception of increased triglyceride levels in the cariprazine 3–6 mg/d group relative to the placebo group. Mean changes in body weight and waist circumference were small and similar for cariprazine and placebo; however, as the study duration was only 3 weeks, these changes should be interpreted accordingly. Mean changes in vital signs were also generally similar among groups; no QTc interval over 500 msec was observed in any treatment group.

This study was limited by the lack of an active comparator, and the short study duration limits analyses of longer-term outcomes. Additionally, conclusions regarding the risk/benefit profile of the different cariprazine doses are difficult due to the flexible-dose design and the lack of power to detect differences between cariprazine dose groups. However, clinicians should take into account individual patient differences and response and tolerability to medication when selecting the appropriate cariprazine dosage for treatment.

CONCLUSION

In patients with manic or mixed episodes associated with bipolar I disorder, cariprazine showed statistically significant improvement versus placebo on the primary, secondary, and all additional efficacy parameters.

Cariprazine was generally well tolerated and exhibited a favorable metabolic profile; incidences of akathisia were greater with cariprazine treatment than with placebo. These results support findings from a previous study[8] in acute and mixed mania suggesting that cariprazine, a D_3 receptor–preferring D_3 and D_2 partial agonist antipsychotic candidate, may be a valuable new treatment option for bipolar I disorder.

Drug names: diazepam (Diastat, Valium, and others), eszopiclone (Lunesta), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), zaleplon (Sonata and others), zolpidem (Ambien, Edluar, and others).

Author affiliations: University Hospitals Case Medical Center, Case Western Reserve School of Medicine, Cleveland, Ohio (Dr Calabrese); Lindner Center of HOPE, Mason, and Department of Psychiatry & Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, Ohio (Dr Keck); Forest Research Institute, Jersey City, New Jersey (Ms Starace and Drs Lu and Durgam); Prescott Medical Communications Group, Chicago, Illinois (Dr Ruth); and Gedeon Richter Plc, Budapest, Hungary (Drs Laszlovszky and Németh).

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