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ORIGINAL RESEARCH

Effect of Cariprazine on Anhedonia in Patients with Bipolar I Depression: Post Hoc Analysis of Three Randomized Placebo-Controlled Clinical Trials

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ABSTRACT

Introduction: Anhedonic symptoms in bipolar I (BP-I) depression are associated with decreased quality of life and impaired functioning. We evaluated the effects of cariprazine in patients with BP-I depression with lower or higher levels of anhedonia at baseline.

Methods: Data were pooled from three clinical trials (NCT01396447, NCT02670538, NCT02670551) analyzing the effects of cariprazine 1.5 and 3 mg/day in adults with BP-I depression. During post hoc analysis, patients were stratified by baseline median Montgomery-Åsberg Depression Rating Scale (MADRS) anhedonia factor score into a lower (score < median) or higher (score ≥ median) anhedonia subgroup. Outcomes included change from baseline to week 6 in MADRS total and anhedonia factor score, with the latter also evaluated after adjusting for other depressive symptoms. Between-group differences in change from baseline to week 6 were compared using least-squares mean differences (LSMD) analyzed via a mixed-effect model for repeated measures.

Results: Median baseline anhedonia factor score was 19, defining the lower (placebo = 211; cariprazine 1.5 mg/day = 200, 3 mg/day = 212) and higher (placebo = 249; cariprazine 1.5 mg/day = 261, 3 mg/day = 250) anhedonia subgroups. In the lower subgroup, cariprazine 1.5 mg/day but not 3 mg/day was superior to placebo in reducing MADRS total (LSMD [95% CI] 1.5 mg/day = − 2.61 [− 4.28, − 0.93], $P = .0024$) and anhedonia factor scores (− 1.70 [− 2.77, − 0.62], $P = .0021$) at week 6. In the higher subgroup, both cariprazine doses were associated with significantly greater reductions than placebo in MADRS total (1.5 mg/day = − 3.01 [− 4.84, − 1.19], $P = .0012$; 3 mg/day = − 3.26 [− 5.12, − 1.40], $P = .0006$) and anhedonia factor scores (1.5 mg/day = − 1.97 [− 3.13, − 0.81], $P = .0009$; 3 mg/day = − 2.07 [− 3.26, − 0.89], $P = .0006$). Anti-anhedonic effects were preserved after adjusting for

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other depressive symptoms, suggesting the effect was not pseudospecific. Patients in the higher subgroup had higher baseline depression and therefore the lower subgroup may have had a floor effect.
Conclusion: Cariprazine demonstrated antidepressant and specific anti-anhedonic effects regardless of baseline anhedonia symptoms in patients with BP-I depression.
Trial Registration: ClinicalTrials.gov identifiers, NCT02670538, NCT02670551, NCT01396447.

PLAIN LANGUAGE SUMMARY

Anhedonia, or the lack of interest or pleasure, is common in patients with bipolar I depression. Cariprazine is a medication approved for the treatment of bipolar I depression. However, its effect on anhedonia is unclear. To understand the effect of cariprazine on anhedonia, we combined data from three bipolar I depression trials. We compared the effect of cariprazine treatment (1.5 mg or 3 mg per day) for 6 weeks against placebo in patients who had lower and higher levels of anhedonia before they started treatment. A total of 1383 patients were included in the study. There were 623 patients with lower anhedonia and 760 with higher anhedonia. Patients with higher anhedonia were more depressed overall than those with lower anhedonia. In patients with lower anhedonia, cariprazine 1.5 mg per day was better than placebo at reducing both anhedonia and depression. In patients with higher anhedonia, both cariprazine doses were better than placebo at reducing anhedonia and depression. Our results suggest that cariprazine reduces symptoms of both depression and anhedonia in patients with bipolar I depression.

Keywords: Anhedonia; Bipolar I disorder; Bipolar I depression; Cariprazine; Atypical antipsychotic; Residual symptoms; Post hoc analysis; Major depressive episode

Key Summary Points

Anhedonia is a common and debilitating symptom in patients with bipolar I disorder and is associated with suicidal ideation, treatment intractability, and increased depression and mania severity.
Cariprazine has proven efficacy in bipolar I depression, but its effects on anhedonia are unknown.
In this post hoc analysis, we evaluated the effects of cariprazine in patients with bipolar I depression with either lower or higher levels of anhedonia at baseline to determine whether cariprazine has specific anti-anhedonic effects.
Cariprazine decreased symptoms of anhedonia and demonstrated a potent antidepressant effect regardless of baseline anhedonia symptoms.
These results demonstrate that cariprazine is a beneficial treatment for bipolar I depression and may also be effective on hard-to-treat anhedonia symptoms.

INTRODUCTION

Individuals with bipolar I (BP-I) depression often present with anhedonia, a symptom that is characterized by markedly diminished interest or pleasure in all or almost all activities and occurs in 52% of patients with BP-I [1–3]. Anhedonic presentation in major depressive episodes consists of a loss of joy, connection, and purpose [4], as well as cognitive deficits and reductions in motivational drive that are negatively associated with functioning and quality of life [5–8]. Anhedonia is associated with increased rates of suicidal ideation, which is common among patients with bipolar disorder [9], independent of depressive symptoms [10–12]. Further, anhedonia is associated with more severe mania in

patients with BP-I as well as comorbidities that differentially affect individuals with bipolar disorders [13–15]. Symptoms of anhedonia often persist even when other depressive symptoms remit, such that more than 20% of outpatients diagnosed with BP-I still have clinically significant anhedonia symptoms even after scoring in the nonclinical range on measures of depression and mania [16]. Further, the effects of BP-I treatments on symptoms of anhedonia have not been extensively studied in clinical trials and there are currently no US Food and Drug Administration (FDA)-approved treatments specific for anhedonia in any indication. Therefore, adequate treatment for this symptom domain persists as an unmet need for patients with BP-I.

Anhedonia primarily associates with dysfunctional anticipatory, consummatory, and motivational reward processing [17]. Dopaminergic signaling supports anticipatory reward processing, while serotonergic and opioid signaling may conversely support consummatory reward processing [18]. In animal models, blunted dopamine transmission increases anhedonic symptoms, whereas manipulation of serotonin transmission produces equivocal effects [19–22]. Mesolimbic dopaminergic signaling from the ventral tegmental area to ventral striatum and nucleus accumbens drives reward signaling [19, 23]; notably, terminal projections of these pathways all contain a high density of dopamine D_3 receptors [24]. Dopamine D_3 agonists have previously demonstrated anti-anhedonic effects in preclinical studies [25, 26] and were validated in one clinical trial [27] of patients with Parkinson's disease: in a prospective, observational clinical trial, results demonstrated that pramipexole, a dopamine agonist with preference for D_3 receptors over D_2 receptors, decreases anhedonia symptoms in patients with Parkinson's disease and moderate or severe depression [27]. Thus, D_3 receptor modulation may similarly represent a promising therapeutic target for the treatment of anhedonia in mood disorders.

Cariprazine is a D_3-preferring D_3/D_2 and 5-HT_{1A} receptor partial agonist and 5-HT_{2B} receptor antagonist that is FDA-approved for the treatment of manic, mixed, and depressive episodes of BP-I and schizophrenia and as an adjunctive treatment for major depressive disorder (MDD). The safety and efficacy of cariprazine in BP-I depression has been demonstrated in three pivotal clinical trials evaluating the change from baseline to week 6 in Montgomery–Åsberg Depression Rating Scale (MADRS) total score, with statistically significant differences versus placebo seen for cariprazine 1.5 mg/day in all three studies [28–30] and for cariprazine 3 mg/day in one study [30]. Pooled analyses of data from these three trials have also demonstrated broad efficacy across a wide range of individual MADRS items [31] and patient clinical characteristics [32]. Additionally, evidence from two preclinical studies demonstrated that cariprazine attenuates anhedonia symptoms in rodent models [33, 34], an effect which may be mediated by dopamine D_3 receptors [33]. Cariprazine has a unique pharmacologic profile with a tenfold greater affinity for D_3 than for D_2 receptors [35], which, along with broad efficacy and preclinical evidence, provides a rationale for investigating its effect on anhedonia in patients with BP-I depression. Thus, in order to explore the potential utility of cariprazine in treating anhedonia in BP-I depression, we conducted a post hoc analysis of patients with BP-I depression from pivotal cariprazine trials presenting with symptoms of anhedonia.

METHODS

Study Design and Patients

Data were pooled from three randomized, double-blind, placebo-controlled clinical trials (RGH-MD-53 [NCT02670538], RGH-MD-54 [NCT02670551], RGH-MD-56 [NCT01396447]) evaluating cariprazine versus placebo for the treatment of BP-I depression. Detailed methodology of each trial has been published previously [28–30]. Briefly, each trial consisted of a 1- to 2-week screening/washout period followed by a 6-week (RGH-MD-53 and -54) or 8-week (RGH-MD-56) double-blind treatment period in which patients were randomized 1:1:1 to receive placebo, cariprazine 1.5 mg/day, or cariprazine 3 mg/day. All patients treated with cariprazine in RGH-MD-53 and RGH-MD-54 were initiated

on 1.5 mg/day, with those assigned to the 3 mg/day group uptitrating to their target dose on day 15. In RGH-MD-56, patients treated with cariprazine were initiated on 0.5 mg/day, which was increased to 0.75 mg/day on day 3, 1 mg/day on day 5, and 1.5 mg/day on day 8 with a final increase to 3 mg/day on day 15 for patients assigned to the 3 mg/day group. The additional treatment arm of 0.75 mg/day in one study (RGH-MD-56) did not separate from placebo on the primary endpoint of MADRS total score. Because of this, and since 0.75 mg/day is not an FDA-approved dose of cariprazine, it was not included in the pooled post hoc analysis. Because no prospective data were collected during this post hoc analysis, ethical approval was not required. During the original trials, all study protocols complied with the Declaration of Helsinki and Good Clinical Practice guidelines and were approved by an institutional review board (US centers) or an ethics committee/government agency (non-US centers). Written informed consent was obtained from all patients included in the original trials.

The primary outcome in all three clinical trials was change from baseline to week 6 in MADRS total score [36]. Included patients were 18 to 65 years old and met *Diagnostic and Statistical Manual of Mental Disorders* (DSM) [1, 37] criteria for BP-I (DSM-5 in RGH-MD-53 and -54; DSM-IV-TR in RGH-MD-56) with a current major depressive episode of ≥ 4 weeks and < 12 months of duration, without psychotic features in the current episode as confirmed by the Mini International Neuropsychiatric Interview (RGH-MD-53 and -54) [38] or the Structured Clinical Interview (RGH-MD-56) [39]. Additionally, patients were required to score ≥ 20 on the 17-item Hamilton Depression Rating Scale (HAM-D) [40] and score ≥ 4 on the Clinical Global Impressions Severity subscale (CGI-S) [41]. Patients were excluded from the constituent studies if they scored > 12 (or > 10 in RGH-MD-56) on the Young Mania Rating Scale (YMRS) [42], reported ≥ 4 episodes of mood disturbance within the previous 12 months, had certain past or current psychiatric diagnoses besides BP-I, were diagnosed with substance use disorder in the previous 6 months, were considered to be at risk of suicide, or had a history of nonresponse in the current depressive episode to ≥ 2 approved bipolar depression agents of adequate dose and duration in the current episode.

Post Hoc Analysis

MADRS anhedonia factor scores, consisting of MADRS item 1 (apparent sadness), item 2 (reported sadness), item 6 (concentration difficulties), item 7 (lassitude), and item 8 (inability to feel) [43], were used to stratify patients at baseline via a median split into either lower (anhedonia factor score less than the median) or higher (anhedonia factor score greater than or equal to the median) anhedonia subgroups. The MADRS anhedonia factor score is frequently used in clinical trials [44, 45] and was used in this analysis because of its high correlation with the Snaith–Hamilton Pleasure Scale [43], a validated anhedonia measure [46, 47]. Outcomes of interest included mean change from baseline to week 6 in MADRS total score and MADRS anhedonia factor score. To ensure the changes in anhedonia factor scores were not driven by changes in overall depressive symptoms, the change from baseline to week 6 in MADRS anhedonia factor scores was also evaluated after adjusting for changes in other depressive symptoms not included in the anhedonia factor score: MADRS items 3–5, 9, and 10 (inner tension, reduced sleep, reduced appetite, pessimistic thoughts, and suicidal thoughts). Finally, the proportion of patients with an anhedonia factor response at week 6, defined as ≥ 50% improvement from baseline, was assessed. All outcomes were analyzed in the pooled intent-to-treat population (ITT), which consisted of all randomized patients who took ≥ 1 dose of study medication and had ≥ 1 post-baseline assessment.

Statistical Analysis

The change from baseline to week 6 in MADRS total score and MADRS anhedonia factor score was analyzed using a mixed-effect model for repeated measures and reported as the least-squares mean change. The model included treatment group, visit, treatment group-by-visit

Table 1 Baseline scores: pooled ITT population and post hoc anhedonia subgroups

Treatment group[a]	Pooled ITT ($n = 1383$)	Lower anhedonia subgroup[b] ($n = 623$)	Higher anhedonia subgroup[c] ($n = 760$)
MADRS total score			
Placebo	30.7 (4.54)	27.4 (3.55)	33.5 (3.28)
Cariprazine 1.5 mg/day	30.9 (4.33)	27.8 (3.17)	33.2 (3.51)
Cariprazine 3 mg/day	31.1 (4.79)	27.5 (3.17)	34.1 (3.70)
Total	30.9 (4.56)	27.6 (3.30)	33.6 (3.51)
MADRS anhedonia factor score			
Placebo	18.5 (2.95)	16.0 (2.04)	20.7 (1.62)
Cariprazine 1.5 mg/d	18.7 (2.67)	16.3 (1.71)	20.6 (1.53)
Cariprazine 3 mg/day	18.8 (2.80)	16.3 (1.62)	20.9 (1.70)
Total	18.7 (2.81)	16.2 (1.81)	20.7 (1.62)

ITT intent-to-treat, *MADRS* Montgomery-Åsberg Depression Rating Scale

[a]*n* values for treatment groups are as follows: pooled ITT, placebo = 460, cariprazine 1.5 mg/day = 461, cariprazine 3 mg/day = 462; lower anhedonia subgroup, placebo = 211, cariprazine 1.5 mg/day = 200, cariprazine 3 mg/day = 212; higher anhedonia subgroup, placebo = 249, cariprazine 1.5 mg/day = 261, cariprazine 3 mg/day = 250

[b]Defined as an anhedonia factor score < 19

[c]Defined as an anhedonia factor score ≥ 19

interaction, and baseline-by-visit interaction. Baseline MADRS total score and baseline MADRS anhedonia factor score were also included in the changes in MADRS total score and MADRS anhedonia factor score models, respectively. The proportion of patients with anhedonia factor response was analyzed using a logistic regression model with study and treatment group as factors and baseline MADRS anhedonia factor score as a covariate; missing values were imputed via last observation carried forward. Similar to many post hoc analyses, *P* values were not corrected for multiple comparisons.

RESULTS

The pooled ITT population consisted of 1383 patients. The average age was 42–44 years, approximately 60% were female, the average duration of the current episode was 3.6 months, and the average duration of BP-I was approximately 15 months [48]. The median MADRS anhedonia factor score was 19, resulting in a total of 623 (45%) patients included in the lower anhedonia subgroup (cariprazine 1.5 mg/day = 200; cariprazine 3 mg/day = 212; placebo = 211) and 760 (55%) patients included in the higher anhedonia subgroup (cariprazine 1.5 mg/day = 261; cariprazine 3 mg/day = 250; placebo = 249). At baseline, the mean MADRS total score was greater in the higher anhedonia subgroup (33.6) compared with the lower anhedonia subgroup (27.6) (Table 1). Baseline MADRS total scores and MADRS anhedonia factor scores were similar across the three treatment arms in each subgroup. Patients in the overall ITT population had a mean (SD) baseline anhedonia factor score of 18.7 (2.81), and patients in the higher and lower anhedonia subgroups had baseline mean (SD) anhedonia factor scores of 20.7 (1.62) and 16.2 (1.81), respectively.

Change in Depression Symptoms

In the lower anhedonia subgroup, cariprazine 1.5 mg/day was associated with significantly greater reductions in MADRS total score relative to placebo, while cariprazine 3 mg/day was associated with a numerically, but not significantly, greater reduction in MADRS total scores relative to placebo (Fig. 1a). For cariprazine 1.5 mg/day, a significant between-group difference versus placebo in MADRS total score change was observed as early as week 2 and maintained through week 6. In the higher anhedonia subgroup, both cariprazine 1.5 mg/day and 3 mg/day were associated with significantly greater reductions in MADRS total scores relative to placebo (Fig. 1b). The difference in MADRS total score change versus placebo was statistically significant for both doses starting at week 2.

Change in Anhedonia Symptoms

In the pooled ITT population, the reduction in MADRS anhedonia factor scores from baseline to week 6 was significantly greater for both cariprazine doses relative to placebo (Fig. 2a), with significant differences observed as early as week 2. Reductions in MADRS anhedonia factor scores were significantly greater than placebo for cariprazine 1.5 mg/day in the lower anhedonia subgroup and for both cariprazine 1.5 mg/day and 3 mg/day in the higher anhedonia subgroup (Fig. 2b, c). Significant differences in MADRS anhedonia factor scores were observed as early as week 2 for cariprazine 1.5 mg/day versus placebo in the lower anhedonia subgroup and for both cariprazine doses versus placebo in the higher anhedonia subgroup.

The statistically significant effects of cariprazine on MADRS anhedonia factor scores persisted after adjusting for changes in other depressive symptoms (Fig. 3), indicating that changes in anhedonia factor scores were not driven by reductions in other depressive symptoms.

Anhedonia Factor Responders

A higher percentage of patients in both cariprazine dose groups relative to placebo met criteria for anhedonia factor response in the lower anhedonia subgroup (cariprazine 1.5 mg/day = 48.0%; cariprazine 3 mg/day = 46.7%; placebo = 39.3%); however, the differences were not statistically significant. In the higher anhedonia subgroup, the percentage of anhedonia factor responders was significantly higher for cariprazine 1.5 mg/day (44.8%) and 3 mg/day (45.6%) compared with placebo (31.7%; both $P<0.01$).

DISCUSSION

In this post hoc analysis, cariprazine demonstrated potent antidepressant and anti-anhedonic effects in patients with BP-I depression regardless of whether they had lower or higher anhedonia scores at baseline. In patients with lower baseline anhedonia levels, cariprazine 1.5 mg/day, but not cariprazine 3 mg/day, was superior to placebo in reducing MADRS total and anhedonia factor scores, whereas both doses of cariprazine were associated with significantly greater reductions than placebo in MADRS total and anhedonia factor scores in patients with higher anhedonia levels at baseline. The lack of significance in the cariprazine 3 mg/day group in patients with lower baseline anhedonia may be indicative of a floor effect, as this subgroup displayed lower anhedonia factor scores as well as lower overall depression scores at baseline, and therefore measures may have been less sensitive to treatment effects. Constituent pivotal trials also indicated a more robust antidepressant effect for cariprazine 1.5 mg/day, which may facilitate separation of this dose from placebo in patients with more mild depression.

Significant differences versus placebo in anhedonia factor score change were observed as early as week 2 for cariprazine 1.5 mg/day in the lower anhedonia subgroup and for both cariprazine doses in the higher anhedonia subgroup; differences were seen as early as week 1 for both dose groups in the overall ITT population. Anhedonia often persists as a residual symptom in major depressive episodes; its presence is associated with suicidal ideation and deteriorated quality of life, and early improvement in anhedonic symptoms is associated with

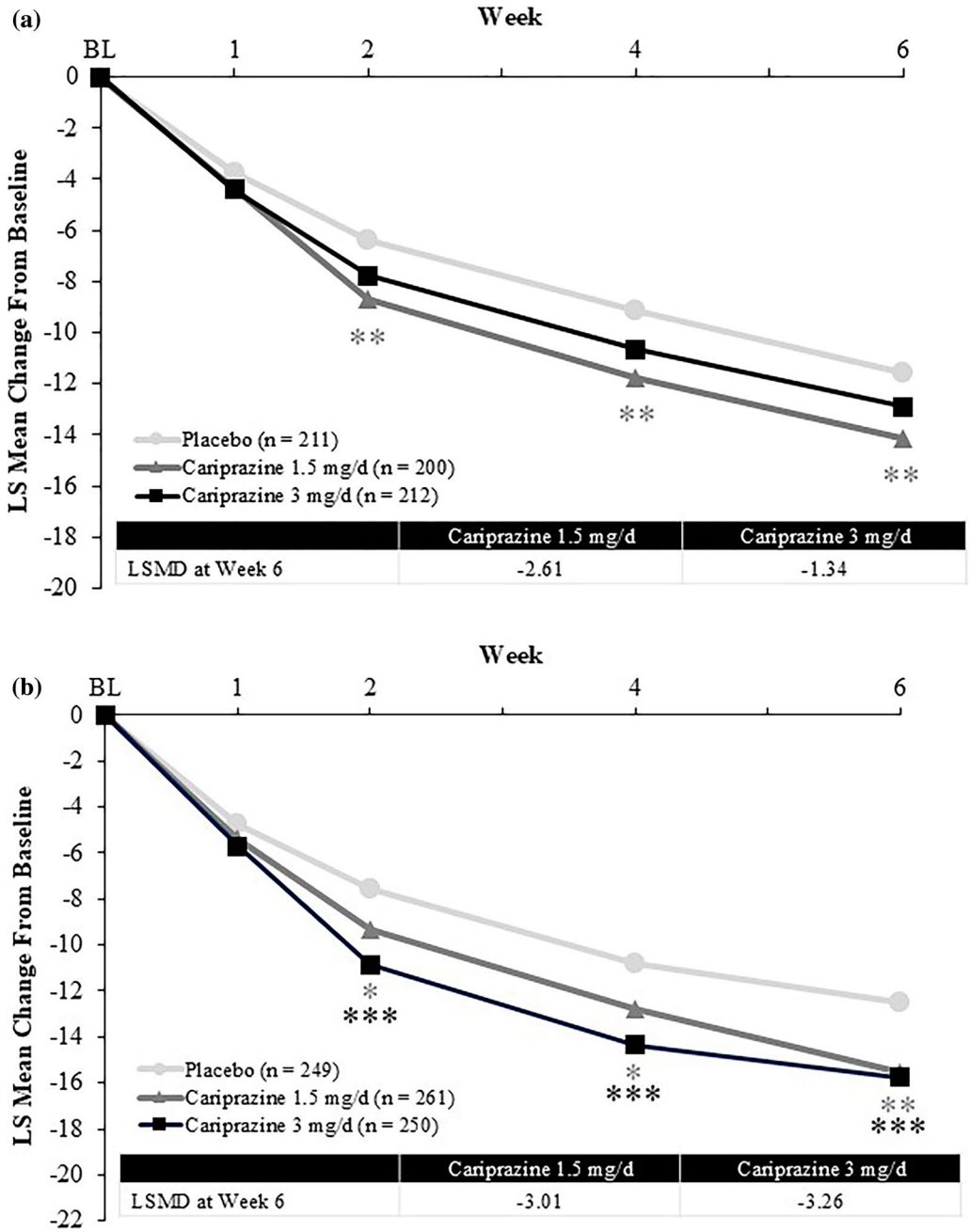
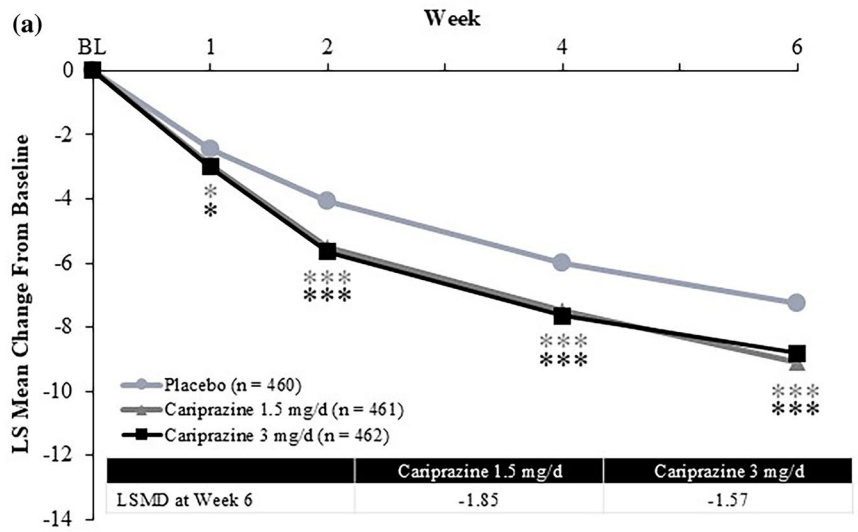
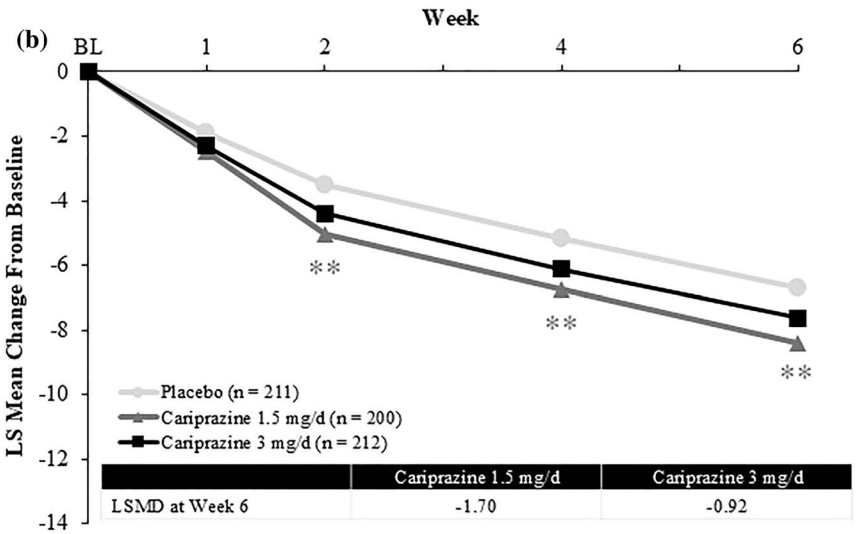


Fig. 1 Change from baseline to week 6 in MADRS total scores by visit. **a** Lower anhedonia subgroup (anhedonia factor score < 19). **b** Higher anhedonia subgroup (anhedonia factor score ≥ 19). ***$P < .001$, **$P < .01$, *$P < .05$ vs placebo. *BL* baseline, *LS* least-squares, *LSMD* least-squares mean difference, *MADRS* Montgomery-Åsberg Depression Rating Scale

improved depressive and anhedonic symptoms later in treatment [10, 11, 16, 49, 50]. Therefore, early improvement in this disabling dimension is likely important to improve patient outcomes. Further, improvement in anhedonia is a strong predictor of improvement in function [6, 7], suggesting that early improvement in anhedonia may also allow patients to start recovering


(a)
Week
BL
1
2
4
6
0
-2
-4
-6
-8
-10
-12
-14
LS Mean Change From Baseline
Placebo (n = 460)
Cariprazine 1.5 mg/d (n = 461)
Cariprazine 3 mg/d (n = 462)
Cariprazine 1.5 mg/d
Cariprazine 3 mg/d
LSMD at Week 6
-1.85
-1.57


(b)
Week
BL
1
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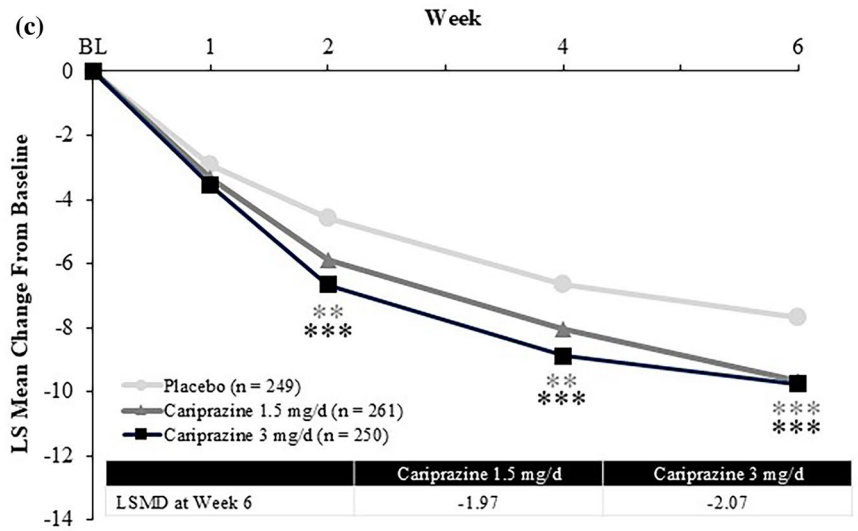
6
0
-2
-4
-6
-8
-10
-12
-14
LS Mean Change From Baseline
Placebo (n = 211)
Cariprazine 1.5 mg/d (n = 200)
Cariprazine 3 mg/d (n = 212)
Cariprazine 1.5 mg/d
Cariprazine 3 mg/d
LSMD at Week 6
-1.70
-0.92


(c)
Week
BL
1
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4
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-2
-4
-6
-8
-10
-12
-14
LS Mean Change From Baseline
Placebo (n = 249)
Cariprazine 1.5 mg/d (n = 261)
Cariprazine 3 mg/d (n = 250)
Cariprazine 1.5 mg/d
Cariprazine 3 mg/d
LSMD at Week 6
-1.97
-2.07

◂**Fig. 2** Change from baseline to week 6 in MADRS anhedonia factor score[a] by visit. **a** ITT population, **b** lower anhedonia subgroup (anhedonia factor score < 19), **c** higher anhedonia subgroup (anhedonia factor score ≥ 19). ***$P < .001$, **$P < .01$, *$P < .05$ vs placebo. [a]Sum of MADRS items 1, 2, 6, 7, and 8 (apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel). *BL* baseline, *ITT* intent-to-treat, *LS* least-squares, *LSMD* least-squares mean difference, *MADRS* Montgomery-Åsberg Depression Rating Scale

function earlier or increase the likelihood of functional recovery.

Importantly, anti-anhedonia benefits with cariprazine were maintained even after adjusting for changes in other depressive symptoms, indicating that cariprazine may exert a specific anti-anhedonic effect separate from improvement in overall depression. Furthermore, compared with patients treated with placebo, more patients treated with cariprazine demonstrated anhedonia factor response, with a statistically significant difference versus placebo in the higher anhedonia group. Together, these results suggest that in addition to proven antidepressant efficacy in patients with BP-I depression, cariprazine may be effective at treating symptoms of anhedonia. These results extend the broad efficacy profile previously established for cariprazine in BP-I depression, which includes efficacy across multiple depressive symptoms [31], varying demographic and clinical characteristics [32], and other symptoms clusters, such as mixed symptoms [51], cognition [52], and anxiety [53].

Anhedonic presentation in BP-I can lead to deleterious outcomes beyond depression, including degrading patients' ability to maintain self-care, daily routines, and interpersonal relationships [49], and severity of anhedonia is comparable across patients with bipolar and unipolar depression [54]. Anhedonic symptoms that persist beyond the resolution of depressive symptoms contribute to continued functional impairment between mood episodes [5], and the presence of anhedonia predicts poor psychosocial functioning despite symptomatic response to antidepressants in patients with MDD [6]. Previous analyses demonstrated the effect of cariprazine on improving function in patients with BP-I depression [55], with superiority versus placebo on subscales measuring interpersonal relationships, autonomy, occupational functioning, and cognitive functioning [55]. Further research is needed to elucidate any mediating, predictive, or synergistic effect between the antidepressant and anti-anhedonia effects of cariprazine on functional recovery.

Although the exact mechanism by which cariprazine improves depressive and anhedonia symptoms is unknown, its D_3-preferring dopamine receptor partial agonism may contribute to its effect on anhedonia. Pharmacologic studies have found that cariprazine displays partial agonist activity at D_3 receptors ($E_{max} = 71\%$), D_2 receptors ($E_{max} = 30\%$), and $5HT_{1A}$ receptors ($E_{max} = 39\%$), with a tenfold greater in vitro affinity for D_3 over D_2 receptors [35]. Cariprazine also showed preferential binding to D_3 receptors in an in vivo occupancy study in patients with schizophrenia, with cariprazine 1 mg/day demonstrating average receptor occupancies of 76% and 45% at D_3 and D_2 receptors, respectively, and cariprazine 3 mg/day demonstrating average receptor occupancies of 92% and 79%, respectively [56]. These pharmacological analyses also showcase that receptor occupancy is dose dependent, with lower doses of cariprazine having higher D_3 over D_2 receptor selectivity than higher doses [35, 56]. Furthermore, a preclinical study found that cariprazine significantly decreased rates of anhedonia in wild-type but not D_3-knockout mice, suggesting that dopamine D_3 receptors mediated the anti-anhedonia properties of cariprazine [33]. A potential anti-anhedonic effect for cariprazine is also supported by results of a phase 3b clinical trial investigating predominant negative symptoms in schizophrenia, a debilitating domain that includes anhedonia as a key symptom [57]. This active-controlled study found that cariprazine was more effective than risperidone in reducing negative symptoms, and importantly, improvement in negative symptoms also resulted in improved functioning. Interestingly, risperidone is a D_2-preferring agent [58] while cariprazine prefers D_3 [35], which may in part drive this differentiated effect of cariprazine on anhedonia.

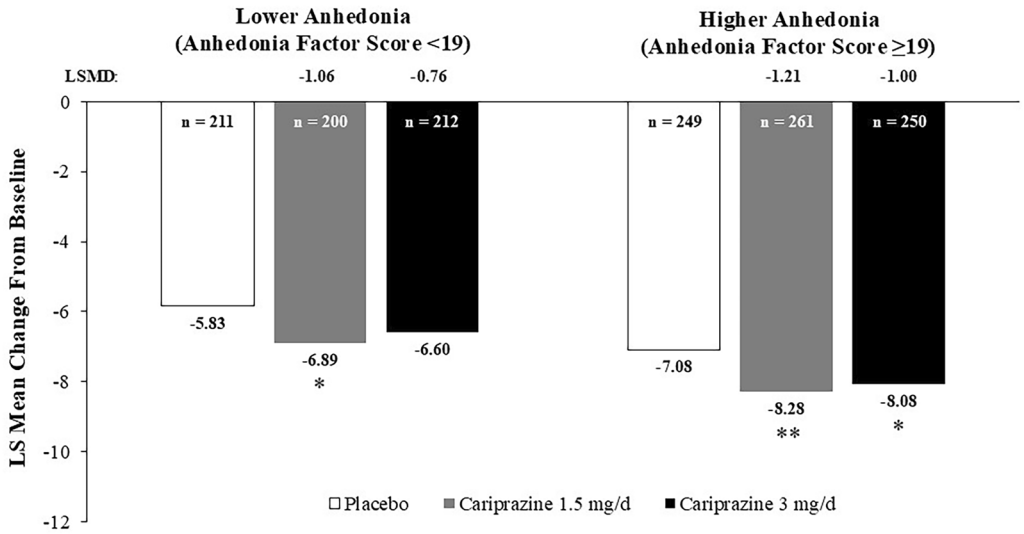

Fig. 3 Change from baseline to week 6 in MADRS anhedonia factor score[a] after adjustment for changes in other depressive symptoms[b]. $^{**}P < .01$, $^{*}P < .05$ vs placebo. [a]Sum of MADRS items 1, 2, 6, 7, and 8 (apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel). [b]Other depressive symptoms included MADRS items 3, 4, 5, 9, and 10 (inner tension, reduced sleep, reduced appetite, pessimistic thoughts, and suicidal thoughts). *LS* least-squares, *LSMD* least-squares mean difference, *MADRS* Montgomery-Åsberg Depression Rating Scale

These results demonstrating the anti-anhedonic effects of cariprazine should be considered in conjunction with the safety and tolerability of cariprazine, which has been described previously for BP-I depression [59]. On the basis of the three trials included in this analysis, adverse events that occurred in ≥5% of either cariprazine treatment group and at twice the rate of placebo were akathisia (1.5 mg/day, 6%; 3 mg/day, 10%; placebo, 2%), nausea (1.5 mg/day, 7%; 3 mg/day, 7%; placebo, 3%), extrapyramidal symptoms (1.5 mg/day, 4%; 3 mg/day, 6%; placebo, 2%), and restlessness (1.5 mg/day, 2%; 3 mg/day, 7%; placebo, 3%). Cariprazine is generally safe and well tolerated for the treatment of BP-I depression, as well as for the treatment of bipolar I mania [59, 60], schizophrenia [61], and MDD (adjunctive to antidepressant therapy) [62].

Limitations

Interpretation of this analysis must consider its limitations: these results are post hoc in nature and were not adjusted for multiple comparisons, and the constituent trials were not powered to detect significant differences in these anhedonia endpoints between patient subgroups. Because the lower anhedonia subgroup by definition included patients with lower anhedonia factor scores, the effects on anhedonia symptoms were likely limited by a floor effect. Patients were not balanced for overall levels of depression between subgroups, and as anhedonia is a core component of depression, patients in the lower anhedonia subgroup had lower overall depression scores. Further, because independently validated measures of anhedonia were not included in the constituent studies, proxy measures (e.g., MADRS anhedonia factor score) were used to identify changes in anhedonia symptoms. Additionally, this analysis was conducted using pooled data from three randomized clinical trials with relatively short study durations of only 6 weeks, which is particularly important given that cariprazine and its metabolites reach steady

state between 1 and 4 weeks [63]. It should also be noted that these trials enrolled patients with BP-I depression rather than specifically patients experiencing anhedonia; although these analyses adjusted for pseudospecificity, correlation between anti-anhedonic and antidepressive effects cannot be entirely ruled out.

CONCLUSION

In this post hoc analysis of pooled data from three BP-I depression clinical trials, cariprazine demonstrated antidepressant and anti-anhedonic effects in patients with bipolar I depression. Significant improvements in anhedonia symptoms were independent of changes in other depressive symptoms. Results of this analysis suggest that, regardless of the presence of higher or lower anhedonia scores at baseline, cariprazine is an effective treatment for BP-I depression that may also be effective on hard-to-treat anhedonia symptoms.

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Data Availability. The datasets generated during the current study are available from AbbVie on reasonable request. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing.

Declarations

Conflict of Interest. Roger S. McIntyre has received research grant support from the Canadian Institute of Health Research (CIHR), Global Alliance for Chronic Diseases (GACD),

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Ethical Approval. No prospective data were collected during this post hoc analysis and therefore ethical approval was not required. During the original trials, all study protocols complied with the Declaration of Helsinki and Good Clinical Practice guidelines and were approved by an institutional review board (US centers) or an ethics committee/government agency (non-US centers). Written informed consent was obtained from all patients included in the trials.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. 2013.
2. Mazza M, Squillacioti MR, Pecora RD, et al. Effect of aripiprazole on self-reported anhedonia in bipolar depressed patients. Psychiatry Res. 2009;30(1–2):193–6.
3. McIntyre RS, Alda M, Baldessarini RJ, et al. The clinical characterization of the adult patient with bipolar disorder aimed at personalization of management. World Psychiatry. 2022;21(3):364–87.
4. Watson R, Harvey K, McCabe C, et al. Understanding anhedonia: a qualitative study exploring loss of interest and pleasure in adolescent depression. Eur Child Adolesc Psychiatry. 2020;29(4):489–99.
5. Whitton A, Pizzagalli DA. Anhedonia in depression and bipolar disorder. Curr Top Behav Neurosci. 2022;58:111–27.
6. Vinckier F, Gourion D, Mouchabac S. Anhedonia predicts poor psychosocial functioning: results from a large cohort of patients treated for major depressive disorder by general practitioners. Eur Psychiatry. 2017;44:1–8.
7. Atre-Vaidya N, Taylor MA, Seidenberg M, et al. Cognitive deficits, psychopathology, and psychosocial functioning in bipolar mood disorder. Neuropsychiatry Neuropsychol Behav Neurol. 1998;11(3):120–6.
8. Wong S, Lee GH, Phan L, et al. Effects of anhedonia on health-related quality of life and functional outcomes in major depressive disorder: a

systematic review and meta-analysis. J Affect Disord. 2024;356:684–98.

9. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. Lancet. 2020;396(10265):1841–56.

10. Ballard ED, Wills K, Lally N, et al. Anhedonia as a clinical correlate of suicidal thoughts in clinical ketamine trials. J Affect Disord. 2017;18:195–200.

11. Ducasse D, Loas G, Dassa D, et al. Anhedonia is associated with suicidal ideation independently of depression: a meta-analysis. Depress Anxiety. 2018;35(5):382–92.

12. Gillissie ES, Le GH, Rhee TG, et al. Evaluating anhedonia as a risk factor in suicidality: a meta-analysis. J Psychiatr Res. 2023;158:209–15.

13. Dimick M, Hird M, Fiksenbaum LM, et al. Severe anhedonia among adolescents with bipolar disorder is common and associated with increased psychiatric symptom burden. J Psychiatr Res. 2021;134:200–7.

14. McIntyre RS. The co-occurrence of depression and obesity: implications for clinical practice and the discovery of targeted and precise mechanistically informed therapeutics. J Clin Psychiatry. 2024;85(2):24com15322.

15. Jawad MY, Meshkat S, Tabassum A, et al. The bidirectional association of nonalcoholic fatty liver disease with depression, bipolar disorder, and schizophrenia. CNS Spectr. 2023;28(5):541–60.

16. Di Nicola MR, Luisa, Battaglia C, Camardese G, et al. Reduced hedonic capacity in euthymic bipolar subjects: a trait-like feature? J Affect Disord. 2012;147(1–3):446–50.

17. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 2011;35(3):537–55.

18. Hoflich A, Michenthaler P, Kasper S, et al. Circuit mechanisms of reward, anhedonia, and depression. Int J Neuropsychopharmacol. 2019;22(2):105–18.

19. Pizzagalli DA. Toward a better understanding of the mechanisms and pathophysiology of anhedonia: are we ready for translation? Am J Psychiatry. 2022;179(7):458–69.

20. Guo CC-G, Verheij MMM, Homberg JR. Knockout of the serotonin transporter in the rat mildly modulates decisional anhedonia. Neuroscience. 2021;469:31–45.

21. Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. Trends Neurosci. 2012;35(1):68–77.

22. Pizzagalli DA. Depression, stress, and anhedonia: toward a synthesis and integrated model. Annu Rev Clin Psychol. 2014;10:393–423.

23. Baik J-H. Stress and the dopaminergic reward system. Exp Mol Med. 2020;52(12):1879–90.

24. Sokoloff P, Foll BL. The dopamine D3 receptor, a quarter century later. Eur J Neurosci. 2017;45(1):2–19.

25. Millan MJ, Brocco M, Papp M, et al. S32504, a novel naphtoxazine agonist at dopamine D3/D2 receptors: III. Actions in models of potential antidepressive and anxiolytic activity in comparison with ropinirole. J Pharmacol Exp Ther. 2004;309(3):936–50.

26. Willner P, Lappas S, Cheeta S, et al. Reversal of stress-induced anhedonia by the dopamine receptor agonist, pramipexole. Psychopharmacology. 1994;115(4):454–62.

27. Lemke MR, Brecht HM, Koester J, et al. Effects of the dopamine agonist pramipexole on depression, anhedonia and motor functioning in Parkinson's disease. J Neurol Sci. 2006;248(1–2):266–70.

28. Durgam S, Earley W, Lipschitz A, et al. An 8-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression. Am J Psychiatry. 2016;173(3):271–81.

29. Earley WR, Burgess MV, Khan B, et al. Efficacy and safety of cariprazine in bipolar I depression: a double-blind, placebo-controlled phase 3 study. Bipolar Disord. 2020;22(4):372–84.

30. Earley W, Burgess MV, Rekeda L, et al. Cariprazine treatment of bipolar depression: a randomized double-blind placebo-controlled phase 3 study. Am J Psychiatry. 2019;176(6):439–48.

31. Yatham LN, Vieta E, McIntyre RS, et al. Broad efficacy of cariprazine on depressive symptoms in bipolar disorder and the clinical implications. Prim Care Companion CNS Disord. 2020;22(5):24841.

32. Patel M, Jain R, Tohen M, et al. Efficacy of cariprazine in bipolar I depression across patient characteristics: a post hoc analysis of pooled randomized, placebo-controlled studies. Int Clin Psychopharmacol. 2021;36(2):76–83.

33. Duric V, Banasr M, Franklin T, et al. Cariprazine exhibits anxiolytic and dopamine D3 receptor-dependent antidepressant effects in the chronic

stress model. Int J Neuropsychopharmacol. 2017;20(10):788–96.

34. Papp M, Gruca P, Lasoń-Tyburkiewicz M, et al. Attenuation of anhedonia by cariprazine in the chronic mild stress model of depression. Behav Pharmacol. 2014;25(5–6):567–74.

35. Kiss B, Horváth A, Némethy Z, et al. Cariprazine (RGH-188), a dopamine D(3) receptor-preferring, D(3)/D(2) dopamine receptor antagonist-partial agonist antipsychotic candidate: in vitro and neurochemical profile. J Pharmacol Exp Ther. 2010;333(1):328–40.

36. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382–9.

37. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text revised. 2000.

38. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59(Suppl 20):20–33.

39. First MB, Williams JBW, Spitzer RL, et al. Structured clinical interview for DSM-IV-TR axis I disorders, clinical trials version (SCID-CT). New York: Biometrics Research, New York State Psychiatric Institute; 2007.

40. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32(1):50–5.

41. Guy W. ECDEU assessment manual for psychopharmacology. US Dept Health, Education, and Welfare Publication (ADM). Rockville: National Institute of Mental Health; 1976. p. 218–222.

42. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978;133:429–35.

43. Cao B, Park C, Subramaniapillai M, et al. The efficacy of vortioxetine on anhedonia in patients with major depressive disorder. Front Psychiatry. 2019;10:17. https://doi.org/10.3389/fpsyt.2019.00017.

44. Zheng W, Gu LM, Sun CH, et al. Comparative effectiveness of repeated ketamine infusions in treating anhedonia in bipolar and unipolar depression. J Affect Disord. 2022;300:109–13.

45. McIntyre RS, Christensen MC. Efficacy of vortioxetine on anhedonia: results from a pooled analysis of short-term studies in patients with major depressive disorder. Neuropsychiatr Dis Treat. 2021;17:575–85.

46. Franken IH, Rassin E, Muris P. The assessment of anhedonia in clinical and non-clinical populations: further validation of the Snaith-Hamilton Pleasure Scale (SHAPS). J Affect Disord. 2007;99(1–3):83–9.

47. Nakonezny PA, Carmody TJ, Morris DW, et al. Psychometric evaluation of the Snaith-Hamilton pleasure scale in adult outpatients with major depressive disorder. Int Clin Psychopharmacol. 2010;25(6):328–33.

48. Yatham LN, Vieta E, McIntyre RS, et al. Broad efficacy of cariprazine on depressive symptoms in bipolar disorder and the clinical implications. Prim Care Companion CNS Disord. 2020;22(5):20m02611.

49. Whitton AE, Kumar P, Treadway MT, et al. Distinct profiles of anhedonia and reward processing and their prospective associations with quality of life among individuals with mood disorders. Mol Psychiatry. 2023;28(12):5272–81.

50. Allen TA, Lam RW, Milev R, et al. Early change in reward and punishment sensitivity as a predictor of response to antidepressant treatment for major depressive disorder: a CAN-BIND-1 report. Psychol Med. 2019;49(10):1629–38.

51. McIntyre RS, Suppes T, Earley W, et al. Cariprazine efficacy in bipolar I depression with and without concurrent manic symptoms: post hoc analysis of 3 randomized, placebo-controlled studies. CNS Spectr. 2020;25(4):502–10.

52. McIntyre RS, Daniel DG, VIeta E, et al. The efficacy of cariprazine on cognition: a post hoc analysis from phase II/III clinical trials in bipolar mania, bipolar depression, and schizophrenia. CNS Spectr. 2023;28(3):319–30.

53. Jain R, McIntyre RS, Cutler AJ, et al. Efficacy of cariprazine in patients with bipolar depression and higher or lower levels of baseline anxiety: a pooled post hoc analysis. Int Clin Psychopharmacol. 2024;39(2):82–92.

54. Rizvi S, Lambert C, Kennedy S. Presentation and neurobiology of anhedonia in mood disorders: commonalities and distinctions. Curr Psychiatry Rep. 2018;20(2):13.

55. Vieta E, Calabrese JR, Whelan J, et al. The efficacy of cariprazine on function in patients with bipolar depression: a post hoc analysis of a randomized controlled trial. Curr Med Res Opin. 2021;37(9):1635–43.

56. Girgis RR, Slifstein M, D'Souza D, et al. Preferential binding to dopamine D3 over D2 receptors by cariprazine in patients with schizophrenia using PET with the D3/D2 receptor ligand [(11)C]-(+)-PHNO. Psychopharmacology. 2016;233(19–20):3503–12.

57. Németh G, Laszlovszky I, Czobor P, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. Lancet. 2017;389(10074):1103–13.

58. Schotte A, Janssen PF, Gommeren W, et al. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology. 1996;124(1–2):57–73.

59. Vraylar [package insert]. Madison, NJ: Allergan; 2022.

60. Earley W, Durgam S, Lu K, et al. Tolerability of cariprazine in the treatment of acute bipolar I mania: a pooled post hoc analysis of 3 phase II/III studies. J Affect Disord. 2017;215:205–12.

61. Earley W, Laszlovszky I, Debelle M, et al. Safety and tolerability of cariprazine in patients with acute exacerbation of schizophrenia: a pooled analysis of four phase II/III randomized, double-blind, placebo-controlled studies. Int Clin Psychopharmacol. 2017;32(6):319–28.

62. Thase ME, Yeung PP, Rekeda L, et al. Safety and tolerability of cariprazine for the adjunctive treatment of major depressive disorder: a pooled analysis of phase 2b/phase 3 clinical trials. Int Clin Psychopharmacol. 2024. https://doi.org/10.1097/YIC.0000000000000528.

63. Nakamura T, Kubota T, Iwakaji A, et al. Clinical pharmacology study of cariprazine (MP-214) in patients with schizophrenia (12-week treatment). Drug Des Devel Ther. 2016;10:327–38.