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Research paper

Cariprazine for the treatment of bipolar mania with mixed features: A post hoc pooled analysis of 3 trials

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ABSTRACT

Background: When bipolar I disorder (BP-I) mania is accompanied by subsyndromal depressive symptoms, a more complicated illness presentation results. To qualify for the mixed features specifier during mania, the *DSM-5* requires ≥3 "non-overlapping" depressive symptoms (DS); notwithstanding, concerns of this definition's ecological validity and implications for timely diagnosis remain.

Methods: Herein, patients were pooled from three similarly-designed pivotal trials of cariprazine compared to placebo for BP-I mania (NCT00488618/NCT01058096/NCT01058668) in post hoc analyses of mixed features using three criteria: ≥3 DS (DSM-5), ≥2 DS, and Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥10. Efficacy of cariprazine compared to placebo was assessed (Week 3) by Young Mania Rating Scale (YMRS) and MADRS scores and rates of mania response and remission.

Results: In pooled patients (N = 1037), cariprazine significantly improved mean YMRS scores compared to placebo for each criterion; LSMDs were ≥3 DS = -3.79 (P = .0248), ≥2 DS = -2.91 (P = .0207), and ≥10 MADRS = -5.49 (P < .0001). More cariprazine- than placebo-treated patients met YMRS response and remission criteria, reaching significance for response in ≥2 DS (34% versus 47%; number-needed-to-treat [NNT] = 8, P = .0483) and ≥10 MADRS

(31% versus 57%, NNT = 4, P < .0001) and for remission in ≥2 DS (27% versus 39%, NNT = 9, P = .0462), ≥10 MADRS (23% versus 44%, NNT = 5, P < .0001). Depressive symptoms were improved compared to placebo, reaching statistical significance in the MADRS ≥10 subgroup (LSMD = -1.59, P = .0082).

Limitations: Post hoc analysis, MADRS < 18 entry criterion may have prevented assessment of MADRS changes.

Conclusions: Cariprazine significantly reduced manic and depressive symptoms in patients with mixed features with differential efficacy across the subgroups analyzed herein.

1. Introduction

Mixed states in psychiatry have historical, phenomenological, conceptual, and clinical implications (McIntyre, 2017). Mixed states in bipolar disorder can present in a wide-range of clinical presentations (e.g. mania with depression, mania with subsyndromal depression, or hypomania with depression). Individuals presenting with a manic episode often manifest subsyndromal depressive symptomatology, and the presence of subsyndromal depressive symptoms during a manic episode can interfere with functional recovery (Gitlin et al., 2011), increase the likelihood of relapse, particularly into depression (Tohen et al., 2006), are longer in duration (Perugi et al., 1997), and are associated with both lower rates of recovery and higher rates of chronicity (Gonzalez-Pinto et al., 2007; Martin-Carrasco et al., 2012). In a systematic review, it was reported that the prevalence of patients with 3 or more symptoms of opposite mood-polarity for patients with bipolar disorder was approximately 35%, (Vazquez et al., 2018) but the percentage of individuals presenting with mixed states has been variably reported reflecting heterogeneity in how mixed states have been operationalized. Moreover, the complexity and hazards posed by mixed states is further underscored by the high rates of suicidality (Gonzalez-Pinto et al., 2007; Goldberg JF and Portera, 1999; Goldberg JF and Portera, 2000; Hantouche EG and Azorin, 2006; Tondo L and Baldessarini, 2003), comorbidity (Gonzalez-Pinto et al., 2007), and greater hospitalizations

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(Shim et al., 2015) associated with mixed states relative to manic symptoms without depressive features. From an interventional perspective, some FDA-approved agents (e.g. lithium) for bipolar mania may be less effective in individuals presenting with mania with mixed features (Freeman et al., 1992). A recent literature review concluded that atypical antipsychotics, newer anticonvulsants and electroconvulsive therapy are currently the best options for the treatment of mixed states in patients with bipolar disorder, but that most have only shown limited effectiveness (Muneer, 2017).

Timely and accurate diagnosis and treatment of mixed episodes is a critical modifiable deficiency in the management of adults with bipolar l disorder (Association, 2013). The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-*IV*-TR) (Association, 2000), defined a mixed state as the syndromal co-occurrence of both a major depressive and manic episode, but this was associated with a relatively high rate of misdiagnosis and consequently the selection and prescription of inappropriate treatments (Kupfer et al., 2011). As a result, the DSM-5 supplanted the previous definition with a new nosological entity, the "with mixed features" specifier (Association, 2013), which generally refers to the presence of a syndromal manic episode with 3 or more depressive symptoms, or a major depressive episode with 3 or more hypomanic symptoms; in both instances the opposite pole symptoms must be "non-overlapping."

Most clinical studies evaluating the efficacy of treatments for acute manic and/or mixed episodes have used the DSM-*IV*-TR criteria (Calabrese et al., 2015; Durgam et al., 2015; Earley et al., 2017; Sachs et al., 2015; Muralidharan et al., 2013), with no agent approved by the FDA for the treatment of acute mania using the DSM-5 "with mixed features" specifier criteria. Post hoc analyses however have been conducted with select agents wherein a proxy definition of mixed features according to DSM-5 were operationalized (McIntyre et al., 2013; Tohen et al., 2014).

Cariprazine, an atypical antipsychotic, is a potent dopamine D_3 and D_2 receptor partial agonist with preferential binding to D_3 receptors and is FDA approved for the treatment of adults with schizophrenia, as well as acute manic, acute mixed, or depressive episodes associated with bipolar I disorder (VRAYLAR, 2019). The three pivotal trials of cariprazine in patients with bipolar I disorder were similarly designed (NCT00488618, NCT01058096, NCT01058668) (Calabrese et al., 2015; Durgam et al., 2015; Sachs et al., 2015); patients had a current manic episode and subsyndromal depressive features were permitted (note that the inclusion/exclusion criteria of the trials required all patients to have Montgomery-Åsberg Depression Rating Scale [MADRS] (Montgomery and Åsberg, 1979) total scores <18).

We hypothesized that cariprazine would be efficacious in patients with mania and mixed features. Thus, the objectives of the present post hoc analyses included determining the frequency of patients from these pooled studies with mania and mixed features meeting the DSM-5 criteria (≥ 3 depressive symptoms) and two proxy definitions: ≥ 2 depressive symptoms (which also includes all patients in the ≥ 3 depressive symptoms group), and a MADRS total score ≥ 10. The rationale for the former proxy definition is that patients with a current manic episode and ≥ 2 depressive symptoms present clinical differences (e.g. greater levels of anxiety (Swann et al., 2009)) and clinical outcomes (e.g. less responsiveness to lithium (Swann et al., 1997)) compared to those with ≤ 1 depressive symptoms, which has led some researchers to hypothesize that the presence of 2 or more depressive symptoms may be sufficient to identify a mixed episode (Tohen et al., 1990; McElroy et al., 1992). The MADRS total score ≥ 10 proxy definition was selected to be a slightly more stringent criterion for remission from depression than was used in previously reported bipolar depression atypical antipsychotic studies, which required a MADRS total score less than or equal to 12 for patients to be considered remissed (Suppes et al., 2010; Jean Endicott and Minkwitz, 2006). The effect of cariprazine treatment of manic and depressive symptoms was compared to placebo in these subpopulations of patients with mania and mixed features.

2. Methods

2.1. Study centers, patient populations, and investigational product

Data from three phase 2/3 clinical trials were pooled. Details of the study designs and patient populations have been previously published (Calabrese et al., 2015; Durgam et al., 2015; Sachs et al., 2015). The study centers were in the following countries: the United States, Russia, India, Romania, Ukraine, Serbia, and Croatia. Patients for each trial were screened and recruited in compliance with the International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki. Each study was approved by institutional review boards for U.S. sites or ethics committees and government agencies for other sites. Patients provided written informed consent after receiving a complete description of the study and prior to initiation.

The studies were randomized, double-blind, placebo-controlled 3-week pivotal trials in adults patients (18–65 years) who met the DSM-*IV*-TR criteria for bipolar I disorder and a current manic or mixed episode (Young Manic Rating Scale [YMRS] total score (Young et al., 1978) ≥ 20, scores ≥ 4 on ≥ 2 of 4 YMRS items: irritability, speech, content, disruptive/aggressive behavior) without rapid cycling or cognitive or psychotic disorders. Patients were voluntarily hospitalized with a primary diagnosis of mania, and hospital admission must have been a result of the current manic episode and must have occurred less than 14 days prior to screening. Patients with MADRS total scores <18 were permitted in the studies, and patients could not be in their first manic episode. Principal exclusion criteria were an axis I disorder other than bipolar I disorder, an axis II disorder of sufficient severity to interfere with the study, substance abuse or dependence (within prior 3 months), suicide risk, or being at imminent risk of harm to self or others.

Specific medications for insomnia, extrapyramidal symptoms, and agitation/restlessness/irritability/hostility were permitted, but other concomitant psychotropic medications were prohibited.

2.2. Treatments

The studies had a washout period (up to 1 week), 3-week double-blind treatment period, and 2-week safety follow-up period. Patients were hospitalized at screening and for at least 2 weeks of the investigational treatment period. In each double-blind treatment period, patients were randomized to placebo or cariprazine (3.0–12.0 mg/d for RGH-MD-31[19] and RGH-MD-32[21] [flexible dose design], and 3.0–6.0 mg/d or 6.0–12.0 mg/d for RGH-MD-33[18] [fixed/flexible dose design]). In RGH-MD-31 and RGH-MD-32 patients were randomized 1:1 to cariprazine or placebo, and RGH-MD-33 patients were randomized 1:1:1 to placebo, cariprazine 3.0–6.0 mg/d, or 6.0–12.0 mg/d.

2.3. Assessments

YMRS and Clinical Global Impressions – Severity (CGI-S) (Guy, 1976) assessments were conducted at screening, baseline, days 2, 4, 7, 11, 14, and 21. Clinical Global Impressions – Improvement (CGI-I) (Guy, 1976) assessments were conducted at days 2, 4, 7, 11, 14, and 21. MADRS was conducted at baseline, screening, days 7, 14, and 21. Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) scores were collected at baseline and days 14 and 21.

For the ≥ 3 depressive symptoms (DSM-5) and ≥ 2 depressive symptoms definitions, the 6 possible depressive symptoms were each linked to a MADRS and/or PANSS item as follows: depressed mood (MADRS item1 or 2), fatigue, loss of energy (MADRS item 7), diminished interest/pleasure (MADRS item 8), psychomotor retardation (PANSS item G7), worthlessness, guilt feelings (MADRS item 9), and suicidal thoughts (MADRS item 10). Symptom presence was defined as a MADRS total score ≥ 1 or PANSS score ≥ 2 for each item. These

criteria were based on prior post hoc analyses of second-generation antipsychotic efficacy in treatment of mixed features (McIntyre et al., 2013; Tohen et al., 2014).

2.4. Statistical analyses

The intent-to-treat (ITT) patient populations (at least 1 dose of study medication and at least 1 post-baseline YMRS assessment) were pooled for post hoc analyses. Efficacy assessments were change from baseline to Week 3 in YMRS and MADRS total scores, and rates of YMRS response (≥50% improvement) and remission (YMRS total score ≤12). The definitions for YMRS response and remission were those used in the original studies of cariprazine efficacy in bipolar I mania (Calabrese et al., 2015; Durgam et al., 2015; Sachs et al., 2015). Change from YMRS or MADRS baseline was analyzed using a mixed-effect model repeated measure (MMRM) approach, and study, treatment group, time, and treatment group-by-time interaction were treated as categorical fixed effects and the baseline value and baseline-by-time interaction as covariates; an unstructured covariance matrix was used to model the covariance of within-patient scores. Changes from baseline for cariprazine compared to placebo were compared at Week 3 using the least-squares mean difference (LSMD). The YMRS response and remission *P*-values were obtained using logistic regression with study and treatment group as factors and baseline as covariate with missing data imputed using last observation carried forward (LOCF). Potential confounders (age, sex, race, and number of previous hospitalizations) were added to the model as covariates in sensitivity analyses.

3. Results

Of 1037 in the ITT population pooled from the original studies, the numbers of patients with mixed features at baseline using the three definitions were: 141 (13.6%) with ≥3 depressive symptoms, 269 (25.9%), with ≥2 depressive symptoms, and 453 (43.7%) with MADRS ≥10 (**Table 1**). Patient demographics and psychiatric history at baseline (**Table 2**) were generally comparable across each definition.

3.1. Effect of cariprazine on mania (YMRS total score)

Cariprazine treatment significantly improved manic symptoms (mean YMRS score changes) from baseline to Week 3 compared to placebo in each definition of mixed features (**Fig. 1**). LSMDs (P-value), effect sizes were: ≥3 depressive symptoms = −3.79 (*P* = .0248), −0.4081; ≥2 depressive symptoms = −2.91 (*P* = .0207), −0.2891; and ≥10 MADRS: −5.49 (*P* < .0001), −0.5362.

3.2. Effect of cariprazine on manic symptoms response

A greater proportion of patients with mixed features met criteria for YMRS response when treated with cariprazine versus placebo (**Fig. 2a**). Differences were statistically significant for cariprazine in the ≥2 depressive symptoms group (47%) versus placebo (34%; *P* = .0483, number needed to treat [NNT] = 8, effect size = 0.2626) and MADRS total score ≥10 group (57%) versus placebo (31%; *P* < .0001, NNT = 4, effect size = 0.5277), and were numerically greater in the ≥3 depressive symptoms group (43%) versus placebo (34%; *P* = .2608, NNT = 11, effect size = 0.1888).

Table 1
Numbers of patients in manic episodes with depressive features at baseline, by definition, in pooled intent-to-treat population (*N* = 1037) by treatment type from pivotal studies: RGH-MD-31, RGH-MD-32, and RGH-MD-33.

	Placebo (*n*)	Cariprazine (*n*)	Total (*N*)
≥3 depressive symptoms*	62	79	141
≥2 depressive symptoms	115	154	269
MADRS total score ≥10	172	281	453

*DSM-5 definition.

3.3. Effect of cariprazine on mania remission

Rates of YMRS remission were greater with cariprazine for each mixed feature criterion compared to placebo (**Fig. 2b**). Cariprazine-treatment numerically improved remission rates in patients with ≥3 depressive symptoms (37%) versus placebo (26%; *P* = .1224, NNT = 9, effect size = 0.2360). Cariprazine significantly improved rates of remission for patients with ≥2 depressive symptoms (39%) versus placebo (27%; *P* = .0462, NNT = 9, effect size = 0.2564) and MADRS total score ≥10 (44%) versus placebo (23%; *P* < .0001, NNT = 5, effect size = 0.4538).

3.4. Effect of cariprazine on depressive symptoms

Depressive symptom improvement was numerically greater with cariprazine compared to placebo (**Fig. 3**), but the results were only statistically significant for the ≥10 MADRS subgroup; MADRS change from baseline to Week 3 versus placebo, LSMDs (P-value), effect sizes for DSM-5 definition (≥3 depressive symptoms) = −1.54 (*P* = .1953), −0.2294; ≥2 depressive symptoms = −0.17 (*P* = .8324), −0.0190; and ≥10 MADRS = −1.59 (*P* = .0082), −0.2610.

3.5. Sensitivity analyses

Age, sex, race, and number of previous hospitalizations were added to each model (Sections 3.1–3.4; **Figs. 1–3**) as covariates in sensitivity analyses; the results were not appreciably affected.

4. Discussion

Depressive symptoms were common in individuals meeting DSM-*IV*-TR criteria for mania in these studies. As expected, a higher frequency of patients in this pooled population met the criteria for mixed features when broader definitions than the DSM-5 were used: ~14% met the DSM-5 criteria for "with mixed features", ~25% had 2 or more depressive symptoms, and ~44% had a MADRS total score of 10 or higher at baseline. The proportion of patients in a current manic episode with ≥3 and ≥2 depressive symptoms were lower than those previously reported in some other studies, possibly because the current analysis used data from studies that excluded patients with MADRS total score ≥18 and thus selected patients with less depressive symptomatology than the general patient population with bipolar I disorder and mania (e.g. clinical judgement in a cross-sectional study of patients with bipolar I disorder who were admitted to specialized units) (Bauer et al., 2005; Vieta et al., 2014; Vieta and Morralla, 2010). The impetus to evaluate the efficacy of cariprazine across broader definitions of mixed features was provided by the observation that mixed features are frequently underrecognized, their association with high levels of morbidity and comorbidity (e.g. alcohol use disorder and cardiovascular disease), and less favorable disease course and outcomes relative to manic episodes without depressive symptoms (McIntyre et al., 2013; McIntyre et al., 2015).

Several mood stabilizers and atypical antipsychotics are recommended for the treatment of mixed episodes (Ostacher et al., 2016). Treatment with more than one agent is very common in adults with mixed features, increasing the likelihood of adverse events and safety concerns. Cariprazine, an atypical antipsychotic, has replicated evidence of efficacy in manic or mixed episodes associated with bipolar I disorder in adults (VRAYLAR, 2019), as well as in the treatment of bipolar I depression with positive results reported for three phase 2/3 trials: Durgam et al. (2016), Earley et al. (2019a) and NCT02670538 (manuscript submitted). (Earley et al., 2019b) Cariprazine efficacy in

Table 2
Patient baseline characteristics by treatment group.

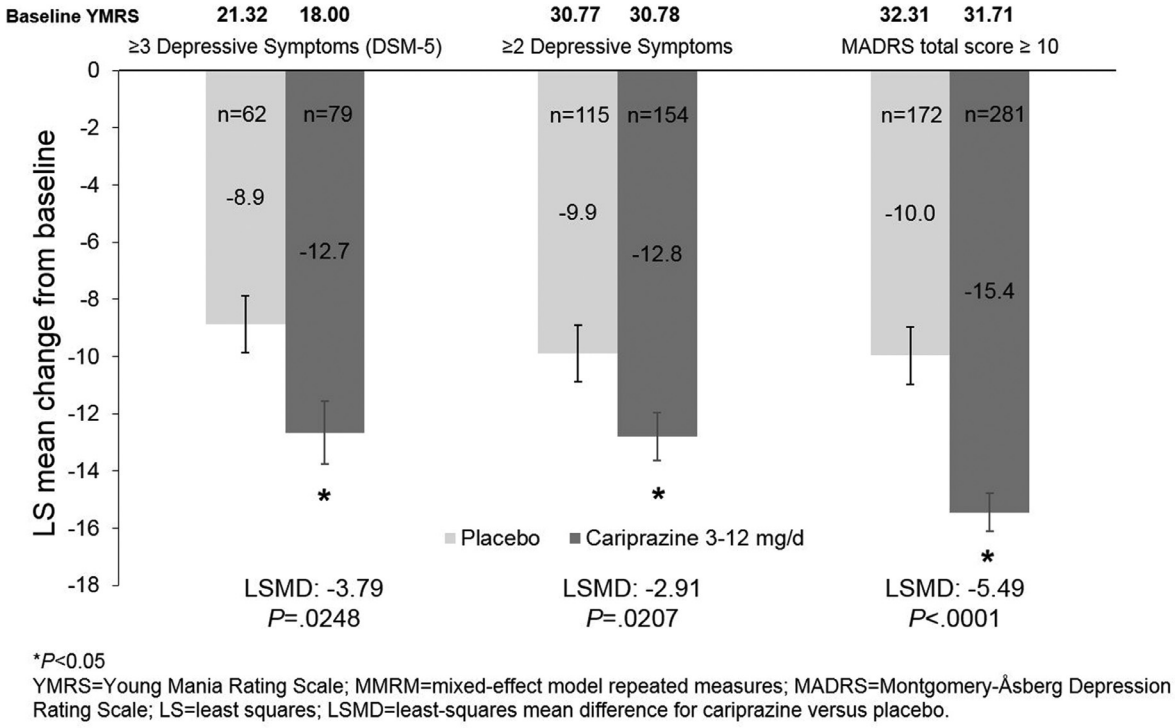
	≥3 depressive symptoms (DSM-5)		≥2 depressive symptoms		MADRS total score ≥10	
	n	%	*n*	%	*n*	%
Female	62	43.97	121	44.98	204	45.03
Male	79	56.03	148	55.02	249	54.97
Race						
White	81	57.45	151	56.13	273	60.26
Black or African American	51	36.17	103	38.29	148	32.67
Asian	5	3.55	10	3.72	25	5.52
Other	4	2.84	5	1.86	7	1.55
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age, years	39.88	11.78	30.37	12.58	40.74	11.08
BMI, kg/m^2	28.70	5.71	28.33	5.37	28.36	5.23
Psychiatric History						
	n	**%**	***n***	**%**	***n***	**%**
Attempted suicide in the past year	49	35.00	92	34.33	138	30.53
Current episode of bipolar I disorder ≤30 days[a]	110	78.01	211	78.44	352	77.70
Current episode of bipolar I disorder >30 days[a]	31	21.99	58	21.56	101	22.30
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Duration of bipolar I disorder, yrs	14.90	9.36	15.26	9.64	15.08	9.68
Age of onset, yrs	31.20	12.70	30.37	12.58	29.55	12.09
Number of previous hospitalizations	4.42	5.43	4.06	4.98	3.76	4.81

BMI = body mass index; *n* = Number of patients within a specific category.
[a] Duration of current episode of bipolar 1 disorder = time between the date of informed consent and the date of onset of current episode of bipolar 1 disorder.

treating depressive symptoms has been hypothesized because it exhibits high affinity and occupancy for dopamine D_3 receptors that are highly expressed in brain regions involved in cognitive function, motivation, and reward-related behavior (Carnicella et al., 2014) and its engagement with these receptors may positively affect cognition (Marder et al., 2016), mood, and/or measures of reward, including reduction of anhedonia (Gross and Drescher, 2012; Nakajima et al., 2013; Papp et al., 2014). The high affinity for, and occupancy of, both D_3 and D_2 receptors by cariprazine is a unique characteristic not found in other atypical antipsychotics.

In the pivotal trials of cariprazine for the treatment of manic and mixed episodes, patients were included based on DSM-*IV*-TR criteria, and those with mixed features were permitted in the trials (Calabrese et al., 2015; Durgam et al., 2015; Sachs et al., 2015). The post hoc analyses herein investigated the efficacy of cariprazine versus placebo in using DSM-5 and proxy criteria for defining patient subsets with mixed features. Because the original studies required a DSM-*IV*-TR based diagnosis of bipolar I disorder with manic or mixed features and other recruitment criteria (e.g., MADRS total scores <18), the pooled population may not have been representative of the entire population with mixed features.

The results of these analyses indicate that cariprazine 3–12 mg/d significantly improved manic symptoms in patients with mania together with ≥3 depressive symptoms, ≥2 depressive symptoms, or MADRS total score ≥10. Additionally, cariprazine 3–12 mg/d significantly increased rates of manic symptom response at Week 3 in



*P<0.05
YMRS=Young Mania Rating Scale; MMRM=mixed-effect model repeated measures; MADRS=Montgomery-Åsberg Depression Rating Scale; LS=least squares; LSMD=least-squares mean difference for cariprazine versus placebo.

Fig. 1. YMRS total score (MMRM) mean (± standard error) change from baseline to week 3 in patients with mixed features.

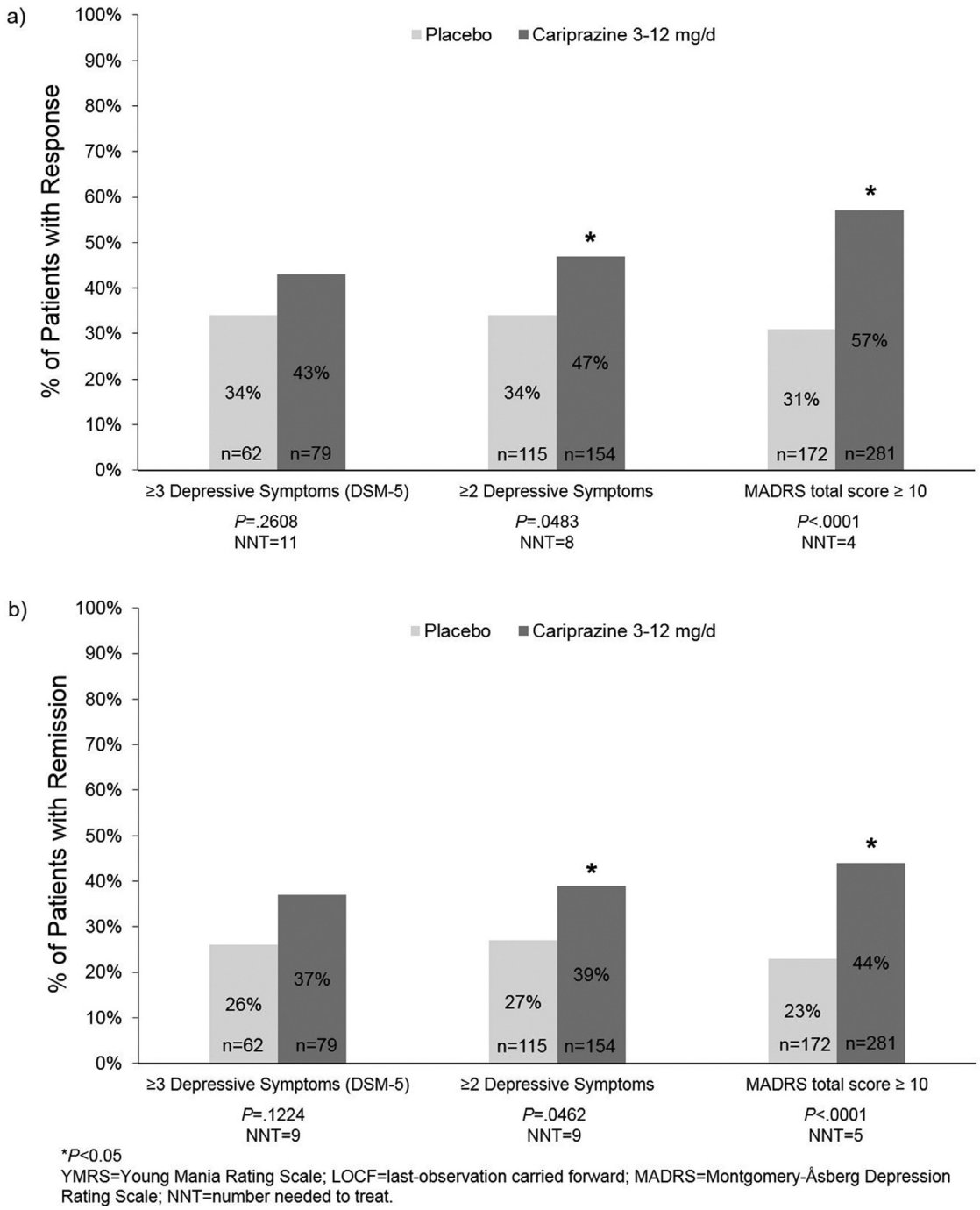


Fig. 2. YMRS total score a) response (≥50% improvement from baseline in total score; LOCF) rates at week 3 in patients with mixed features, and b) remission (total score ≤12; LOCF) at week 3 in patients with mixed features.

patients with ≥2 depressive symptoms or MADRS total score ≥10, but rates were only numerically improved in patients with the DSM-5 definition of mixed features (≥3 depressive symptoms). Rates of remission from manic symptoms were also significantly improved in the ≥2 depressive symptoms or MADRS total score ≥10 subpopulations. The inability to detect statistically significant differences in manic symptom improvement compared to placebo in patients with ≥3 depressive symptoms may be partially attributed to small sample size ($n < 80$ for each treatment group).

Depressive symptom improvement was numerically greater with cariprazine compared to placebo for each subgroup of patients with mixed features, but it was only statistically significant for the MADRS total score ≥10 group. A possible explanation for the lack of significant reduction in MADRS total scores in 2 of the 3 groups is the relatively low levels of depressive symptoms of all patients due to the inclusion criteria (MADRS total score <18 at baseline) in the original studies. For example, it may be difficult to detect significant reductions in depressive symptoms when patients entered the study with few symptoms.

In this pooled population, mean YMRS scores did not increase from baseline to week 3, but the mean MADRS scores decreased, indicating the lack of induction of mania or "manic switch" when the depressive symptoms of bipolar I disorder were treated. Notably, treatment of depressive symptoms in patients with bipolar I disorder with conventional antidepressants can increase the risk of mood destabilization, particularly the induction of hypomanic and manic episodes, with long-term monotherapy use (Altshuler et al., 1995; McGirr et al., 2016).

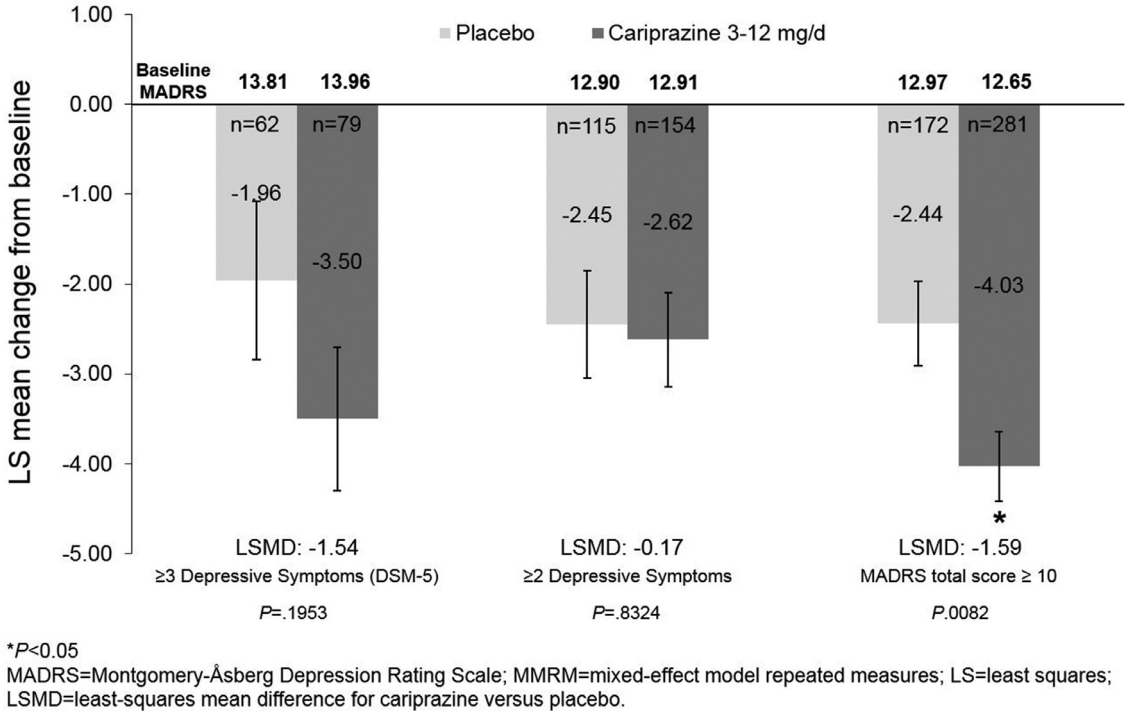


Fig. 3. MADRS total score (MMRM) change from baseline to week 3 in patients with mixed features.

Identification of pharmacological agents that are effective in treating mania with either symptomatic or subsyndromal levels of depression is of high clinical value due to the prevalence of patients with mixed features and the consequences of these episodes when untreated. This study analyzed several definitions of mixed features, including the DSM-5 criteria and other definitions that may represent subsyndromal levels of depression. Results indicate that cariprazine may be effective in treating manic and depressive symptoms in patients with mixed features as defined by the DSM-5 and other criteria. The results suggest that cariprazine may lower manic symptoms, induce remission from mania, and decrease depressive symptoms while not increasing the risk of manic or depressive switch. Additional future research may be warranted to evaluate the efficacy of cariprazine in patients with other depressive conditions such as bipolar II depression and treatment-resistant bipolar disorder.

4.1. Limitations

There are methodological aspects that limit the inferences from and interpretations of these analyses. First, these analyses were conducted post hoc; the original studies were not specifically designed to evaluate the efficacy of cariprazine in patients using the DSM-5 and two proxy definitions of mixed features. Also, the proxy definitions of mixed features (≥ 2 depressive symptoms and MADRS total score ≥ 10) have only been investigated or validated in two previous studies. Next, the results may not be generalizable to certain other patients because they are limited by the inclusion and exclusion criteria of the original studies; for example, patients with suicidal behavior and certain psychiatric diagnoses were excluded. The flexible and fixed/flexible dose designs of the original studies prevent the analysis of the efficacy of individual cariprazine doses, and the lack of an active comparator prevents the direct assessment of relative efficacy. The requirement of a DSM-*IV*-TR-based diagnosis of bipolar I disorder with mixed or manic features in the primary studies may have prevented the inclusion of all patients with mixed features in these analyses. Additionally, the relatively short 3-week duration of treatment in the original studies may have impaired the ability to observe effects on depressive symptoms that might require longer treatment, and also limit translation of results to clinical practice. Finally, a MADRS total score <18 was an inclusion criterion in each of the original studies; as such, patients had relatively low baseline depressive symptoms and the ability to assess MADRS total score changes may have been limited.

4.2. Conclusions

Cariprazine 3–12 mg/d was efficacious as both an antimanic and antidepressive therapy in the treatment of patients with mixed features defined by mania with a MADRS total score ≥ 10. Manic symptoms were significantly improved in patients with ≥ 2 depressive symptoms and using some measures in patients with the DSM-5 mixed features criteria (≥ 3 depressive symptoms). Cariprazine may represent a novel treatment option for treating mixed features associated with bipolar I disorder.

Disclosure

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Author statement

The authors have read and approved the final version of the manuscript "*Cariprazine for the Treatment of Bipolar Mania with Mixed Features: A Post Hoc Pooled Analysis of 3 Trials*" being submitted. We confirm that it is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Drs. Roger S. McIntyre, Prakash S. Masand, Willie Earley, and Mehul Patel made substantial contributions to the conception, design, and interpretation of the analyses, provided input and revisions to the drafting of the manuscript, read and approved the final current version of the manuscript, agree to be held accountable for all aspects of the manuscript, and ensure that questions related to the accuracy or integrity of any part of the work will be appropriately investigated and resolved.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.07.020.

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