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The efficacy of cariprazine on cognition: a post hoc analysis from phase II/III clinical trials in bipolar mania, bipolar depression, and schizophrenia

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Abstract

Objective. To investigate the effect of cariprazine on cognitive symptom change across bipolar I disorder and schizophrenia.

Methods. Post hoc analyses of 3- to 8-week pivotal studies in bipolar I depression and mania were conducted; one schizophrenia trial including the Cognitive Drug Research System attention battery was also analyzed. Outcomes of interest: Montgomery-Åsberg Depression Rating Scale [MADRS], Functioning Assessment Short Test [FAST], Positive and Negative Syndrome Scale [PANSS]). LSMDs in change from baseline to end of study were reported in the overall intent-to-treat population and in patient subsets with specified levels of baseline cognitive symptoms or performance.

Results. In patients with bipolar depression and at least mild cognitive symptoms, LSMDs were statistically significant for cariprazine vs placebo on MADRS item 6 (3 studies; 1.5 mg=−0.5 [P<.001]; 3 mg/d=−0.2 [P<.05]) and on the FAST Cognitive subscale (1 study; 1.5 mg/d=−1.4; P=.0039). In patients with bipolar mania and at least mild cognitive symptoms, the LSMD in PANSS Cognitive subscale score was statistically significant for cariprazine vs placebo (3 studies; −2.1; P=.001). In patients with schizophrenia and high cognitive impairment, improvement in power of attention was observed for cariprazine 3 mg/d vs placebo (P=.0080), but not for cariprazine 6 mg/d; improvement in continuity of attention was observed for cariprazine 3 mg/d (P=.0012) and 6 mg/d (P=.0073).

Conclusion. These post hoc analyses provide preliminary evidence of greater improvements for cariprazine vs placebo across cognitive measures in patients with bipolar I depression and mania, and schizophrenia, suggesting potential benefits for cariprazine in treating cognitive symptoms.

Introduction

Cognition encompasses discrete yet overlapping processes including, but not limited to, executive functions (eg, planning, behavioral initiation and monitoring, and impulse control), attention, memory, and processing speed.[1] Although bipolar disorder and schizophrenia are distinct diagnostic entities based on their clinical presentations, neurocognitive impairment is recognized as a core feature of both disorders[2]; approximately 40% to 60% of patients with bipolar disorder and up to 75% of patients with schizophrenia experience cognitive deficits.[3,4] While some studies have found comparable degrees of cognitive impairment in patients with bipolar disorder and schizophrenia,[5–10] others indicate that patients with schizophrenia have more severe and/or pervasive impairment.[11–13] In both disorders, however, cognitive deficits are associated with worse outcomes and diminished quality of life, including more hospitalizations, longer duration of illness, positive and negative psychotic symptoms, nonremission status, and lower psychosocial functioning.[14,15] As no therapeutic agent is currently approved to treat cognitive impairment in patients with bipolar disorder or schizophrenia, cognitive deficits are widely recognized as an unmet medical need and a novel treatment target in these illnesses.[14,16]

While dopamine dysregulation has been implicated in the pathophysiology of both bipolar disorder and schizophrenia,[17,18] evidence from animal and human research suggests that the dopaminergic system also plays a role in cognitive function.[19–21] Specifically, dopamine D_3 receptors appear to be associated with cognitive functioning in healthy individuals and in those with neuropsychiatric disorders,[21,22] with evidence that domains of memory, attention, learning,

processing speed, social recognition, and executive function are potentially enhanced by D_3 receptor blockade and impaired by D_3 receptor agonism.[21] As such, cognitive performance in individuals with a neuropsychiatric disorder may be improved by D_3 receptor blockade,[21] suggesting that a dopamine antagonist/partial-agonist agent that more potently targets D_3 receptors than D_2 receptors could have potentially beneficial effects on cognition.[23] It is important to note, however, that cognition is a complex concept, and although clinical observations support the role of dopamine D_3 in cognitive function in patients with schizophrenia and bipolar I disorder, cognitive deficits may have a heterogenous origin and other factors, including receptors other than dopamine D_3, could be involved.

Cariprazine is a dopamine D_3-preferring D_3/D_2 receptor partial agonist and serotonin 5-HT_{1A} receptor partial agonist that is approved by the U.S. Food and Drug Administration to treat adults with depressive (1.5-3 mg/d) or manic/mixed (3-6 mg/d) episodes associated with bipolar I disorder and schizophrenia (1.5-6 mg/d). The pharmacology of cariprazine is unique among dopamine modulating agents, demonstrating almost 10-fold greater affinity for D_3 than D_2 receptors in vitro,[23] as well as high and balanced in vivo occupancy of D_3 and D_2 receptors.[24] In support of a potential advantage for treating cognitive symptoms, cariprazine has demonstrated efficacy in animal models of cognitive impairment,[25,26] with evidence that procognitive effects were mediated by the dopamine D_3 receptor.[26] The efficacy of cariprazine was established in randomized, double-blind, placebo-controlled pivotal phase 2/3 clinical trials for the treatment of depressive episodes associated with bipolar I disorder (3 trials),[27–29] acute manic/mixed episodes associated with bipolar I disorder[30–32] (3 trials), and schizophrenia (3 trials)[33–35]; cariprazine has also demonstrated broad efficacy across individual symptoms and symptom domains in each approved indication.[36–39]

To investigate the effects of cariprazine on cognitive symptoms across the indications of bipolar I disorder and schizophrenia, we conducted post hoc analyses of data relevant to cognitive symptom change. As the constituent studies were not prospectively designed to assess cognition, these post hoc analyses were exploratory and they were based on available measures in each indication.

In bipolar I disorder, most of the presented analyses were based on pooled data from the pivotal studies in bipolar depression and mania; an additional post hoc analysis that was based on a cognitive measure collected in one bipolar depression study is also presented. Pooled cognition analyses in schizophrenia have been previously reported[36,37]; results from a computerized battery of cognitive tests that was conducted in one pivotal study in patients with schizophrenia (RGH-MD-04) are reported here as a supportive analysis.

Methods

Study designs and participants

Post hoc analyses were conducted on data from phase 2/3, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trials of cariprazine in bipolar I depression, bipolar I mania, and schizophrenia. Patients in the constituent studies gave informed written consent; study protocols were approved by institutional review board (U.S. centers) or ethics committee/government agency (non-U.S. centers).

Detailed methods of the bipolar I depression studies,[27–29] the bipolar mania studies,[30–32] and RGH-MD-04 in schizophrenia[33] have been previously published. Briefly, each study had a washout period of up to 1 week, followed by a 6-week (bipolar depression studies and schizophrenia study) or 3-week (bipolar mania studies) double-blind evaluation period, and a 2-week safety follow-up. Adult patients (bipolar I disorder: 18-65 years; RGH-MD-04 [schizophrenia]: 18-60 years) met *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR or DSM-5)[40,41] criteria for bipolar I disorder (acute manic/mixed or depressive episode) or schizophrenia depending on the disorder under investigation; patients with bipolar I mania and schizophrenia were hospitalized during screening and for at least the first 2 weeks of treatment. Post hoc analyses were conducted in the respective intent-to-treat populations modified by pooling and the application of subgroup criteria (mITT).

Participants in the constituent studies met inclusion and exclusion criteria that are typical of criteria used in clinical studies of bipolar I disorder and schizophrenia. In the bipolar depression studies, participants were required to have a Hamilton Depression Rating Scale ($HAMD_{17}$) total score ≥20 and an item 1 score ≥2,[42] and a Clinical Global Impression-Severity (CGI-S) score ≥4.[43] In the bipolar I mania studies, participants were required to have a Young Mania Rating Scale (YMRS) total score ≥20 and a score ≥4 on at least 2 of 4 YMRS items (irritability, speech, content, and disruptive/aggressive behavior)[44] and a Montgomery-Åsberg Depression Rating Scale (MADRS) total score <18.[45] In the RGH-MD-04 schizophrenia study, participants were required to have a Positive and Negative Syndrome Scale (PANSS) total score ≥80 and ≤120 and a score ≥4 on at least 2 of 4 PANSS items (Delusions, Hallucinatory Behavior, Conceptual Disorganization, and Suspiciousness/Persecution Items),[46] and a CGI-S score ≥4. Key exclusion criteria in each study included a DSM axis I diagnosis other than the disorder under investigation, alcohol- or substance-related disorders within a specified timeframe (3 months for bipolar mania and schizophrenia and 6 months for bipolar depression), risk for suicide, and previous nonresponse to approved treatment or treatment resistance.

Bipolar I depression

To analyze cognitive symptoms in adult patients with bipolar I disorder and a current depressive episode, 6-week data were pooled from all 3 pivotal cariprazine studies.[27–29] In RGH-MD-53 (NCT02670538) and RGH-MD-54 (NCT02670551), patients were randomized (1:1:1) to receive placebo, or cariprazine 1.5 or 3 mg/d; in RGH-MD-56 (NCT01396447), patients were randomized (1:1:1:1) to receive placebo or cariprazine 0.75, 1.5, or 3 mg/d. The double-blind period was 6 weeks in RGH-MD-53 and -54, and 8 weeks in RGH-MD-56; the primary efficacy endpoint was week 6 in all studies. Cariprazine 0.75 mg/d was not included in these analyses since it is below the recommended dose for bipolar depression. The primary efficacy outcome in all 3 studies was change from baseline to week 6 in MADRS total score. The Functioning Assessment Short Test (FAST),[47] a 24-item clinician-rated scale that assesses 6 areas of functioning in patients with bipolar disorder (ie, autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time), was administered as an additional efficacy assessment in RGH-MD-56 only; changes in FAST outcomes were assessed from baseline to end of the 8-week double-blind period.

Post hoc analyses evaluated changes from baseline to week 6 in MADRS Concentration Item (item 6) score and MADRS total

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score in the overall mITT population (all patients who received study treatment and had at least 1 postbaseline efficacy assessment) and in 2 patient subgroups with greater levels of cognitive symptoms (at least mild cognitive symptoms = item 6 score ≥3; at least moderate cognitive symptoms = item 6 score ≥4). Scores on item 6 range from 0 (no difficulty in concentration) to 6 (unable to read or converse without great initiative). In RGH-MD-56 only, cognitive functioning was also evaluated by changes from baseline to week 8 in FAST total score, FAST Cognitive Functioning subscale score, and FAST Cognitive item scores in the mITT population and in a patient subset with baseline cognitive symptoms defined as a FAST Cognitive Functioning subscale score ≥2 on 2 or more of 5 cognitive items. The FAST Cognitive Functioning subscale is scored as the sum of 5 items (Ability to Concentrate on a Book/Film, Make Mental Calculations, Solve a Problem Adequately, Remember Newly Learned Names, and Learn New Information); scores range from 0 (no difficulty) to 3 (severe difficulty) for each item, with higher scores indicating greater impairment.

Bipolar I mania

To analyze cognitive symptoms in adult patients with manic or mixed episodes associated with bipolar I disorder, data were pooled from all 3 pivotal 3-week cariprazine studies.[30–32] In RGH-MD-31 (NCT00488618) and RGH-MD-32 (NCT01058096), patients were randomized (1:1) to receive placebo or flexible-dose cariprazine 3 to 12 mg/d; in RGH-MD-33 (NCT01058668), patients were randomized (1:1:1) to receive placebo or fixed/flexible dose cariprazine 3 to 6 mg/d or 6 to 12 mg/d. The primary efficacy outcome in each bipolar mania study was change from baseline to week 3 in YMRS total score; the PANSS was also administered as an additional efficacy outcome in each study.

Post hoc analyses evaluated changes from baseline to day 21 in PANSS Cognitive subscale score,[33,48] PANSS Cognitive subscale individual item scores, and YMRS total score. The items of the PANSS Cognitive subscale are P2 (Conceptual Disorganization), N5 (Difficulty in Abstract Thinking), N7 (Stereotyped Thinking), G10 (Disorientation), and G11 (Poor Attention), with scores ranging from 1 (absent) to 7 (extreme). Outcomes were assessed in the mITT population and in a subset of patients with greater cognitive symptoms, defined as PANSS Cognitive subscale score ≥15 (representing an average score of 3 [mild severity] on each item of the 5-item subscale). Changes from baseline were also evaluated in a less restrictive subset defined as patients with a baseline PANSS Cognitive subscale score greater than or equal to the median (median = 11).

Schizophrenia

Cognitive symptom outcomes from all 3 pivotal 6-week cariprazine studies in adult patients with acute exacerbation of schizophrenia and from a 26-week study in patients with schizophrenia and predominant negative symptoms have been previously analyzed and reported.[36,37] To objectively evaluate the effect of cariprazine on cognitive symptoms in schizophrenia, performance-based outcomes from the Cognitive Drug Research (CDR) system attention battery,[49] which was an additional efficacy parameter in pivotal study RGH-MD-04 (NCT01104766),[33] were investigated. The CDR system attention battery consists of 3 brief and highly sensitive tests (simple reaction time, digit vigilance, and choice reaction time) organized into factors; power of attention (PoA) and continuity of attention (CoA) factors were reported. In RGH-MD-04, patients with a current psychotic episode <2 weeks in duration were randomized (1:1:1:1) to receive placebo, cariprazine 3 mg/d, cariprazine 6 mg/d, or aripiprazole 10 mg/d (included for assay sensitivity).

Statistical analyses

Change in MADRS, PANSS, and FAST assessments were analyzed using a mixed-effects model for repeated measures with an unstructured covariance matrix including study, baseline score, treatment, visit, and treatment-by-visit interaction, and baseline-by-visit interaction as covariates. All statistical tests were 2-sided at the 5% significance level; *P* values were not adjusted for multiple comparisons. Median changes and *P* values for CDR system attention battery outcomes were analyzed using the Wilcoxon rank-sum test based on a last observation carried forward approach.

Results

Bipolar depression

Patient disposition

There was a total of 1383 patients in the pooled mITT bipolar depression population (Table 1). At baseline, 88.4% of patients had at least mild cognitive symptoms (MADRS item 6 score ≥3) and 66.0% had at least moderate cognitive symptoms (MADRS item 6 score ≥4); baseline MADRS item 6 and total scores were similar in placebo- and cariprazine-treated groups. In RGH-MD-56, 393 patients had baseline and postbaseline FAST scores and were included in the mITT population. Mean baseline FAST total score in the mITT population was 38.8, indicating a population with moderate-to-severe functional impairment.[50] A total of 75.8% of patients had baseline cognitive symptoms (FAST Cognitive score of ≥2 on at least 2 of the 5 items; Table 1).

Changes in cognitive and depressive symptoms: MADRS item 6 and total score

In the pooled mITT population, least squares (LS) mean change from baseline to week 6 in MADRS concentration item (item 6) was −1.2 for placebo, −1.6 for cariprazine 1.5 mg/d, and −1.4 for cariprazine 3 mg/d; differences vs placebo were statistically significant for cariprazine 1.5 mg/d ($P < .0001$) and 3 mg/d ($P = .0365$). The difference in mean change from baseline in MADRS item 6 was statistically significant for cariprazine 1.5 and 3 mg/d vs placebo in patients with at least mild cognitive symptoms (item 6 score ≥3) and at least moderate cognitive symptoms (item 6 score ≥4; Figure 1A). In patients with at least mild cognitive symptoms, the LS mean change from baseline to week 6 was −1.3 for placebo, −1.8 for 1.5 mg/d ($P < .0001$), and −1.5 for 3 mg/d ($P = .0292$); in patients with at least moderate cognitive symptoms, the LS mean change was −1.5 for placebo, −1.9 for 1.5 mg/d ($P < .0001$), and −1.7 for 3 mg/d ($P = .0366$).

The difference in mean change from baseline in MADRS total score (depressive symptoms) was statistically significant in favor of cariprazine vs placebo for patients with at least mild cognitive symptoms and at least moderate cognitive symptoms (Figure 1B). LS mean change in MADRS total score was −12.0 for placebo, −15.1 for cariprazine 1.5 mg/d ($P < .0001$), and −14.7 for 3 mg/d ($P = .0001$) in patients with at least mild cognitive symptoms and

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Table 1. Bipolar Depression: Subsets with Greater Cognitive Symptoms at Baseline

Populations and assessments	Placebo	Cariprazine 1.5 mg/d	Cariprazine 3 mg/d
Pooled mITT[a] (RGH-MD-53, -54, and -56), n	460	461	462
MADRS concentration item score ≥3, n (%)	404 (87.8)	411 (89.2)	407 (88.1)
MADRS concentration item score at baseline, mean (SD)	3.9 (0.6)	3.8 (0.6)	3.9 (0.6)
MADRS total score at baseline, mean (SD)	31.4 (4.2)	31.4 (4.1)	31.7 (4.6)
MADRS concentration item score ≥4, n (%)	303 (65.9)	307 (66.6)	303 (65.6)
MADRS concentration item score at baseline, mean (SD)	4.1 (0.4)	4.1 (0.4)	4.2 (0.4)
MADRS total score at baseline, mean (SD)	32.3 (3.9)	32.1 (4.0)	32.7 (4.4)
RGH-MD-56 mITT,[a] n	132	135	126
FAST Cognitive score ≥2 on ≥2 items, n (%)	100 (75.8)	105 (77.8)	93 (73.8)
FAST Cognitive score at baseline, mean (SD)	9.5 (2.3)	9.5 (2.4)	9.7 (2.5)
FAST total score at baseline, mean (SD)	42.8 (10.5)	42.4 (11.7)	43.3 (11.7)

Abbreviations: FAST, Functional Assessment Short Test; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent to treat.
[a]mITT is defined as all randomized patients who took at least 1 dose of double-blind study drug and had at least 1 postbaseline efficacy score.

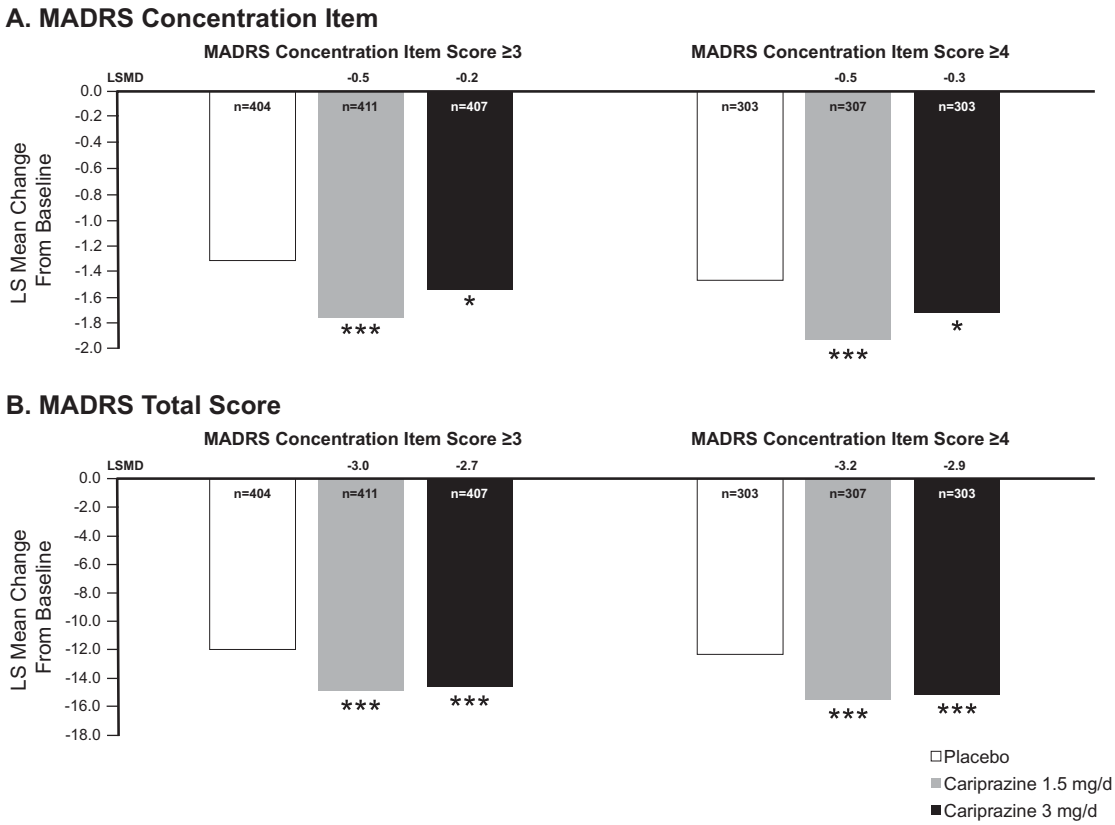

Figure 1. MADRS change from baseline to week 6 in patients with bipolar depression and cognitive symptoms. Differences in change from baseline on the (A) MADRS Concentration item and (B) MADRS total score were statistically significant in favor of cariprazine 1.5 and 3 mg/d vs placebo for patients in higher and lower cognitive symptom subgroups. *P < .05 and ***P < .001 vs placebo. Abbreviations: LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale.

−12.3 for placebo, −15.6 for 1.5 mg/d (P < .0001), and −15.2 for 3 mg/d (P < .0006) in patients with at least moderate cognitive symptoms.

Change in functioning: FAST Cognitive subscale score, item scores, and total score

In the overall ITT population, the difference in change from baseline to week 8 in FAST Cognitive subscale score was statistically significant in favor of cariprazine 1.5 mg/d vs placebo (LSMD = −1.2; P = .0035); the difference for cariprazine 3 mg/d vs placebo was not statistically significant (LSMD = −0.5). In patients with baseline cognitive symptoms (scores ≥2 on at least 2 of 5 FAST Cognitive subscale items), the difference in change from baseline in FAST Cognitive subscale score was statistically significant in favor of cariprazine 1.5 mg/d vs placebo (LSMD = −1.4; P = .0039); the difference for cariprazine 3 mg/d vs placebo was not statistically

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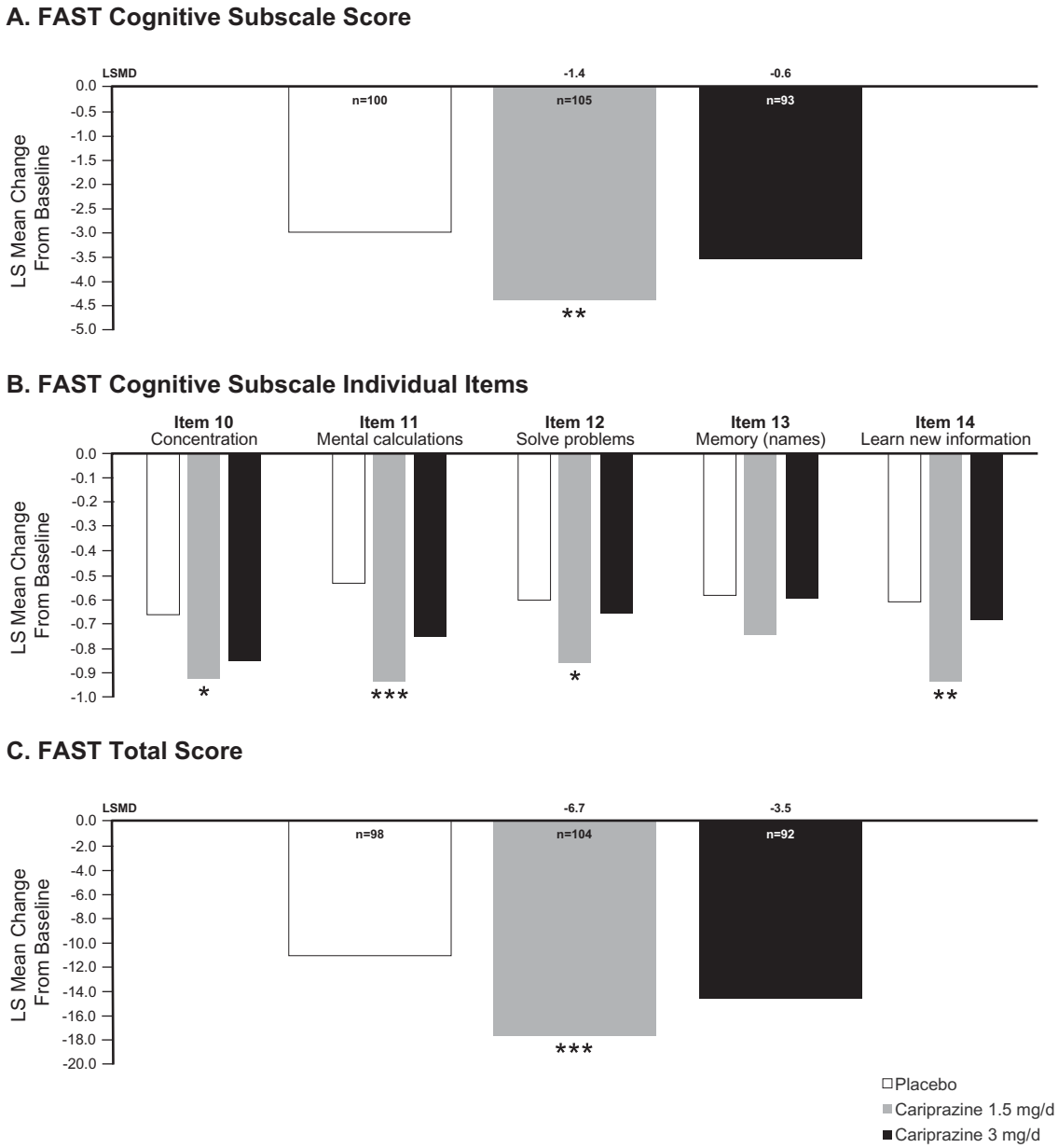

Figure 2. FAST change from baseline to week 8 in patients with bipolar depression and cognitive symptoms (FAST Cognitive subscale item score ≥2 on at least 2 of 5 items). (A) The difference in change from baseline on the FAST Cognitive subscale was significantly different for cariprazine 1.5 mg/d vs placebo. (B) Changes from baseline in FAST individual item scores were significantly different for cariprazine 1.5 mg/d vs placebo on all items except Memory. (C) Change from baseline in FAST total score was significantly different than placebo for cariprazine 1.5 mg/d.
*P < .05, **P < .01, and ***P < .001 vs placebo. Abbreviations: FAST, Functional Assessment Short Test; LS, least squares.

significant (LSMD = −0.6; Figure 2A). Also of note, changes from baseline were significantly different in favor of cariprazine 1.5 mg/d vs placebo on 4 of 5 individual symptom items included in the FAST Cognitive subscale (ie, Concentration, Mental Calculations, Solve Problems, and Learn New Information); no statistically significant differences vs placebo were seen for cariprazine 1.5 mg/d on the "Memory For a New Name" item or for cariprazine 3 mg/d on any item (Figure 2B). In the subset of patients with baseline cognitive symptoms, the difference in change from baseline in FAST total score was also statistically significant for cariprazine 1.5 mg/d (LSMD = −6.7; P = .0009) vs placebo, suggesting overall functional improvement in this group; cariprazine 3 mg/d was not significantly different than placebo (LSMD = −3.5; Figure 2C).

Bipolar mania

Patient disposition

There were a total of 1012 patients in the pooled mITT bipolar mania population (Table 2). Baseline PANSS Cognitive subscale scores and YMRS total scores were similar in the cariprazine and placebo groups in the mITT population. Similar PANSS Cognitive subscale scores and YMRS total scores for cariprazine and placebo were also noted at baseline in the subset with PANSS Cognitive subscale score ≥15 and in the subset with a baseline PANSS Cognitive subscale score at or above the median (Table 2). More than half of all patients had a baseline PANSS Cognitive subscale score at or above the median (11), whereas 17.2% of patients had PANSS Cognitive subscale score ≥15 (Table 2).

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Change in cognitive symptoms: PANSS Cognitive subscale score and item scores

In the pooled mITT population, mean change from baseline to day 21 in PANSS Cognitive subscale score was −2.2 for cariprazine and −1.3 for placebo, with a statistically significant LSMD in favor of cariprazine over placebo (−0.9; $P < .0001$). In patients with PANSS Cognitive subscale score ≥15, the difference in change from baseline to day 21 was statistically significant in favor of cariprazine vs placebo ($P = .0002$); in patients with a PANSS Cognitive subscale score above the median, a statistically significant difference in favor of cariprazine vs placebo was again noted ($P < .0001$; Figure 3A). In patients with a PANSS Cognitive subscale score ≥15, changes from baseline to day 21 were significantly different in favor of cariprazine vs placebo on all individual PANSS Cognitive subscale items except for "Disorientation" (Figure 3B). For patients with a baseline PANSS Cognitive subscale score at or above the median, LSMDs were also statistically significant in favor of cariprazine on 4 of 5 items (P2: −0.4, $P < .0001$; N5: −0.2, $P = .0127$; N7: −0.1, $P = .1246$; G10: −0.1, $P = .0392$; G11: −0.3, $P = .0002$); unlike the subset with baseline PANSS Cognitive subscale score ≥15, the difference on item N7 was not statistically significant, although the difference on item G10 was statistically significant (data not shown).

Change in mania symptoms: YMRS total score

The difference in mean change from baseline to day 21 in manic symptoms was statistically significant in favor of cariprazine vs placebo in the subset of patients with baseline PANSS Cognitive subscale score ≥15 (LSMD = −8.6; $P < .0001$); a smaller, but statistically significant mean difference was also noted for cariprazine vs placebo in the subset with baseline PANSS Cognitive subscale scores at or above the median (LSMD = −5.6; $P < .0001$; Figure 4).

Schizophrenia

Patient disposition

A total of 520 patients were included in the mITT population of schizophrenia study RGH-MD-04 (Table 3). The high cognitive impairment subsets included patients with scores above or equal to the median PoA time (≥1545.1 ms) and below or equal to the median COA score (≤88).

Changes in cognition performance measures: CDR system power of attention and continuity of attention

In the mITT population, the median (SD) change from baseline to week 6 in PoA (ms) was 27.3 (597.5) for placebo, −59 (595.1; $P = .0036$) for cariprazine 3 mg/d, 5.7 (781.8; $P = .1272$) for cariprazine 6 mg/d, and 44.2 (828.1; $P = .4104$) for aripiprazole 10 mg/d; differences vs placebo were statistically significant for cariprazine 3 mg/d, but not for cariprazine 6 mg/d or aripiprazole (P values based on Wilcoxon rank-sum). Differences in PoA change were also statistically significant for both doses of cariprazine vs aripiprazole (cariprazine 3 mg/d, $P = .0006$; cariprazine 6 mg/d, $P = .0260$). In patients with a PoA score above or equal to the median PoA at baseline (high cognitive impairment), the difference in median change from baseline to week 6 was statistically significant in favor of cariprazine 3 mg/d vs placebo ($P = .0080$) and vs aripiprazole ($P = .0064$); differences vs placebo were not significant for cariprazine 6 mg/d ($P = .2974$) or aripiprazole ($P = .4443$; Figure 5A).

For CoA score in the mITT population, the median (SD) change from baseline to week 6 was 0 (11.7) for placebo, 2 (10.5; $P = .0005$) for cariprazine 3 mg/d, 1 (14.1; $P = .0168$) for cariprazine 6 mg/d, and 0 (13.9; $P = .1685$) for aripiprazole 10 mg/d; differences vs placebo were statistically significant for cariprazine 3 and 6 mg/d, but not for aripiprazole 10 mg/d. In patients with a CoA score below or equal to the median CoA at baseline (higher cognitive impairment), the median change from baseline to week 6 was significantly higher, indicating improvement, in favor of all treatment groups vs placebo (cariprazine 3 mg/d, $P = .0012$; cariprazine 6 mg/d, $P = .0073$; aripiprazole, $P = .0160$); there were no other statistically significant differences between other individual groups (Figure 5B).

Discussion

In multiple post hoc analyses conducted to evaluate the effect of cariprazine on cognitive symptoms, greater improvement was seen across a range of outcomes for cariprazine-treated patients with bipolar I disorder (depressive and manic episodes) and schizophrenia. These post hoc results support earlier evidence of improvement demonstrated in animal models of cognitive impairment [25,26] and suggest a potential role for cariprazine in treating cognitive symptoms across indications. Given that cognitive dysfunction in serious mental illnesses is associated with decreased quality of life

Table 2. Bipolar Mania: Baseline Scores Overall and in Subsets with Greater Cognitive Symptoms at Baseline

Population and assessments	Placebo	Cariprazine
Pooled mITT[a] Population, n	419	593
PANSS Cognitive subscale score at baseline, mean (SD)	10.9 (3.3)	11.2 (3.4)
YMRS total score at baseline, mean (SD)	31.7 (5.6)	32.4 (5.4)
PANSS Cognitive subscale score ≥15, n (%)	71 (16.9)	103 (17.4)
PANSS Cognitive subscale score at baseline, mean (SD)	16.1 (1.9)	16.6 (2.1)
YMRS total score at baseline, mean (SD)	33.9 (5.5)	34.1 (5.6)
PANSS Cognitive subscale score ≥ median, n (%)	213 (50.8)	335 (56.5)
PANSS Cognitive subscale score at baseline, mean (SD)	13.5 (2.3)	13.6 (2.5)
YMRS total score at baseline, mean (SD)	32.1 (5.6)	32.7 (5.2)

Note: Median PANSS cognitive subscale score = 11.
Abbreviations: mITT, modified intent to treat; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale.
[a]mITT is defined as all randomized patients who took at least 1 dose of double-blind study drug and had at least 1 postbaseline Cognitive subscale PANSS assessment.

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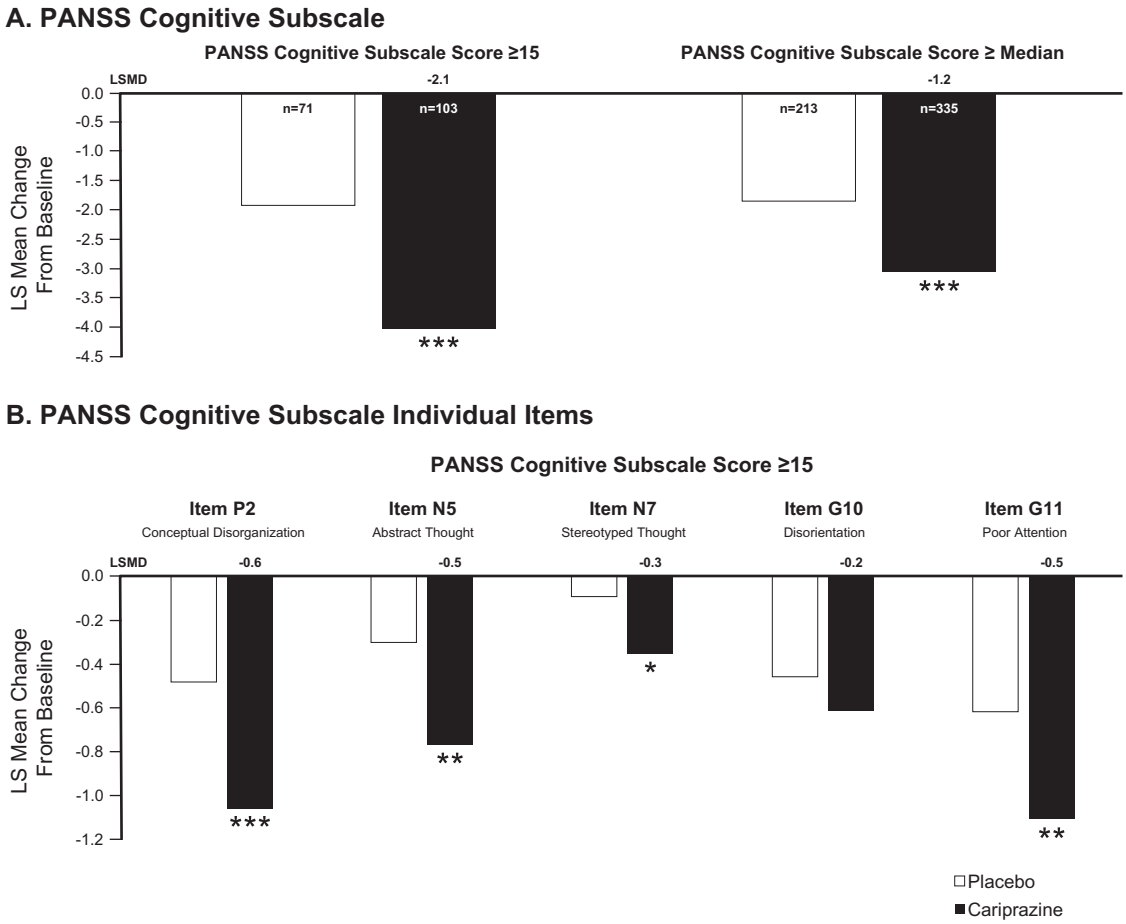

Figure 3. PANSS Cognitive subscale change from baseline to day 21 in patients with bipolar mania and cognitive symptoms. (A) The difference in change from baseline was statistically significant for cariprazine vs placebo in patients with cognitive symptoms defined as PANSS Cognitive subscales score ≥15 and greater than or equal to the median. (B) On individual subscale items, differences were statistically significant in favor of cariprazine on each item except Disorientation for patients with subscales score ≥15. *P < .05, **P < .01, and ***P < .001 vs placebo. Abbreviations: LS, least squares; PANSS, Positive and Negative Syndrome Scale.

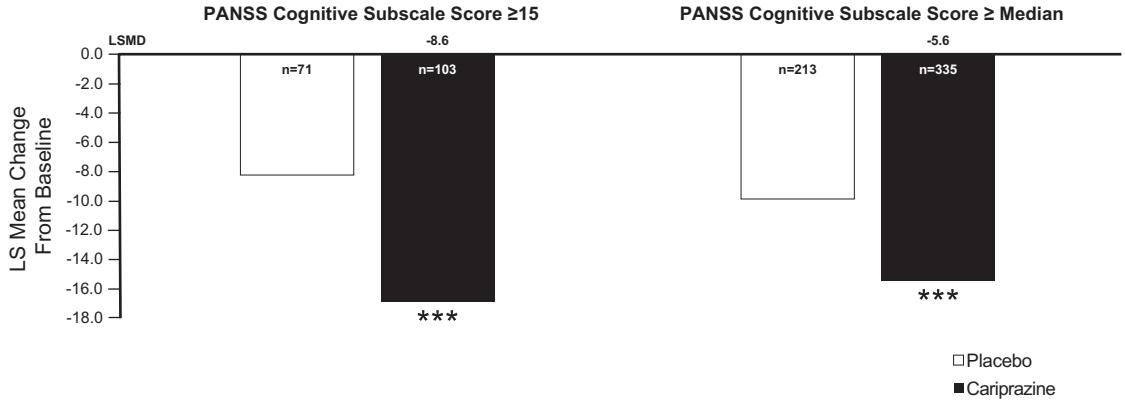

Figure 4. Change from baseline in YMRS total score at day 21 in patients with bipolar mania and cognitive symptoms. The difference in change from baseline in manic symptoms was statistically significant for cariprazine vs placebo in patients with cognitive symptoms defined as PANSS Cognitive subscales score ≥15 and greater than or equal to the median. ***P < .001 vs placebo. Abbreviations: LS, least squares; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale.

and worse functional outcomes, cognitive symptoms should be considered a critical clinical and therapeutic target for patients with schizophrenia and bipolar I disorder.[16,51]

In patients with bipolar disorder, the pattern of cognitive impairment is broad and heterogenous, with evidence suggesting that cognitive symptoms and depression may amplify each other in producing disability.[52,53] In these pooled post hoc analyses of data from patients with bipolar depression, greater improvement was observed for cariprazine vs placebo on measures of cognition, depression, and functioning in the overall population and in subsets of patients with greater cognitive symptoms. Since evidence points to a gap between clinical outcomes and functional recovery

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Table 3. Schizophrenia: Performance-Based Measures at Baseline Overall and in Subsets with Cognitive Impairment at Baseline

	Placebo		Cariprazine 3 mg/d		Cariprazine 6 mg/d		Aripiprazole 10 mg/d	
mITT[a] Population	n	Median (SD)	n	Median (SD)	n	Median (SD)	n	Median (SD)
Baseline PoA Score, median (SD); ms	129	1547.3 (961.1)	124	1550.1 (855.0)	137	1551.4 (904.2)	130	1527.6 (718.4)
Baseline CoA Score, median (SD)	128	88 (14.9)	122	87 (13.9)	135	87 (14.2)	130	88 (12.9)
High Cognitive Impairment (≥1545.1 ms; Median PoA)								
Baseline PoA Score, median (SD); ms	65	2114.5 (1090.7)	62	2233.7 (895.7)	69	2062.7 (1016.5)	63	2148.5 (767.6)
High Cognitive Impairment (≤88; Median CoA)								
Baseline CoA Score, median (SD)	68	80.5 (16.6)	73	80.0 (14.4)	73	78.0 (14.3)	66	80.0 (13.9)

Abbreviations: CoA, continuity of attention; mITT, modified intent to treat; ms, milliseconds; PoA, power of attention.
[a]mITT is defined as all randomized patients who took at least 1 dose of double-blind investigational product and had at least one postbaseline PoA or CoA assessment.

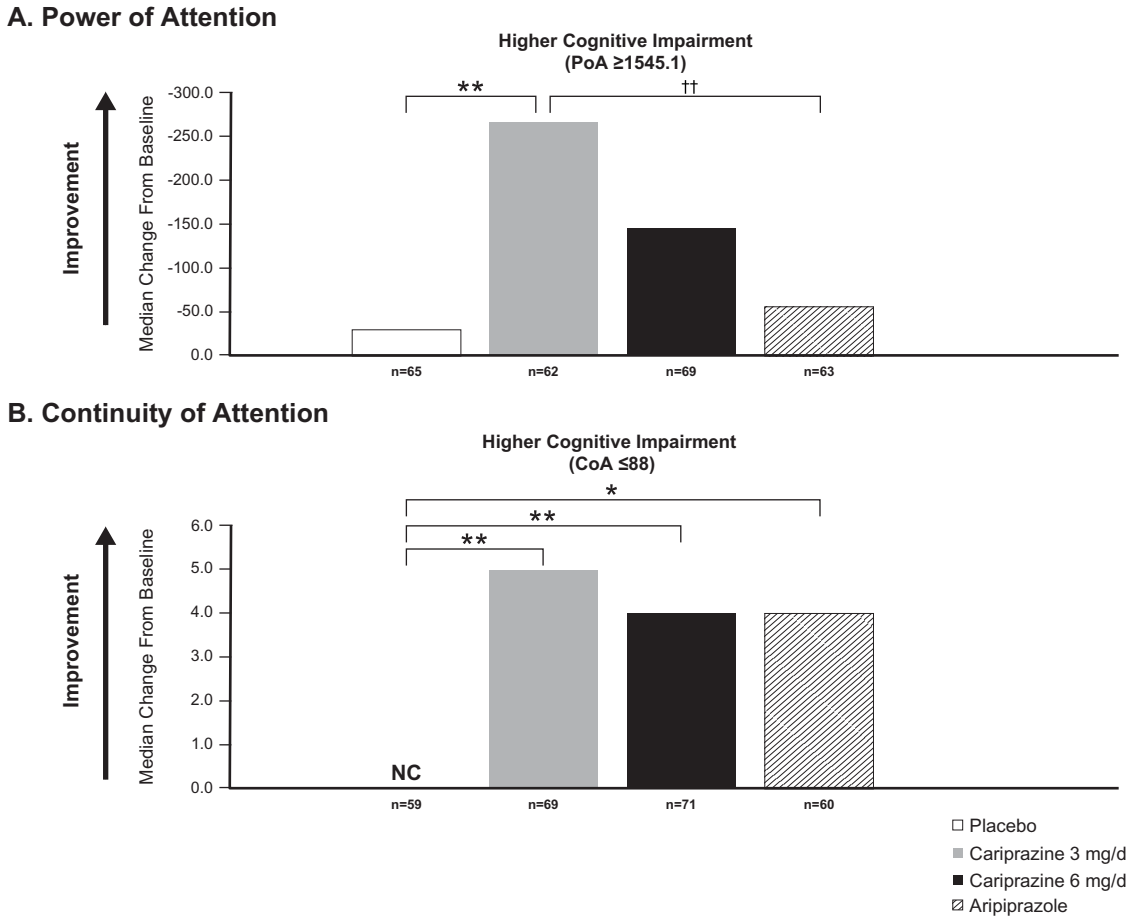

Figure 5. Change from baseline to week 6 in CDR attention battery. (A) In patients with schizophrenia and high cognitive impairment, the difference in median change from baseline to week 6 was statistically significant in favor of cariprazine 3 mg/d vs placebo and aripiprazole; differences vs placebo were not significant for cariprazine 6 mg/d or aripiprazole. (B) In patients with higher cognitive impairment, median change from baseline to week 6 was significantly higher (improvement) in favor of all treatment groups vs placebo; there were no statistically significant differences between other individual groups.
*P < .05 vs placebo, **P < .01 vs placebo, and $^{\dagger\dagger}P$ < .01 vs aripiprazole. P values based on Wilcoxon rank-sum test. Abbreviations: COA, continuity of attention; NC, no change; PoA, power of attention.

in patients with bipolar disorder,[54] findings that cariprazine 1.5 mg/d improved cognitive and depressive symptoms as well as functioning in patients with bipolar depression is an interesting clinical outcome. Furthermore, in patients with manic or mixed bipolar I disorder episodes and cognitive symptoms at baseline, significant improvement for cariprazine vs placebo was observed in cognitive symptoms (ie, change from baseline in PANSS Cognitive subscale and on 4 of 5 individual subscale items) as well as in manic symptoms (ie, change in YMRS total score), demonstrating that manic symptom efficacy was not compromised by the presence of baseline cognitive symptoms.

The neurocognitive profile of patients with schizophrenia is characterized by deficits across numerous cognitive domains accompanying general intellectual impairment, which may predate illness onset.[2] To augment previously published findings reporting subjective cognitive outcomes in cariprazine-treated patients with

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schizophrenia,[36,37] post hoc analyses were conducted on data from cariprazine RGH-MD-04, a pivotal trial in which a computerized, performance-based attention battery, the CDR system, was administered.[33] When the PoA factor, an outcome measuring focused attention, and the CoA factor, an outcome measuring sustained attention, were analyzed in the overall ITT population, the difference vs placebo was significant for cariprazine 3 mg/d ($P = .0036$), but not for cariprazine 6 mg/d or aripiprazole.[33] When PoA was analyzed in patients with baseline attentional impairment, significantly greater median change from baseline on the PoA was again noted for cariprazine 3 mg/d vs placebo, as well as for cariprazine 3 mg/d vs the active-comparator aripiprazole. As the speed scores from the PoA attentional tasks reflect the intensity of concentration at that particular moment,[55] faster responses suggest that more cognitive processes and high levels of effortful concentration were being used. When the CoA factor was examined, significantly greater median change from baseline was seen for both cariprazine 3 and 6 mg/d vs placebo. The CoA reflects the ability to sustain concentration,[55] with greater change from baseline suggesting that cariprazine-treated patients were able to sustain focus on a single task for a more prolonged period than placebo-treated patients. Of note, these findings support previous evidence of cognitive symptom improvement in RGH-MD-04, which was shown by statistically significant differences in favor of cariprazine 3 and 6 mg/d vs placebo ($P < .001$ both doses) in change from baseline on the PANSS Cognitive subscale.[33]

While these CDR system factor results provide an objective assessment of attention in one schizophrenia trial, additional evidence of a treatment effect for cariprazine in cognitive symptoms has been suggested in pooled post hoc analyses of data from the pivotal studies in patients with acute exacerbation of schizophrenia.[37,56] Namely, statistically significant improvement for cariprazine 1.5 to 9 mg/d vs placebo has been noted in change from baseline to week 6 on various outcomes including PANSS Cognitive subscale (LSMD = −1.47; $P < .001$),[56] each individual item of the PANSS Cognitive subscale ($P < .001$ each item),[56] and the PANSS Disorganized Thought factor (LSMD = −2.0; effect size = 0.47; $P < .0001$).[37] The PANSS 6-item Disorganized Thought factor consists of the Difficulty in Abstract Thinking, Mannerisms and Posturing Disorientation, Poor Attention, Disturbance of Volition, Preoccupation, and Conceptual Disorganization items. Additional evidence of cognitive symptom improvement for cariprazine was also observed in a 26-week study of patients with schizophrenia and persistent, predominant negative symptoms.[36] Of note, differences in change from baseline were statistically significant for cariprazine 4.5 mg/d vs risperidone 4 mg/d (the active-comparator) on both the PANSS Cognitive subscale (LSMD = −0.53; $P = .028$) and the PANSS Disorganized Thought factor (LSMD = −0.63; $P = .05$). Since the severity of cognitive dysfunction has been related to psychosis as well as to negative symptoms in patients with schizophrenia and bipolar disorder,[57] the favorable findings for cariprazine in cognitive symptom domains in patients with documented negative symptoms may be of particular interest.

Although currently available medications can effectively treat depressive and manic symptom states in bipolar I disorder and psychosis in schizophrenia, evidence of treatment efficacy for illness-related cognitive symptoms is limited, and to date, there is no well-established pharmacologic treatment for cognitive impairment. In addition to cariprazine, preclinical and clinical studies of several other newer atypical antipsychotics (eg, lurasidone, brexpiprazole, and lumateperone) have demonstrated procognitive effects that are likely related to their dopaminergic mechanisms.[58,59] A systematic review of studies investigating cognitive enhancement with novel pharmacologic agents (eg, mifepristone, galantamine, and donepezil) in bipolar disorder yielded disappointing or preliminary results without convincing effects.[3,60] Furthermore, because cognitive difficulties can persist during periods of euthymia for patients with bipolar I disorder, it is interesting to note that adjunctive lurasidone was more effective than treatment as usual in improving cognition in euthymic patients with reduced cognitive functioning.[61] In schizophrenia, studies of change in cognitive deficits in patients treated with atypical antipsychotics have been equivocal, with some results suggesting a greater potential for improvement in cognitive symptoms for atypical vs conventional antipsychotic agents[62,63] and others not supporting this finding.[64] In meta-analyses of prospective clinical studies, atypical antipsychotics were found to have mild effects in cognitive deficits in schizophrenia, with specific atypicals differentially effective within certain cognitive domains.[63]

Although cognitive deficits are a complex problem with a potentially heterogenous etiology, the unique mechanism of action of cariprazine may offer benefits in the treatment of cognition through its activity at the dopamine D_3 receptor, which has been identified as a treatment target for cognitive symptoms.[65] Unlike other dopamine D_2 and D_3 dopamine receptor antagonists or partial agonists, cariprazine has a higher potency for the D_3 receptor than does dopamine itself, which results D_3 receptor blockade.[66] With almost 10-fold greater affinity for D_3 than D_2 receptors in vitro,[23] cariprazine also shows high in vivo occupancy at both dopamine D_2 and D_3 receptors at clinically relevant doses.[24,67] Cariprazine has demonstrated dopamine D_3-dependent procognitive effects in an animal study,[26] further suggesting the potential for an efficacy advantage in cognitive symptoms in patients with serious mental illness. Of additional interest, since cariprazine has greater preference for occupying dopamine D_3 receptors vs D_2 receptors at lower doses,[24] greater effects for lower doses of cariprazine on cognitive symptoms in both bipolar depression and schizophrenia in our current analyses are consistent with its pharmacologic profile.

These analyses have several limitations including their post hoc nature and lack of adjustment for multiple comparisons, which is typical of post hoc evaluations. Since thorough neuropsychological evaluations were not performed, our findings should be considered relevant to cognitive symptoms, but not necessarily to cognitive deficits or social cognition, which are separate domains that are profoundly impaired in bipolar disorder and schizophrenia.[68] Because cognition was not a primary outcome in any of the studies and objective measures of cognition were not included in most cases, analyses were based on cognition-relevant rating scale measures that were included in the study protocols. For example, MADRS item 6 (Concentration Item) was used in post hoc analyses of the bipolar depression studies since concentration is considered a subdomain of higher-level cognitive processes (ie, executive function).[69] As global cognitive functioning requires the coordination and effective use of component cognitive abilities, change in concentration could influence cognitive function, but this item alone is not considered a measure of cognition. Interpretation of some outcomes is limited by the use of rating scale measures that were not specifically designed to investigate cognitive function. Moreover, since cognitive symptoms are closely related to affective and psychotic symptom loads, determining whether treatment effects are attributable to improvement in subjective cognitive function vs overall symptom improvement is difficult. Furthermore, no path analysis was conducted to determine whether

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improvement in cognition items was independent of improvement in other items and adjustments were not made for common conditions in bipolar disorder and schizophrenia, such as obesity, that may affect cognitive outcomes.[70,71] The constituent studies were of short duration, there was no objective measure to determine whether cognition was influenced by emotion or was independent of it, and the studies were not designed to detect treatment differences in patient subsets; patients were required to meet stringent inclusion and exclusion criteria, which may limit the ability to generalize these results to other bipolar I disorder or schizophrenia populations. Although patient characteristics such as age, sex, age of onset, number of affective or psychotic episodes, comorbid conditions, and concomitant medications may affect cognitive functioning, our analyses did not control for these variables. Differences in the available measures of cognition, doses, and cognitive impairment definitions precluded pooling data across indications for analysis. Finally, the small sample size of some subsets may also reduce the stability and certainty of results.

In conclusion, cariprazine improved cognitive symptoms, function, and performance vs placebo in these exploratory post hoc analyses of patients with bipolar I disorder and schizophrenia. Furthermore, the greater improvements vs placebo reported previously for primary outcomes in the original studies (mania measured by YMRS and depression measured by MADRS) were also observed in these post hoc analyses of patient subsets with worse cognitive symptoms. Although manic and depressive symptoms associated with bipolar I disorder and exacerbation of schizophrenia can be well controlled with pharmacologic agents, treatment of cognitive symptoms remains an unmet need in patients with serious mental illness.[72] These analyses provide preliminary evidence, suggesting that cariprazine may have potential benefits on cognitive symptoms in patients with bipolar I disorder and schizophrenia. As such, future prospectively designed acute and long-term trials investigating cariprazine and cognition are warranted.

Additional information

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

Previous presentations

Presented at the American Psychiatric Association (APA) Annual Meeting, May 18-21, 2019; the American College of Neuropsychopharmacology (ACNP) Annual Meeting, December 8-11, 2019; the Neuroscience Education Institute (NEI) Virtual Poster Library, posted online July 2, 2020.

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