Broad Efficacy of Cariprazine on Depressive Symptoms in Bipolar Disorder and the Clinical Implications

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ABSTRACT

Introduction: Bipolar disorder is a complex mood disorder characterized by a chronic and subtle course of fluctuating manic/hypomanic and depressive symptoms. Cariprazine, a dopamine D_3-preferring D_3/D_2 receptor partial agonist with serotonin 5-HT_{1A} receptor partial agonist and serotonin 5-HT_{2A} antagonist properties, is approved to treat manic and depressive episodes of bipolar disorder. Post hoc analyses evaluated efficacy across symptoms in bipolar depression.

Methods: Pooled data were analyzed from 3 phase 2 or 3, randomized, double-blind, placebo-controlled studies of adults with bipolar disorder and a major depressive episode. Mean change from baseline to week 6 in Montgomery-Asberg Depression Rating Scale (MADRS) total score and individual item scores were analyzed in individual dose groups (1.5 mg/d, 3 mg/d) and overall cariprazine (1.5–3 mg/d). Pooled safety was evaluated via adverse events.

Results: A significantly greater difference in mean change from baseline in MADRS total score was seen for each cariprazine dose group versus placebo (least squares mean difference vs placebo: 1.5–3 mg/d = −2.6, 1.5 mg/d = −2.8, 3 mg/d = −2.4) ($P < .001$ all). Significant differences versus placebo were seen on all individual MADRS items except inner tension for the overall cariprazine group ($P < .05$). Cariprazine was generally well tolerated.

Conclusions: Cariprazine demonstrated broad efficacy across symptoms of depression in bipolar disorder. In previous post hoc analyses, cariprazine also demonstrated broad efficacy across manic symptoms, suggesting that it is effective across the wide range of symptoms on the bipolar spectrum. A 1.5-mg/d starting dose and slow titration resulted in lower rates of some adverse events in the bipolar depression studies versus the mania studies.

Trial Registration: ClinicalTrials.gov identifiers: NCT01396447, NCT02670538, NCT02670551

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Bipolar disorder is a complex and disabling mood disorder that is characterized by a chronic and subtle course of fluctuating manic, hypomanic, and depressive symptoms.[1,2] On the bipolar spectrum, bipolar depression is the leading cause of morbidity in patients with bipolar disorder,[3] with major depressive disorder (MDD), dysthymia, and dysphoric mixed states accounting for a far greater percentage of time spent unwell than manic symptoms.[4–9] For example, a systematic review[10] of studies of long-term course in clinically treated patients with bipolar I disorder concluded that depressive symptoms account for approximately 70% of the time spent unwell with the disorder. The excess burden of depressive symptoms compared with manic symptoms in bipolar disorder is underscored by greater long-term dysfunction, worse psychosocial impairment, more lost work productivity, worse cognitive impairment, and diminished quality of life.[11] Comorbidities are common,[12] adding to the symptom burden and complicating the clinical picture. Effective treatment across the spectrum of bipolar symptoms is a necessity for patients with this complex disorder.

Although diagnosing bipolar disorder may not be challenging if a patient presents with blatant manic symptoms, 50% of individuals with bipolar disorder seek treatment during a depressive episode.[13] As such, misdiagnosis is common, especially if a patient is seen early in the course of illness and corroborating information that would establish a history of hypomania or mania is lacking.[3] Unipolar depression is the initial misdiagnosis for 60% of patients with bipolar disorder,[14] although approximately 20% of patients initially diagnosed with MDD subsequently experience a manic or hypomanic episode, resulting in a revised diagnosis of bipolar I or II disorder.[15] Misdiagnosis as MDD is especially problematic given the progressive nature of bipolar disorder, the potential for mistreatment with antidepressants, and delayed initiation of effective treatment.[16] Antidepressant monotherapy is not recommended for bipolar depression because of the lack of evidence for efficacy and abiding safety concerns, including the risk for rapid cycling or treatment-emergent mania.[16,17]

Approximately half of all patients with mental illness are treated in primary care.[18] To promote timely and accurate diagnosis and effective treatment of bipolar disorder, it is important that all clinicians recognize when symptoms such as mania, hypomania, depression, subsyndromal depression, or anxiety are part of the bipolar spectrum. Although several medications are US Food and Drug Administration approved to treat bipolar mania, only cariprazine, quetiapine

Clinical Points

- Cariprazine is 1 of only 2 treatments that has demonstrated efficacy in both mania and depression associated with bipolar I disorder and is approved for both of these indications.
- Cariprazine demonstrated efficacy across the symptoms of depression in patients with bipolar I disorder.
- Cariprazine is easy to use, as the starting dose of 1.5 mg is the therapeutic dose, and it is generally well tolerated.

(immediate and extended release), lurasidone, and combination fluoxetine/olanzapine are approved to treat bipolar depression. Of these agents, only cariprazine and quetiapine are approved to treat both manic and depressive symptoms. Cariprazine is a dopamine D_3-preferring D_3/D_2 receptor partial agonist with serotonin 5-HT_{1A} receptor partial agonist and serotonin 5-HT_{2A} antagonist properties. As demonstrated in preclinical studies, this unique D_3 receptor affinity may mediate antianhedonic, procognitive, and antidepressant-like effects and improve social memory deficits,[19–22] suggesting that it may have broad utility to treat a range of symptoms in bipolar disorder.

The efficacy, safety, and tolerability of cariprazine (3–12 mg/d) in manic or mixed episodes of bipolar I disorder were established in 3 randomized clinical trials[23–25]; the recommended dose range in bipolar mania is 3–6 mg/d.[26] The indication for bipolar depression was based on efficacy and safety outcomes in 3 subsequent randomized studies[27–29] in patients with bipolar I disorder who were experiencing a major depressive episode. In these trials, 3 fixed cariprazine doses (0.75 mg [1 study], 1.5 mg, and 3 mg [each study]) were evaluated on the primary endpoint, change from baseline to week 6 in Montgomery-Asberg Depression Rating Scale (MADRS)[30] total score. In each trial, a statistically significant difference was seen in favor of cariprazine 1.5 mg/d versus placebo, while cariprazine 3 mg separated from placebo in 1 study (RGH-MD-54) and was numerically better in 2 studies (RGH-MD-56 and -53); 0.75 mg did not separate from placebo. The recommended cariprazine dose in bipolar depression is 1.5 mg/d or 3 mg/d.[26]

To explore the efficacy of cariprazine across the debilitating symptoms of bipolar depression, we conducted post hoc analyses of pooled data from the 3 clinical trials in bipolar depression. For these findings to have a clinically useful context for primary care physicians, the efficacy and safety profile of cariprazine across mania and other symptoms of bipolar disorder is also presented so treatment decisions can be made in the best interest of the whole patient.

METHODS

Study Design and Patients

Data from 3 bipolar depression studies (RGH-MD-56 [NCT01396447, July 2011–January 2014], RGH-MD-53 [NCT02670538, March 2016–January 2018], and RGH-MD-54 [NCT02670551, March 2016–July 2017]) were pooled for analyses. The studies were similarly designed phase 2 or 3, randomized, placebo-controlled, double-blind, multicenter, parallel-group, fixed-dose studies of adult patients with bipolar disorder experiencing a major depressive episode; detailed methods were published previously.[27–29] Briefly, all studies consisted of a screening period (up to 14 days) followed by double-blind treatment and a 1-week safety follow-up period; the double-blind period was 8 weeks in RGH-MD-56 and 6 weeks in RGH-MD-53 and RGH-MD-54, although the primary endpoint was week 6 in all studies. In RGH-MD-56, patients were randomized (1:1:1:1) to placebo, cariprazine 0.75 mg/d, cariprazine 1.5 mg/d, or cariprazine 3 mg/d; patients randomized to cariprazine were initiated on 0.5 mg/d and uptitrated to target doses of 0.75 mg/d, 1.5 mg/d, or 3 mg/d by day 15, after which the dose was fixed. In RGH-MD-53 and RGH-MD-54, patients were randomized (1:1:1) to placebo, cariprazine 1.5 mg/d, or cariprazine 3 mg/d; cariprazine-treated patients were initiated at a therapeutic 1.5-mg/d dose and patients in the 3-mg/d group were uptitrated to the target dose on day 15. All patients gave informed written consent after study procedures and the potential side effects of the intervention were fully explained; study protocols were approved by the institutional review board (US centers) or ethics committee/government agency (non-US centers).

Male or female outpatients (18–65 years of age) with a diagnosis of bipolar I disorder and a current major depressive episode according to *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) criteria (*DSM-IV-TR*[31] in RGH-MD-56; *DSM-5*[32] in RGH-MD-53 and RGH-MD-54) participated in the studies. Clinical inclusion criteria required that patients have a 17-item Hamilton Depression Rating Scale (HDRS-17)[33] total score ≥ 20 and an item 1 score ≥ 2. Exclusion criteria included a score ≥ 12 (or > 10 in RGH-MD-56) on the Young Mania Rating Scale (YMRS),[34] *DSM* axis I diagnosis other than bipolar I disorder, alcohol- or substance-related disorders (within 6 months), and risk for suicide (investigator judged or rating scale assessment). Patients with nonresponse to 2 or more treatment trials of adequate dose and duration with an approved bipolar depression agent in the current depressive episode were also ineligible.

Post hoc Analyses

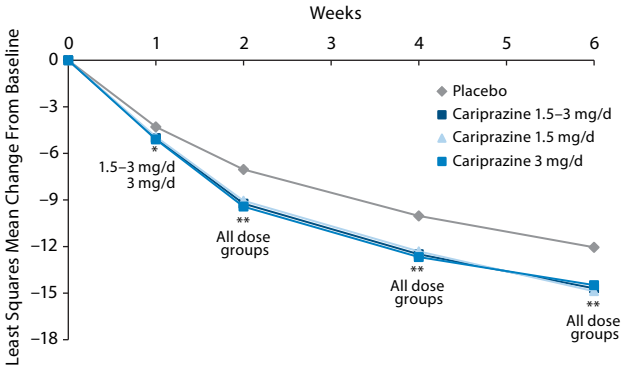
Data from the 3 bipolar depression studies were pooled and analyzed in individual dose groups (1.5 mg/d or 3 mg/d) and overall cariprazine (pooled 1.5 and 3 mg/d); the 0.75-mg/d dose was not included in these analyses because it is not within the recommended dose range for cariprazine. Post hoc outcomes of interest were mean change from baseline to the end of week 6 in MADRS total score and individual item scores. Pooled safety and tolerability in the recommended dose range for bipolar depression from these 3 studies were also investigated via reports of adverse events (AEs).

Table 1. Demographic and Baseline Characteristics (pooled ITT population)

Characteristic	Placebo n = 460	Cariprazine n = 923
Male, n (%)	188 (40.9)	350 (37.9)
Age, mean (SD), y	44.2 (12.0)	42.4 (11.7)
Race, n (%)		
White	342 (74.4)	697 (75.5)
Black/African American	108 (23.5)	197 (21.3)
Other	10 (2.2)	29 (3.1)
Body mass index, mean (SD)	31.3 (6.3)	31.2 (6.5)
Age at onset, mean (SD), y	28.5 (11.3)	26.8 (10.7)
Duration of bipolar I, mean (SD), mo	15.4 (10.2)	15.0 (9.8)
Duration of current depressive episode, mean (SD), mo	3.6 (2.6)	3.6 (2.5)
MADRS total score, mean (SD)	30.7 (4.5)	31.0 (4.6)

Abbreviations: ITT = intent to treat, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 1. MADRS Total Score Change by Week (pooled ITT population)



*$P < .05$ (cariprazine vs placebo).
**$P < .001$ (cariprazine vs placebo).
Abbreviations: ITT = intent to treat, MADRS = Montgomery-Asberg Depression Rating Scale.

Statistical Analyses

MADRS outcomes were based on the pooled intent-to-treat (ITT) population (all patients in the safety population with a baseline and ≥ 1 postbaseline MADRS total score assessment). Change from baseline to week 6 in MADRS total and individual item scores was analyzed using a mixed-effects model for repeated measures (MMRM) with study, treatment group, visit, and treatment group-by-visit as factors and baseline MADRS scores and baseline-by-visit interaction as covariates. *P* values were not adjusted for multiple comparisons; all statistical tests were 2-sided at the 5% significance level. AEs were analyzed using descriptive statistics; no inferential statistics were performed for this safety parameter.

RESULTS

Patient Disposition and Demographics

The pooled ITT population comprised 1,383 patients (placebo = 460, cariprazine = 923 [1.5 mg/d = 461, 3 mg/d = 462]). In each constituent study, baseline and demographic characteristics were similar between groups; characteristics of the pooled placebo and cariprazine groups are presented in Table 1. Mean baseline MADRS total scores in the placebo and cariprazine groups indicated a population with moderate depression.[35]

MADRS Total Score

Improvement in depressive symptoms was demonstrated by significantly greater mean change from baseline in MADRS total score for each cariprazine dose group versus placebo at week 6; the least squares mean difference (LSMD) in favor of cariprazine versus placebo was −2.6 for 1.5–3 mg/d, −2.8 for 1.5 mg/d, and −2.4 for 3 mg/d. A significant difference in favor of cariprazine versus placebo was seen as early as week 1 for overall cariprazine and cariprazine 3 mg/d and week 2 for cariprazine 1.5 mg/d; significant differences versus placebo persisted from the point of separation through week 6 for all groups (Figure 1).

MADRS Individual Items

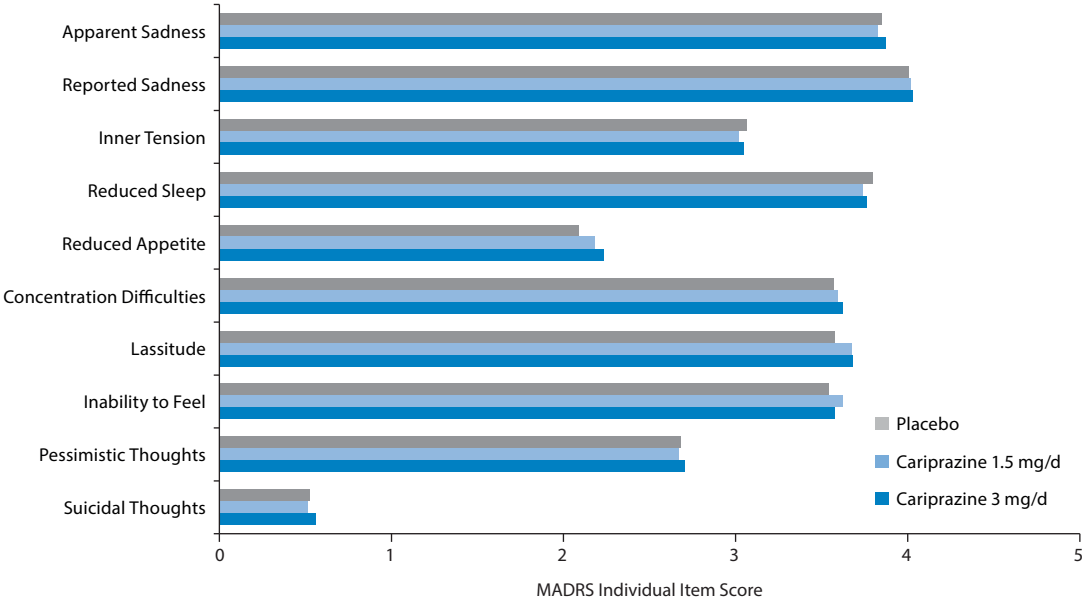
To investigate efficacy across individual depressive symptoms, the single items of the MADRS were analyzed. The severity of mean baseline scores on all individual MADRS items except suicidal thoughts ranged from 2 (mild symptoms) to 4 (moderate symptoms) (Figure 2).

Improvement across depressive symptoms was shown by statistically significant LSMDs versus placebo in mean change from baseline on all individual MADRS items except inner tension in the combined 1.5- to 3-mg/d dose group and on most items in the 1.5-mg and 3-mg individual dose groups (Figures 3A and B). Mean changes in suicidal thoughts were small, but the differences were still significant in favor of cariprazine for the overall and 3-mg/d groups; small mean changes are most likely due to low baseline scores on this item.

Safety and Tolerability in Bipolar Depression

In a pooled post hoc analysis of safety data from the clinical studies of cariprazine in patients with bipolar depression (RGH-MD-53, -54, and -56), recommended doses were generally well tolerated. Overall, few patients discontinued from the studies due to AEs, with similar rates for cariprazine (6%) and placebo (5%). The only AEs that occurred in ≥ 5% of patients and at least twice the rate of placebo were nausea, akathisia, restlessness, and extrapyramidal symptoms. Akathisia was the most common treatment-emergent AE, but it rarely resulted in discontinuation from a study (1.5 mg/d = 1%, 3 mg/d = 2%). The most common AEs occurring in more cariprazine- than placebo-treated patients are presented in Figure 4. Cariprazine had a neutral metabolic profile, with similar proportions of cariprazine- and placebo-treated patients having shifts in fasting total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides. Weight increase was minimal (mean change < 1 kg) in both dose groups.

Figure 2. Severity at Baseline: MADRS Individual Item Scores (pooled ITT population)

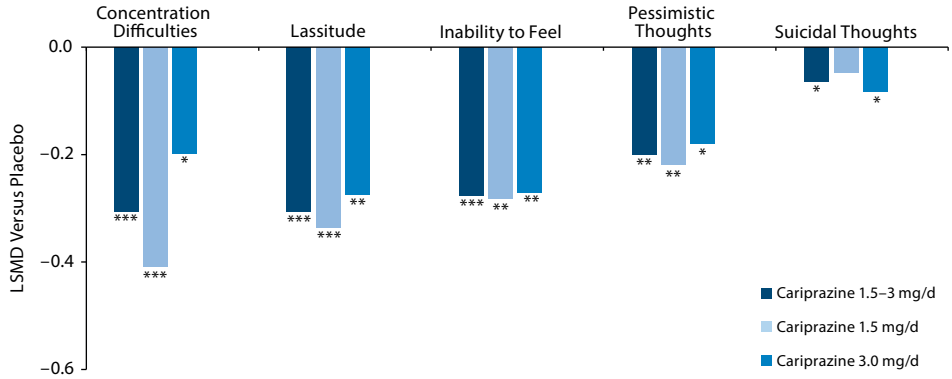


Abbreviations: ITT = intent to treat, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 3. MADRS Individual Items: Mean Difference for Cariprazine Versus Placebo[a]

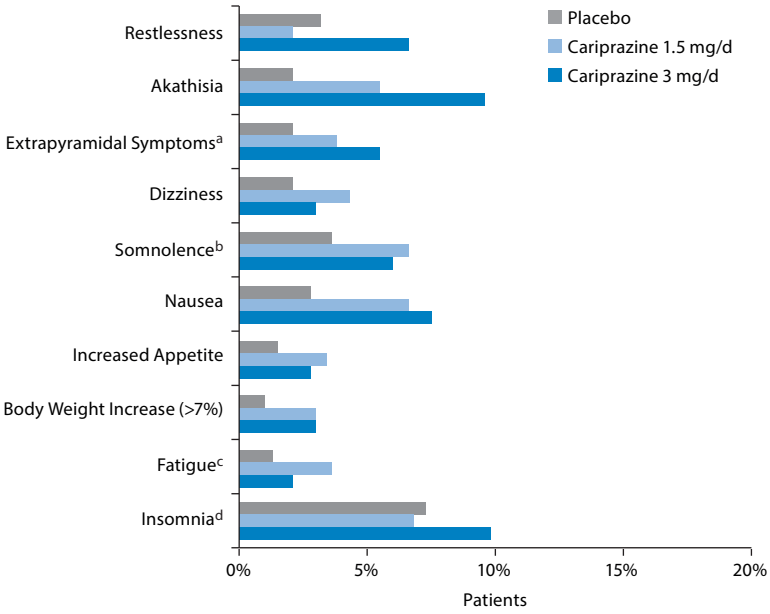
A. Items 1 to 5

B. Items 6 to 10



[a]Bars represent the LSMD in favor of cariprazine versus placebo.
*$P < .05$ (cariprazine vs placebo).
**$P < .01$ (cariprazine vs placebo).
***$P < .001$ (cariprazine vs placebo).
Abbreviations: LSMD = least squares mean difference, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 4. Adverse Events Occurring in ≥ 2% of Cariprazine-Treated Patients and > Placebo (pooled bipolar depression trials)



[a]Extrapyramidal symptoms terms = drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle tightness, musculoskeletal stiffness, myoclonus, oculogyric crisis, salivary hypersecretion, tardive dyskinesia, tremor.
[b]Somnolence terms = hypersomnia, sedation, somnolence.
[c]Fatigue terms = asthenia, fatigue, malaise.
[d]Insomnia terms = initial insomnia, insomnia, insomnia related to another mental condition, middle insomnia, sleep disorder terminal insomnia.

DISCUSSION

As the only dopamine antagonist/partial agonist approved to treat both bipolar mania and depression, cariprazine occupies a unique place in the bipolar disorder treatment armamentarium. Although several agents are approved to treat symptoms of bipolar mania, few agents have proven efficacy in treating acute bipolar depression. For example, in 23 clinical trials that evaluated the efficacy of 9 different agents in monotherapy, only olanzapine (2 trials), lurasidone (1 trial), quetiapine (5 trials), and cariprazine (3 trials) were more effective than placebo in improving depressive symptoms in patients with bipolar depression.[36] Our post hoc analyses of pooled data from these same 3 cariprazine trials extended its evidence for efficacy in bipolar depression by demonstrating improvement across a wide range of individual depressive symptoms in patients with bipolar I disorder. Significant differences versus placebo were seen on all MADRS individual items except inner tension for the cariprazine 1.5- to 3-mg/d group. Further, since sadness, lassitude, and inability to feel are key symptoms that clinicians regularly encounter in primary care settings and ones that they may struggle to assess in the context of bipolar disorder, it is noteworthy that cariprazine had strong effects on these individual MADRS items, suggesting it as a treatment option that could help address problematic symptoms in the clinic.

Beyond efficacy in bipolar depression, cariprazine has also demonstrated robust efficacy in bipolar mania. In a post hoc analysis of data from the 3 positive clinical trials in patients with acute manic or mixed episodes associated with bipolar I disorder,[23–25] the difference in change from baseline to week 3 in Young Mania Rating Scale (YMRS)[34] total score was statistically significant in favor of a cariprazine versus placebo at all assessments from visit 1 on day 4 to the last visit on day 21 ($P < .001$).[37] In subsequent investigations of broad efficacy across the individual symptoms of mania based on data from these same 3 studies, equally robust efficacy was demonstrated by statistically significant differences in favor of cariprazine over placebo in mean change from baseline to week 3 on all 11 individual items of the YMRS ($P < .001$).[38] Together with the results from our bipolar depression analyses, these post hoc outcomes suggest that cariprazine has strong efficacy across both overall and individual manic and depressive symptoms, which is an important characteristic for a bipolar treatment given the changeable and wide-ranging symptoms that are typical of this disorder.

Symptoms other than depression and mania are also common and burdensome in bipolar disorder. Anxiety, which may occur as another symptom or as a comorbid condition of bipolar disorder, is frequently associated with increasing symptom severity, frequency of episodes, higher suicide rates, and decreasing response to therapy in bipolar disorder.[39] In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, 51% of patients had at least 1 type of lifetime anxiety disorder.[40] The

effect of cariprazine on anxiety symptoms was explored in 2 of the bipolar depression studies via the Hamilton Anxiety Rating Scale (HARS),[41] which was included as an additional efficacy measure. In both studies,[28,29] the mean difference in change from baseline to week 6 in HARS total scores was statistically significant in favor cariprazine 1.5 mg/d versus placebo ($P < .05$). While this finding suggests that anxiety symptoms in patients with bipolar depression may improve with cariprazine treatment, especially at the 1.5-mg/d dose, additional analyses are warranted to further explore this common and debilitating aspect of bipolar disorder.

Adding to the challenges of treating bipolar disorder, there is increasing evidence that manic or depressive episodes with mixed features are common, presenting in 25%–35% of all mood episodes.[42] Mixed episodes are associated with worse clinical characteristics including earlier age at onset, increased frequency of psychotic symptoms, higher risk of suicide, higher rates of comorbidities including substance use, longer time to remission, more severe course of illness, and worse prognosis.[43] Importantly, post hoc analyses of data from the clinical trials of cariprazine in patients with acute bipolar mania[23–25] and bipolar depression[27–29] have shown preliminary efficacy for mixed features in both bipolar I mania and depression.[44,45] Collectively, post hoc results suggest that cariprazine could benefit patients with bipolar mania or depression by treating symptoms across the bipolar spectrum, including symptoms associated with more complex presentations of bipolar disorder.

Efficacy only represents part of the overall treatment picture for bipolar disorder since good safety and tolerability are important aspects of clinical success. Medication side effects were reported as a factor that is significantly associated with treatment nonadherence in bipolar patients in the United States, a troubling finding since nonadherence in bipolar disorder is common and associated with poor clinical outcomes.[46] Many agents used to treat bipolar disorder are associated with clinically significant AEs (eg, weight gain, metabolic issues, extrapyramidal symptoms [EPS], sedation, hyperprolactinemia),[47] but different agents have different safety profiles.[48] In an analysis of pooled data from the clinical trials in bipolar depression (RGH-MD-53, -54, and -56), approved doses of cariprazine were generally well tolerated and few patients discontinued from the studies due to AEs. Akathisia was the most common treatment-emergent AE, but it resulted in low rates of discontinuation (1%–2%). Cariprazine also had a neutral metabolic profile and caused minimal weight increase (mean change < 1 kg).[26]

Of additional note, better tolerability was observed in the cariprazine bipolar depression studies versus the bipolar mania studies on several measures including study completion (78% vs 71%), treatment-emergent AEs (60% vs 80%), serious AEs (1% vs 6%), and discontinuations due to AEs (7% vs 12%).[37,49] This tolerability advantage is most likely related to lower maximum doses and slower titration used in the bipolar depression studies compared with the bipolar mania studies. Specifically, patients in 2 of the bipolar depression studies were initiated on a therapeutic 1.5-mg/d dose (lower starting doses were used in RGH-MD-56) and patients in the 3-mg/d dose group were not uptitrated from 1.5 mg/d to 3 mg/d until day 15. Conversely, patients in the bipolar mania studies received 1.5 mg on day 1 and 3 mg on day 2, with incremental 3-mg increases to a maximum of 12 mg/d within the first week of treatment. Although efficacy was shown across the 3- to 12-mg/d dose range in the bipolar mania studies, lower doses were just as effective as higher doses,[23] and some side effects occurred at lower rates with lower doses.[37] This finding was considered a factor in determining the recommended 3- to 6-mg/d dose range for patients with acute mania.

Limitations of these analyses include their post hoc nature and the lack of an active comparator. The constituent studies were not powered to detect treatment differences in individual symptoms, and as is typical in post hoc evaluations, *P* values were not adjusted for multiple comparisons, so random chance could have had a role in determining statistically significant differences. Patients with bipolar II disorder, rapid cycling, significant manic symptoms, and most other psychiatric comorbidities were excluded from participation in the constituent studies, limiting the ability to generalize these findings to other populations on the bipolar spectrum.

Deconstructing a mood episode into individual symptom components may provide useful information about symptoms within the fluctuating and changeable environment of bipolar disorder. In these analyses, statistically significant differences versus placebo in change from baseline in MADRS total score and individual items demonstrated the efficacy of cariprazine in treating symptoms across bipolar depression, suggesting that improvement could encompass full syndromal episodes, subsyndromal episodes, and individual residual symptoms. Results from similar individual YMRS item analyses in patients with bipolar mania further established broad efficacy for cariprazine across the wide-ranging symptoms that comprise bipolar disorder. Additionally, safety analyses suggest that starting with the 1.5-mg/d recommended dose and uptitrating slowly may provide a tolerability advantage. Balance is key in managing the capricious symptoms of bipolar disorder—ideal treatment should support mood stability across the spectrum of manic and depressive symptoms while offering patients a tolerable side effect profile. Because treatment with cariprazine offers both broad spectrum efficacy and tolerability benefits, primary and specialty care providers may consider it a good treatment option for their patients with bipolar I depression.

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Additional information: Data inquiries can be submitted at https://www.allerganclinicaltrials.com/en/patient-data/.

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