

Effects of Cariprazine on Cognition in Patients With Bipolar Mania or Mixed States: Post Hoc Analysis From 3 Randomized, Controlled Phase III Studies

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Abstract

Introduction. Cariprazine, a dopamine D3-preferring D3/D2 and serotonin 5-HT1A receptor partial agonist, is approved for the treatment of schizophrenia and for depressive, manic, or mixed episodes associated with bipolar I disorder. Previous post hoc analyses have demonstrated that cariprazine was effective versus placebo for improving cognitive symptoms in patients with schizophrenia or bipolar depression. This post hoc analysis evaluated the effects of cariprazine on cognitive symptoms in patients with acute manic or mixed bipolar episodes.

Methods. Data from 3 phase II/III, randomized, double-blind, placebo-controlled studies in patients with manic or mixed episodes associated with bipolar I disorder (NCT00488618, NCT01058096, NCT01058668) were pooled and analyzed. Patients were randomized to placebo or flexibly dosed cariprazine (3-12 mg/d, 3-6 mg/d, or 6-12 mg/d [1 study only]) for 3 weeks of double-blind treatment; all dose groups were combined for the pooled analysis. Cognitive symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) Cognitive subscale (sum of PANSS items P2, N5, N7, G10, G11); a score of 15 or greater at baseline indicated the presence of cognitive symptoms. Mean changes from baseline to week 3 in PANSS cognitive subscale/item scores and Young Mania Rating Scale (YMRS) total score were evaluated in the overall intent-to-treat (ITT) population and in the subgroup of patients with baseline cognitive symptoms. A mixed-effects model for repeated measures (MMRM) was used to impute missing values.

Results. Of the 1012 patients in the ITT population, 174 (placebo=71; cariprazine=103) had a PANSS Cognitive subscale score of 15 or greater at baseline. At week 3, the cariprazine group demonstrated significantly greater mean improvement than the placebo group on PANSS cognitive subscale scores in both the ITT population (-2.2 vs -1.3; $P<.0001$) and the subgroup with baseline cognitive symptoms (-4.0 vs -1.9; $P=.0002$). In patients with baseline cognitive symptoms, improvement was significantly greater for cariprazine- versus placebo-treated patients on YMRS total score (-16.7 vs -8.2; $P<.0001$) and the individual PANSS cognitive subscale items of conceptual disorganization (-1.1 vs -0.5; $P=.0004$), difficulty in abstract thinking (-0.8 vs -0.3; $P=.0044$), stereotyped thinking (-0.3 vs -0.1; $P=.0350$), and poor attention (-1.1 vs -0.6; $P=.0043$).

Conclusion. In patients with manic or mixed episodes associated with bipolar I disorder, cariprazine versus placebo was effective in improving cognitive symptoms in the overall patient population as well as in patients with baseline cognitive symptoms. In addition, cariprazine versus placebo also demonstrated efficacy in improving manic symptoms in patients with baseline cognitive symptoms. These results suggest that cariprazine may provide benefits for the treatment of cognitive symptoms in patients with bipolar I mania. **Funding.** AbbVie Inc.

Evaluation of MADRS Severity Thresholds in Patients With Bipolar Depression

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Abstract

Introduction. The Montgomery-Åsberg Depression Rating Scale (MADRS) is commonly used for the assessment of depressive symptom changes in patients with major depressive disorder (MDD) or bipolar depression. Categories of depression severity that correspond to ranges of MADRS total score have been previously reported in patients with MDD, but it appears that MADRS severity ranges have not been reported for patients with bipolar I disorder. The objective of this study was to evaluate MADRS total score ranges that correspond with different grades of depression severity in patients with bipolar I depression.

Methods. Data were pooled from 3 randomized, double-blind, placebo-controlled, 6- or 8-week trials of cariprazine in patients with bipolar I depression. MADRS severity ranges were evaluated using an anchor-based approach with the clinician-rated, 7-category Clinical Global Impression-Severity (CGI-S) scale. CGI-S has previously been used to determine severity thresholds in MDD. Correlations between MADRS total score and CGI-S score were assessed in the pooled dataset at week 6; placebo and active treatment arms were pooled together. Youden index from receiver operating characteristic (ROC) curves was used to determine the optimal threshold for MADRS total score corresponding to each CGI-S severity level.

Results. The pooled dataset included 1523 patients with bipolar depression. Mean CGI-S scores were highly correlated with mean MADRS total scores at week 6 ($r=.87$; $P<.0001$), with MADRS total scores increasing with CGI-S severity. Using the ROC curves, MADRS total score ranges corresponding to each CGI-S severity category were estimated as follows: score of 0-6 for "normal, not at all ill", 7-12 for "borderline mentally ill", 13-18 for "mildly ill", 19-23 for "moderately ill", 24-36 for "markedly ill", 37-39 for

“severely ill”, and 40 or greater for “extremely ill”. Area under the curve (AUC) values for these cutoffs ranged from 0.930 to 0.997, representing outstanding sensitivity and specificity.

Conclusions. Utilizing data from 3 recent clinical trials of subjects with bipolar depression, we were able to identify MADRS

severity thresholds. These empirical findings may help clinicians to understand and contextualize MADRS results from bipolar clinical research and apply to their patients in practice.

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