Neuropsychiatric Disease and Treatment

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

# Efficacy and Clinical Relevance of Adjunctive Cariprazine Treatment in Patients with Major Depressive Disorder: Post Hoc Analyses from a Phase III Study

George I Papakostas[1], Prakash S Masand[2], Anita H Clayton[3], Vladimir Maletic[4,†], Julie L Adams[5], Ludmyla Rekeda[6], Manpreet Kaur Singh[7], Majid Kerolous[8]

[1]Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA; [2]Academic Medicine Education Institute, Duke-NUS, Singapore, Singapore; [3]Department of Psychiatry & Neurobehavioral Sciences, University of Virginia School of Medicine, Charlottesville, VA, USA; [4]Department of Psychiatry and Behavioral Science, University of South Carolina School of Medicine, Greenville, SC, USA; [5]Global Development, Psychiatry, AbbVie, North Chicago, IL, USA; [6]Biostatistics, AbbVie, North Chicago, IL, USA; [7]Department of Psychiatry and Behavioral Sciences, UC Davis Medical Center, Sacramento, CA, USA; [8]Neuroscience Clinical Development, AbbVie, North Chicago, IL, USA

[†]Dr. Vladimir Maletic passed away on December 11, 2024

Correspondence: Majid Kerolous, Neuroscience Clinical Development, AbbVie, 1 N. Waukegan Road, North Chicago, IL, 60064, USA, Tel + 1 862 261 7425, Email majid.kerolous@abbvie.com



**Objective:** Efficacy analyses that go beyond the primary outcome of major depressive disorder (MDD) clinical trials and consider clinical relevance, response range, disease severity, and patient subpopulations may inform clinical decision-making. This post hoc analysis assessed clinically relevant outcomes associated with adjunctive cariprazine for MDD.

**Methods:** Data from a randomized controlled trial (NCT03738215) of cariprazine 1.5 or 3 mg/d + antidepressant therapy (ADT) versus placebo + ADT were analyzed. Change from baseline to week 6 in Montgomery–Åsberg Depression Rating Scale (MADRS) total score was assessed and number of patients achieving thresholds of MADRS response (≥5, ≥10, ≥15, ≥20, and ≥25 points) were determined. MADRS severity shifts were reported as the proportion of patients with no change or worsened severity, 1, ≥1, and ≥2 category improvements. Other efficacy characterizations included improvements in each MADRS item score and MADRS total score improvement across demographic-defined (age, sex, race) patient subgroups, baseline ADT response, and number of prior ADTs.

**Results:** More patients treated with adjunctive cariprazine versus placebo had MADRS total score improvements across all response thresholds and achieved ≥1 MADRS severity category improvement. Adjunctive cariprazine was associated with numerically greater improvements versus placebo in all individual MADRS items, with statistically significant improvements in 7/10 items. Adjunctive cariprazine was also associated with MADRS total score reductions, regardless of patient demographics, baseline ADT response, or number of prior ADTs.

**Conclusion:** Results suggest that adjunctive cariprazine provides clinically meaningful improvements in depressive symptoms, with efficacy ranging across individual depressive symptoms and in diverse subpopulations.

**Keywords:** cariprazine, atypical antipsychotics, major depressive disorder, post hoc analysis, full range of efficacy

## Introduction

Major depressive disorder (MDD) is characterized by a range of emotional, cognitive, and physical symptoms, including persistent sadness, loss of interest, difficulty concentrating, and changes in sleep.[1,2] As one of the most common mental illnesses, with an estimated lifetime prevalence of 20.6% in the United States,[3] MDD impacts individuals across all sexes, ages, and races. The diverse patient population and heterogeneity of MDD symptoms make a "one-size-fits-all" approach to treatment difficult.[4–6] Therefore, establishing the clinical relevance of efficacy across diverse patient

https://doi.org/10.2147/NDT.S561112
Received: 16 August 2025
Accepted: 12 March 2026
Published: 1 April 2026

populations is of significant clinical importance for MDD treatment. However, providing effective treatment remains a major clinical challenge, with only approximately one-third of patients achieving remission following initial antidepressant therapy (ADT).[7] Augmentation of ongoing ADT with atypical antipsychotic agents is an effective treatment approach for patients with MDD who have an inadequate response to ADT, as supported by the results of several meta-analyses.[8–11]

Although statistically significant mean treatment response vs placebo is a valuable indicator of efficacy in clinical trials, this measure alone may be difficult to interpret in clinical settings where outcomes are impacted by complexities such as symptom severity, concomitant treatment, and symptom heterogeneity. Alternative assessments, including measures of the range of responses at endpoint,[12] may be more relevant in clinical practice. For example, analysis of individual patient responses can aid clinicians' understanding of treatment nuance, as treatment associated with a seemingly small mean effect may still provide meaningful benefits to some patients. Categorical shifts in illness severity (eg, when illness improves from a more to a less severe category) are intuitive measures of well-being[13] and may help set treatment expectations for patients As some treatments may be more effective than others at improving certain symptoms,[9,14,15] identifying treatment effects on individual symptoms may help clinicians determine the most appropriate course of treatment.[14] When a treatment is used in conjunction with ADT, evaluating its efficacy in the context of ADT class, as well as a patient's prior ADT usage and response, may provide valuable insights. Information gleaned from alternative efficacy analyses can aid both clinicians and patients in identifying treatment strategies that may provide clinically meaningful benefits for patients with MDD.

Cariprazine is a dopamine $D_3$-preferring $D_3/D_2$ and serotonin 5-$HT_{1A}$ receptor partial agonist that is approved by the US Food and Drug Administration for the treatment of schizophrenia and manic, mixed, or depressive episodes of bipolar I disorder and as adjunctive treatment in MDD. The efficacy of cariprazine as an adjunctive treatment for adults with MDD was established in one phase 2b flexible-dose study[16] and one Phase 3 fixed-dose study;[17] in both studies, the primary efficacy outcome was change from baseline in Montgomery–Åsberg Depression Rating Scale (MADRS) total score.[18] In the flexible-dose study, significant differences in the primary outcome were demonstrated for cariprazine 2 to 4.5 mg/d + ADT versus placebo but not for cariprazine 1 to 2 mg/d + ADT.[16] In the fixed-dose study, significant differences in the primary outcome were demonstrated for cariprazine 1.5 mg/d + ADT versus placebo; numerical improvements in favor of cariprazine 3 mg/d + ADT were observed, but the differences did not achieve statistical significance.[17] In both MDD studies, cariprazine treatment was adjunctive to patients' ongoing ADT and was generally well tolerated. In addition, cariprazine demonstrated broad efficacy in reducing depressive symptoms across diverse patient demographics and characteristics in patients with bipolar I depression;[19] however, little is known regarding the efficacy of adjunctive cariprazine across diverse demographic groups in patients with MDD.

In order to assess the effects of adjunctive cariprazine on clinically meaningful patient outcomes beyond the primary endpoint, we conducted post hoc analyses of the positive phase 3 pivotal fixed-dose study to examine patient-level changes across the full range of MADRS total score response and the proportion of patients who experienced categorical shifts in disease severity. To evaluate the broad efficacy of adjunctive cariprazine, we examined improvements across individual depressive symptoms and assessed MADRS total score improvements in patient subgroups defined by demographics and ADT characteristics.

# Methods

## Study Design and Patients

Post hoc analyses were conducted using data from a positive, phase 3, fixed-dose, randomized, double-blind, placebo-controlled, parallel-group study (NCT03738215) of cariprazine as an adjunct to ADT in adults with MDD and inadequate response to ADT monotherapy. Detailed study methods were previously published.[17] In brief, the study included a washout of prohibited psychotropic medications during a 1- to 2-week screening period (with up to 7 additional days if needed), followed by 6 weeks of double-blind treatment and a 4-week safety follow-up period. During the double-blind treatment period, patients continued taking the same ADT at the same dosage they were taking at baseline; no study medication was taken during the 4-week safety follow-up period. Patients were randomized 1:1:1 to receive placebo +

ADT, cariprazine 1.5 mg/d + ADT, or cariprazine 3 mg/d + ADT. All patients treated with cariprazine were initiated at the 1.5 mg/d dose; patients in the 1.5 mg/d group remained at that dosage, while patients in the 3 mg/d group were up-titrated to 3 mg/d on day 15. The primary efficacy endpoint was change from baseline to week 6 in MADRS total score.[18] Included patients (18–65 years of age) met *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5)[2] criteria for MDD (per the Structured Clinical Interview for DSM-5) and had a current major depressive episode (MDE) of ≥8 weeks and <24 months' duration. A modified, clinician-rated version of the Antidepressant Treatment Response Questionnaire (ATRQ) assessed prior antidepressant exposure and response within the current MDE.[20] Eligible patients had inadequate response (<50% improvement) with 1 to 3 prior ADTs of adequate dose and duration (≥6 weeks at or above the minimum dosage per package insert, with ≥3 weeks at a dosage above the minimum). A complete list of ongoing ADTs used by patients in this study has been previously published.[17] Clinical inclusion criteria included a 17-item Hamilton Depression Rating Scale (HAMD 17)[21] total score ≥22 and an item 1 (depressed mood) score ≥2. Exclusion criteria were typical of clinical studies in MDD and included current manic episode (Young Mania Rating Scale score >12),[22] current psychiatric diagnoses other than MDD, substance use disorder (previous 3 months), suicide risk, or history of nonresponse to >3 antidepressant trials of adequate dose and duration of treatment (in current MDE).

## Post Hoc Analyses

The effects of cariprazine on depressive symptoms were evaluated in the modified intent-to-treat (mITT) population, consisting of all randomized participants who took ≥1 dose of study drug and had ≥1 postbaseline assessment of MADRS total score.

Full-range clinical improvement was determined by patient-level response, defined as the proportion of patients achieving increasing levels of MADRS total score improvement from baseline to week 6 (total score point reduction ≥5, ≥10, ≥15, ≥20, and ≥25) and analyzed using descriptive statistics. Missing values were imputed using the last observation carried forward. Clinically meaningful shifts in MADRS severity categories were also evaluated by examining the proportion of patients who shifted from one MADRS severity category (normal ≤6; mild = 7–19; moderate = 20–34; severe ≥35) to another. MADRS severity shifts were reported as no change or worsened severity, 1 category improvement, ≥1 category improvement, or ≥2 category improvement. For example, a 1 category improvement could be a shift from severe to moderate and a 2-category improvement could be a shift from severe to mild.

To investigate adjunctive cariprazine efficacy across different depressive symptoms, improvements in individual MADRS items were analyzed. The MADRS is composed of 10 items that assess apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts; each item is rated on a 0–6 scale for a total possible score of 0 to 60.[18] Least squares (LS) mean changes from baseline to week 6 in MADRS individual item scores were analyzed using a mixed-effects model for repeated measures (MMRM). The change from baseline to week 6 in MADRS total score was examined across diverse patient subgroups using MMRM. For demographic-defined subgroups, treatment effects of cariprazine 1.5 mg/d or 3 mg/d + ADT versus placebo + ADT were determined using point estimates (95% CI) of treatment differences across patient subgroups stratified by age, race, or sex. Two subgroups, White and non-White (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, or multiple races), were used for stratification by patient-reported race. For stratification based on ADT response at baseline, patients were stratified into 2 subgroups: those who had ≥25% to <50% response or those who had <25% response to ADT, as measured by a modified, clinician-rated version of ATRQ.[20] For subjects with multiple observations of previous ADT response (n = 22), only the highest response level was selected. Patients were also stratified into subgroups defined by the number of prior inadequate responses to ADT in the current depressive episode. Mean change from baseline to end of week 6 in MADRS total score was examined in subgroups of patients stratified according to the class of their ongoing ADT (selective serotonin reuptake inhibitor [SSRI], which included vilazodone and vortioxetine, which are serotonin reuptake inhibitors with other serotonin receptor effects; serotonin norepinephrine reuptake inhibitor [SNRI]; dopamine norepinephrine reuptake inhibitor [DNRI]; or tricyclic antidepressant [TCA]); these data were analyzed using descriptive statistics.

## Results

A total of 751 patients were included in the mITT population (placebo + ADT = 249; cariprazine 1.5 mg/d + ADT = 250; cariprazine 3 mg + ADT = 252). Demographic and baseline characteristics are presented in Table 1. Baseline demographics were generally similar across the adjunctive cariprazine and adjunctive placebo arms. Most patients were female (73.4%); the mean patient age was between 43.2 and 46.5 years. The majority of patients were White (82.3%), followed by Black or African American (14.5%), Asian (2.1%), Native Hawaiian or Other Pacific Islander (0.5%), American Indian or Alaska Native (0.3%), or multiple races (0.3%). Per study design, all patients had ≥1 prior ADT failure; the number of prior ADT failures was similar across treatment groups, with most patients (~85%) having failed 1 prior ADT. MADRS total score at baseline was also similar across treatment groups (placebo + ADT = 31.9; cariprazine 1.5 mg/d + ADT = 32.8; cariprazine 3 mg/d + ADT = 32.7).

The primary efficacy measure, change from baseline to week 6 in MADRS total score, was statistically significant in favor of cariprazine 1.5 mg/d + ADT versus placebo + ADT (LS mean change from baseline to week 6: cariprazine 1.5 mg/d + ADT = −14.1; placebo + ADT = −11.5; $P<0.01$). For cariprazine 3 mg/d + ADT-treated patients, the LS mean change from baseline in MADRS total score was numerically greater than for placebo + ADT-treated patients (cariprazine 3 mg/d + ADT = −13.1; placebo + ADT = −11.5); however, the difference was not statistically significant.

### Full Range of MADRS Clinical Improvement with Adjunctive Cariprazine

Compared with patients treated with adjunctive placebo, a greater proportion of patients treated with adjunctive cariprazine 1.5 or 3 mg/d had MADRS total score improvements of ≥5, ≥10, ≥15, and ≥20 points from baseline to week 6; a greater proportion of patients treated with cariprazine 1.5 mg/d + ADT than patients treated with placebo + ADT improved by ≥25 points (Figure 1). A smaller proportion of adjunctive cariprazine-treated patients worsened or had no change in MADRS total score relative to adjunctive placebo-treated patients (placebo + ADT = 8%; cariprazine + ADT: 1.5 mg/d = 4%, 3 mg/d = 5%). Nearly half of patients treated with cariprazine 1.5 mg/d + ADT and 43% of patients treated with cariprazine 3 mg/d + ADT improved by ≥15 points on the MADRS total score. Further, one-third of patients who received adjunctive cariprazine 1.5 mg/d experienced an improvement of ≥20 points from baseline in MADRS total score.

### MADRS Severity Shifts

At baseline, the majority of patients (64%) had moderate MDD; 35% had severe and 1.5% had mild MDD. A smaller proportion of patients treated with cariprazine + ADT (1.5 mg/d = 32%; 3 mg/d = 33%) compared with patients treated with placebo + ADT (41%) did not improve or worsened in MADRS severity category (Figure 2A). A larger proportion

**Table 1** Demographic and Baseline Characteristics (Modified ITT Population)

| Baseline Characteristic | Placebo + ADT (n = 249) | CAR 1.5 mg/d + ADT (n = 250) | CAR 3 mg/d + ADT (n = 252) | Overall (N = 751) |
|---|---|---|---|---|
| Sex, n (%) | | | | |
| Male | 68 (27.3) | 60 (24.0) | 72 (28.6) | 200 (26.6) |
| Female | 181 (72.7) | 190 (76.0) | 180 (71.4) | 551 (73.4) |
| Race, n (%) | | | | |
| American Indian or Alaska Native | 1 (0.4) | 1 (0.4) | 0 | 2 (0.3) |
| Asian | 5 (2.0) | 4 (1.6) | 7 (2.8) | 16 (2.1) |
| Black or African American | 42 (16.9) | 37 (14.8) | 30 (11.9) | 109 (14.5) |
| Multiple | 0 | 2 (0.8) | 0 | 2 (0.3) |
| Native Hawaiian or Other Pacific Islander | 1 (0.4) | 3 (1.2) | 0 | 4 (0.5) |
| White | 200 (80.3) | 203 (81.2) | 215 (85.3) | 618 (82.3) |
| Age, mean (SD), y | 46.5 (11.9) | 43.2 (13.6) | 44.8 (13.3) | 44.8 (13.0) |
| Weight, mean (SD), kg | 86.4 (24.1) | 85.3 (22.7) | 82.0 (21.1) | 84.6 (22.7) |
| MADRS total score, mean (SD) | 31.9 (5.7) | 32.8 (5.0) | 32.7 (4.9) | 32.5 (5.2) |

**Abbreviations**: ADT, antidepressant therapy; CAR, cariprazine; ITT, intent to treat; MADRS, Montgomery–Åsberg Depression Rating Scale.

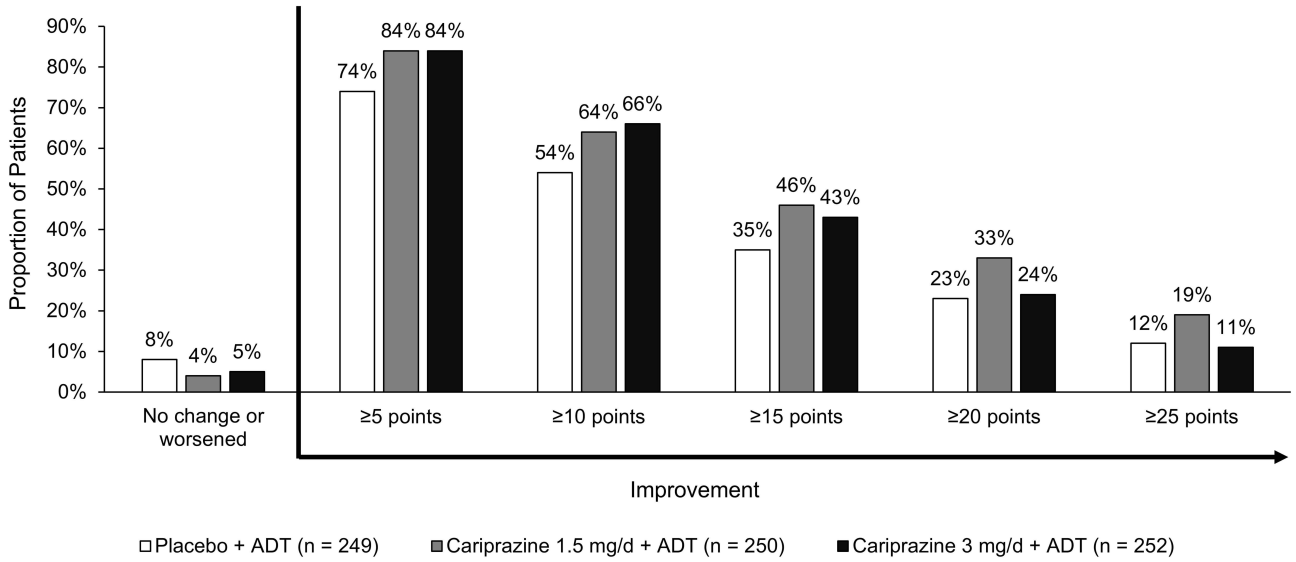


**Figure 1** Patient-Level Response: Full Range of MADRS Score Improvement at End of Week 6.
**Abbreviations**: ADT, antidepressant therapy; MADRS, Montgomery–Åsberg Depression Rating Scale.

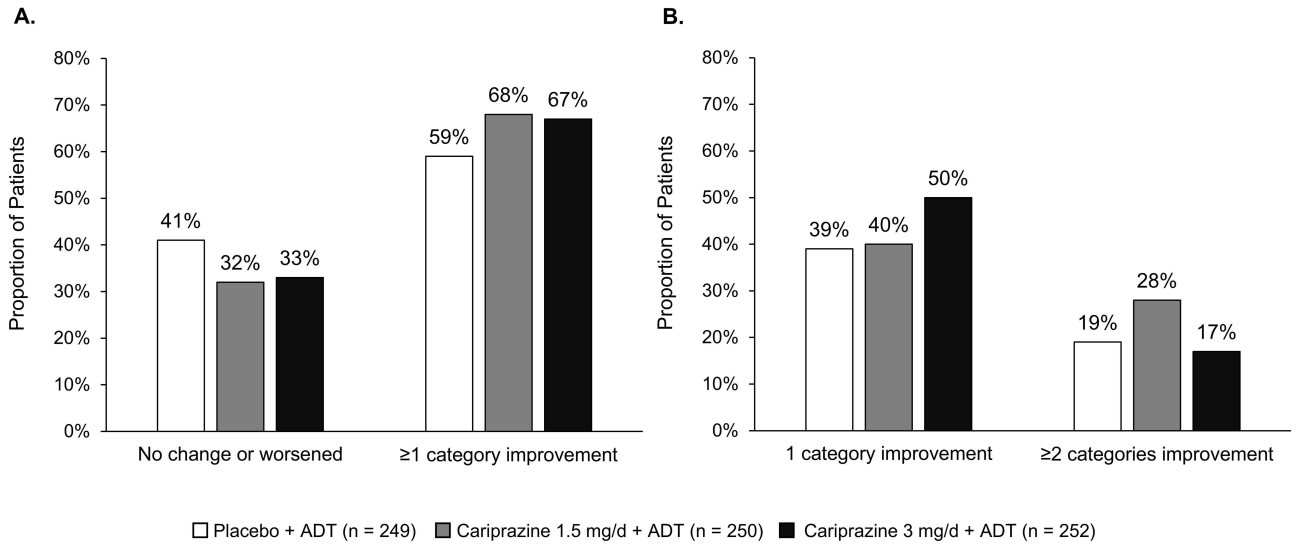


**Figure 2** MADRS Severity Category Shifts From Baseline to Week 6. (**A**) Proportion of patients with no change or worsened in MADRS severity category or with improved MADRS severity category. (**B**) Proportion of patients with MADRS severity improvements of 1 category or ≥2 categories.
**Abbreviations**: ADT, antidepressant therapy; MADRS, Montgomery–Åsberg Depression Rating Scale.

of patients treated with cariprazine + ADT (1.5 mg/d = 68%, 3 mg/d = 67%) versus placebo + ADT (59%) improved by ≥1 MADRS severity category. Half of the patients treated with cariprazine 3 mg/d + ADT improved by 1 MADRS severity category; 40% of cariprazine 1.5 mg/d + ADT-treated patients and 39% of placebo + ADT-treated patients improved by 1 category (Figure 2B). A larger proportion of patients treated with cariprazine 1.5 mg/d + ADT (28%) than cariprazine 3 mg/d + ADT (17%) and placebo + ADT (19%) improved by ≥2 MADRS severity categories.

## MADRS Individual Items

Baseline scores on individual MADRS items were similar across placebo + ADT and cariprazine + ADT treatment groups (Table 2). Examination of LS mean change from baseline to week 6 on individual MADRS items revealed that treatment with cariprazine 1.5 mg/d + ADT was associated with significantly greater reduction from baseline versus


https://doi.org/10.2147/NDT.S561112

**Table 2** Baseline Individual MADRS Scores (Modified ITT Population)

| Individual MADRS Items Scores, Mean (SD) | Placebo + ADT (n = 249) | CAR 1.5 mg/d + ADT (n = 250) | CAR 3 mg/d + ADT (n = 252) |
|---|---|---|---|
| Apparent sadness | 3.9 (0.85) | 3.9 (0.77) | 3.9 (0.84) |
| Reported sadness | 4.0 (0.75) | 4.2 (0.67) | 4.1 (0.70) |
| Inner tension | 3.1 (0.96) | 3.2 (1.01) | 3.3 (1.00) |
| Reduced sleep | 3.8 (1.11) | 3.9 (1.07) | 3.8 (1.04) |
| Reduced appetite | 2.4 (1.61) | 2.6 (1.64) | 2.6 (1.67) |
| Concentration difficulties | 3.7 (1.00) | 3.7 (0.90) | 3.8 (0.97) |
| Lassitude (lack of energy) | 3.8 (0.94) | 3.9 (0.91) | 4.0 (0.79) |
| Inability to feel | 3.7 (1.00) | 3.7 (0.89) | 3.7 (0.79) |
| Pessimistic thoughts | 2.9 (1.16) | 2.9 (1.21) | 2.9 (1.14) |
| Suicidal thoughts | 0.6 (0.78) | 0.7 (0.92) | 0.7 (0.85) |

**Abbreviations**: ADT, antidepressant therapy; CAR, cariprazine; ITT, intent to treat; MADRS, Montgomery-Åsberg Depression Rating Scale.

placebo + ADT on 7 items: apparent sadness, reported sadness, reduced appetite, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts (Figure 3). The improvement from baseline was also statistically significant in favor of cariprazine 3 mg/d + ADT versus placebo + ADT on 3 items: reported sadness, reduced appetite, and lassitude (Figure 3).

## Adjunctive Cariprazine Efficacy Across Demographic-Defined Patient Subgroups

Change from baseline to week 6 in MADRS total score was examined across patient subgroups defined by age (<55 years old: 1.5 mg/d, n = 174; 3 mg/d, n = 155; placebo, n = 159; ≥55 years old: 1.5 mg/d, n = 57; 3 mg/d, n = 68; placebo, n = 72), sex (female: 1.5 mg/d, n = 178; 3 mg/d, n = 161; placebo, n = 166; male: 1.5 mg/d, n = 53; 3 mg/d, n = 62; placebo, n = 65), or race (White: 1.5 mg/d, n = 188; 3 mg/d, n = 190; placebo, n = 185; non-White: 1.5 mg/d, n = 43; 3 mg/d, n = 33; placebo, n = 46). Overall, patients treated with adjunctive cariprazine had reductions in depressive symptoms, regardless of age, sex, or race (Figure 4). In general, trends seen in the total population were also similar across patient subgroups, with numerically larger effects for cariprazine 1.5 mg/d + ADT relative to 3 mg/d + ADT. Among patients treated with cariprazine 1.5 mg/d + ADT, the point estimates (95% CI) of treatment difference vs placebo in the <55

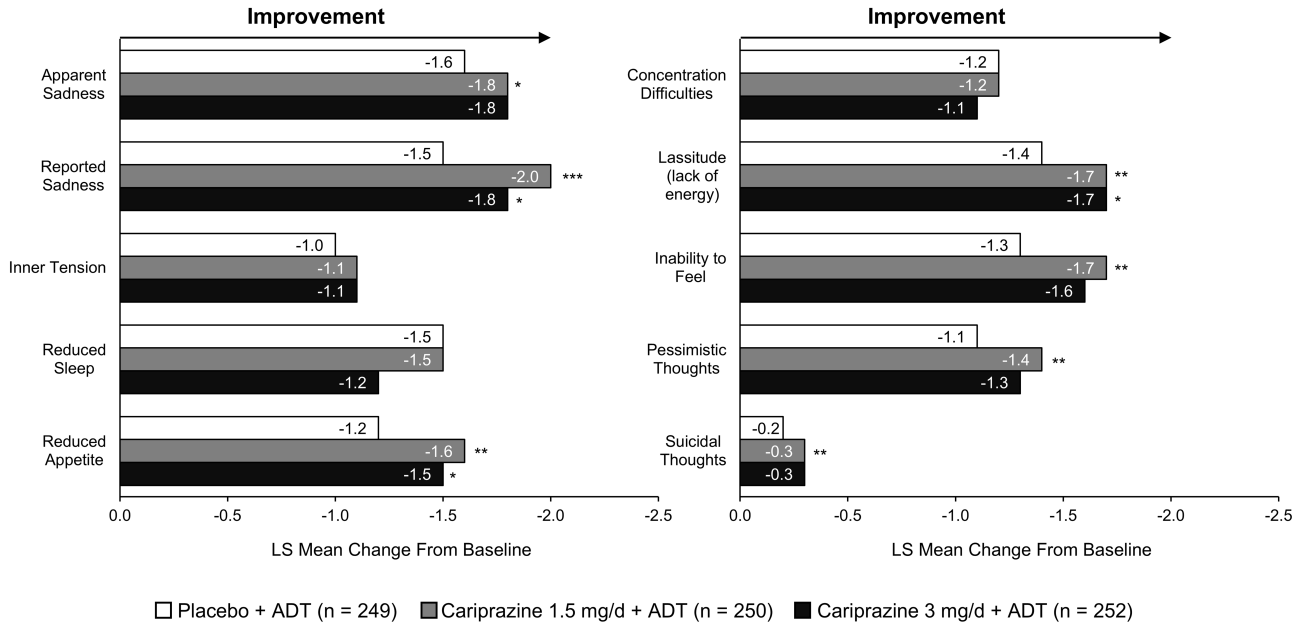


**Figure 3** Change From Baseline to the End of Week 6 in MADRS Individual Item Scores. *$P$<0.05, **$P$<0.01, ***$P$<0.001 vs placebo + ADT.
**Abbreviations**: ADT, antidepressant therapy; LS, least squares; MADRS, Montgomery–Åsberg Depression Rating Scale.


https://doi.org/10.2147/NDT.S561112

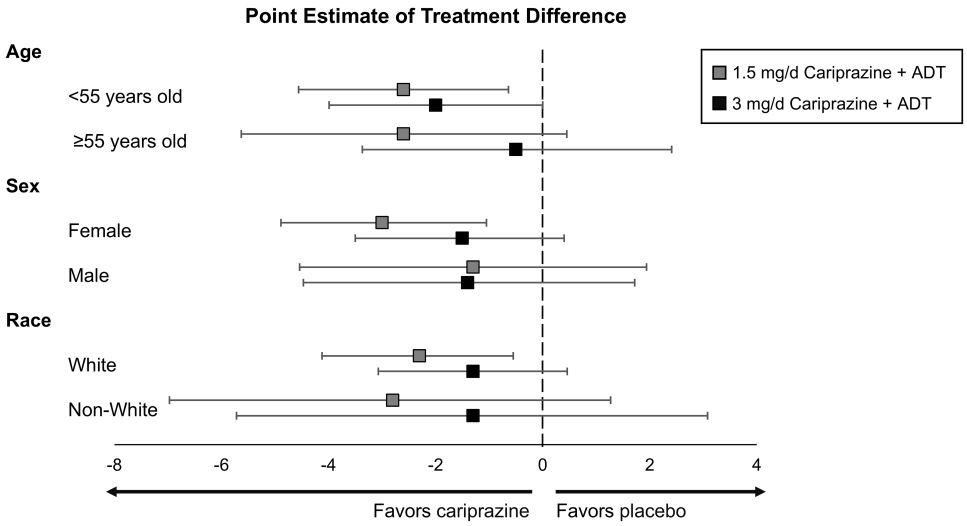


**Figure 4** Adjunctive Cariprazine Treatment Effects on Change from Baseline to Week 6 in MADRS Total Score by Patient Demographics.
**Abbreviations**: ADT, antidepressant therapy; MADRS, Montgomery–Åsberg Depression Rating Scale.

years old (−2.6 [−4.6, −0.6]) and ≥55 years old (−2.6 [−5.6, 0.5]) subgroups were similar. Patients in the <55 years old subgroup treated with cariprazine 3 mg/d + ADT had numerically larger treatment effects relative to patients in the ≥55 years old subgroup (−2.0 [−4.0, 0.0] vs −0.5 [−3.4, 2.4]). In male patients, similar treatment effects were observed in the 1.5 mg/d + ADT (−1.3 [−4.5, 1.9]) and 3 mg/d + ADT (−1.4 [−4.5, 1.7]) treatment groups. A numerically larger treatment effect was seen in female patients treated with cariprazine 1.5 mg/d + ADT (−3.0 [−4.9, −1.1]) relative to those treated with cariprazine 3 mg/d + ADT (−1.5 [−3.5, 0.4]). Among patients treated with cariprazine 1.5 mg/d + ADT, treatment effects were numerically larger in the non-White patient subgroup (−2.8 [−7.0, 1.3]) compared with the White patient subgroup (−2.3 [−4.1, −0.6]), though there was a large amount of variability, likely due to the small sample size. Similar treatment effects were observed in the White (−1.3 [−3.1, 0.5]) and non-White patient subgroups (−1.3 [−5.7, 3.1]) in patients treated with cariprazine 3 mg/d + ADT.

## Adjunctive Cariprazine Efficacy Across ADT-Defined Patient Subgroups

At baseline, 34.9% of patients (n = 261) had an ADT response level <25% and 65.1% of patients (n = 486) had an ADT response level ≥25% to <50%. LS mean reductions in MADRS total score were numerically greater for adjunctive cariprazine treatment compared with adjunctive placebo treatment in subgroups of patients with <25% and ≥25% to <50% baseline ADT response levels (Figure 5). In patients who had an ADT baseline response level ≥25% to <50%, the difference in MADRS improvement between cariprazine 1.5 mg/d + ADT and placebo + ADT treatment was statistically significant (LS mean difference [LSMD] [95% CI], −2.3 [−4.2, −0.3]) in favor of adjunctive cariprazine, while the 3 mg/d + ADT group had greater improvement compared with placebo + ADT, though the difference failed to reach significance. Among patients who had an ADT baseline response level <25%, those treated with either cariprazine 1.5 or 3 mg/d + ADT had a numerically greater reduction in LS mean MADRS total score compared with patients treated with placebo + ADT.

During the current MDD episode, most patients (86.0%, n = 644) had an inadequate response to 1 previous ADT, and 14.0% (n = 105) of patients had an inadequate response to 2 or 3 previous ADTs. Patients treated with cariprazine 1.5 mg/d + ADT had numerically greater improvements in MADRS total score compared with those treated with placebo + ADT, regardless of whether they had an inadequate response to 1 or 2 to 3 previous ADTs (Figure 6). In patients treated with cariprazine 1.5 mg/d + ADT with an inadequate response to 1 ADT, the LSMD [95% CI] vs placebo was statistically significant (−2.3 [−4.1, −0.6]); however, in patients with inadequate responses to 2 to 3 previous ADTs treated with cariprazine 1.5 mg/d + ADT, the effect of treatment did not reach statistical significance, despite a large LSMD [95% CI] vs placebo (−3.2 [−7.1, 0.8]). Patients treated with cariprazine 3 mg/d + ADT in both previous ADT-defined patient

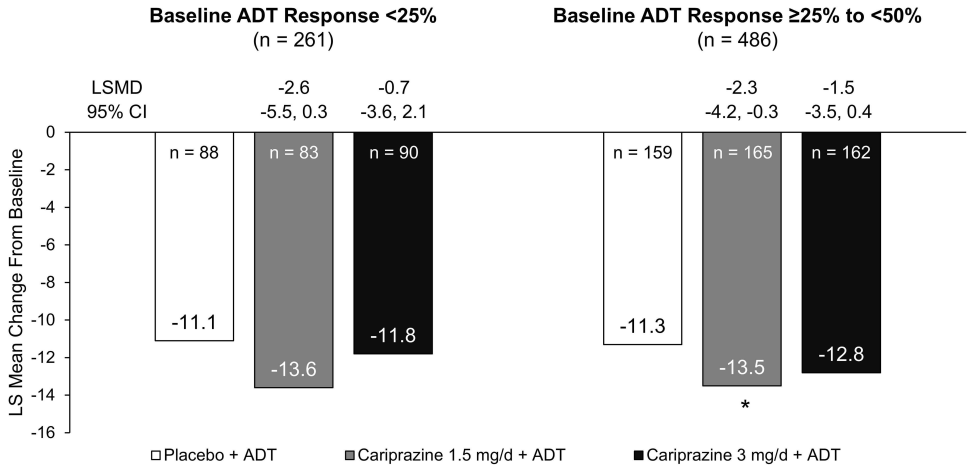


**Figure 5** Change From Baseline to the End of Week 6 in MADRS Total Score by Baseline ADT Response[a]. *95% CI for LSMD did not cross 0. [a]Two patients had baseline ADT responses >50% and were not included in the analysis.
**Abbreviations**: ADT, antidepressant therapy; LS, least squares; LSMD, LS mean difference; MADRS, Montgomery–Åsberg Depression Rating Scale.

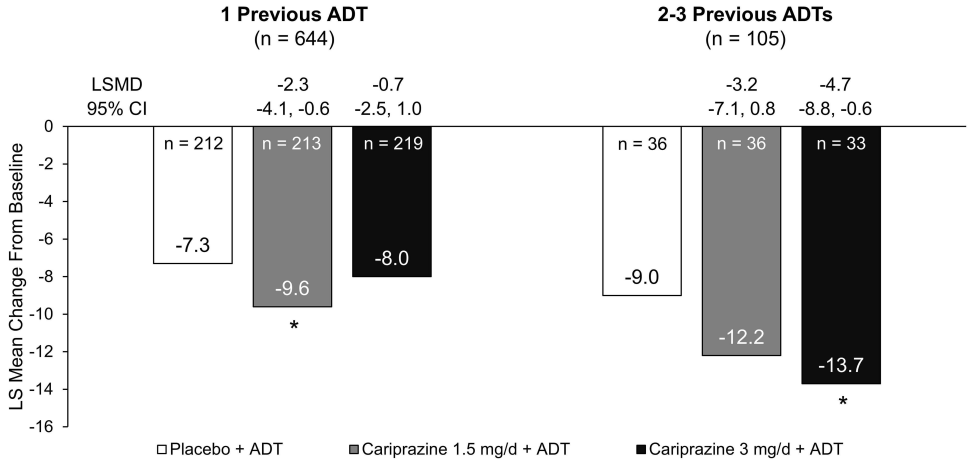


**Figure 6** Change From Baseline to the End of Week 6 in MADRS Total Score by Number of Previous ADTs in Current Episode[a]. *95% CI for LSMD did not cross 0. [a]Two patients were missing baseline ADT data and were not included in the analysis.
**Abbreviations**: ADT, antidepressant therapy; LS, least squares; LSMD, LS mean difference; MADRS, Montgomery–Åsberg Depression Rating Scale.

subgroups had numerically greater MADRS total score improvements compared with those treated with placebo + ADT (Figure 6). Though the LSMD [95% CI] vs placebo in patients with an inadequate response to 1 ADT was modest and did not reach statistical significance for the cariprazine 3 mg/d + ADT group (−0.7 [−2.5, 1.0]), improvement in patients with an inadequate response to 2 to 3 ADTs was statistically significant in favor of cariprazine 3 mg/d + ADT (−4.7 [−8.8, −0.6]).

Trends in MADRS total score improvements from baseline to week 6 were similar in patients who had an SSRI, SNRI, DNRI, or TCA as their ongoing concomitant ADT (Supplemental Figure 1).

## Discussion

This post hoc analysis of data from a fixed-dose study of adjunctive cariprazine in patients with MDD and inadequate response to ongoing ADT expanded characterization of adjunctive cariprazine efficacy. In patients treated with adjunctive cariprazine, MADRS total score improvements were observed across varying response-level thresholds, and most patients improved by at least 1 MADRS severity category. Improvements were seen across a range of depressive symptoms and across multiple patient demographic subgroups. Collectively, these results support the importance of

examining outcomes beyond the primary endpoint to evaluate the benefit of treatment and suggest that adjunctive cariprazine is associated with clinically relevant improvements in depressive symptoms.

Although a significant difference in mean change on a rating scale measure is the most common way efficacy versus placebo is measured for a drug in a clinical trial, this outcome alone may not capture change that is clinically meaningful; for example, small mean changes could still represent meaningful improvement for patients with MDD who experience severe illness or previous treatment nonresponse.[7] In the primary study, statistically significant differences versus placebo were only observed for adjunctive cariprazine 1.5 mg/d on the protocol-defined primary efficacy measure; however, in post hoc analysis, patient-level response with adjunctive cariprazine 3 mg/d was comparable to that of adjunctive cariprazine 1.5 mg/d, with similar proportions of patients in both dosage groups experiencing improvements of ≥5, ≥10, and ≥15 points in MADRS total score from baseline. Of note, over 40% of patients in the 3 mg/d group experienced at least a 15-point improvement in MADRS total score, a magnitude of change that could be considered relevant to patient well-being. To put these findings into context, in prior analyses, an improvement of 7 to 9 points in MADRS total score was considered minimally improved in patients with MDD,[23] a 6-point change was a clinically meaningful improvement,[24] and a 12-point change was a clinically substantial improvement in patients with prior inadequate responses to ADTs,[24] suggesting that adjunctive cariprazine treatment likely resulted in clinically meaningful improvements in depressive symptoms for some patients.

Because increased MDD severity is associated with cardiovascular comorbidities, changes in sleep, and functional disability,[25–28] reducing disease severity is an important treatment goal. A larger proportion of patients treated with adjunctive cariprazine relative to adjunctive placebo improved by ≥1 MADRS severity category, and fewer patients treated with adjunctive cariprazine experienced no change or worsened disease severity. Moreover, a larger proportion of patients treated with adjunctive cariprazine 1.5 mg/d versus adjunctive placebo improved by ≥2 severity categories. These results are particularly noteworthy given that most patients had moderate or severe disease severity at baseline. This analysis may provide clinicians with a more intuitive evaluation of MDD severity improvement than mean change in total MADRS score.[13]

Individual depressive symptoms, as assessed by MADRS, can be grouped into 3 principal components that relate to distinct aspects and neurochemical disturbances associated with MDD: dysphoria, which includes pessimistic thoughts, suicidal thoughts, and reported sadness; retardation, which includes lassitude, inability to feel, concentration difficulties and apparent sadness; and vegetative symptoms, which includes reduced sleep, reduced appetite, and inner tension.[29] Treatment with adjunctive cariprazine 1.5 mg/d was associated with broad efficacy across a range of symptoms, with statistically significant improvements vs placebo on 7 items: apparent sadness, reported sadness, reduced appetite, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. In addition, both adjunctive cariprazine dosages were associated with significant improvement in at least 1 symptom from each of the 3 MADRS principal components, highlighting the effectiveness of adjunctive cariprazine in providing meaningful relief to patients experiencing depressive symptoms that encompass the full range of MDD pathology. These results are consistent with previous findings demonstrating the efficacy of adjunctive cariprazine in treating a broad spectrum of symptoms associated with MDD, including difficult-to-treat symptoms that contribute to functional impairment, such as anhedonia[30] and anxiety.[17,31] Together, these findings provide clinically useful efficacy assessments of adjunctive cariprazine treatment and underscore the importance of examining treatment effects across a range of symptoms.

Post hoc analyses across demographic-defined patient subgroups suggest that adjunctive cariprazine may be associated with depressive symptom improvements, regardless of age, sex, or race. Overall, treatment effects were similar across demographic subgroups but did vary based on adjunctive cariprazine dosage. In most cases, treatment effects were larger with adjunctive cariprazine 1.5 mg/d versus 3 mg/d, mirroring trends observed in the overall patient population. Generally, similar treatment effects were seen in the White and non-White patient subgroups, though data were variable, likely due to the small sample size of non-White patient subgroup. Finding relatively similar treatment effects in the White and non-White patient subgroups is particularly promising given the racial disparities present in nearly all aspects of MDD, including symptom severity and treatment response.[32,33] Together, results suggest that adjunctive cariprazine may reduce depressive symptoms across a spectrum of patients with MDD; however, future studies examining efficacy across patient demographics in larger patient populations are needed to draw definitive conclusions.

For patients with a partial but inadequate response to ADT, augmenting treatment may have advantages over switching (eg, additive benefit to ADT); however, little is known about how prior ADT use or baseline ADT response might impact adjunctive treatment efficacy[7,34] In this study, patients with partial but inadequate response to baseline ADT (≥25% to <50%) treated with adjunctive cariprazine 1.5 mg/d saw significant improvement in depressive symptoms. Patients with ≥25% to <50% ADT response at baseline treated with adjunctive cariprazine 3 mg/d also saw reduced depressive symptoms, as did patients with <25% baseline ADT response treated with adjunctive cariprazine, though the difference versus adjunctive placebo failed to reach statistical significance for these comparisons. Adjunctive cariprazine was generally associated with reduced depressive symptom severity, regardless of the number of prior inadequate responses to ADTs. Of note, the largest symptom improvement was seen with adjunctive cariprazine 3 mg/d among patients who had inadequate responses to multiple ADTs, suggesting that higher cariprazine dosages may benefit some difficult-to-treat patient subpopulations, though the small sample size should be considered when interpreting results. These findings suggest cariprazine may have broad efficacy as an adjunctive treatment in patients with MDD and inadequate response to ADT, regardless of baseline ADT response level or number of prior inadequate ADT responses.

Any measures of a treatment's efficacy should be considered within the context of its safety and tolerability. While these study findings suggest adjunctive cariprazine 3 mg/d may provide clinically meaningful improvements for some patients, this treatment group experienced higher rates of study discontinuation due to adverse events compared with adjunctive cariprazine 1.5 mg/d and placebo treatment groups, though rates were still relatively low (7.1%).[17] In the overall safety population, the most common adverse events occurring in ≥5% of patients in either adjunctive cariprazine treatment group and twice the rate of placebo were akathisia (1.5 mg/d, 5.2%; 3 mg/d, 7.9%; placebo, 0.8%) and nausea (1.5 mg/d, 7.9%; 3 mg/d, 6.3%; placebo, 2.4%).[17] Nearly all treatment-emergent adverse events were mild or moderate in severity, and overall safety outcomes were consistent with the established safety profile of cariprazine.[17] Moreover, a previous analysis assessing the number needed to treat/harm for adjunctive cariprazine treatment in patients with MDD found that cariprazine has a favorable risk/benefit ratio.[35]

Findings should be interpreted within the context of the limitations of both the primary study and post hoc analyses. The primary study was too short to enable inferences about the longer-term impact of adjunctive cariprazine treatment in MDD. Future open-label and real-world or comparative effectiveness studies can build upon the granularity of the short-term effects described here. The primary study did not include an active comparator to inform comparative effectiveness or clinical guidelines for sequencing of treatment. The strict inclusion and exclusion criteria may limit the generalizability to other patient populations. Most participants had only 1 previous ADT failure, so results may not be generalizable to patients with several previous ADT failures. The relatively smaller subgroup sample sizes should be considered when drawing conclusions based on efficacy measures across patient subpopulations. As the primary study consisted of mostly White patients, only 2 subgroups were used to stratify patients across racial demographics; future studies are needed to examine adjunctive cariprazine in patients across multiple individual racial subgroups. Analyses were post hoc and did not adjust for multiple comparisons. Finally, while results suggest that some patients may have achieved clinically meaningful benefit from treatment with adjunctive cariprazine 3 mg/d, findings should be interpreted with caution as this treatment group did not meet the primary efficacy endpoint.

## Conclusion

In summary, our analyses provide a detailed picture of the clinical relevance and practice utility of adjunctive cariprazine for the treatment of depressive symptoms in patients with MDD. Compared with the adjunctive placebo group, the adjunctive cariprazine 1.5 mg and 3 mg/d groups had a larger proportion of patients who experienced potentially clinically meaningful improvements in MADRS total score and MDD severity. Adjunctive cariprazine treatment demonstrated efficacy across multiple individual depressive symptoms and was generally associated with symptomatic improvement regardless of a patient's demographics, baseline ADT response, ADT history, or class of ongoing ADT. Our findings suggest that adjunctive cariprazine is an effective and clinically meaningful treatment option for patients with MDD who have an inadequate response to ADT alone and highlight the value of assessing patient response through a variety of analyses.

## Previous Presentations

Presented at the Neuroscience Education Institute (NEI) Congress, November 3-6, 2022; the Psych Congress, September 17-20, 2022; the Psych Congress, September 6-10, 2023.

## Data Sharing Statement

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 (eg, 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 from AbbVie 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/.

## Ethics Approval and Consent

The original study (NCT03738215) was approved by institutional review boards (U.S. sites) or ethics committees and government agencies (European sites) listed in Supplemental Table 1 and performed in accordance with the International Conference on Harmonization Good Clinical Practice guideline and the Declaration of Helsinki. All participants provided written informed consent prior to study initiation.

## Acknowledgments

Medical writing support was provided by Lacy Goode, PhD, from Citrus Health Group, Inc. (Chicago, Illinois) and was funded by AbbVie (North Chicago, Illinois).

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. No honoraria or payments were made for authorship.

## Disclosure

G.I. Papakostas has served as a consultant for Abbott, Alkermes, AstraZeneca, Avanir, BrainsWay, Bristol Myers Squibb, Cephalon, Dey Pharma, Eli Lilly, Evotec, GlaxoSmithKline, Inflabloc Pharmaceuticals, Jazz, Lundbeck, Methylation Sciences, Novartis, Otsuka, Pamlab, Pfizer, Pierre Fabre Laboratories, Ridge Diagnostics (formerly Precision Human Biolaboratories), Shire, Sunovion, Takeda, Theracos, and Wyeth; on behalf of Massachusetts General Hospital, he has served as a consultant for Acadia, Alphasigma USA, Axsome Therapeutics, Boston Pharmaceuticals, Cala Health, Genentech, Genomind, Janssen Global Services, Johnson & Johnson, Mylan, One Carbon Therapeutics, Osmotica Pharmaceutical, Sage, and Taisho; he has received honoraria for lectures or consultancy from Abbott, Acadia, Alkermes, Alphasigma USA, Asopharma America Central Y Caribe, AstraZeneca, Avanir, Bristol-Myers Squibb, BrainsWay, Cephalon, Dey Pharma, Eli Lilly, Evotec, Forest, GlaxoSmithKline, Inflabloc Pharmaceuticals, Grunbiotics, Hypera, Jazz, Lundbeck, Medichem Pharmaceuticals, Meiji Seika Pharma, Novartis, Otsuka, Pamlab,

Pfizer, Pharma Trade SAS, Pierre Fabre Laboratories, Ridge Diagnostics, Shire, Sunovion, Takeda, Theracos, Titan Pharmaceuticals, and Wyeth; he has received research support (paid to hospital) from AstraZeneca, Bristol Myers Squibb, Cala Health, Forest, NIMH, Mylan, Neuralstem, Pamlab, the Patient-Centered Outcomes Research Institute, Pfizer, Johnson & Johnson, Ridge Diagnostics, Sunovion, Tal Medical, and Theracos; and he has served on the speakers bureaus for Bristol-Myers Squibb and Pfizer. P.S. Masand has served as a consultant for AbbVie, Intra-Cellular Therapies, Karuna Therapeutics, Neumora Therapeutics, and Neurocrine Biosciences; has served on speaker's bureaus for AbbVie, Bristol Myers Squibb, Neurocrine Biosciences, and Vanda Pharmaceuticals; and has stock ownership in Relmada Therapeutics. A.H. Clayton reports research and grant support from Janssen; Neumora Therapeutics; Neurocrine Biosciences; Otsuka; Relmada Therapeutics, Inc.; Reunion Neuroscience, Inc.; and S1 Biopharma; consultant or advisory board fees from AbbVie, Inc.; ACCUMIN; Actinogen; AdhereTech; Axsome Therapeutics; Biogen, Inc.; Initiator Pharma; Intra-cellular Therapies; Janssen Research & Development, LLC; LIVANOVA PLC; MycoMedica Life Sciences, PBC; Neumora Therapeutics, Inc.; Neurocrine Biosciences; P/S/L Group Services; Reunion Neuroscience, Inc.; Seaport Therapeutics; S1 Biopharma; Sirtsei Pharmaceuticals, Inc.; and Vella Bioscience, Inc.; shares/restricted stock units of Mediflix LLC and S1 Biopharma, Inc.; and royalties or copyrights from Ballantine Books/Random House, Changes in Sexual Functioning Questionnaire, and Guilford Publications. V. Maletic received speaking/consulting fees from: AbbVie/Allergan, Acadia Pharmaceuticals, Inc., Alfasigma, USA, Inc., Alkermes, Inc., Biogen, Boehringer Ingelheim, Cerevel Therapeutics, LLC, Corium, Intra-Cellular Therapies, Ironshore, Janssen, LivaNova, Lundbeck A/S, Jazz Pharmaceuticals, Neurelis, Neumora, Noven Pharmaceuticals Inc, Otsuka America Pharmaceutical, Inc., Pax Medica, Relmada Therapeutics, Sage Pharmaceuticals, Sunovion Pharmaceuticals Inc., Supernus Pharmaceuticals, Inc., Takeda Pharmaceutical Company Limited, Tris Pharma. J. L. Adams, L. Rekeda, and M. Kerolous are employees of AbbVie and may hold stock. M.K. Singh has received research support from the National Institutes of Health, the Patient Centered Outcomes Research Institute, the Brain and Behavior Foundation, Advanced Neuromodulation Systems, and AbbVie Inc. She is on a data safety monitoring board for a study funded by the National Institute of Mental Health. She has in the past 3 years consulted for or been on an advisory board for AbbVie Inc., Alkermes, Alto Neuroscience, Boehringer-Ingelheim, Johnson and Johnson, Karuna Therapeutics, Inc., Neumora, and Skyland Trail. She receives honoraria from the American Academy of Child and Adolescent Psychiatry and royalties from American Psychiatric Association Publishing and Thrive Global.

The authors report no other conflicts of interest in this work.

## References


1. Rush AJ. The varied clinical presentations of major depressive disorder. *J Clin Psychiatry*. 2007;68 Suppl 8:4–10.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. *Fifth Edition* ed. 2013.
3. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry*. 2018;75(4):336–346. doi:10.1001/jamapsychiatry.2017.4602
4. Kennedy SH, Ceniti AK. Unpacking major depressive disorder: from classification to treatment selection. *Can J Psychiatry*. 2018;63(5):308–313. doi:10.1177/0706743717748883
5. Fried EI, Nesse RM. Depression is not a consistent syndrome: an investigation of unique symptom patterns in the STAR*D study. *J Affect Disord*. 2015;172:96–102. doi:10.1016/j.jad.2014.10.010
6. Ostergaard SD, Jensen SO, Bech P. The heterogeneity of the depressive syndrome: when numbers get serious. *Acta Psychiatr Scand*. 2011;124(6):495–496. doi:10.1111/j.1600-0447.2011.01744.x
7. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905–1917. doi:10.1176/ajp.2006.163.11.1905
8. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am J Psychiatry*. 2009;166(9):980–991. doi:10.1176/appi.ajp.2009.09030312
9. Spielmans GI, Berman MI, Linardatos E, Rosenlicht NZ, Perry A, Tsai AC. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. *Focus*. 2016;14(2):244–265. doi:10.1176/appi.focus.140202
10. Vazquez GH, Bahji A, Undurraga J, Tondo L, Baldessarini RJ. Efficacy and tolerability of combination treatments for major depression: antidepressants plus second-generation antipsychotics vs. esketamine vs. lithium. *J Psychopharmacol*. 2021;35(8):890–900. doi:10.1177/02698811211013579
11. Papakostas GI, Shelton RC, Smith J, Fava M. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. *J Clin Psychiatry*. 2007;68(6):826–831. doi:10.4088/jcp.v68n0602
12. Mathis MV, Muoio BM, Andreason P, et al. The US Food and Drug Administration's perspective on the new antipsychotic pimavanserin. *J Clin Psychiatry*. 2017;78(6):e668–e673. doi:10.4088/JCP.16r11119

13. Culpepper L, Mathews M, Ghori R, Edwards J. Clinical relevance of vilazodone treatment in patients with major depressive disorder: categorical improvement in symptoms. *Prim Care Companion CNS Disord*. 2014;16(1):PCC.13m01571. doi:10.4088/PCC.13m01571
14. Mulder R, Hamilton A, Irwin L, et al. Treating depression with adjunctive antipsychotics. *Bipolar Disord*. 2018;20 Suppl 2:17–24. doi:10.1111/bdi.12701
15. Voineskos D, Daskalakis ZJ, Blumberger DM. Management of treatment-resistant depression: challenges and strategies. *Neuropsychiatr Dis Treat*. 2020;16:221–234. doi:10.2147/NDT.S198774
16. Durgam S, Earley W, Guo H, et al. Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. *J Clin Psychiatry*. 2016;77(3):371–378. doi:10.4088/JCP.15m10070
17. Sachs GS, Yeung PP, Rekeda L, Khan A, Adams JL, Fava M. Adjunctive cariprazine for the treatment of patients with major depressive disorder: a randomized, double-blind, placebo-controlled phase 3 study. *Am J Psychiatry*. 2023;180(3):241–251. doi:10.1176/appi.ajp.20220504
18. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389. doi:10.1192/bjp.134.4.382
19. Patel M, Jain R, Tohen M, Maletic V, Earley WR, Yatham LN. 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. doi:10.1097/YIC.0000000000000344
20. Chandler GM, Iosifescu DV, Pollack MH, Targum SD, Fava M. RESEARCH: validation of the Massachusetts general hospital antidepressant treatment history questionnaire (ATRQ). *CNS Neurosci Ther*. 2010;16(5):322–325. doi:10.1111/j.1755-5949.2009.00102.x
21. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62. doi:10.1136/jnnp.23.1.56
22. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133:429–435. doi:10.1192/bjp.133.5.429
23. Leucht S, Fennema H, Engel RR, Kaspers-Janssen M, Lepping P, Szegedi A. What does the MADRS mean? Equipercentile linking with the CGI using a company database of mirtazapine studies. *J Affect Disord*. 2017;210:287–293. doi:10.1016/j.jad.2016.12.041
24. Turkoz I, Alphs L, Singh J, et al. Clinically meaningful changes on depressive symptom measures and patient-reported outcomes in patients with treatment-resistant depression. *Acta Psychiatr Scand*. 2021;143(3):253–263. doi:10.1111/acps.13260
25. Almas A, Forsell Y, Iqbal R, Janszky I, Moller J. Severity of depression, anxious distress and the risk of cardiovascular disease in a Swedish population-based cohort. *PLoS One*. 2015;10(10):e0140742. doi:10.1371/journal.pone.0140742
26. Whitton AE, Pizzagalli DA. Anhedonia in depression and bipolar disorder. *Curr Top Behav Neurosci*. 2022;58:111–127. doi:10.1007/7854_2022_323
27. Wescott DL, Taylor ML, Klevens AM, Franzen PL, Roecklein KA. Waking up on the wrong side of the bed: depression severity moderates daily associations between sleep duration and morning affect. *J Sleep Res*. 2024;33(3):e14010. doi:10.1111/jsr.14010
28. Morin RT, Nelson C, Bickford D, Insel PS, Mackin RS. Somatic and anxiety symptoms of depression are associated with disability in late life depression. *Aging Mental Health*. 2020;24(8):1225–1228. doi:10.1080/13607863.2019.1597013
29. Suzuki A, Aoshima T, Fukasawa T, et al. A three-factor model of the MADRS in major depressive disorder. *Depress Anxiety*. 2005;21(2):95–97. doi:10.1002/da.20058
30. McIntyre RS, Maletic V, Masand P, et al. The effect of adjunctive cariprazine on symptoms of anhedonia in patients with major depressive disorder. *J Affect Disord*. 2025;385:119366. doi:10.1016/j.jad.2025.05.026
31. Fava M, Masand PS, Maletic V, Chen C, Adams JL, Kerolous M. Efficacy of adjunctive cariprazine on anxiety symptoms in patients with major depressive disorder: post hoc analysis of a randomized placebo-controlled trial. *J Clin Psychiatry*. 2025;86(2):24m15506.
32. Bailey RK, Mokonogho J, Kumar A. Racial and ethnic differences in depression: current perspectives. *Neuropsychiatr Dis Treat*. 2019;15:603–609. doi:10.2147/NDT.S128584
33. Murphy E, Hou L, Maher BS, et al. Race, genetic ancestry and response to antidepressant treatment for major depression. *Neuropsychopharmacology*. 2013;38(13):2598–2606. doi:10.1038/npp.2013.166
34. Thase ME. Update on partial response in depression. *J Clin Psychiatry*. 2009;70 Suppl 6:4–9. doi:10.4088/JCP.8133su1c.01
35. Citrome L, Reda I, Kerolous M. Adjunctive cariprazine for the treatment of major depressive disorder: number needed to treat, number needed to harm, and likelihood to be helped or harmed. *J Affect Disord*. 2024. doi:10.1016/j.jad.2024.10.040