Am J of Geriatric Psychiatry 33:4 (2025) 372–386

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ajgponline.org

Regular Research Article

Effect of Cariprazine on Outcomes in Older-aged and Younger-aged Patients with Bipolar I Disorder: A Post-hoc Analysis

Nicolas Garel, MD, MSc, FRCPC, Annemieke Dols, MD, PhD, Jun Yu, PhD, Christine Di Cresce, PhD, Soham Rej, MD, MSc, FRCPC, Martha Sajatovic, MD

ARTICLE INFO

Article history:
Received November, 25 2024
Revised December, 24 2024
Accepted December, 27 2024

Key Words:
Cariprazine
older age bipolar disorder
bipolar mania
bipolar depression

ABSTRACT

Objectives: *To evaluate cariprazine in adults with older- and younger-age bipolar I disorder (OABD-I and YABD-I) and compare treatment effects between them.* ***Design and setting:*** *Pooled post-hoc analysis of studies in depressive or acute manic/mixed episodes associated with bipolar I disorder.* ***Participants:*** *475/1383 patients (34.3%) in 3 depression trials and 238/1037 patients (23.0%) in 3 manic/mixed trials were OABD-I.* ***Interventions:*** *Depression: placebo, cariprazine 1.5 mg/day, 3.0 mg/day, pooled 1.5-3.0 mg/day. Manic/mixed: placebo, cariprazine 3.0-6.0 mg/day, and 9.0-12.0 mg/day.* ***Measurements:*** *Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression of Severity (CGI-S), and Young Mania Rating Scale (YMRS).* ***Results:*** *In bipolar I depression, mean change from baseline in MADRS was significantly greater for the pooled cariprazine group vs. placebo in OABD-I (−13.72 vs. −11.98; $p < 0.05$) and for each cariprazine group vs. placebo among YABD-I. There was no significant difference in treatment effect between OABD-I and YABD-I for either individual cariprazine group vs. placebo.*

For mania/mixed states, mean change in YMRS was significantly greater for cariprazine 3.0-6.0 mg/day vs. placebo in OABD-I (−19.04 vs. −12.45; $p < 0.001$) and for both cariprazine groups in YABD-I (−12.49, −19.66 and −18.05 for placebo, cariprazine 3.0−6.0 mg/day and 9.0−12.0 mg/day, respectively [both $p < 0.0001$ vs. placebo]. There was no significant difference in

From the Department of Psychiatry and Addictology (NG), Faculty of Medicine, University of Montreal, Montréal, Québec, Canada; Research Centre (NG), Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, Québec H2 × 0A9, Canada; Department of Psychiatry (AD), UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands; AbbVie Inc. (JY), Sugar Land, TX; AbbVie Corp. (CDC), Saint-Laurent, Québec, Canada; Department of Psychiatry (SR), Jewish General Hospital/Lady Davis Institute, Montreal, Québec, Canada; Department of Psychiatry (SR), McGill University, Montreal, Québec, Canada; University Hospitals Cleveland Medical Center (MS), Cleveland, OH; and the Case Western Reserve University School of Medicine (MS), Cleveland, OH. Send correspondence and reprint requests to Nicolas Garel, MD, MSc, FRCPC, Centre Hospitalier de l'Université de Montréal (CRCHUM), 900 Saint-Denis Street, Montréal, Québec H2 × 0A9, Canada. e-mail: nicolas.garel@umontreal.ca

https://doi.org/10.1016/j.jagp.2024.12.006

treatment effect between OABD-I and YABD-I for cariprazine 3.0−6.0 mg/day vs. placebo; there was a significantly higher treatment effect for cariprazine 9.0 −12.0 mg/day vs. placebo in the YABD-I subpopulation vs. OABD-I (4.20; $p < 0.05$). ***Conclusions:*** *Cariprazine appears to be effective for both depressive and manic/mixed episodes of bipolar I disorder, regardless of age.* (Am J Geriatr Psychiatry 2025; 33:372−386)

Editorial accompaniment, please see page 387.

Highlights

- **What is the primary question addressed by this study?**
  Is cariprazine effective for the treatment of older adults with bipolar I disorder (OABD-I: aged ≥50 years)?
- **What is the main finding of this study?**
  Cariprazine is efficacious for both depressive and manic episodes of bipolar I disorder regardless of age; and the currently recommended dose ranges for cariprazine are appropriate for all ages.
- **What is the meaning of the finding?**
  The analyses provide reassurance that treatment with cariprazine is appropriate and similar for both older and younger patients with bipolar I disorder.

INTRODUCTION

The International Society of Bipolar Disorder (ISBD) task force on older adults with bipolar disorder (BD) has defined older-age bipolar disorder (OABD) as BD in individuals aged 50 years or older.[1]

The prevalence of BD in older adults is conservatively estimated to be 0.5%−1.0%, lower than in younger adults.[1−3] However, approximately 10% of inpatients and 6% of outpatients within the geriatric psychiatry subpopulation have BD,[4] and these patients are some of the highest users of psychiatric and physical health services.[5] The number of individuals with OABD is expected to increase with the global aging demographic.[1,6]

In OABD, depressive and cognitive symptoms tend to be more common and severe relative to younger-aged bipolar disorder (YABD; adults <50 years), while symptoms of mania or hypomania are often less prominent.[7] Research suggests that, as individuals with BD continue to age, there are progressively shorter inter-episode intervals and more frequent relapses after mood episodes.[8]

Published, prospective research analyzing efficacy and safety of medication treatments for individuals with OABD is minimal.[7] This paucity of evidence supporting effective treatments among the growing OABD population and the lack of emphasis on issues related to the OABD population included in current guidelines demonstrates a need for further analysis of existing data to ensure they receive appropriate care.[9] Indeed, there has only been one prospective randomized controlled trial (RCT) on the treatment of acute mania exclusively in the OABD population,[10] and none for the treatment of acute depressive episodes in OABD.[1,11]

Cariprazine is a potent dopamine D_3-preferring D_3/D_2 receptor partial agonist and serotonin 5-HT_{1A} receptor partial agonist; part of the second-generation atypical antipsychotic class.[12] Efficacy and safety of cariprazine have been demonstrated for the treatment of people aged 18 to 65 with bipolar I disorder, in 3 pivotal studies in individuals with acute depressive episodes (at doses of 0.75 to 3.0 mg/day) and 3 pivotal studies in individuals with acute manic/mixed episodes (at doses of 3.0 to 12.0 mg/day).[13−18]. In the United States, cariprazine is approved for the acute management of manic/mixed episodes and depressive episodes associated with bipolar I disorder, the treatment of schizophrenia, and adjunctive therapy to antidepressants for the treatment of major depressive disorder. There are no specified dosing or indication differences between adults and older adults.[19] In the

present study, we performed a pooled post-hoc analysis to compare the efficacy and safety of cariprazine vs. placebo in OABD-I and YABD-I subpopulations, for both acute depressive and mania/mixed episodes. We also compared the treatment effect of cariprazine in OABD-I and YABD-I populations.

METHODS

Post-hoc analyses were performed by pooling data from three pivotal studies evaluating cariprazine in the treatment of depressive episodes associated with bipolar I disorder (bipolar I depression) or from three pivotal studies of cariprazine in the treatment of manic or mixed episodes associated with bipolar I disorder.[13–18] All of the trials were in adults (aged 18 to 65 years old) and were placebo-controlled. The studies for bipolar I depression (NCT02670538, NCT02670551, NCT01396447) were conducted from 2011 to 2018 in the US, Ukraine, Russia, Bulgaria, Croatia, Serbia, Slovakia, Estonia, Lithuania, Poland, Canada, and Colombia. The studies for bipolar mania (NCT00488618, NCT01058096, NCT01058668) were conducted from 2007 to 2011 in the US, Russia, Ukraine, Croatia, Serbia, and India.

Acute Depressive Episodes

The acute bipolar I depression trials evaluated cariprazine at fixed doses of 0.75 mg, 1.5 mg or 3.0 mg/day. The primary efficacy outcome of these trials was change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to week 6. Change in Clinical Global Impression of Severity (CGI-S) score from baseline to week 6 was a secondary outcome, while change in Young Mania Rating Scale (YMRS) score from baseline to week 6 was included among the safety measures to assess for switches in mood polarity.

Acute Manic/Mixed Episodes

The acute mania/mixed trials evaluated cariprazine at flexible doses ranging from 3.0 to 12.0 mg/day. The primary efficacy outcome of these studies was change in the YMRS total score from baseline to week 3. Change in CGI-S score and MADRS score from baseline to week 3 were secondary and additional outcomes included in all three trials.

Analyses

For the current analyses, data were drawn from pooled intent-to-treat (ITT) populations (≥1 postbaseline measurement of the primary efficacy outcome) and safety populations (≥1 dose of investigational product).

In the bipolar I depression data set, the results presented focus on the 1.5 mg/day and 3.0 mg/day doses, as well as a pooled cariprazine group (1.5 or 3.0 mg/day) vs. placebo. The 0.75 mg/day data from the single trial that included this dose were omitted.

In the manic/mixed episodes data set, results were stratified based on modal daily dose of cariprazine to generate data for 3.0 to 6.0 mg/day and 9.0 to 12.0 mg/day vs. placebo. While results with both doses are presented, the Food and Drug Administration (FDA)-approved dose range for manic/mixed episodes is 3.0 to 6.0 mg/day.

The pooled cariprazine dose arm was chosen for inclusion in the bipolar I depression analyses based on its inclusion in prior publications on this medication as a treatment for bipolar I depression.[13]

In the ITT populations, individual or pooled cariprazine groups were compared to placebo for the primary and secondary outcome measurements listed above for OABD-I (age ≥50 years) and YABD-I (age ≤49 years) populations. To evaluate changes in outcome measures, least squares mean (LSM) change from baseline and least squares mean difference of change (LSMD) vs. placebo were calculated using a mixed-effects model for repeated measures (MMRM).

In the current investigation, MMRM analyses were carried out to determine if there were differences in outcomes between the OABD-I and YABD-I populations. In each model, the change in the outcome is the dependent variable (*i.e.*, bipolar I depressive episodes: MADRS; mania/mixed episodes: YMRS), while covariates were baseline scores on the outcome in question, visit, treatment, age group, and the interaction item of treatment and age group.

Additional analyses of the bipolar I depression pooled data included MADRS response and remission rates, and changes in the MADRS concentration and sleep items from baseline. Additional analyses of the mania/mixed pooled data included YMRS

response and remission rates and changes in YMRS sleep and irritability items from baseline.

RESULTS

Bipolar I Depression Baseline Characteristics

The pooled ITT population from the 3 bipolar I depression trials consisted of 1383 patients, of which 475 (34.3%) were OABD-I patients and 908 (65.7%) were YABD-I patients. Except for age, the OABD-I and YABD-I populations and treatment groups were balanced for demographics, psychiatric history, and mean baseline MADRS, CGI-S, and YMRS scores (Table 1). Similar percentages of OABD-I (84.3%) and YABD-I (76.9%) patients completed the trials.

Bipolar I Depression Efficacy

MADRS total score

At week 6, for the OABD-I population, mean change in MADRS total score from baseline was significantly greater for the pooled cariprazine group vs. placebo (LSM change from baseline −13.72 vs. −11.98; LSMD vs. placebo −1.74; 95% CI −3.46 to −0.03; $p < 0.05$; Fig. 1). However, the mean changes from baseline for the individual cariprazine dose groups (1.5 or 3.0 mg/day) were not significantly different from placebo.

In the YABD-I population, mean change in MADRS total score from baseline was significantly greater for both cariprazine dose groups and the pooled group vs. placebo. LSM change from baseline was −12.09 for placebo, −15.47 for cariprazine 1.5 mg/day (LSMD vs. placebo −3.39, 95% CI −5.00 to −1.78; $p < 0.0001$), −14.84 for cariprazine 3.0 mg/day (LSMD vs. placebo −2.76, 95% CI −4.39 to −1.13; $p < 0.001$), and −15.17 for the pooled cariprazine group (LSMD vs. placebo −3.10, 95% CI −4.51 to −1.68; $p < 0.0001$).

MMRM analysis of mean change in MADRS total score from baseline indicated no significant treatment difference between OABD-I and YABD-I populations for individual or pooled cariprazine groups vs. placebo for each dose-specific comparison (Fig. 1).

Other MADRS analyses

In both the MADRS response (≥50% total score reduction) and remission (total score ≤10) analyses (Figures S1 and S2), each of the YABD-I cariprazine dose groups were associated with significantly greater rates of response and remission compared to placebo. In the OABD-I population, none of the individual cariprazine groups reached statistical significance for MADRS response rate vs. placebo, while the pooled cariprazine group had a significantly higher remission rate vs. placebo.

MADRS sub-item analyses

For mean change in MADRS concentration score from baseline (Figure S3), statistically significant differences were noted for the cariprazine 1.5 mg/day and pooled cariprazine groups vs. placebo in both the OABD-I and YABD-I populations, but not for cariprazine 3.0 mg/day vs. placebo in either population. For mean change in the MADRS sleep item score from baseline (Figure S4), no cariprazine dose group achieved a statistically significant difference vs. placebo among the OABD-I or YABD-I populations.

CGI-S

Among OABD-I patients, mean changes from baseline vs. placebo were significantly greater for the cariprazine 1.5 mg/day and pooled cariprazine groups, but not for the cariprazine 3.0 mg/day group (Fig. 2). In the YABD-I subgroup, all cariprazine individual and pooled dose groups had significantly greater mean changes from baseline vs. placebo. MMRM analysis of CGI-S indicated no significant treatment difference between OABD-I and YABD-I populations for any cariprazine group vs. placebo for each dose-specific comparison (Fig. 2).

Bipolar I Depression Safety

Safety summary

Discontinuations due to adverse events in the OABD-I population were 6.6% for placebo, and 2.8%, 7.0% and 5.0% for cariprazine 1.5 mg/day, 3.0 mg/day, and pooled groups, respectively. In the YABD-I population, 4.2% of placebo-treated patients

TABLE 1. Baseline Characteristics, Pooled Bipolar-I Depression Trials

Demographics – Pooled ITT Population		Older-aged Bipolar-I Disorder (OABD-I) Patients (Age ≥ 50 years)				Younger-age Bipolar-I Disorder (YABD-I) Patients (Age ≤ 49 years)			
		Placebo (*n* = 179)	Cariprazine			PBO (*n* = 281)	Cariprazine		
			1.5 mg/d (*n* = 142)	3.0 mg/d (*n* = 154)	Pooled CAR (*n* = 296)		1.5 mg/d (*n* = 319)	3.0 mg/d (*n* = 308)	Pooled CAR (*n* = 627)
Mean age, years (SD)		56.3 (4.11)	55.9 (4.29)	55.4 (3.99)	55.6 (4.13)	36.4 (8.48)	35.8 (8.55)	36.5 (8.35)	36.1 (8.46)
Female, %		90 (50.3)	85 (59.9)	95 (61.7)	180 (60.8)	182 (64.8)	209 (65.5)	184 (59.7)	393 (62.7)
Race, n (%)	White	141 (78.8)	115 (81)	120 (77.9)	235 (79.4)	201 (71.5)	231 (72.4)	231 (75)	462 (73.7)
	Black	36 (20.1)	25 (17.6)	32 (20.8)	57 (19.3)	72 (25.6)	72 (22.6)	68 (22.1)	140 (22.3)
	Other	2 (1.1)	2 (1.4)	2 (1.3)	4 (1.4)	8 (2.8)	16 (5)	9 (2.9)	25 (4)
Mean weight, kg (SD)		81.41 (15.92)	83.19 (17.68)	83.08 (17.51)	83.13 (17.56)	85.89 (21.77)	85.22 (22.62)	84.33 (20.60)	84.78 (21.64)
Mean BMI, kg/m^2 (SD)		28.33 (5.19)	29.05 (6.06)	29.15 (5.71)	29.10 (5.87)	29.98 (7.47)	29.64 (7.55)	29.29 (7.27)	29.47 (7.41)
Mean MADRS score (SD)		30.8 (4.64)	30.9 (4.20)	31.0 (4.61)	31.0 (4.41)	30.6 (4.49)	30.8 (4.39)	31.1 (4.88)	31.0 (4.63)
Mean CGI-S score (SD)		4.5 (0.52)	4.5 (0.57)	4.5 (0.55)	4.5 (0.56)	4.5 (0.53)	4.5 (0.55)	4.5 (0.54)	4.5 (0.55)
Mean YMRS score (SD)		3.8 (2.17)	3.9 (2.31)	4.0 (2.27)	4.0 (2.28)	4.4 (2.42)	4.2 (2.29)	4.1 (2.30)	4.1 (2.30)

Psychiatry history, Safety Population		Older-aged Bipolar-I Disorder (OABD-I) Patients (Age ≥ 50 years)				Younger-age Bipolar-I Disorder (YABD-I) Patients (Age ≤ 49 years)			
		Placebo (*n* = 181)	Cariprazine			PBO (*n* = 287)	Cariprazine		
			1.5 mg/d (*n* = 145)	3.0 mg/d (*n* = 157)	Pooled CAR (*n* = 302)		1.5 mg/d (*n* = 325)	3.0 mg/d (*n* = 312)	Pooled CAR (*n* = 637)
Mean age of onset of current episode, years (SD)		55.9 (4.15)	55.5 (4.3)	55.1 (4.0)	55.3 (4.14)	36.0 (8.51)	35.5 (8.52)	36.2 (8.38)	35.8 (8.45)
Mean duration of current episode, months (SD)		3.35 (2.45)	3.46 (2.42)	3.11 (1.94)	3.28 (2.19)	3.79 (2.58)	3.87 (2.63)	3.75 (2.54)	3.81 (2.59)
Duration of current episode, n (%)	≤3 mos	108 (59.7)	87 (60)	95 (60.5)	182 (60.3)	146 (50.9)	166 (51.1)	161 (51.6)	327 (51.3)
	>3 to 6 mos	48 (26.5)	34 (23.4)	52 (33.1)	86 (28.5)	83 (28.9)	94 (31.7)	99 (31.7)	193 (30.3)
	>6 to 12 mos	25 (13.8)	24 (16.6)	10 (6.4)	34 (11.3)	58 (20.2)	65 (20)	52 (16.7)	117 (18.4)
Mean no. of prior manic/mixed episodes (SD)		4.5 (4.15)	4.4 (4.33)	4.4 (4.98)	4.4 (4.67)	4.8 (6.04)	4.2 (4.37)	4.5 (5.21)	4.3 (4.80)
Mean no. of prior depressive episodes (SD)		7.0 (6.38)	6.9 (5.48)	7.8 (11.35)	7.3 (9.02)	6.9 (7.80)	7.1 (7.59)	6.3 (6.56)	6.7 (7.11)

Notes: ITT population consisted of patients with at least one postbaseline MADRS result; Safety population consisted of patients who had taken at least 1 dose of study medication.

BMI: body mass index; CAR: cariprazine; CGI-S: Clinical Global Impression of Severity; d: day; ITT: intent-to-treat; MADRS: Montgomery-Asberg Depression Rating Scale; PBO: placebo; SD: standard deviation; YMRS: Young Mania Rating Scale.

discontinued due to adverse events, as did 6.2%, 8.3%, and 7.2% of cariprazine 1.5 mg/day, 3.0 mg/day, and pooled groups, respectively (Table 2). A higher proportion of patients treated with cariprazine experienced akathisia in both the OABD-I population and the YABD-I population (Table 2). A complete list of the most common individual treatment-emergent adverse events is shown in Table 2. Discontinuation due to akathisia was ≤3% across all treatment groups in both patient populations (Table S1).

Risk of mood polarity switch

Analysis of changes in YMRS total scores from baseline to week 6 (Fig. 3) did not suggest a risk of manic switch. Among OABD-I patients and YABD-I patients, there were no significant differences between any individual or pooled cariprazine dose groups and placebo in YMRS change from baseline. MMRM analysis showed no significant treatment difference for any comparison of cariprazine vs. placebo between OABD-I and YABD-I populations.

Bipolar I Mania/Mixed Baseline Characteristics

The pooled ITT population from the 3 manic/-mixed trials consisted of 1037 patients, of which 238 (23.0%) were OABD-I patients and 799 (77.0%) were YABD-I patients. The OABD-I and YABD-I populations and treatment groups were balanced for demographics (apart from age), psychiatric history, and mean baseline YMRS, CGI-S, and MADRS scores (Table 3). Similar percentages of OABD-I (74.1%) and YABD-I (68.9%) patients completed the trials.

FIGURE 1. Changes in MADRS scores from baseline to week 6, bipolar I depression, by treatment and age group, pooled data, ITT. CAR: cariprazine; ETD: estimated treatment difference; ITT: intent-to-treat; LSM: least squares mean; LSMD: least squares mean difference vs. placebo; MADRS: Montgomery-Åsberg Depression Rating Scale; MMRM: mixed model for repeated measures, treatment effect (cariprazine vs. placebo) for OABD-I vs. YABD-I population; OABD-I: older-age bipolar I disorder; YABD: younger-aged bipolar I disorder.

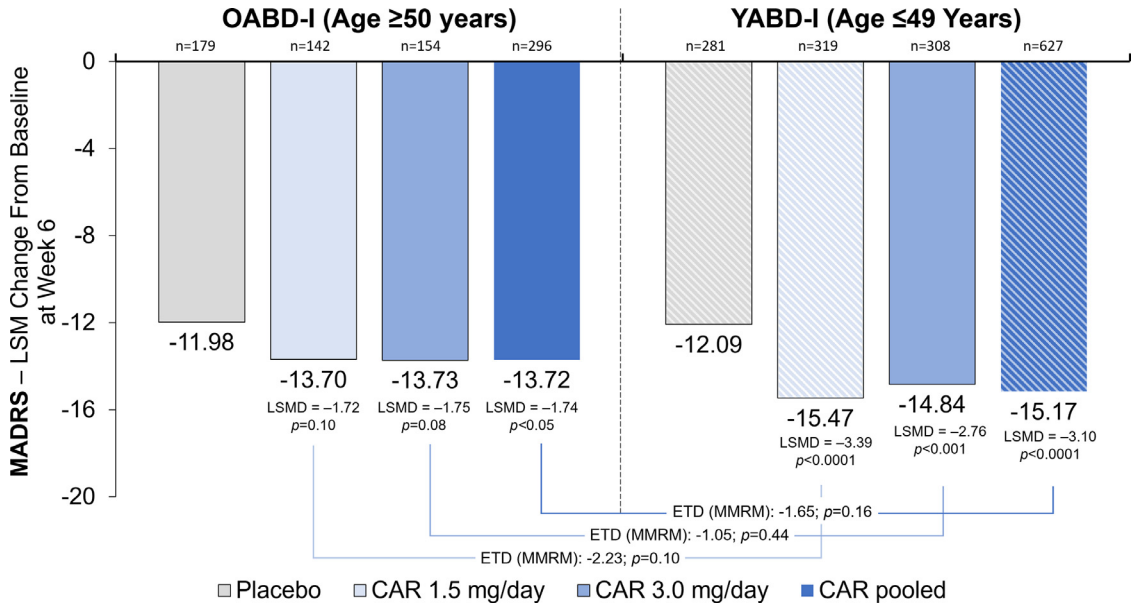


FIGURE 2. Changes in CGI-S from baseline to week 6, bipolar I depression, by treatment and age group, pooled data, ITT. CAR: cariprazine; CGI-S: Clinical Global Impression of Severity; ETD: estimated treatment difference; ITT: intent-to-treat; LSM: least squares mean of change from baseline; LSMD: least squares mean difference vs. placebo; MMRM: mixed model for repeated measures, treatment effect (cariprazine vs. placebo) for OABD-I vs. YABD-I population; OABD-I: older-age bipolar I disorder; YABD: younger-aged bipolar I disorder.

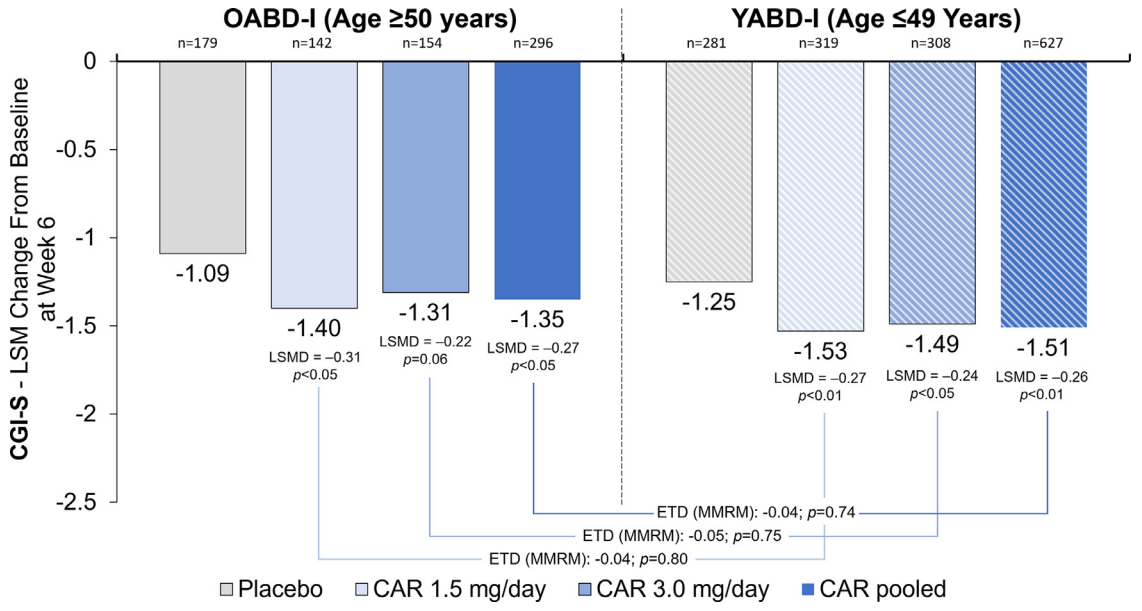
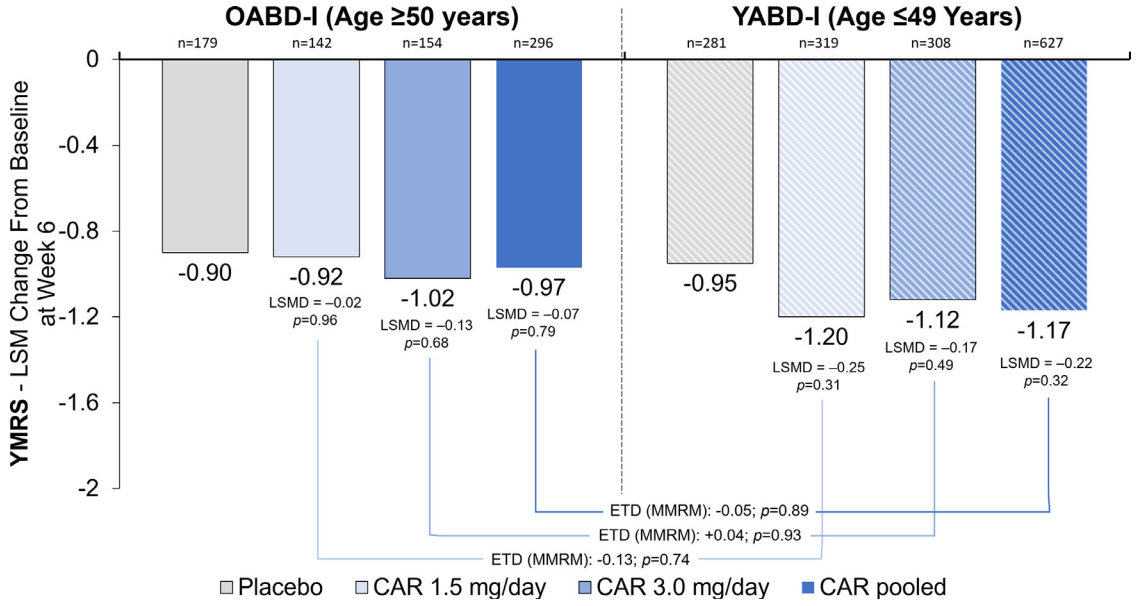


TABLE 2. Safety Summary, Pooled Bipolar-I Depression Trials (Safety Population)

	Older-aged Bipolar-I Disorder (OABD-I) Patients (Age ≥ 50 years)				Younger-age Bipolar-I Disorder (YABD-I) Patients (Age ≤ 49 years)			
	Placebo (*n* = 179)	Cariprazine			PBO (*n* = 281)	Cariprazine		
		1.5 mg/d (*n* = 142)	3.0 mg/d (*n* = 154)	Pooled CAR (*n* = 296)		1.5 mg/d (*n* = 319)	3.0 mg/d (*n* = 308)	Pooled CAR (*n* = 627)
Any TEAE, n (%)	81 (44.8)	71 (49.0)	80 (51.0)	151 (50.0)	156 (54.4)	191 (58.8)	191 (61.2)	382 (60)
Serious AE, n (%)	3 (1.7)	3 (2.1)	2 (1.3)	5 (1.7)	9 (3.1)	2 (0.6)	2 (0.6)	4 (0.6)
AE leading to discontinuation, n (%)	12 (6.6)	4 (2.8)	11 (7.0)	15 (5.0)	12 (4.2)	20 (6.2)	26 (8.3)	46 (7.2)
Akathisia	1 (0.6)	5 (3.4)	11 (7.0)	16 (5.3)	9 (3.1)	21 (6.5)	34 (10.9)	55 (8.6)
Diarrhoea	-	-	-	-	13 (4.5)	17 (5.2)	5 (1.6)	22 (3.5)
Headache	9 (5.0)	11 (7.6)	15 (9.6)	26 (8.6)	34 (11.8)	20 (6.2)	20 (6.4)	40 (6.3)
Insomnia	12 (6.6)	7 (4.8)	12 (7.6)	19 (6.3)	18 (6.3)	17 (5.2)	28 (9.0)	45 (7.1)
Nausea	5 (2.8)	8 (5.5)	7 (4.5)	15 (5.0)	8 (2.8)	23 (7.1)	28 (9.0)	51 (8.0)
Restlessness	-	-	-	-	10 (3.5)	8 (2.5)	27 (8.7)	35 (5.5)
Somnolence	-	-	-	-	10 (3.5)	12 (3.7)	19 (6.1)	31 (4.9)

Notes: AE: adverse event; CAR: cariprazine; d: day; TEAE: treatment-emergent adverse event.

FIGURE 3. Changes in YMRS total score from baseline to week 6, bipolar I Depression, by Treatment and Age Group, Pooled Data, ITT. CAR: cariprazine; ETD: estimated treatment difference; ITT: intent-to-treat; LSM: least squares mean; LSMD, least squares mean difference vs. placebo; MMRM: mixed model for repeated measures, treatment effect (cariprazine vs. placebo) for OABD-I vs. YABD-I population; OABD-I: older-age bipolar I disorder; YABD: younger-aged bipolar I disorder; YMRS: Young Mania Rating Scale.



Bipolar I Mania/Mixed Efficacy

YMRS total score

At week 3, for the OABD-I population, mean change in YMRS total score from baseline was significantly greater for the cariprazine 3.0 to 6.0 mg/day group vs. placebo (LSM change from baseline −19.04 vs.−12.45; LSMD vs. placebo −6.59; 95% confidence interval [CI] −10.12 to −3.06; p < 0.001; Fig. 4). However, the mean change from baseline for

TABLE 3. Baseline Characteristics, Pooled Bipolar-I Manic / Mixed Trials

Demographics & characteristics—Pooled ITT Population		Older-aged Bipolar-I Disorder (OABD-I) Patients (Age ≥ 50 years)			Younger-age Bipolar-I Disorder (YABD-I) Patients (Age ≤ 49 years)		
		PBO (*n* = 95)	Cariprazine		PBO (*n* = 334)	Cariprazine	
			3-6 mg/d (*n* = 67)	9-12 mg/d (*n* = 76)		3-6 mg/d (*n* = 189)	9-12 mg/d (*n* = 276)
Mean age, years (SD)		54.8 (3.93)	55.5 (3.98)	54.4 (3.29)	34.5 (8.82)	35.8 (9.22)	34.6 (9.10)
Female, n (%)		44 (46.3)	33 (49.3)	36 (47.4)	126 (37.7)	78 (41.3)	103 (37.3)
Race, n (%)	White	60 (63.2)	55 (82.1)	36 (47.4)	141 (42.2)	99 (52.4)	119 (43.1)
	Black	22 (23.2)	9 (13.4)	30 (39.5)	80 (24.0)	57 (30.2)	68 (24.6)
	Asian	13 (13.7)	2 (3.0)	9 (11.8)	107 (32.0)	32 (16.9)	86 (31.2)
	Other	0	1 (1.5)	1 (1.3)	6 (1.8)	1 (0.5)	3 (1.1)
Mean weight, kg (SD)		80.81 (16.52)	80.49 (15.96)	79.26 (18.19)	76.57 (19.76)	79.92 (18.63)	74.53 (19.84)
Mean BMI, kg/m^2 (SD)		28.67 (5.63)	27.87 (4.85)	27.58 (5.21)	26.5 (5.6)	27.58 (5.79)	26.12 (5.78)
Mean YMRS Score (SD)		31.2 (6.32)	33.8 (5.53)	32.4 (4.9)	32.0 (5.45)	31.7 (5.39)	32.5 (5.43)
Mean CGI-S Score (SD)		4.7 (0.72)	4.8 (0.58)	4.8 (0.57)	4.7 (0.64)	4.6 (0.66)	4.7 (0.65)
Mean MADRS Score (SD)		9.3 (4.0)	9.1 (3.64)	10.2 (3.9)	8.8 (4.11)	9.3 (3.87)	8.8 (4.01)

Psychiatry history, Safety Population		Older-aged Bipolar-I Disorder (OABD-I) Patients (Age ≥ 50 years)			Younger-age Bipolar-I Disorder (YABD-I) Patients (Age ≤ 49 years)		
		Placebo (*n* = 96)	Cariprazine		Placebo (*n* = 337)	Cariprazine	
			3-6 mg/d (*n* = 67)	9-12 mg/d (*n* = 76)		3-6 mg/d (*n* = 189)	9-12 mg/d (*n* = 276)
Mean age of onset of BP-I, years (SD)		40.7 (11.51)	35.8 (12.32)	38.5 (12.80)	27.0 (9.98)	24.8 (9.63)	27.9 (9.79)
Mean duration of current episode, days (SD)		26.3 (33.76)	20.8 (22.06)	21.6 (23.87)	38.9 (208.45)	27.2 (27.17)	36.7 (148.78)
Duration of current episode, n (%)	≤7 days	15 (15.6)	13 (19.4)	14 (18.4)	43 (12.8)	17 (8.8)	31 (11.2)
	>7 to 14 days	35 (36.6)	30 (44.8)	33 (43.4)	137 (40.7)	73 (37.8)	109 (39.5)
	>14 to 21 days	14 (14.6)	7 (10.4)	9 (11.8)	51 (15.1)	30 (15.5)	40 (14.5)
	>21 days	32 (33.3)	17 (25.4)	20 (26.3)	106 (31.5)	73 (37.8)	96 (34.8)
Mean no. of prior manic/mixed episodes (SD)		10.6 (9.94)	10.1 (11.89)	10.6 (11.77)	7.9 (7.76)	9.9 (11.51)	7.7 (8.55)
Mean no. of prior depressive episodes (SD)		3.5 (2.24)	3.2 (2.04)	3.9 (1.97)	2.8 (2.17)	3.2 (2.18)	2.7 (2.12)

Notes: ITT population consisted of patients with at least 1 postbaseline YMRS result; Safety population consisted of patients who had taken at least 1 dose of study medication.

BMI: body mass index; CAR, cariprazine; CGI-S, Clinical Global Impression of Severity; d, day; ITT, intent-to-treat; MADRS, Montgomery-Asberg Depression Rating Scale; PBO, placebo; SD, standard deviation; YMRS, Young Mania Rating Scale.

the cariprazine 9.0 to 12.0 mg/day group was not significantly different from placebo (Fig. 4).

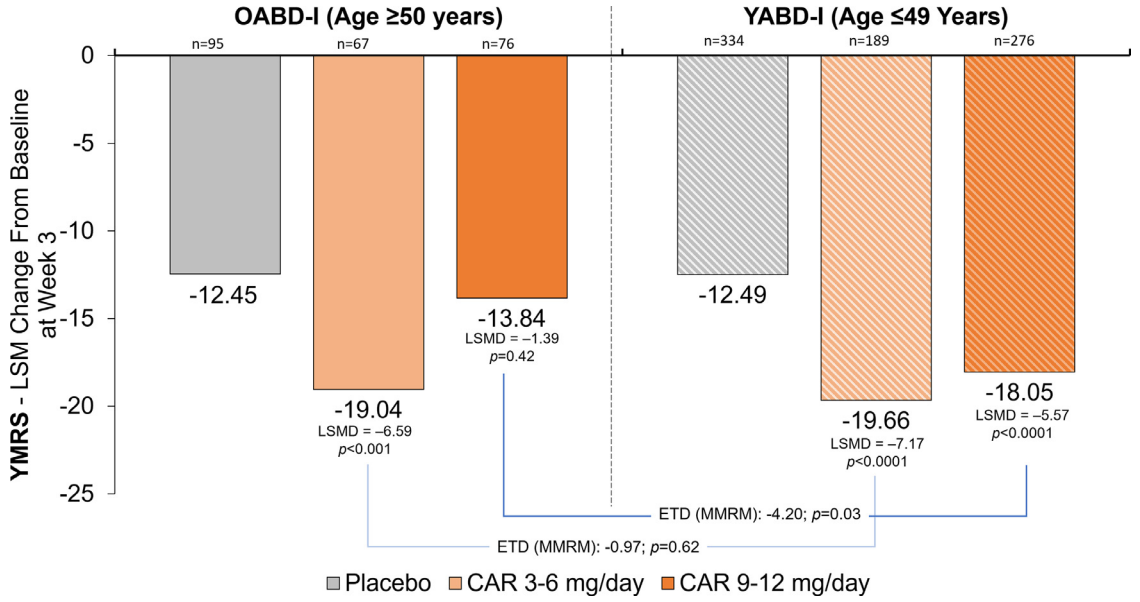
In the YABD-I population, mean change from baseline in YMRS total score was significantly greater for both cariprazine dose groups vs. placebo. LSM changes from baseline for placebo and cariprazine 3.0 to 6.0 mg/day groups were −12.49 and −19.66, respectively (LSMD vs. PBO −7.17; 95% CI −9.20 to −5.14, $p < 0.0001$), while for the cariprazine 9.0 to 12.0 mg/day group, it was −18.05 (LSMD vs. PBO −5.57, $p < 0.0001$).

MMRM analysis of YMRS total scores indicated no significant treatment difference between OABD-I and YABD-I populations for cariprazine 3.0 to 6.0 mg/day vs. placebo. There was, however, a significantly higher treatment effect for the cariprazine 9.0 to12.0 mg/day group vs. placebo in the YABD-I group vs. the OABD-I group (estimated treatment difference 4.20; standard error 1.89; $p < 0.05$; Fig. 4).

YMRS sub-item analyses

YMRS response and remission rates were also evaluated (Figures S5 and S6), as were changes in YMRS sleep and irritability items (Figures S7 and S8). Across all these analyses in the YABD-I population, both

FIGURE 4. Changes in YMRS total score from baseline to week 3, bipolar I mania/mixed, by treatment and age group, pooled data, ITT. CAR: cariprazine; ETD: estimated treatment difference; ITT: intent-to-treat; LSM: least squares mean; LSMD: least squares mean difference vs. placebo; MMRM: mixed model for repeated measures, treatment effect (cariprazine vs. placebo) for OABD-I vs. YABD-I population; OABD-I: older-age bipolar I disorder; YABD: younger-aged bipolar I disorder; YMRS: Young Mania Rating Scale.



cariprazine doses separated significantly from placebo. In the OABD-I population, the 3.0 to 6.0 mg/day cariprazine group separated from placebo in all these analyses except YMRS sleep score, whereas the 9.0 to 12.0 mg/day cariprazine group did not achieve significant differences in any of the analyses.

CGI-S

In the OABD-I subgroup, mean change from baseline was significantly greater for the cariprazine 3.0 to 6.0 mg/day group vs. placebo, but not for the cariprazine 9.0 to 12.0 mg/day group vs. placebo (Fig. 5). In the YABD-I subgroup, both cariprazine dose groups had significantly greater mean changes from baseline vs. placebo. MMRM analysis of CGI-S scores indicated no difference between OABD-I and YABD-I populations for cariprazine 3.0 to 6.0 mg/day vs. placebo or for cariprazine 9.0 to 12.0 mg/day vs. placebo.

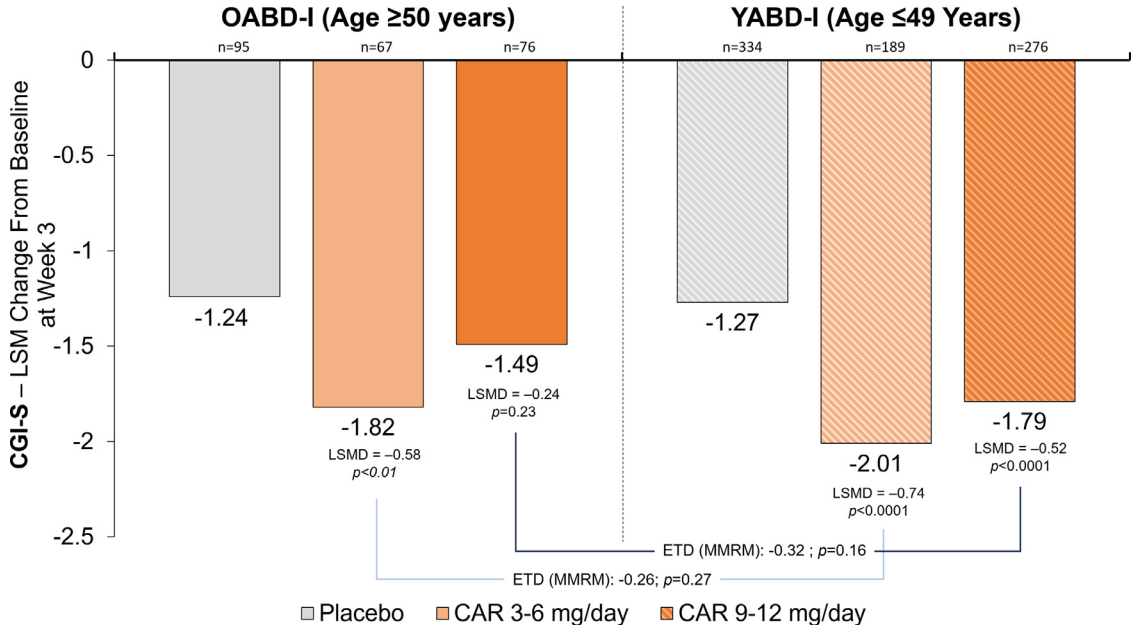
Risk of mood polarity switch

Overall, the MADRS results did not suggest a risk of depressive switch with cariprazine treatment (Fig. 6). Among OABD-I patients, there were no significant differences between either cariprazine dose group compared to placebo in mean change of total MADRS score from baseline. In the YABD-I analysis, there was a significant difference in favor of cariprazine for the 3.0 to 6.0 mg/day group vs. placebo and no significant difference between the higher-dose group and placebo. MMRM analysis indicated no difference for the comparison of cariprazine 3.0 to 6.0 mg/day or 9.0 to 12.0 mg/day vs. placebo between OABD-I and YABD-I populations.

Bipolar I Mania/Mixed Safety

Discontinuations due to adverse events in the OABD-I population were 7.3%, 7.5%, and 17.1% for placebo, cariprazine 3.0 to 6.0 mg/day, and cariprazine 9.0 to 12.0 mg/day, respectively. In the YABD-I population, the rates of discontinuations due to adverse events were 7.1%, 12.4%, and 10.9% for placebo, cariprazine 3.0 to 6.0 mg/day, and cariprazine 9.0 to 12.0 mg/day, respectively (Table 4). A higher proportion of patients treated with cariprazine experienced akathisia vs. placebo in both the OABD-I (3.1% of the placebo group, 16.4% of the cariprazine 3.0 to

FIGURE 5. Changes in CGI-S from baseline to week 3, bipolar I mania/mixed, by treatment and age group, pooled data, ITT. CAR: cariprazine; ETD: estimated treatment difference; ITT: intent-to-treat; LSM: least squares mean; LSMD: least squares mean difference vs. placebo; MMRM: mixed model for repeated measures, treatment effect (cariprazine vs. placebo) for OABD-I vs. YABD-I population; OABD-I: older-age bipolar I disorder; YABD: younger-aged bipolar I disorder.



6.0 mg/day group and 15.8% of the cariprazine 9.0 to 12.0 mg group) and YABD-I populations (5.0% of the placebo group, 20.7% of the cariprazine 3.0 to 6.0 mg/day group and 21.7% of the cariprazine 9.0 to 12.0 mg/day group). A complete list of the most common individual treatment-emergent adverse events is shown in Table 4. Discontinuation due to akathisia was ≤3% across all treatment groups in both populations (Table S2).

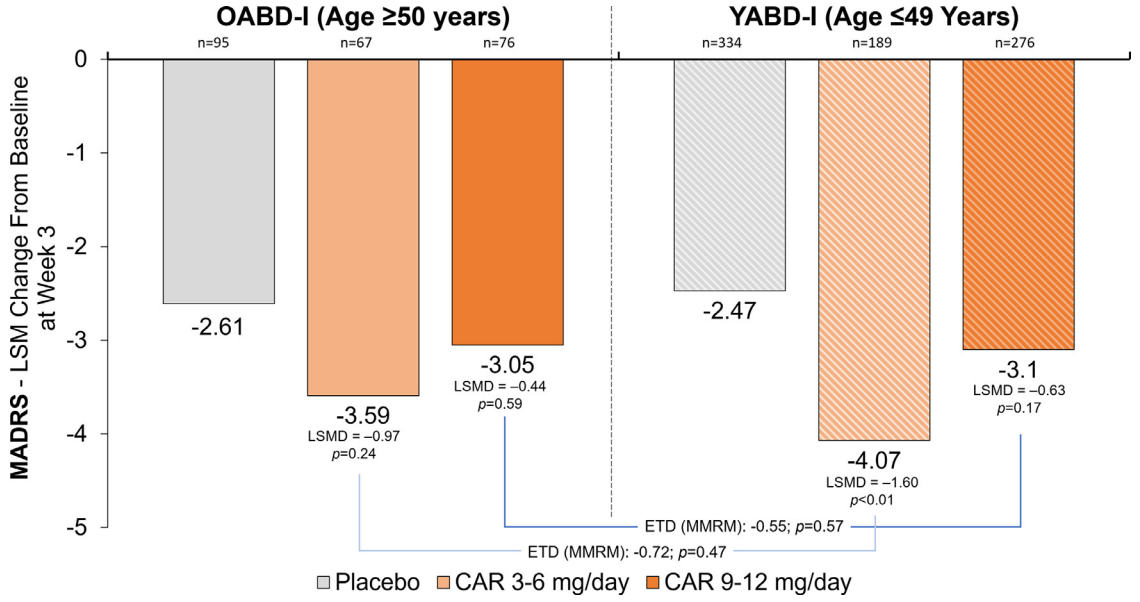
DISCUSSION

This post-hoc analysis of 6 pooled pivotal RCTs of cariprazine in both acute bipolar I depression and acute bipolar I mania/mixed episodes provides evidence to inform the pharmacologic management of OABD-I. Treatment of OABD-I is based on very limited evidence, particularly in the setting of acute episodes of bipolar depression, which tend to be more frequent and severe in older adults.[7] The only prospective RCT in the OABD-I setting was of lithium and divalproex in mania/mixed episodes of bipolar I disorder.[10] Other published research in OABD has included small open-label studies, case series or post-hoc analyses suggesting benefit of quetiapine, asenapine, aripiprazole or risperidone, in older individuals with acute mania/mixed episodes;[20–24] and quetiapine, lurasidone and lamotrigine in older individuals with acute bipolar depression, however the cut-off age for OABD varies across studies.[25–29]

The current analysis suggests that cariprazine has significant treatment effects at approved doses for both episodes of acute depression and mania/mixed episodes in OABD-I patients. These benefits were also evident in the secondary outcome of CGI-S scores, which may be a more inclusive representation of overall treatment effectiveness.

In the OABD-I sample from the acute bipolar I depression trials, the primary outcome analysis showed that only the pooled cariprazine dose group led to a statistically significant improvement vs. placebo in mean change from baseline in MADRS total score. In the YABD-I population, all cariprazine dose groups showed improved MADRS total score vs. placebo, possibly due to the higher number of patients

FIGURE 6. Changes in MADRS Scores from Baseline to Week 3, Bipolar I Mania/Mixed, by Treatment and Age Group, Pooled Data, ITT. CAR, cariprazine; ETD, estimated treatment difference; ITT, intent-to-treat; LSM, least squares mean; LSMD, least squares mean difference vs. placebo; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed model for repeated measures, treatment effect (cariprazine vs. placebo) for OABD-I vs. YABD-I population OABD-I, older-age bipolar I disorder; YABD, younger-aged bipolar I disorder.



and comparatively larger statistical power. However, across the analyses, findings consistently suggest that the 1.5 mg/day cariprazine dose is at least as efficacious as the 3.0 mg dose in both the OABD-I and YABD-I populations. This was reflected in the secondary outcomes: in the analysis of CGI-S scores among OABD-I patients and the analysis of the concentration item of the MADRS for both OABD-I and YABD-I patients, the cariprazine 1.5 mg/day group significantly separated from placebo, while the 3.0 mg/day group did not.

Recognizing that real-life dosing needs to be evaluated on a patient-by-patient basis, our findings support the recommended starting dose of 1.5 mg/day for cariprazine for individuals with acute episodes of bipolar I depression, regardless of age. More generally, this suggests that individuals with bipolar I depression respond similarly to treatment regardless of age. The tolerability of cariprazine was generally similar across OABD-I and YABD-I populations from the bipolar I depression clinical development program. Consistent with findings in the safety analyses across the development program, there were increased rates of akathisia in patients treated with cariprazine; this is not specific to either OABD-I or YABD-I patients. Of interest, the incidence of akathisia was lower for the OABD-I population than in YABD-I.

In OABD-I patients with acute mania/mixed episodes, the lower cariprazine dose range (3.0 to 6.0 mg/day) resulted in significantly higher mean change from baseline in YMRS score vs. placebo, while the higher-dose group (9.0 to 12.0 mg/day) did not. Similar findings were seen for YMRS response and remission rates and for mean change from baseline in CGI-S. By contrast, the effects of cariprazine were significantly greater than placebo in the YABD-I population for both doses across all efficacy analyses, except for mean change from baseline in MADRS score. The rates of discontinuation due to adverse events were numerically higher for the 9.0 to 12.0 mg/day compared to the 3.0 to 6.0 mg/day cariprazine group in OABD-I, but not in YABD-I. These findings suggest that for OABD-I, there is an ideal therapeutic range for cariprazine, from 3.0 to 6.0 mg/day. The 3.0 to 6.0 mg/day dose is also an effective dose for the YABD-I population (although the benefit extends beyond the recommended maximum dose of

TABLE 4. Safety Summary, Pooled Bipolar-I Manic / Mixed Trials (Safety Population)

	Older-aged Bipolar-I Disorder (OABD-I) Patients (Age ≥ 50 years)			Younger-age Bipolar-I Disorder (YABD-I) Patients (Age ≤ 49 years)		
Placebo (*n* = 96)	**Cariprazine**	**3-6 mg/d (*n* = 67)**	**Placebo (*n* = 337) 9-12 mg/d (*n* = 76)**		**Cariprazine 3-6 mg/d (*n* = 189)**	**9-12 mg/d (*n* = 276)**
Any TEAE, n (%)	60 (62.5)	50 (74.6)	64 (84.2)	228 (67.7)	160 (82.9)	212 (76.8)
Serious AE, n (%)	3 (3.1)	3 (4.5)	2 (2.6)	8 (2.4)	5 (2.6)	6 (2.2)
AE leading to discontinuation, n (%)	7 (7.3)	5 (7.5)	13 (17.1)	24 (7.1)	24 (12.4)	30 (10.9)
Abdominal Discomfort	2 (2.1)	4 (6.0)	7 (9.2)	-	-	-
Agitation	5 (5.2)	1 (1.5)	4 (5.3)	-	-	-
Akathisia	3 (3.1)	11 (16.4)	12 (15.8)	17 (5.0)	40 (20.7)	60 (21.7)
Constipation	7 (7.3)	5 (7.5)	12 (15.8)	17 (5.0)	11 (5.7)	29 (10.5)
Diarrhoea	2 (2.1)	4 (6.0)	6 (7.9)	19 (5.6)	7 (3.6)	14 (5.1)
Dizziness	3 (3.1)	3 (4.5)	4 (5.3)	15 (4.5)	16 (8.3)	15 (5.4)
Dry Mouth	1 (1.0)	2 (3.0)	4 (5.3)			
Dyspepsia	6 (6.3)	3 (4.5)	7 (9.2)	12 (3.6)	14 (7.3)	23 (8.3)
Extrapyramidal Disorder	6 (6.3)	6 (9.0)	4 (5.3)	16 (4.7)	21 (10.9)	49 (17.8)
Headache	12 (12.5)	11 (16.4)	14 (18.4)	43 (12.8)	23 (11.9)	30 (10.9)
Hypertension	1 (1.0)	2 (3.0)	4 (5.3)	-	-	-
Insomnia	6 (6.3)	6 (9.0)	8 (10.5)	20 (5.9)	17 (8.8)	20 (7.2)
Mania	2 (2.1)	2 (3.0)	6 (7.9)	-	-	-
Nausea	5 (5.2)	5 (7.5)	6 (7.9)	26 (7.7)	27 (14.0)	31 (11.2)
Pain in Extremity	-	-	-	4 (1.2)	10 (5.2)	8 (2.9)
Restlessness	3 (3.1)	4 (6.0)	4 (5.3)	7 (2.1)	14 (7.3)	18 (6.5)
Salivary Hypersecretion	1 (1.0)	4 (6.0)	2 (2.6)	-	-	-
Tremor	0	3 (4.5)	8 (10.5)	14 (4.2)	7 (3.6)	19 (6.9)
Vision Blurred	0	3 (4.5)	4 (5.3)	-	-	-
Vomiting	0	3 (4.5)	4 (5.3)	18 (5.3)	22 (11.4)	24 (8.7)

Notes: AE: adverse event; CAR: cariprazine; d: day; TEAE: treatment-emergent adverse event.

6.0 mg/day of cariprazine into the 9.0 to 12.0 mg/day range). These findings support the current recommended dosing range of cariprazine 3.0 to 6.0 mg/day for acute manic/mixed episodes of bipolar I disorder, regardless of age.

Reassuringly, these data suggest a low risk of treatment-emergent affective switch (from depression to mania or vice-versa) with cariprazine in both OABD-I and YABD-I populations. Similar to bipolar I depression analyses, safety was consistent with the original manic/mixed development program. There were increased rates of akathisia in patients treated with cariprazine in both OABD-I and YABD-I patients relative to placebo; these rates were numerically lower in the OABD-I population. However, the studies were not designed to compare adverse events between groups. It is possible that the OABD population may under-report akathisia, assuming it to be normal, while the YABD population may be more vigilant for this known adverse event and report it more actively. In general, drug-induced movement disorders or motor side effects are more common and persistent among older patients receiving antipsychotic medications.[30]

Replicated findings from the Global Aging & Geriatric Experiments in Bipolar Disorder (GAGE-BD) database studies found that bipolar disorder symptom severity is associated with poorer functioning in OABD, highlighting the importance of aggressively targeting symptoms regardless of age.[31,32] The current findings provide support on the choice of pharmacologic treatment options to effectively improve symptoms and functioning across the lifespan for people with bipolar disorder, while being well tolerated.

Key strengths of this analysis include the robustness of the source data—6 double-blind, placebo-controlled RCTs with a substantial number of patients aged 50 years or older (n = 475 OABD-I in bipolar I depression trials; n = 238 OABD-I in manic/mixed trials)—and the availability of data across different cariprazine doses.

In addition to the lack of a comparator arm in these studies, there are inherent limitations to these data

associated with the post-hoc nature of the analyses—i.e., the original studies were not prospectively designed to detect statistical differences across OABD-I and YABD-I subgroups. While these post-hoc data are helpful in the setting of limited research, new prospective studies in the OABD-I population would be welcome for any treatment used to treat bipolar disorders in adults. In terms of data limitations, ethnicity information was unavailable in the original trials and was accordingly not included in this analysis. Lastly, because there are global differences in companies with pharmaceutical marketing rights to cariprazine, indications may differ across countries. For example, while cariprazine is approved for the acute management of manic/mixed episodes and acute depression associated with bipolar 1 disorder in the United States and Canada, outside of North America it is only approved for the treatment of schizophrenia.[19,33]

In conclusion, treatment of OABD-I and YABD-I patients with cariprazine is similarly efficacious and well-tolerated for acute depressive episodes or acute manic/mixed episodes associated with bipolar I disorder.

CONCLUSIONS

This post-hoc analysis confirms the efficacy of cariprazine at the recommended dosing ranges across adult age groups for the management of acute depressive or manic/mixed episodes of bipolar I disorder. Within the adult patient population, age is not related to cariprazine treatment differences within the FDA-approved dose ranges. Future research should prospectively evaluate this and other treatments for acute and maintenance phases among OABD-I.

ACKNOWLEDGMENTS

AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Assistance with writing this manuscript was provided by Jordanna Bermack, David Haberl, Ian Hellstrom, and Scott Moffatt, of liV Medical Education Agency, funded by AbbVie Corporation. Original research relating to this manuscript was funded by Forest Laboratories LLC, an Allergan affiliate (Jersey City, New Jersey) and Gedeon Richter Plc (Budapest, Hungary). AbbVie and authors thank all the trial investigators and the patients who participated in the clinical trials that contributed to this manuscript.

AUTHORS CONTRIBUTIONS

Nicolas Garel: Conceptualization, Methodology, Writing (original draft, review, editing), Supervision.

Annemieke Dols: Conceptualization, Methodology, Writing (Original Draft, Review, Editing), Supervision.

Jun Yu: Methodology, Statistical Analysis, Review and Editing.

Christine Di Cresce: Conceptualization, Methodology, Writing (original draft, review, editing), Supervision.

Soham Rej: Conceptualization, Methodology, Writing (Original Draft, Review, Editing), Supervision.

Martha Sajatovic: Conceptualization, Methodology, Writing (Original Draft, Review, Editing), Supervision.

DISCLOSURES

*NG is currently receiving a grant from Le **Reseau québécois sur le suicide**, les troubles de l'humeur et les troubles associés.*

AD has received unrestricted grants from the VCVGZ, ZonMw and the Massey Bowden award.

JY is an employee of AbbVie Inc. (USA) and holds stock.

CDC is an employee of AbbVie Corporation (Canada) and holds stock.

SR has a salary award from the Fonds de recherche du Québec — Santé (FRQS), has grants from Mitacs, the Canadian Institutes for Health Research (CIHR), Mind and Life Institute, Doggone Foundation, the Jewish General Hospital Foundation, and the Social Sciences and Humanities Research Council of Canada (SSHRC), was on one steering committee meeting for Abbvie for a postmarketing observational study in 2022, and owns shares of Aifred Health.

MS has received research grants in the past 3 years from Neurelis, Intra-Cellular, Merck, Otsuka, Alkermes, International Society for Bipolar Disorders (ISBD), National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), Patient-Centered Outcomes

Research Institute (PCORI); consultant in the past year: Alkermes, Otsuka, Janssen, Lundbeck, Teva, received royalties in the past year from Springer Press, Johns Hopkins University Press, Oxford Press, UpToDate, and compensation for preparation of/participation in CME activities past year from American Physician's Institute (CME-toGo), Psychopharmacology Institute, American Epilepsy Society, Clinical Care Options,.

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 (e.g., protocols and Clinical Study Reports), 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.

This 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 and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and 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.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

You may also contact the corresponding author, NG, for additional information regarding the data that support the findings of this analysis.

The data from this article was presented at the 36th European College of Neuropsychopharmacology (ECNP) Congress, Barcelona, Spain, 7–10 October, 2023, to congress attendees.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jagp.2024.12.006.

References

1. Sajatovic M, Strejilevich SA, Gildengers AG, et al: A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. Bipolar Disord 2015; 17:689–704
2. Kessler RC, Berglund P, Demler O, et al: Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62:593–602
3. Hirschfeld RMA, Calabrese JR, Weissman MM, et al: Screening for bipolar disorder in the community. J Clin Psychiatry 2003; 64:53–59
4. Depp CA, Jeste DV: Bipolar disorder in older adults: a critical review. Bipolar Disord 2004; 6:343–367
5. Yu C, Sylvestre J-D, Segal M, et al: Predictors of psychiatric rehospitalization in older adults with severe mental illness. Int J Geriatr Psychiatry 2015; 30:1114–1119
6. Jeste DV, Alexopoulos GS, Bartels SJ, et al: Consensus statement on the upcoming crisis in geriatric mental health: research agenda for the next 2 decades. Arch Gen Psychiatry 1999; 56:848–853
7. Yatham L.N., Kennedy S.H., Parikh S.V., et al.: Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018; 20:97—170.
8. Arnold I, Dehning J, Grunze A, et al: Old age bipolar disorder—epidemiology, aetiology and treatment. Medicina (Kaunas) 2021; 57:587
9. Dols A, Kessing LV, Strejilevich SA, et al: Do current national and international guidelines have specific recommendations for older adults with bipolar disorder? A brief report. Int J Geriatr Psychiatry 2016; 31:1295–1300
10. Young RC, Mulsant BH, Sajatovic M, et al: GERI-BD: a randomized double-blind controlled trial of lithium and Divalproex in the treatment of mania in older patients with bipolar disorder. Am J Psychiatry 2017; 174:1086–1093
11. Beunders AJM, Orhan M, Dols A: Older age bipolar disorder. Curr Opin Psychiatry 2023; 36:397–404
12. 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; 333:328–340
13. 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; 176:439–448
14. 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; 22:372–384
15. 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; 173:271–281
16. Sachs GS, Greenberg WM, Starace A, et al: Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. J Affect Disord 2015; 174:296–302
17. Calabrese JR, Keck PE, Starace A, et al: Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated

with bipolar I disorder: a double-blind, placebo-controlled study. J Clin Psychiatry 2015; 76:284–292
18. Durgam S, Starace A, Li D, et al: The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. Bipolar Disord 2015; 17:63–75
19. VRAYLAR® (cariprazine): Prescribing information. AbbVie Inc, 2024
20. Sajatovic M, Calabrese JR, Mullen J: Quetiapine for the treatment of bipolar mania in older adults. Bipolar Disord 2008; 10: 662–671
21. Baruch Y, Tadger S, Plopski I, et al: Asenapine for elderly bipolar manic patients. J Affect Disord 2013; 145:130–132
22. Sajatovic M, Dines P, Fuentes-Casiano E, et al: Asenapine in the treatment of older adults with bipolar disorder. Int J Geriatr Psychiatry 2015; 30:710–719
23. Sajatovic M, Coconcea N, Ignacio RV, et al: Aripiprazole therapy in 20 older adults with bipolar disorder: a 12-week, open-label trial. J Clin Psychiatry 2008; 69:41–46
24. Madhusoodanan S, Brenner R, Araujo L, et al: Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia in 11 geriatric patients: a case series. J Clin Psychiatry 1995; 56:514–518
25. Sajatovic M, Calabrese JR, Mullen J: Quetiapine for the treatment of bipolar mania in older adults. Bipolar Disord 2008; 10:662–671
26. Sajatovic M, Forester BP, Tsai J, et al: Efficacy of lurasidone in adults aged 55 years and older with bipolar depression: post hoc analysis of 2 double-blind, placebo-controlled studies. J Clin Psychiatry 2016; 77:e1324–e1331
27. Forester BP, Sajatovic M, Tsai J, et al: Safety and effectiveness of long-term treatment with Lurasidone in older adults with bipolar depression: post-hoc analysis of a 6-month, open-label study. Am J Geriatr Psychiatry 2018; 26:150–159
28. Robillard M, Conn DK: Lamotrigine use in geriatric patients with bipolar depression. Can J Psychiatry 2002; 47:767–770
29. Sajatovic M, Gildengers A, Jurdi RKA, et al: Multisite, open-label, prospective trial of lamotrigine for geriatric bipolar depression: a preliminary report. Bipolar Disord 2011; 13:294–302
30. Saltz BL, Robinson DG, Woerner MG: Recognizing and managing antipsychotic drug treatment side effects in the elderly prim care companion. J Clin Psychiatry 2004; 6:14–19
31. Sajatovic M, Dols A, Rej S, et al: Bipolar symptoms, somatic burden, and functioning in older-age bipolar disorder: analyses from the Global Aging & Geriatric Experiments in Bipolar Disorder Database project. Bipolar Disord 2022; 24:195–206
32. Sajatovic M, Rej S, Almeida OP, et al: Bipolar symptoms, somatic burden and functioning in older-age bipolar disorder: a replication study from the global aging & geriatric experiments in bipolar disorder database (GAGE-BD) project. Int J Geriatr Psychiatry 2024; 39:e6057
33. VRAYLAR® (cariprazine): Product monograph. AbbVie Corporation, 2024