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Efficacy of cariprazine in bipolar I depression across patient characteristics: a post hoc analysis of pooled randomized, placebo-controlled studies

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Patients who experience bipolar depression have diverse demographic and clinical characteristics that have the potential to impact treatment. The efficacy of cariprazine in bipolar I depression was evaluated in patient subgroups defined by baseline demographic and clinical characteristics. Post hoc analyses of data from three randomized, double-blind, placebo-controlled trials in bipolar I depression (NCT01396447, NCT02670538 and NCT02670551) evaluated mean change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total scores for pooled cariprazine 1.5–3 mg/d versus placebo in subgroups defined by demographic and clinical characteristics. The least-squares mean difference in MADRS total score change from baseline was statistically significant for cariprazine 1.5–3 mg/d versus placebo in all patient subgroups analyzed ($P<0.05$ all subgroups): demographic characteristics (age, sex, white or black race and obese/nonobese BMI); episode characteristics (defined by current episode duration, number of previous manic/mixed and depressive episodes, and prior bipolar disorder medication use) and disease severity (groups above and below Clinical Global Impressions-Severity and MADRS cutoff scores). Cariprazine 1.5–3 mg/d consistently improved depressive symptoms in all patient subgroups without regard to differences in baseline demographic and clinical characteristics, suggesting broad efficacy across a spectrum of patients with bipolar I depression.

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Introduction

Bipolar I disorder is a chronic and recurrent psychiatric disorder that is characterized by manic, depressive and mixed symptom episodes (Grande *et al.*, 2016). In a nationally representative sample of adults in the USA, 12-month prevalence of bipolar I disorder was 1.5%, whereas lifetime prevalence was 2.1% (Blanco *et al.*, 2017). An important contributor to high levels of functional disability and reduced quality of life, bipolar disorder is also frequently associated with medical and psychiatric comorbidity, premature mortality, long-term dysfunction, psychosocial impairment and lost work productivity (Blanco *et al.*, 2017). Bipolar disorder initially presents as a depressive episode in 50–80% of patients (O'Donovan and Alda, 2020) and depressive episodes are identified as the leading cause of morbidity in patients with bipolar disorder, accounting for the majority of time spent unwell with the disorder (Forte *et al.*, 2015). Bipolar disorder affects people across a wide-ranging continuum regardless of nationality, ethnic origin, socioeconomic status, sex or age.

While bipolar disorder is seen in all patient populations, it is interesting to note that certain clinical characteristics, including early age of onset, mixed states, psychosis, substance abuse, medication nonadherence and comorbid anxiety disorders, are known predictors of poor outcome in bipolar disorder (Kemp *et al.*, 2010). For example, childhood-onset bipolar disorder usually has a worse prognosis than does later onset illness and it is associated with long delays to first treatment, more episodes, more comorbidities, rapid cycling, severe mania and depression, and fewer days well (Treuer and Tohen, 2010). In this vein, evaluating if patient and disease characteristics moderate treatment effects in bipolar I disorder may be a valuable avenue of investigation. Some findings already suggest that this is the case, as seen in studies showing that lithium and olanzapine were associated with better outcomes when treatment was started early in the course of a manic episode (Ketter *et al.*, 2006, Kessing *et al.*, 2014).

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Beyond mania, the potential that treatment effects may be moderated by the baseline characteristics of patients with bipolar depression has also been supported by some literature. For instance, in a post hoc analysis investigating aripiprazole in patients stratified by baseline severity of bipolar depression, differences versus placebo were statistically significant in patients with more severe depression, but not in patients with less severe depression (Thase *et al.*, 2012). Of additional interest, olanzapine had greater efficacy in patients with bipolar depression and baseline melancholic features compared with patients without melancholic features, although no differential treatment effects were seen for other baseline traits (e.g. age, sex and age of onset) (Tohen *et al.*, 2013). Given the possibility that treatment effects can be moderated by clinical and demographic characteristics in patients with bipolar I disorder, it is important to investigate how patients with different baseline characteristics respond to dopamine antagonist/partial agonists (DAPAs) in the treatment of bipolar I depression.

Although there are several first-line acute treatment options for manic episodes associated with bipolar I disorder (e.g. DAPAs, lithium and valproate), there are fewer treatments for bipolar I depression (Yatham *et al.*, 2018). Cariprazine, fluoxetine/olanzapine combination, lurasidone and quetiapine (immediate- and extended-release) are the only US Food and Drug Administration-approved treatments for bipolar depression, with only cariprazine and quetiapine approved to treat both bipolar I disorder mania and depression. Cariprazine is a broad spectrum DAPA with dopamine D_3-preferring D_3/D_2 and serotonin 5-HT_{1A} receptor partial agonist properties. In addition to indications for acute manic/mixed episodes (USA; 3-6 mg/day) and depressive episodes (USA; 1.5 or 3 mg/d) in bipolar I disorder, cariprazine is also approved to treat adults with schizophrenia (USA and European Union; 1.5-6 mg/day). The efficacy of cariprazine in bipolar depression was demonstrated in three pivotal phase 2b/3 randomized, double-blind, placebo-controlled trials (Durgam *et al.*, 2016; Earley et al., 2019, 2020). Because evidence has shown that patient factors can moderate treatment effects in bipolar disorder, these post hoc investigations were planned to evaluate whether cariprazine efficacy differed across baseline characteristics in patients with bipolar depression. Data were analyzed in patient subgroups categorized by baseline demographic characteristics, psychiatric history and clinical features.

Methods

The constituent studies were conducted at study centers in North America, South America and Europe. Study protocols complied with the Declaration of Helsinki and Good Clinical Practice guidelines; written informed consent was obtained from all study participants.

Study design

Post hoc analyses were performed using pooled data from the three similarly designed randomized, double-blind, placebo-controlled trials of cariprazine in bipolar I depression [RGH-MD-56 (NCT01396447), RGH-MD-53 (NCT02670538) and RGH-MD-54 (NCT02670551)] (Durgam *et al.*, 2016; Earley et al., 2019, 2020). Detailed methods have been previously published (Durgam *et al.*, 2016; Earley et al., 2019, 2020). Briefly, all studies consisted of a screening and no-drug washout period (up to 14 days) followed by double-blind treatment and a 1-week safety follow-up. The double-blind period was 8 weeks in RGH-MD-56 and 6 weeks in RGH-MD-53- and -54, with a week 6 primary endpoint in all studies.

In RGH-MD-56, patients were randomized (1:1:1:1) to placebo, cariprazine 0.75 mg/day, cariprazine 1.5 mg/day or cariprazine 3 mg/day. Patients randomized to cariprazine were initiated on 0.5 mg/day and up-titrated to a 0.75, 1.5 or 3 mg/day target dose by day 15, after which the dose was fixed; 0.75 mg/day was not included in post hoc analyses because it was only investigated in one trial and it is not in the recommended cariprazine dose range. Patients in RGH-MD-53 and -54 were randomized (1:1:1) to placebo, cariprazine 1.5 mg/day or 3 mg/day; cariprazine-treated patients were initiated at a therapeutic 1.5 mg/day dose and patients in the 3 mg/day group were up-titrated to the target dose on day 15.

In each trial, the primary and secondary outcome parameters were changed from baseline to week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score (Montgomery and Asberg, 1979) and Clinical Global Impressions-Severity (CGI-S) score (Guy, 1976), respectively. Additional assessments included the Young Mania Rating Scale (YMRS) total score (Young *et al.*, 1978), which was used to monitor manic symptoms, and the Hamilton Anxiety Rating Scale total score (Hamilton, 1959), which evaluated anxiety symptoms in RGH-MD-53 and -54.

Patients

Patients included in the constituent studies were 18–65 years of age with a Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnosis of bipolar I disorder (DSM-IV-TR in RGH-MD-56 and DSM-5 in RGH-MD-53 and -54) and a current major depressive episode ≥4 weeks' and <12 months' duration. Key clinical inclusion criteria comprised a 17-item Hamilton Depression Rating Scale ($HAMD_{17}$) total score ≥20 and Item 1 (depressed mood) score ≥2 (Hamilton, 1960), CGI-S score ≥4 and YMRS total score ≤10 (RGH-MD-56) or <12 (RGH-MD-53 and -54). Exclusion criteria included DSM axis I diagnosis other than bipolar I disorder, alcohol/substance-related disorders (within 6 months) and risk for suicide (investigator judged or rating scale assessment). Patients with nonresponse to two or more treatment trials with an approved bipolar depression agent at

an adequate dose and duration in the current depressive episode were also ineligible. Participants had normal physical and laboratory findings, or findings that were judged by investigators not to be clinically significant.

Post hoc analyses

Post hoc analyses were conducted in patient subgroups categorized by selected demographic characteristics, episode characteristics, disease severity and use of prior medications. Subgroups were selected based on their potential association with clinical outcomes in bipolar depression. Demographic subgroups were stratified by median age (<45 years and ≥45 years), sex, race, ethnicity and BMI ≥30 (obese) and <30 (nonobese). Disease history subgroups were classified by a median duration of the current episode (≤2.77 or >2.77 months), a median number of previous lifetime manic/mixed episodes (≤2 or >2 previous episodes) and depressive episodes (≤4 or >4 previous episodes), and predominant mood polarity (manic or depressive). Disease severity was investigated in patient subgroups categorized by baseline CGI-S scores ≤4 (normal to moderately ill) or >4 (markedly ill to extremely ill) and MADRS total score stratified by the median baseline score (<31 or ≥31). Prior medication use was evaluated in patient subgroups according to who did or did not take bipolar disorder medications or prior DAPAs within 4 weeks of randomization into a constituent study; included bipolar disorder medications were lithium, DAPAs, or anticonvulsants (e.g. lamotrigine, divalproex and carbamazepine). To investigate efficacy among patients who were treatment-naïve or in early-stage treatment, prior medication use was also evaluated in a subgroup of patients who had received one or fewer lifetime bipolar medications.

Patient-level data were pooled from the three similarly designed cariprazine bipolar depression clinical trials to provide larger subgroups and improved power for post hoc analysis. Least-squares mean change from baseline in MADRS total score in patient subgroups defined by baseline characteristics was analyzed for the combined 1.5-3 mg/day dose group versus placebo using a mixed-effects model for repeated measures in the pooled intent-to-treat (ITT) population. Statistical significance of the least-squares mean difference (LSMD) between cariprazine and placebo was determined at the 0.05 level.

Results

Patient disposition and baseline characteristics

A total of 1383 patients (placebo = 460, cariprazine 1.5 mg/day = 461 and cariprazine 3.0 mg/day = 462 participants) were included in the pooled ITT population; post hoc results were evaluated in a pooled cariprazine 1.5 and 3.0 mg/day treatment group ($n = 923$). In each constituent study, baseline and demographic characteristics were similar between groups; pooled baseline characteristics have been previously described (Yatham *et al.* 2020b). Approximately 60% of patients in each treatment group were women and about 75% identified their race as white; approximately 9% of participants reported Hispanic ethnicity, although the sample size was insufficient to obtain reliable results in these analyses. The mean duration of bipolar disorder was 15 years for cariprazine- and placebo-treated patients; mean MADRS total scores at baseline were approximately 31 in both groups, indicating a patient population with a moderate-to-severe level of depression (Muller *et al.*, 2003).

Post hoc patient subgroup analyses

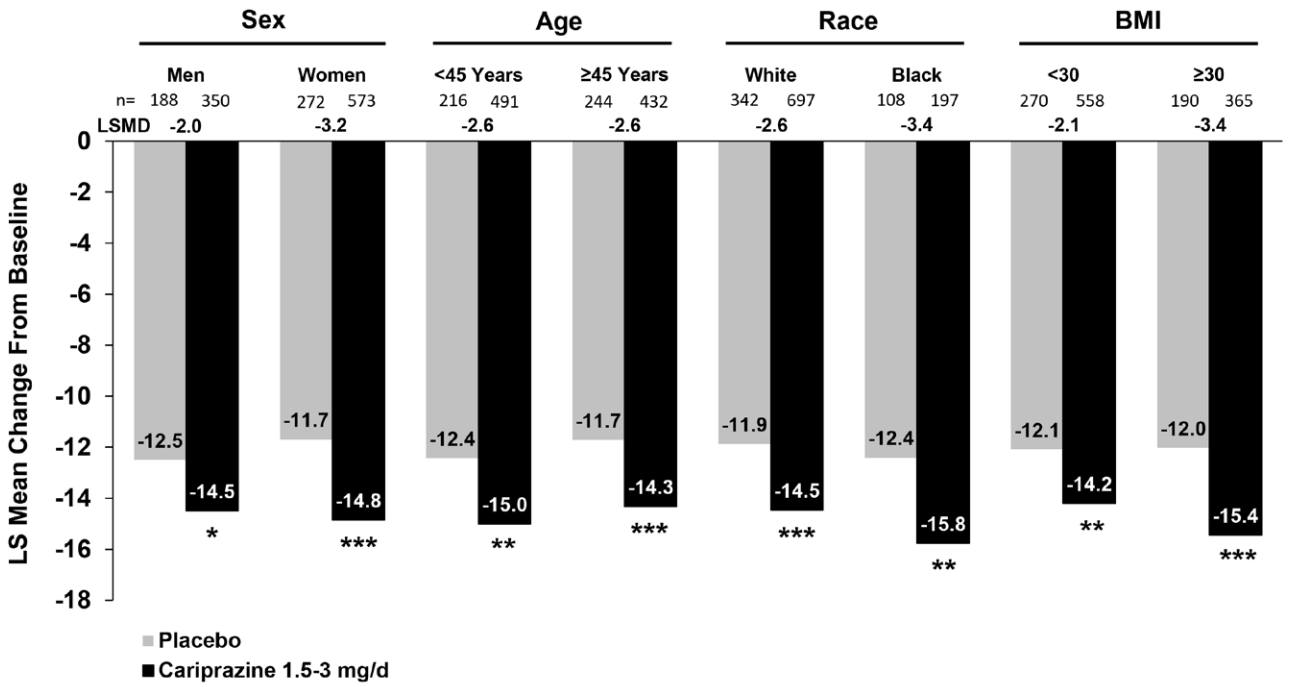
Demographic characteristics

Least-squares mean change from baseline to week 6 in MADRS total score was significantly greater for cariprazine 1.5–3.0 mg/day versus placebo in all subsets defined by sex, age, race and BMI (Fig. 1). The LSMD and associated 95% confidence interval (CI) in MADRS total score change was statistically significant in favor of cariprazine over placebo in subgroups of male [–2.0 (–3.7 and –0.3); $P = 0.0203$] and female [–3.2 (–4.6 and –1.7); $P < 0.0001$] patients. Similarly, the difference in MADRS total score change for cariprazine versus placebo was statistically significant for patients <45 years old [–2.6 (–4.2, –1.0); $P = 0.0016$] and ≥45 years old [–2.6 (–4.1, –1.1); $P = 0.0007$], with the same magnitude of change in each group. When race was investigated, significant differences in MADRS change for cariprazine versus placebo were noted in white [–2.6 (–3.8, –1.3); $P < 0.0001$] and black [–3.4 (–5.8, –0.9); $P = 0.0071$] patient subgroups. Finally, differences in favor of cariprazine were also significant for patients categorized as nonobese [BMI <30 kg/m^2; –2.1 (–3.5, –0.7); $P = 0.0035$) and obese [BMI ≥30 kg/m^2; –3.4 (–5.1, –1.7); $P = 0.0001$].

Episode characteristics

When efficacy was investigated by episode features, the least-squares mean change in MADRS total score was significantly greater for cariprazine- versus placebo-treated patients across all subgroups defined by episode (Fig. 2). Adjusted mean differences for cariprazine versus placebo were similar in subgroups defined by the duration of the current depressive episode above the median [>2.77 months; LSMD = –2.9 (–4.5, –1.3); $P = 0.0004$] and below the median [≤2.77 months; LSMD = –2.4 (–3.9, –1.0); $P = 0.0013$]. When the number of previous manic episodes was investigated, the LSMDs in MADRS total score change were statistically significant for cariprazine over placebo in patients with >2 previous manic/mixed episodes [LSMD = –3.3 (–4.8, –1.8); $P < 0.0001$] as well as in patients with ≤2 manic/mixed episodes [LSMD = –1.9 (–3.5, –0.4); $P = 0.0153$]. Similarly, when the number of previous depressive episodes was considered, the LSMDs in MADRS change were again statistically significant in favor of cariprazine versus placebo in patients with ≤4 previous episodes depressive episodes [–2.4 (–3.9, –0.9); $P = 0.0015$] and in patients with >4 previous depressive episodes [–2.9 (–4.6, –1.3); $P = 0.0004$]. Differences in MADRS total score change were also

Fig. 1



*P<.05, **P<.01, ***P<.001 versus placebo.

Montgomery-Åsberg Depression Rating Scale total score change from baseline in demographic subgroups (pooled intent-to-treat population). BMI, body mass index; LS, least squares; LSMD, least-squares mean difference.

significant for cariprazine in patients with predominant manic polarity [–2.2 (–4.1, –0.2); P = 0.0313] and in patients with predominant depressive polarity [–2.9 (–4.2, –1.6); P < 0.0001].

Disease severity

In analyses investigating disease severity, the least-squares mean change from baseline in MADRS total score was significantly greater for cariprazine versus placebo in all patient subgroups regardless of the severity of disease (Fig. 3). LSMDs were statistically significant in favor of cariprazine versus placebo in patients with CGI-S scores indicating marked to extreme illness [score >4; –3.2 (–4.8, –1.5); P = 0.0002] and in patients with scores indicating mild or moderate illness [score ≤4; –2.2 (–3.7, –0.8); P = 0.0027]. Similarly, the difference in MADRS change was also statistically significant for cariprazine in the subgroup with higher severity defined as MADRS total baseline scores at or above the median [score ≥31; –3.6 (–5.2, –2.0); P < 0.0001] and lower severity defined as MADRS total baseline scores below the median [score <31; –1.6 (–3.0, –0.10; P = 0.0304].

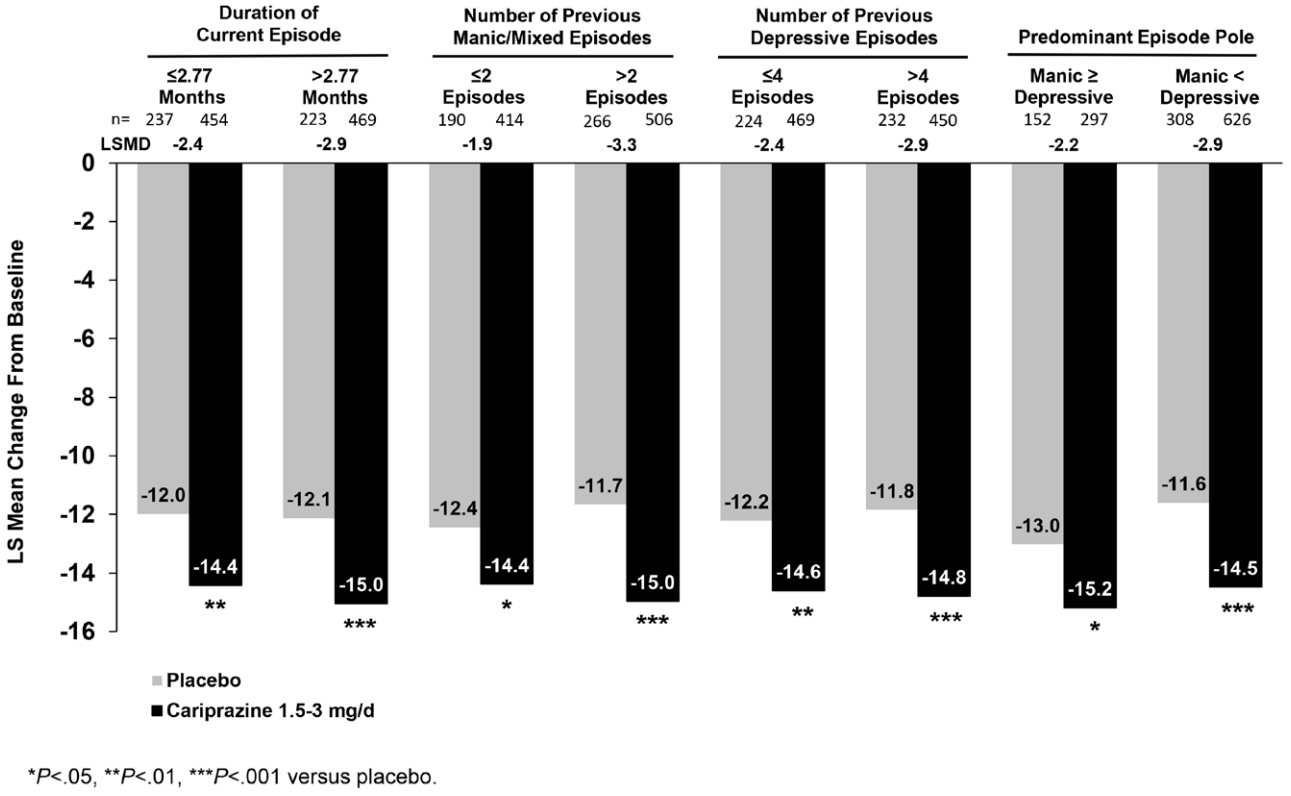
Use of prior medications

When efficacy was investigated in terms of prior medication use, the least-squares mean change in MADRS total score from baseline was significantly greater for cariprazine versus placebo in subgroups of patients who had received bipolar disorder medication within 4 weeks of randomization into a constituent study and in those who had not (Fig. 3). The LSMD in favor of cariprazine was –3.1 (–5.2, –1.0; P = 0.0040) for patients who received prior bipolar medications within 4 weeks and –2.5 (–3.8, –1.2; P = 0.0002) for patients who had not. Similar results were observed when prior DAPAs were considered, with a statistically significant difference in MADRS change observed for cariprazine over placebo in patients who took a DAPA within 4 weeks of randomization [–3.0 (–5.6, –0.4); P = 0.0254] and those who did not [–2.6 (–3.8, –1.4); P < 0.0001). Finally, to evaluate cariprazine in the early stages of treatment, efficacy in patients who were either treatment-naïve or who had been treated with only one prior bipolar medication over their lifetime (placebo = 366; cariprazine = 749) was explored. Among these patients, the difference in MADRS total score change was again statistically significant in favor of cariprazine versus placebo [–2.8 (–4.0, –1.6); P < 0.0001].

Discussion

Given that bipolar I disorder is diagnosed across a wide spectrum of patients with diverse demographic and clinical characteristics, it is important that the medications used to treat symptoms are reliably effective across diverse patient populations. In post hoc analysis of data

Fig. 2



*P<.05, **P<.01, ***P<.001 versus placebo.

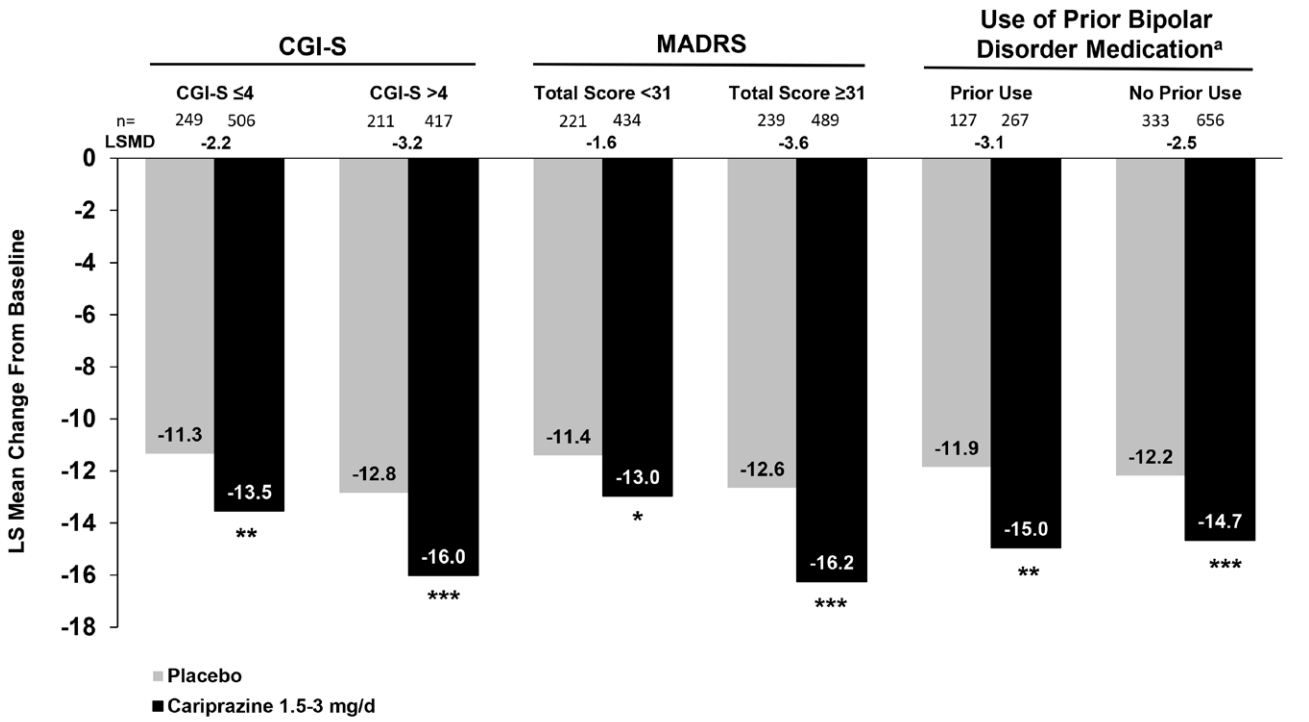
Montgomery-Åsberg Depression Rating Scale total score change from baseline in episode characteristics (pooled intent-to-treat population). LS, least squares; LSMD, least-squares mean difference.

from patients with bipolar depression, cariprazine 1.5–3 mg/day was consistently more effective than placebo in treating depressive episodes associated with bipolar I disorder, with statistically significant reductions in MADRS scores observed for cariprazine regardless of younger or older age, sex, white or black race, duration of illness, disease severity and whether or not patients received prior medication for bipolar disorder. These results extend previous findings that demonstrated the overall efficacy of cariprazine in patients with depressive episodes associated with bipolar I disorder (Durgam *et al.*, 2016; Earley *et al.*, 2019; Earley *et al.*, 2020) and support broad efficacy as demonstrated by significant treatment effects across the individual symptoms of mania (Vieta *et al.*, 2015) and depression (Yatham *et al.* 2020b).

Characterizing the efficacy of pharmacologic treatments in select subgroups of patients with bipolar disorder may help inform clinical management in light of the wide-ranging symptoms, frequent comorbidities and variable treatment responses associated with this heterogeneous illness. For example, the presence of comorbid anxiety symptoms in patients with bipolar depression has been associated with increased disease severity and decreased treatment success, including lower rates of response and remission (Tohen *et al.*, 2007). Similarly, patients with bipolar disorder and mixed features often experience greater symptom severity, increased risk of suicide and poor clinical outcomes with lower rates of treatment response and greater risk of episode recurrence (Betzler *et al.*, 2017). Of note, efficacy for cariprazine in patients with bipolar depression and concurrent manic or anxiety symptoms has been demonstrated in prior pooled post hoc analyses of data from the bipolar depression studies, expanding our current findings to patients with these features. Namely, in patients with bipolar depression and concurrent manic symptoms, significantly greater improvements in depressive symptoms were demonstrated for cariprazine 1.5 and 3 mg/day compared with placebo after 6 weeks of treatment (McIntyre *et al.*, 2020). In an additional analysis, cariprazine 1.5 mg/day was effective in improving both depression and anxiety symptoms in a subgroup of patients with bipolar depression and high levels of baseline anxiety (Yatham *et al.*, 2020a). These results, in concert with the present analysis, suggest that cariprazine has broad efficacy across many patient subgroups and may confer benefit for patients with more complex disease presentations.

Of further interest, psychiatric disease characteristics have also previously been associated with variations in bipolar disorder treatment response. For example, in

Fig. 3



[a]Medications limited to those received within 4 weeks of randomization
*P<.05, **P<.01, ***P<.001 versus placebo.

Montgomery-Åsberg Depression Rating Scale total score change from baseline by disease severity and use of prior medications (pooled intent-to-treat population). CGI-S, clinical global impressions-severity; LS, least squares; LSMD, least-squares mean difference; MADRS, montgomery-asberg depression rating scale.

one clinical study, patients with acute bipolar depression were found to have a predominant lifetime depressive polarity, with considerably more frequent depressive episodes than manic episodes and generally poorer response to treatment, particularly among men (Vieta *et al.*, 2009). Additionally, the number of manic episodes has been associated with reduced response to pharmacologic treatment as seen in studies of lithium and olanzapine in which patients with a greater number of lifetime episodes had worse treatment responses than patients with fewer prior episodes (Franchini *et al.*, 1999; Ketter *et al.*, 2006; Berk *et al.*, 2011; Swann *et al.*, 2013). Data such as these have long suggested that earlier identification and accurate diagnosis are critical to improved patient outcomes in bipolar disorder across several domains, including social adjustment, episode frequency, rate of hospitalization and risk of suicide (Conus *et al.*, 2014).

In light of findings that clinical characteristics can influence treatment outcomes in bipolar disorder, it is important to note that in our analyses cariprazine was consistently effective in all subgroups of patients with bipolar depression regardless of psychiatric disease characteristics. Cariprazine was effective in both predominant manic and depressive episode types, with a slightly greater treatment effect in patients with predominant depressive episodes, and regardless of the number of prior manic/mixed episodes, with similar efficacy versus placebo in patients with two or less and three or more prior episodes. Similarly, patients with five or more depressive episodes had equivalent efficacy to those with four or fewer episodes, suggesting that cariprazine may be effective regardless of the number of previous depressive episodes. Treatment of bipolar depression is associated with a number of major clinical challenges, including the availability of only a small number of approved treatments with proven efficacy (Baldessarini *et al.*, 2020).

To assess whether the prior treatment had any impact on cariprazine efficacy, patient subgroups were also analyzed based on recent treatment history. The efficacy of cariprazine was similar in subgroups of patients stratified by whether or not they were taking bipolar medication or DAPA within the 4 weeks prior to randomization, suggesting that using cariprazine after other agents are discontinued does not compromise efficacy in patients with bipolar depression. In addition, cariprazine was also effective in a subgroup of patients that was treatment naïve or

had received only one prior lifetime bipolar medication, which implies that cariprazine can be effectively initiated early in the course of illness. Collectively, these results suggest that cariprazine has utility for patients across the lifespan of bipolar disorder, with advantages as an early-line treatment or as a treatment later in the course of illness after other agents have been tried.

These analyses had several limitations, including the relatively small sample size of some patient subgroups, which could increase statistical variability. In order to maximize the sample size, cariprazine 1.5 and 3 mg/day doses were pooled for these analyses, which limited the conclusions that can be drawn about the effectiveness of specific doses. For many parameters, clinically meaningful cutoffs were either not available or would have provided too small of a sample due to inclusion/exclusion criteria. In these cases, patient subgroups were defined using a median cutoff; this method provided subgroups of similar size, but the clinical relevance of these cutoffs may be uncertain.

Conclusion

In these pooled post hoc subgroup analyses, cariprazine 1.5-3 mg/day consistently improved depressive symptoms in all patient subgroups without regard to differences in baseline demographic and clinical characteristics, suggesting broad efficacy among patients with bipolar depression. Although studies of other pharmacotherapies have shown that some clinical characteristics can moderate treatment effects in bipolar disorder, our post hoc analyses demonstrated that cariprazine was effective in patients regardless of demographic characteristics, disease stage, disease severity, or whether or not patients had received prior medication for bipolar disorder. Along with proven efficacy in treating episodes and symptoms of both bipolar mania and depression, these results additionally demonstrate that cariprazine has broad efficacy in bipolar depression and may suggest advantages in the clinic, where efficacy is required across the spectrum of mood episodes and patient characteristics.

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Conflicts of interest

M.P. is an employee and shareholder of AbbVie. R.J. has served as a consultant to Addrenex, Allergan (now AbbVie), Avanir, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Otsuka, Pamlab, Pfizer, Shionogi, Shire, Sunovion, Supernus, Takeda, and Teva; paid speaker for Addrenex, Alkermes, Allergan (now AbbVie), Lilly, Lundbeck, Merck, Neos Therapuetics, Otsuka, Pamlab, Pfizer, Rhodes, Shionogi, Shire, Sunovion, Takeda, and Tris Pharmaceuticals; received research support from Allergan (now AbbVie), AstraZeneca, Lilly, Lundbeck, Otsuka, Pfizer, Shire, and Takeda; and served on advisory board for Addrenex, Alkermes, Avanir, Forum, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Otsuka, Pamlab, Pfizer, Shionogi, Shire, Sunovion, Supernus, Takeda, and Teva. M.T. has been a consultant for AstraZeneca, Abbott, BMS, Lilly, GSK, J&J, Otsuka, Roche, Lundbeck, Elan, Allergan (now AbbVie), Alkermes, Merck, Minerva, Neuroscience, Pamlab, Alexza, Forest (now AbbVie), Teva, Sunovion, Gedeon Richter, and Wyeth. He was an employee at Lilly (1997–2008). His spouse is a former employee at Lilly (1998–2013). V.M. has served as a consultant for AbbVie, Acadia Pharmaceuticals, Inc., Alfasigma, USA, Inc., Alkermes, Inc., Allergan, Eisai-Purdue, Intra-Cellular Therapies, Janssen, Lundbeck A/S, Otsuka America Pharmaceutical, Inc., Sage Pharmaceuticals, Sunovion Pharmaceuticals, Inc., Supernus Pharmaceuticals, Inc., Takeda Pharmaceutical Company Limited; on speakers bureau for AbbVie, Acadia, Alkermes, Inc., Allergan, Eisai, Ironshore, Intra-Cellular, Janssen, H. Lundbeck A/S, Otsuka America Pharmaceutical, Inc., Sunovion, Supernus Pharmaceuticals Inc., Takeda Pharmaceutical Company Limited, and his spouse has served on a speakers bureau for Otsuka. W.R.E. is an employee of AbbVie, and shareholder of AbbVie, AstraZeneca and Eli Lilly. L.N.Y. has received research support from or served as a consultant or speaker for Alkermes, Allergan (now AbbVie), AstraZeneca, Bristol-Myers Squibb, the Canadian Psychiatric Foundation, Canadian Institutes of Health Research, Dainippon Sumitomo, Forest, GlaxoSmithKline, Intracellular Therapeutics, Johnson & Johnson, Lilly, Lundbeck, Merck, NARSAD, Novartis, Otsuka, Pfizer, Servier, the Stanley Foundation, Sunovion, Teva, Valeant, and Wyeth.

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