Received: 22 May 2017 | Accepted: 12 October 2017

DOI: 10.1111/ijcp.13037

ORIGINAL PAPER

WILEY THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Global improvement with cariprazine in the treatment of bipolar I disorder and schizophrenia: A pooled post hoc analysis

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Funding information
Forest Research Institute, Inc., an Allergan affiliate; Gedeon Richter Plc

Summary

Introduction: Global rating scale measures are useful for assessing the clinical relevance of patient change. Cariprazine, a dopamine D_3 and D_2 receptor partial agonist, is FDA-approved for the adult treatment of acute manic/mixed episodes of bipolar I disorder and schizophrenia. Post hoc evaluations of Clinical Global Impressions-Severity (CGI-S) scores from the cariprazine pivotal trials in both indications were conducted.

Methods: Data from 3 bipolar mania and 3 schizophrenia trials were pooled by indication (bipolar disorder = 1033; schizophrenia = 1466). Cariprazine- and placebo-treated patients were categorised by baseline CGI-S scores; the proportion of patients who improved from more severe categories at baseline to less severe categories at end-point was evaluated using a logistic regression model. Correlations between Young Mania Rating Scale and Positive and Negative Syndrome Scale total score changes and category shifts were also evaluated.

Results: In both disease states, more cariprazine- than placebo-treated patients had improved CGI-S scores at end-point; more placebo-treated patients had worse end-point scores. More cariprazine- vs placebo-treated patients shifted from the extremely/severely ill to mildly ill/better category (bipolar disorder = 55% vs 36%, odds ratio [OR] = 2.1; $P = .09$; schizophrenia = 42% vs 18%, OR = 3.4, $P<.01$). ORs was statistically significant in favour of cariprazine in shifts from marked and moderate illness to borderline/normal in both indications ($P < .05$). Correlations between rating scale improvement and category shift were greatest in patients with extreme/severe baseline illness for bipolar disorder (−0.853) and schizophrenia (−0.677).

Conclusions: Post hoc analyses showed that more cariprazine- than placebo-treated patients with bipolar mania or schizophrenia had statistically significant and clinically meaningful CGI-S improvement.

1 | INTRODUCTION

In clinical trials of bipolar mania and schizophrenia, the efficacy of a pharmacological intervention is frequently determined by measuring change in symptom severity on an efficacy rating scale such as the Young Mania Rating Scale (YMRS)[1] or the Positive and Negative Syndrome Scale (PANSS).[2] Although mean change in score on a symptom-based rating scale is a routinely employed measure to determine treatment effect in drug research, there are few standard benchmarks for determining clinically significant improvement and

it may be difficult to interpret the clinical relevance of the results.[3] In contrast, a global rating scale may be more useful for assessing the clinical relevance of patient change, and when used in addition to a symptom-specific rating scale, the aggregate outcomes may provide a comprehensive view of patient improvement or deterioration.

The Clinical Global Impressions (CGI) Scale[4] was designed to provide a clinician-rated view of a patient's global functioning before and after the initiation of study medication in clinical trials across psychiatric disease states.[5] Used in virtually all trials in psychiatric indications to suit regulatory requirements, the measure comprises 2 companion components, CGI-Severity (CGI-S) and -Improvement (CGI-I). At each study visit, an experienced clinician makes an informed judgement about the overall status of a patient including severity of illness and the impact of the illness on functioning; ratings take into account all available information, including patient history, symptoms, behaviour and psychosocial condition.[5] CGI anchor scores are connected to established clinical descriptions; the resulting global impression is meant to provide a useful outcome to help clinicians determine the clinical relevance of patient change.

Cariprazine, a dopamine D_3 and D_2 receptor partial agonist that preferentially binds to D_3 receptors, is approved by the US Food and Drug Administration for the treatment of adult patients with schizophrenia (1.5 to 6 mg/d) and manic or mixed episodes associated with bipolar I disorder (3 to 6 mg/d). Cariprazine has demonstrated efficacy in three 3-week randomised, double-blind, placebo-controlled studies in bipolar mania[6-8] and three 6-week randomised, double-blind, placebo- and active-controlled studies in schizophrenia.[9-11] In each of these studies, a significant difference vs placebo was seen in change from baseline on the primary efficacy measure (YMRS total score in the bipolar mania studies and PANSS total score in the schizophrenia studies); the CGI-S was the secondary efficacy measure in each study. In one additional study conducted in patients with schizophrenia (RGH-MD-03),[12] cariprazine did not separate from placebo on the primary efficacy parameter, change from baseline in PANSS total score.

To better characterise the clinical relevance of cariprazine treatment in improving disease severity, we conducted post hoc analyses based on CGI-S data from the positive randomised, controlled studies in bipolar disorder and schizophrenia. In practice, evaluating patient change using the global CGI-S rating in addition to assessing mean change on an efficacy rating scale may provide a clinically meaningful and statistically sound way of assessing of patient progress over time.

What's known

The Clinical Global Impressions Scale (CGI) is a validated rating scale that is regularly used in clinical trials. A global view of the patient, including illness severity, level of distress and impairment, and the impact of the illness on functioning is captured through informed clinical judgement. Beyond use in clinical trials, the CGI has utility for practicing clinicians who wish to track patient progress over time.

What's new

In post hoc analyses, greater improvements in CGI-Severity (CGI-S) measures were seen in cariprazine- vs placebo-treated patients with bipolar disorder or schizophrenia. Clinically relevant shifts to less severe disease were also apparent in both disease states. This suggests that cariprazine was associated with clinically meaningful improvement and clinicians may be able to assess improvement based on clinical judgement as well as rating scale change.

2 | METHODS

2.1 | Study design and patients

To assess CGI-S outcomes in patients with bipolar mania, data were pooled from 3 positive phase II/III, randomised, 3-week double-blind placebo-controlled studies. RGH-MD-31 (NCT00488618)[7] and RGH-MD-32 (NCT01058096)[8] were flexible-dose studies with cariprazine 3-12 mg/d; RGH-MD-33 (NCT01058668)[6] was a fixed/flexible-dose study with 2 cariprazine treatment arms (3-6 mg/d or 6-12 mg/d).

To assess CGI-S outcomes in patients with schizophrenia, data were pooled from the 3 positive phase II/III, randomised, 6-week double-blind placebo- and active-controlled trials. RGH-MD-04 (NCT01104766)[9] was a fixed-dose study (cariprazine 3 mg/d or 6 mg/d); aripiprazole was included as an active control. RGH-MD-05 (NCT01104779)[11] was a fixed/flexible-dose study with 2 cariprazine treatment arms (3-6 mg/d or 6-9 mg/d). RGH-MD-16 (NCT00694707)[10] was a fixed-dose study (cariprazine 1.5 mg/d, 3 mg/d or 4.5 mg/d); risperidone was included as an active control. Cariprazine doses were pooled for post hoc analyses in each disease state (schizophrenia, 1.5-9 mg/d; bipolar mania, 3-12 mg/d).

Detailed methods of the included studies have been previously published.[6-11] Briefly, each study had a washout period of up to 1 week, followed by 3 weeks (bipolar mania studies) or 6 weeks (schizophrenia studies) of double-blind treatment and a 2-week safety follow-up period. Patients met *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR)[13] criteria for bipolar I disorder (acute manic or mixed episode) or schizophrenia (acute exacerbation); all patients were hospitalised during screening and for at least the first 2 weeks of treatment.

Inclusion and exclusion criteria for participants were typical of clinical studies in schizophrenia and bipolar I. Patients who participated in the constituent bipolar I disorder studies were 18-65 years of age and were required to have a YMRS score ≥ 20 and a score ≥ 4 on at least 2 of 4 YMRS items (irritability, speech, content, disruptive/aggressive behaviour); patients with rapid cycling were excluded. Patients who participated in the constituent schizophrenia studies were 18-60 years of age and were required to have a current psychotic episode with a duration of <2 weeks, CGI-S score ≥ 4 (moderately ill or worse), PANSS total score ≥ 80 and ≤ 120, and a score of ≥ 4 (moderate or higher) on at least 2 of the following 4 PANSS items: delusions, hallucinatory behaviour, conceptual disorganisation or suspiciousness/persecution.

Patients were excluded from the bipolar I disorder and schizophrenia studies for DSM-IV-TR axis I diagnoses other than bipolar mania or

schizophrenia, respectively; various other psychiatric conditions, substance abuse and suicide risk were exclusionary. Concurrent medical conditions that could interfere with the conduct of the study, confound the interpretation of results or endanger the patient's well-being were additional criteria for exclusion. Drugs with psychotropic activity were prohibited except for lorazepam (for agitation, hostility and restlessness), eszopiclone, zolpidem, chloral hydrate or zaleplon (for insomnia), and diphenhydramine, benztropine or propranolol (for extrapyramidal symptoms).

2.2 | Post hoc analyses

Post hoc analyses were conducted on patient data collected from the CGI-S administered during the constituent studies; data were pooled by disease state. The 7-point scale has anchor scores of 1 (normal, not at all ill), 2 (borderline mentally ill), 3 (mildly ill), 4 (moderately ill), 5 (markedly ill), 6 (severely ill) or 7 (among the most extremely ill patients). Analyses included all patients from the constituent studies in each disease state who received study medication and had ≥ 1 postbaseline CGI-S assessment. The distribution of CGI-S scores by severity (ie, severely or extremely ill [CGI-S ≥ 6], markedly ill [CGI-S = 5], moderately ill [CGI-S = 4], mildly ill [CGI-S = 3]) was summarised at baseline and end of treatment to ascertain the number and percentage of cariprazine- and placebo-treated patients whose CGI-S scores improved, remained the same or worsened after treatment. End of treatment was defined as the last available assessment in the double-blind period; no inferential statistics were conducted.

Category shift analyses were conducted to determine the percentage of cariprazine- and placebo-treated patients who shifted from a more severe illness category at baseline to a less severe category at the end of treatment. The shift categories for analysis were defined as "severely or extremely ill (CGI-S ≥ 6) to mildly ill or better (CGI-S ≤ 3)"; "markedly ill or worse (CGI-S ≥ 5) to borderline ill/normal (CGI-S ≤ 2)"; and "moderately ill or worse (CGI-S ≥ 4) to borderline ill/normal (CGI-S ≤ 2)." Patients were categorised by baseline CGI-S score; between-group comparison of categorical improvement at end-point was analysed using a logistic regression model with study, treatment group and corresponding baseline value as explanatory variables; missing data were imputed using the last observation carried forward (LOCF) approach. Odds ratios (ORs), 95% confidence intervals (CIs) and *P* values were calculated for each comparison of cariprazine vs placebo; *P* values were not adjusted for multiple comparisons and all statistical tests were 2-sided at the 5% significance level.

Analyses were also conducted to determine if the CGI-S shift to less severe illness categories correlated with mean changes from baseline in YMRS and PANSS total score for patients with bipolar mania and schizophrenia, respectively. Pearson's correlation coefficients were determined for the relationship between categorical shift and change in rating scale total score using a generalised linear mixed model with CGI-S shift and change from baseline in YMRS or PANSS total score as responses, and study, treatment and the corresponding baseline value as a covariate in the joint model.

A post hoc sensitivity analysis was conducted to assess the robustness of the CGI-S analyses in patients with schizophrenia. This analysis included data from RGH-MD-03,[12] the negative exploratory cariprazine study in schizophrenia.

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

Data from 1037 patients were included in the pooled bipolar mania population (placebo = 429, cariprazine = 608); the CGI-S subgroups comprised data from 1033 patients with a rating of moderately ill or worse (CGI-S ≥ 6: 97 [9.4%]; CGI-S = 5: 540 [52.3%]; CGI-S = 4: 396 [38.3%]). In the pooled schizophrenia population, data were included from 1466 patients (placebo = 442, cariprazine = 1024) and the CGI-S subgroups comprised all patient data (CGI-S ≥ 6: 161 [11.0%]; CGI-S = 5: 872 [59.5%]; CGI-S = 4: 433 [29.5%]). Demographic and baseline characteristics of the pooled populations by CGI-S severity baseline score are presented in Table 1. In both disease states, the majority of patients were markedly ill (CGI-S = 5) at baseline; age, gender and disease characteristics were generally similar among baseline severity subgroups. Race distribution differed slightly across severity subgroups in both disease states. Mean age at onset and duration of illness were similar across baseline severity subgroups; mean number of hospitalisations was higher in the most severe baseline subgroup in both disease states.

3.2 | CGI-S score distribution

At baseline, the majority of patients were markedly (bipolar mania = 52%; schizophrenia = 60%) or moderately ill (bipolar mania = 38%; schizophrenia = 30%); fewer patients were severely or extremely ill at baseline (bipolar mania = 9%; schizophrenia = 11%). Only 4 patients with bipolar disorder and no patients with schizophrenia were mildly ill or better at baseline.

3.2.1 | Bipolar mania

Change in the distribution of CGI-S scores from baseline to the end of treatment showed that a higher percentage of cariprazine- vs placebo-treated patients improved to a CGI-S score corresponding to less severe illness at end-point, regardless of the baseline severity score (Figure 1 A-C). Most patients with scores indicating severe or extreme illness at baseline (Figure 1A) improved to a less severe illness score at week 3; more placebo- than cariprazine-treated patients remained severely/extremely ill at end-point. In patients with CGI-S scores indicating marked illness at baseline (Figure 1B), 64% of cariprazine-treated patients and 40% of placebo-treated patients improved to a score of mildly ill or better at week 3; similar percentages of patients in each group had end-point scores indicating moderate illness. End-point scores indicated that 18% of cariprazine- and 41% of placebo-treated patients remained markedly ill or worse at week 3. In patients

TABLE 1 Demographic and baseline characteristics by disease state (pooled populations)

	CGI-S ≥ 6 Severely or extremely ill		CGI-S = 5 Markedly ill		CGI-S = 4 Moderately ill	
Bipolar mania	**Placebo n = 42**	**CAR n = 55**	**Placebo n = 212**	**CAR n = 328**	**Placebo n = 174**	**CAR n = 222**
Baseline demographics						
Age, mean (SD), y	38.2 (12.0)	39.0 (11.8)	38.8 (11.7)	40.4 (12.2)	39.4 (11.5)	39.1 (10.9)
Men, n (%)	27 (64.3)	33 (60.0)	125 (59.0)	192 (58.5)	106 (60.9)	130 (58.6)
Race, n (%)						
White	24 (57.1)	34 (61.8)	97 (45.8)	161 (49.1)	79 (45.4)	112 (50.5)
Black	6 (14.3)	11 (20.0)	48 (22.6)	92 (28.0)	48 (27.6)	59 (26.6)
Asian	10 (23.8)	8 (14.5)	61 (28.8)	69 (21.0)	45 (25.9)	48 (21.6)
Other	2 (4.8)	2 (3.6)	6 (2.8)	6 (1.8)	2 (1.1)	3 (1.4)
Disease characteristics						
Age of onset, mean (SD), y	26.1 (10.1)	25.0 (9.2)	25.8 (10.1)	26.6 (10.5)	26.4 (10.7)	26.5 (10.3)
Duration of illness, mean (SD), y	12.1 (9.3)	14.0 (11.0)	13.0 (9.2)	13.9 (10.2)	13.0 (8.7)	12.7 (9.0)
Previous hospitalisations for mania, mean (SD)	3.3 (3.7)	4.1 (4.2)	2.6 (3.5)	2.7 (3.4)	1.7 (2.9)	2.4 (3.5)
Schizophrenia	**Placebo n = 50**	**CAR n = 111**	**Placebo n = 261**	**CAR n = 611**	**Placebo n = 131**	**CAR n = 302**
Baseline demographics						
Age, mean (SD), y	37.0 (11.4)	36.7 (10.8)	35.8 (11.0)	36.6 (10.2)	39.4 (11.1)	37.4 (10.0)
Men, n (%)	35 (70.0)	80 (72.1)	177 (67.8)	411 (67.3)	89 (67.9)	222 (73.5)
Race, n (%)	—	—	—	—	—	—
White	25 (50.0)	51 (45.9)	125 (47.9)	291 (47.6)	48 (36.6)	134 (44.4)
Black	13 (26.0)	39 (35.1)	63 (24.1)	144 (23.6)	48 (36.6)	86 (28.5)
Asian	6 (12.0)	13 (11.7)	56 (21.5)	145 (23.7)	27 (20.6)	61 (20.2)
Other	4 (8.0)	4 (3.6)	10 (3.8)	14 (2.3)	5 (3.8)	10 (3.3)
Disease characteristics						
Age of onset, mean (SD), y	24.8 (8.8)	25.0 (8.5)	24.7 (8.5)	25.5 (8.5)	26.8 (10.0)	26.2 (8.3)
Duration of illness, mean (SD), y	12.2 (9.8)	11.8 (8.7)	11.1 (9.1)	11.1 (9.1)	12.6 (10.7)	11.2 (9.2)
Previous psychiatric hospitalisations, mean (SD)	6.6 (5.3)	6.9 (7.0)	5.1 (5.4)	6.1 (7.0)	5.9 (9.9)	5.8 (7.2)

CAR, cariprazine.

with baseline scores indicating moderate illness (Figure 1C), 70% of cariprazine- and 60% of placebo-treated patients improved to scores indicating mild illness or better at end-point; 3% of cariprazine patients and 7% of placebo patients had worse scores at the end of treatment.

3.2.2 | Schizophrenia

CGI-S scores improved at end-point in a higher percentage of cariprazine- vs placebo-treated patients with schizophrenia regardless of CGI-S severity score at baseline (Figures 2A-C). In patients with scores indicating severe or extreme illness at baseline (Figure 2A), approximately three quarters of cariprazine-treated compared with less than half of placebo-treated patients had score improvement at week 6. Most cariprazine patients with a severe/extreme baseline score had a week 6 score that corresponded to mild illness; the majority of placebo-treated patients remained at a score indicating severe or extreme illness following double-blind treatment. In patients who had scores indicating marked illness at baseline (Figure 2B), scores for 67% of cariprazine-treated patients and 53% of placebo-treated patients had improved at week 6; the most common score in each group corresponded to mild illness. CGI-S scores worsened to a score indicating severe/extreme illness for 3 times as many placebo-treated patients as cariprazine-treated patients. In patients with scores indicating moderate illness at baseline (Figure 2C), approximately 60% of cariprazine-treated patients and 46% of placebo-treated patients improved to scores corresponding to mild illness or better at week 6. More placebo- than cariprazine-treated patients remained at the score indicating moderate illness at week 6 and more placebo-treated patients (12%) than cariprazine-treated patients (9%) had worse CGI-S scores at end-point.

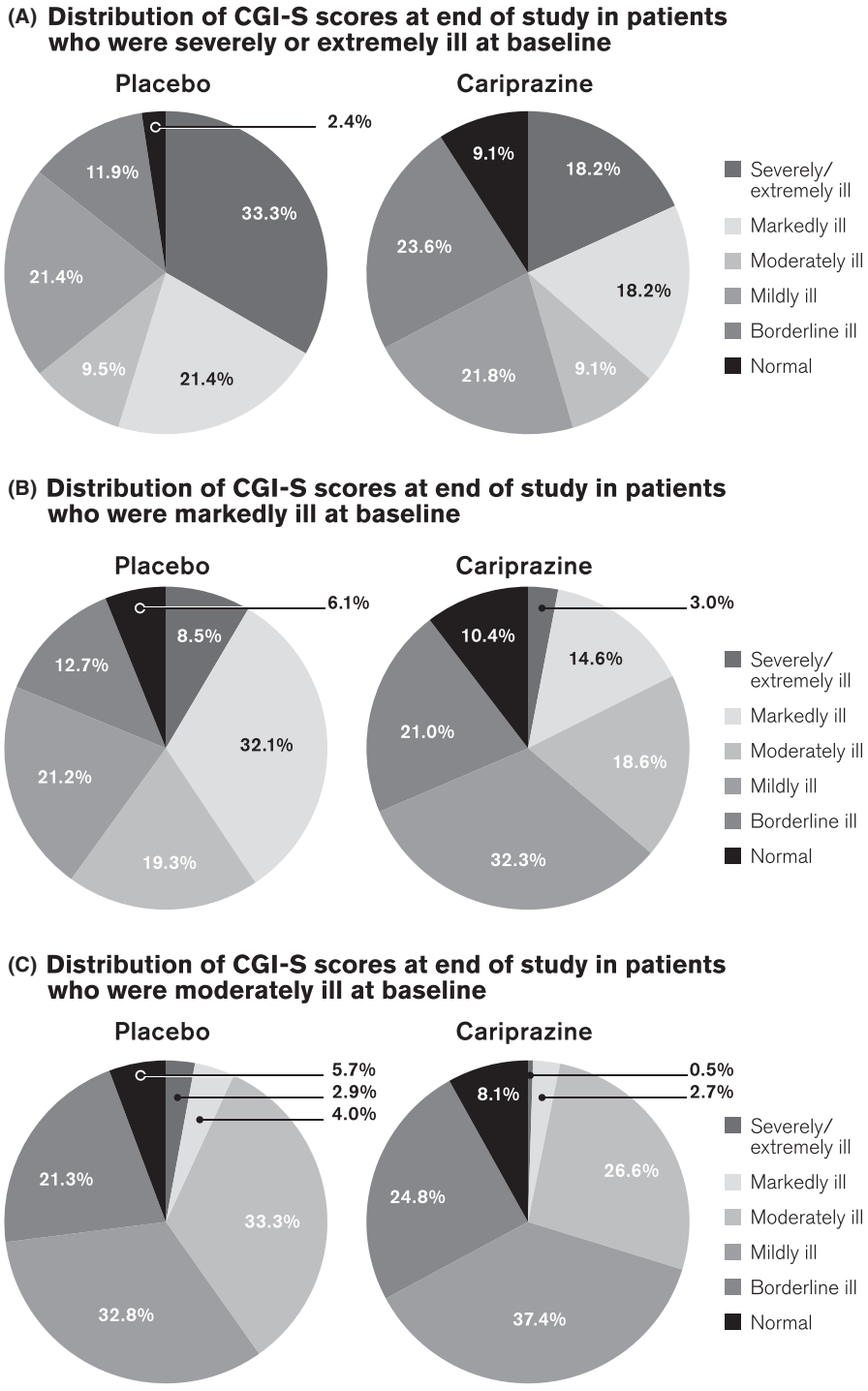

FIGURE 1 Bipolar mania: distribution of CGI-S scores at the end of treatment in patients with (A) severe/extreme, (B) marked or (C) moderate baseline illness severity. A higher percentage of cariprazine- than placebo-treated patients improved to a CGI-S score corresponding to less severe illness at end-point in each baseline illness category. Distribution of CGI-S scores by severity: normal = 1; borderline ill = 2; mildly ill = 3, moderately ill = 4; markedly ill = 5; severely/extremely ill ≥ 6

3.3 | Categorical CGI-S improvement

In both disease states, a higher percentage of cariprazine-treated patients than placebo-treated patients shifted to a less severe category of illness in each shift analysis (Figure 3A and B).

3.3.1 | Bipolar mania

In patients with bipolar mania, the odds of shifting to a less severe illness category were of similar magnitude in favour of cariprazine-treated patients in each shift category. The shift from extremely or severely ill (CGI-S ≥ 6) to mildly ill or better (CGI-S ≤ 3) occurred in 30 (55%) cariprazine patients and 15 (36%) placebo patients; however, the OR (2.1) was not statistically significant (P = .0898), which may have been because of the low number of patients in the group. A shift from markedly ill or worse (CGI-S ≥ 5) to borderline ill or normal (CGI-S ≤ 2) occurred in 121 (32%) cariprazine patients and 46 (18%) placebo patients, with a statistically significant OR (2.1) in favour of cariprazine-treated patients (P = .0002). A shift from moderately ill or worse (CGI-S ≥ 4) to borderline ill or normal (CGI-S ≤ 2)

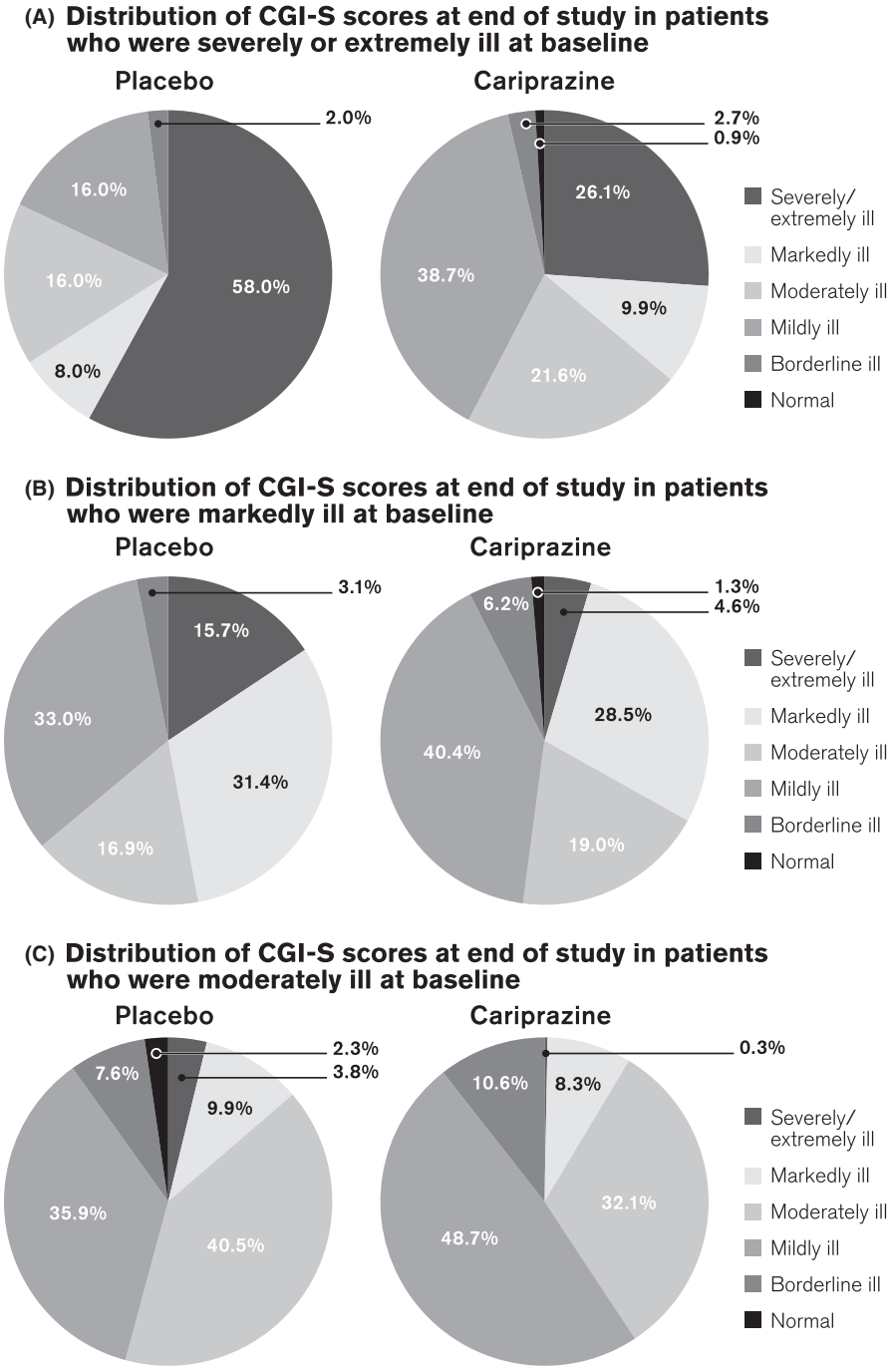

FIGURE 2 Schizophrenia: distribution of CGI-S scores at the end of treatment in patients with (A) severe/extreme, (B) marked, or (C) moderate baseline illness severity. A higher percentage of cariprazine- than placebo-treated patients improved to a CGI-S score corresponding to less severe illness at end-point in each baseline illness category. Distribution of CGI-S scores by severity: normal = 1; borderline ill = 2; mildly ill = 3, moderately ill = 4; markedly ill = 5; severely/extremely ill ≥ 6

was noted in 194 (32%) cariprazine patients and 93 (22%) placebo patients, with a statistically significant OR (1.7) in favour of cariprazine vs placebo (P = .0003).

3.3.2 | Schizophrenia

The percentage of patients in the extremely or severely ill baseline disease category who shifted to a less severe disease category was considerably larger than the percentage of patients who shifted in the less severe baseline categories. In the extremely or severely ill (CGI-S ≥ 6) baseline disease category, 47 (42%) cariprazine patients and 9 (18%) placebo patients shifted to the mildly ill or better category (CGI-S ≤ 3) at week 6; the odds of shifting (3.4) were statistically significant in favour of cariprazine-treated patients vs placebo-treated patients (P = .0038). In the markedly ill or worse (CGI-S ≥ 5) baseline disease category, 50 (7%) cariprazine patients and 9 (3%) placebo patients shifted to the borderline ill or normal (CGI-S ≤ 2) disease category at week 6; the odds of shifting (2.3) were statistically significant in favour of cariprazine-treated patients vs placebo-treated patients (P = .0222). In the moderately ill or worse (CGI-S ≥ 4) baseline disease category, 82 (8%) cariprazine patients and 22 (5%) placebo patients shifted to the borderline ill or normal (CGI-S ≤ 2) disease category at week 6; the odds for cariprazine- vs placebo-treated patients (1.6) were again statistically significant (P = .0494).

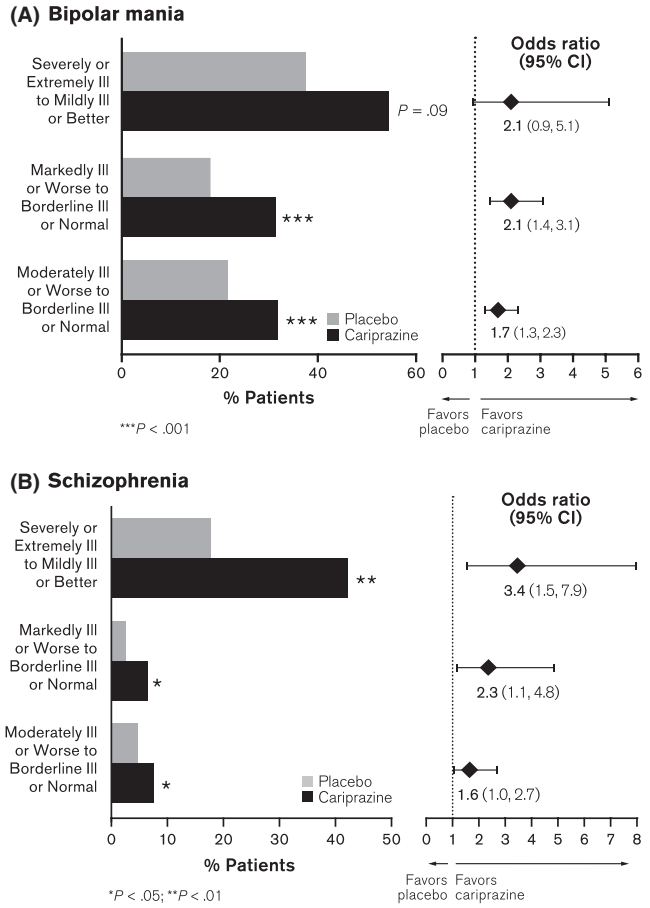

FIGURE 3 Categorical improvements in CGI-S scores in patients with (A) bipolar mania or (B) schizophrenia. Shifts were defined as extremely or severely ill (CGI-S ≥ 6) to mildly ill or better (CGI-S ≤ 3), markedly ill or worse (CGI-S ≥ 5) to borderline ill or normal (CGI-S ≤ 2), and moderately ill or worse (CGI-S ≥ 4) to borderline ill or normal (CGI-S ≤ 2). *P<.05; **P<.01; ***P<.001

A sensitivity analysis that included the results of the negative exploratory cariprazine study in schizophrenia was conducted (RGH-MD-03).[12] The primary findings of our post hoc analysis were supported by the category shift from severely or extremely ill at baseline to mildly ill or better at the end of double-blind treatment; the odds of shifting remained statistically significant for cariprazine vs placebo (51 patients [34%]) vs 11 patients [16%]; OR = 2.84 [95% CI = 1.33, 6.09], P = .0072). In shifts to borderline ill or no symptoms, more cariprazine- vs placebo-treated patients shifted from the markedly ill or worse category (53 [6%] patients vs 13 [3%] patients; OR = 1.72 [95% CI = 0.92, 3.21]; P = .0879) and from the moderately ill or worse category (91 [7%] patients vs 29 [5%] patients; OR = 1.39 [95% CI = 0.90, 2.15]; P = .1351), but the differences were not statistically significant.

3.4 | Categorical CGI-S improvement and symptom severity

The least squares mean differences (LSMDs) and associated 95% CIs in change from YMRS total score baseline for patients with bipolar mania were statistically significant in favour of cariprazine vs placebo in the extremely or severely ill (CGI-S ≥ 6) category (−7.3 [−12.72, −1.82]; P = .0094), the markedly ill or worse (CGI-S ≥ 5) category (−6.9 [−8.84, −5.01]; P < .0001), and in the moderately ill or worse (CGI-S ≥ 4) category (−5.3 [−6.75, −3.93] P < .0001). The LSMDs (95% CI) in change from PANSS total score baseline for patients with schizophrenia were also statistically significant in favour of cariprazine vs placebo across the baseline levels of CGI-S severity: extremely or severely ill (CGI-S ≥ 6) = −11.7 (−19.12, −4.29), P = .0022; markedly ill or worse (CGI-S ≥ 5) = −8.9 (−11.50, −6.25), P < .0001; and moderately ill or worse (CGI-S ≥ 4) = −7.7 (−9.85, −5.61), P < .0001. The correlations for change from baseline in rating scale scores and shifts to a less severe CGI-S illness category were small to moderate in most severity categories (Table 2). Correlations between category shift and mean rating scale change were larger for patients with the most severe illness at baseline and in patients with bipolar mania relative to patients with schizophrenia. Cariprazine- and placebo-treated patients with bipolar disorder and schizophrenia who shifted to a less severe CGI-S category had considerably larger changes from baseline in YMRS and PANSS total scores, respectively.

4 | DISCUSSION

The efficacy of cariprazine in patients with mania associated with bipolar I disorder and in patients with schizophrenia was established in randomised, double-blind, placebo-controlled trials of 3- and 6 weeks' duration, respectively. Although important evidence of symptom improvement with cariprazine treatment vs placebo was seen via significantly different mean changes from baseline in YMRS or PANSS total score in these trials, a statistically significant outcome may be difficult to interpret in a clinical practice setting. To demonstrate that cariprazine treatment resulted in clinically meaningful, as well as statistically significant improvement, we conducted post hoc analyses using the clinician-rated CGI-S scale to evaluate changes in the global impression of bipolar and schizophrenia disease severity. Clinician global ratings are the most suitable method of determining meaningful change from a clinical perspective.[3]

Change in the distribution of CGI-S scores demonstrated that a higher percentage of cariprazine- vs placebo-treated patients had scores indicating less severe disease at the end of treatment across baseline severity in both disease states. In patients with bipolar mania, the most common end-point score for cariprazine-treated patients corresponded to mild or borderline illness; scores corresponding to normal were noted in at least 8% of patients following treatment. In patients with schizophrenia across baseline disease severity scores, the most common CGI-S score for cariprazine-treated patients at week 6 corresponded to mild illness; a small percentage of patients with baseline scores indicating severe/extreme or marked illness attained scores corresponding to normal at week 6. Additionally, more placebo- than cariprazine-treated patients had worse end of treatment scores in both disease states.

In our CGI-S categorical shift analyses, a greater percentage of cariprazine- than placebo-treated patients shifted to a less severe CGI-S

TABLE 2 Joint correlation between CGI-S category shift and rating scale change from baseline at end of double-blind treatment

Bipolar mania	Baseline CGI-S category and shift category	n		YMRS total score change mean (SD)		Correlation coefficient between CGI-S shift and YMRS change
		PBO	CAR	PBO	CAR	
	Patients with extreme or severe illness (CGI-S ≥ 6)	42	55	−10.4 (12.7)	−18.5 (14.9)	−.853
	Shift to score ≤ 3	15	30	−24.5 (6.1)	−30.1 (7.6)	
	No shift	27	25	−2.6 (7.6)	−4.6 (7.5)	
	Patients with marked illness or worse (CGI-S ≥ 5)	254	383	−10.4 (12.5)	−17.7 (12.1)	−.634
	Shift to score ≤ 2	46	121	−26.9 (6.6)	−28.4 (6.1)	
	No shift	208	262	−6.8 (10.5)	−12.8 (10.9)	
	Patients with moderate illness or worse (CGI-S ≥ 4)	428	605	−10.7 (12.0)	−16.5 (11.5)	−.624
	Shift to score ≤ 2	93	194	−24.1 (6.9)	−26.3 (6.4)	
	No shift	335	411	−7.0 (10.3)	−11.9 (10.4)	
Schizophrenia	**Baseline CGI-S category and shift category**	**n**		**PANSS total score change mean (SD)**		**Correlation coefficient between CGI-S shift and PANSS total score change**
		PBO	**CAR**	**PBO**	**CAR**	
	Patients with extreme or severe illness (CGI-S ≥ 6)	50	111	−8.5 (20.9)	−20.3 (22.4)	−.677
	Shift to score ≤ 3	9	47	−35.0 (17.3)	−38.4 (13.0)	
	No shift	41	64	−2.6 (16.7)	−6.9 (18.0)	
	Patients with marked illness or worse (CGI-S ≥ 5)	311	722	−9.9 (20.0)	−18.7 (19.6)	−.379
	Shift to score ≤ 2	9	50	−49.6 (8.5)	−47.5 (11.4)	
	No shift	302	672	−8.7 (19.0)	−16.6 (18.3)	
	Patients with moderate illness or worse (CGI-S ≥ 4)	442	1024	−10.9 (19.3)	−18.5 (18.8)	−.395
	Shift to score ≤ 2	22	82	−42.5 (13.4)	−43.1 (12.1)	
	No shift	420	942	−9.2 (18.2)	−16.4 (17.7)	

CAR, cariprazine; CGI-S, Clinical Global Impressions-Severity; PANSS, Positive and Negative Syndrome Scale; PBO, placebo; YMRS, Young Mania Rating Scale.

category at the end of treatment in each category analysed in both disease states. The odds of shifting to a less severe CGI-S category were statistically significant in favour of cariprazine vs placebo for all category shift analyses except for the shift from severe/extreme illness to mildly ill or better in patients with bipolar mania. The magnitudes of the odds in all shift categories were similar, however, and the small number of patients in the severe/extreme shift category may have made it difficult to detect a significant difference. The greatest odds of shifting to a less severe CGI-S category were observed in the severely or extremely ill to mildly ill or better category in patients with schizophrenia suggesting that lack of active treatment was most detrimental to patients with schizophrenia who had the most severe illness at baseline.

It is noteworthy that in patients who were in the severely ill and markedly ill (or worse) categories at baseline, a shift to mildly ill or borderline ill/normal, respectively, encompasses at least 3 steps of categorical improvement; similarly, a shift to borderline ill or normal in patients who were moderately ill or worse at baseline reflects at least 2 steps of improvement. It is reasonable to suggest that shifts representing more than one level of improvement would be considered clinically relevant and would represent meaningful change in patients with either bipolar mania or schizophrenia. In diseases that carry high burdens of functional, occupational and social impairment, such as bipolar disorder and schizophrenia, any degree of improvement can be meaningful to a patient. In our analyses, however, the ability to quantify that improvement exceeded 1 or 2 categorical steps supports the suggestion that improvement was highly clinically relevant in some cariprazine-treated patients. Referencing patient change with this type of outcome is an intuitively descriptive way to monitor patient improvement or deterioration over time.

Although remission, the absence or near absence of symptoms, in bipolar disorder and schizophrenia is an attainable goal, operational definitions are not standardised in either disease state, which makes evaluation of this outcome more challenging. The International Society for Bipolar Disorders (ISBD) Task Force has reported that the most commonly used definition of remission in bipolar mania is

a YMRS score < 12; remission has been further operationalised as a CGI-Bipolar Disorder Scale severity score ≤ 2 (borderline ill) for both mania and depression.[14] In our post hoc category shift analyses, significantly more cariprazine-treated patients than placebo-treated patients with bipolar disorder shifted to borderline ill (CGI-S = 2) or normal (CGI-S = 1), which would suggest that these patients reached symptomatic remission with treatment. Residual symptoms after resolution of a major affective episode in patients with bipolar disorder are associated with significant risk of rapid relapse or recurrence.[15] As such, attaining near symptom-free status for patients with bipolar mania suggests a stable recovery, with greater potential for regaining and retaining premorbid functional status.

The Remission in Schizophrenia Working Group (RSWG) has proposed PANSS-based remission criteria for schizophrenia that has cross-scale correspondence and a relationship with DSM-IV criteria.[16] In a study investigating the reliability of CGI-S for evaluating remission, a CGI-Schizophrenia Scale severity score ≤ 3 (mildly ill) corresponded to RSWG remission criteria.[17] In our post hoc category shift analyses, significantly more cariprazine- than placebo-treated patients with schizophrenia shifted to a category with end-point CGI-S scores ≤ 3 regardless of the level of baseline disease severity. This would suggest that more cariprazine- than placebo-treated patients attained remission of symptoms corresponding to RSWG criteria. Although higher percentages of patients with bipolar disorder met the relevant remission threshold than did patients with schizophrenia, the category shift appears to an operative indication of remission in patients with either disorder.

Across baseline levels of disease severity in both indications, cariprazine-treated patients had larger mean changes in YMRS or PANSS total score than placebo-treated patients; cariprazine-treated patients with schizophrenia had mean PANSS total score change that exceeded the 15-point reduction threshold that correlates with one level of CGI-S improvement.[18] Placebo- and cariprazine-treated patients who shifted to a less severe CGI-S category had considerably greater mean rating scale change than patients who did not shift, suggesting that clinicians may be able to assess improvement based on clinical judgement as well as rating scale change. For both bipolar disorder and schizophrenia, the statistical analysis of the relationship between categorical improvement and rating scale score change yielded the largest correlation coefficient in the most severe baseline illness category where room for improvement was the greatest; patients in this CGI-S baseline category who did not shift during treatment had minimal rating scale improvement indicating that treatment provided less benefit for them. Although CGI-S category shifts correlated well with improvements in symptom scales, the moderate magnitude of the correlations suggests that each of these outcomes may be measuring additional factors that are complementary to the other outcome.

In the constituent studies, scores at end-point on the CGI-I, the companion component of the CGI-S, supported our post hoc observations of improvement in global disease severity. Across each cariprazine dose that was evaluated, mean CGI-I scores at end-point were between much improved (CGI-I = 2) and minimally improved (CGI-I = 3) and significantly different than placebo in the bipolar disorder studies at week 3 ($P < .001$ each)[6-8] and in the schizophrenia studies at week 6 ($P < .01$ each).[9-11] Additionally, in a previous post hoc pooled analysis of data from the constituent bipolar disorder studies, the rate of CGI-I response (score ≤ 2, much/very much improved) was significantly greater for cariprazine- (64%) vs placebo-treated (42%) patients ($P < .0001$),[19] providing further support for our analyses. Improvements in both CGI-S and CGI-I suggest that global impressions were consistent across the components of the CGI Scale and cariprazine-treated patients with bipolar mania or schizophrenia experienced significantly greater global improvement than placebo-treated patients did.

The CGI has been validated as a clinical outcome measure for routine use in inpatient psychiatric settings in patients with a variety of diagnoses.[20] The advantages of the scale include its established utility in psychiatric research, sensitivity to change, easy administration, usefulness across diagnostic subgroups and reliability when administered by a skilled clinician.[20] Given these properties, the CGI can be readily adapted for use in clinical practice, where it can help a clinician consistently track interventions over the course of care.[5] However, limitations associated with the CGI Scale have also been cited, including its lack of consistency, unreliability and being too general to provide meaningful information about clinical status or treatment response.[21] Scoring is dependent on the clinical judgement of the rater and there are no universally established scoring guidelines for the 7 anchor points; as such, variability in scoring could occur.[5] In spite of these limitations, however, the CGI-S has been shown to be well correlated with other scales across a range of psychiatric indications.[5] Collective experiences suggest that using a global impression of illness severity in addition to mean change on an efficacy rating scale may provide an integrated approach for assessing clinically meaningful patient improvement in research or clinical practice settings.

Although these analyses were post hoc and have inherent limitations, they allowed for the evaluation of CGI-S data from large numbers of patients with bipolar I disorder or schizophrenia. As is typical in post hoc evaluations, *P* values were not adjusted for multiple comparisons, which may have allowed random chance to play a role in determining statistically significant differences. The short duration of the constituent studies further limits interpretation of these findings. Stringent inclusion and exclusion criteria limit the ability to generalise results to other populations of patients with bipolar I disorder or schizophrenia; of note, patients with bipolar II disorder, rapid cycling, significant depressive symptoms and treatment-resistant schizophrenia were excluded from participation. As previously discussed, the CGI-S has psychometric limitations including lack of standard scoring guidelines; these post hoc analyses were adjusted for study site to help lessen the potential for inter-rater variability in CGI-S scoring. From a statistical perspective, correlating implicit CGI-S ratings with explicitly calculated efficacy scale mean changes may be problematic, but finding a correlation between category shifts and rating scale improvement helped to substantiate our CGI-S findings nonetheless.

Statistical significance is not the same as clinical relevance. While small numerical differences on a rating scale may produce statistically

significant change in a large sample size, a change is only clinically meaningful if it improves patient function and informs the treatment path forward. In our post hoc analyses, higher percentages of cariprazine-treated patients than placebo-treated patients had improved CGI-S scores and shifted from a more severe baseline category of disease to a less severe category at end-point. This was true for patients with either bipolar mania or schizophrenia, although the magnitude of improvement was generally greater for patients with bipolar mania than for patients with schizophrenia. The correlation between the clinician-based CGI-S outcomes and YMRS or PANSS improvement for patients with bipolar I disorder or schizophrenia, respectively, supports the less empirical CGI-S outcome with statistically based findings. Collectively, our post hoc analyses of CGI-S outcomes showed that treatment with cariprazine produced clinically relevant, as well as statistically significant, improvement in patients with manic or mixed episodes associated with bipolar I disorder and in patients with schizophrenia.

ACKNOWLEDGEMENTS

Supported by funding from Forest Research Institute, Inc, an Allergan affiliate, Jersey City, NJ, USA, and Gedeon Richter Plc, Budapest, Hungary. Forest Research Institute, Inc, an Allergan affiliate, and Gedeon Richter Plc. were involved in the study design, collection (via contracted clinical investigator sites), analysis and interpretation of data, and the decision to present these results. Writing assistance and editorial support for this manuscript were provided by Carol Brown, MS, of Prescott Medical Communications Group, Chicago Illinois, a contractor of Allergan.

DISCLOSURES

Stephen Volk has received grant/research support from Eli Lilly, Forest Laboratories, Inc., Merck, Otsuka Pharmaceuticals, and Sunovion Pharmaceuticals; and is a stock shareholder for MannKind Corporation and Arena Pharmaceuticals. Robert E. Litman acknowledges a potential conflict of interest as a member of the speaker's bureau for Johnson & Johnson and Otsuka. Suresh Durgam, Kaifeng Lu, and Willie Earley acknowledge a potential conflict of interest as employees of Allergan. György Németh and István Laszlovszky acknowledge a potential conflict of interest as employees of Gedeon Richter Plc.

AUTHOR CONTRIBUTIONS

All authors had access to the study data that supported this publication. Suresh Durgam and Willie Earley contributed to concept/design of the studies, protocol development and data analysis/interpretation. Kaifeng Lu was involved in the study design, statistical analysis and interpretation of data. György Németh and István Laszlovsky contributed to the design of the studies and interpretation of data. Stephen Volk and Robert Litman contributed to the analyses and interpretation of data. All authors contributed to the drafting and/or critical revision of the manuscript, and have approved the final version.

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How to cite this article: Durgam S, Earley W, Lu K, et al. Global improvement with cariprazine in the treatment of bipolar I disorder and schizophrenia: A pooled post hoc analysis. *Int J Clin Pract*. 2017;71:e13037. https://doi.org/10.1111/ijcp.13037