response with esketamine+AD vs AD+placebo at endpoint (rates 63.4% vs 49.5%, respectively) yielded an NNT value of 8, and MADRS remission at endpoint (48.2% vs 30.3%) resulted in a NNT vs AD+placebo of 6. NNH values vs AD+placebo were <10 for the adverse events (AE) of dissociation (26.1% vs 3.7%), vertigo (26.1% vs 2.8%), nausea (26.1% vs 6.4%), dizziness (20.9% vs 4.6%), and dysgeusia (24.3% vs 11.9%), the NNH values were 5, 5, 6, 7, and 9, respectively. Discontinuation rates due to AE (7.0% vs 0.9%) yielded a NNH of 17. LHH comparing MADRS remission vs discontinuation was 17/6, or approximately 3. The pattern of results was similar for the other acute studies and for the pooled data combining all 3 acute studies. Maintenance use of esketamine (dose 56-84 mg once-weekly or once-every-other-week) plus an oral AD demonstrated NNT values <10 for relapse and/or maintenance of remission in favor of esketamine+AD vs AD+placebo, a NNT of 4 was observed for outcome of relapse in patients with stable response at the time of randomization (relapse rates were 25.8% vs 57.6%, respectively). In the maintenance study, discontinuation rates due to an AE (2.6% vs 2.1%) yielded a non-significant NNH value of 178.

CONCLUSION: The low NNT values <10 for efficacy outcomes suggest potential benefits of esketamine+AD for both acute and maintenance use. LHH was favorable: esketamine+AD was 3 times more likely to result in acute remission vs discontinuation due to an AE.

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Incidence and Characteristics of Akathisia and Restlessness During Cariprazine Treatment for Bipolar I Disorder

Leslie Citrome, MD, MPH[1]*;*
Lakshmi N. Yatham, MBBS, FRCPC, MBA[2]*;*
Mehul Patel, PharmD[3]*; and Willie R. Earley, MD*[4]

[1] Clinical Professor, Department of Psychiatry and Behavioral Sciences, New York Medical College, Valhalla, New York
[2] Professor and Head, Department of Psychiatry, University of British Columbia, Vancouver, Canada
[3] Medical Director, Global Medical Affairs – Psychiatry, Allergan, Madison, New Jersey
[4] Associate Vice President, Clinical Development-CNS, Allergan, Madison, New Jersey

ABSTRACT: Study Objective: Akathisia and restlessness are common adverse events associated with atypical antipsychotic use; in severe cases, symptoms may lead to treatment discontinuation. Cariprazine, a dopamine D3/D2 receptor partial agonist with preferential binding to D3 receptors, is approved for the treatment of schizophrenia (1.5–6 mg/d), and manic or mixed (3–6 mg/d) and depressive episodes (1.5–3 mg/d) associated with bipolar I disorder. Pooled post hoc analyses were conducted to characterize the incidence and severity of cariprazine-related akathisia and restlessness in patients who participated in bipolar disorder studies.

METHOD: All studies were Phase II/III multicenter, randomized, double-blind, placebo-controlled, parallel-group studies in patients with bipolar I disorder who were currently experiencing a manic/mixed (NCT00488618, NCT01058096, NCT01058668) or depressive (NCT01396447, NCT02670538, NCT02670551) mood episode. Patients received flexibly dosed cariprazine 3-12 mg/d (day 1: 1.5 mg; day 2: 3 mg; subsequent up-titration in 3-mg increments if needed) or placebo in the bipolar mania studies and fixed-dose cariprazine 1.5 mg/d, 3 mg/d (slow titration to 1.5 mg [day 8] and 3 mg [day 15] or initiation at 1.5 mg with escalation to 3 mg on day 15), or placebo in the bipolar depression studies. The incidence, severity, and timing of treatment-emergent adverse events (TEAEs) of akathisia and restlessness were evaluated in this analysis.

RESULTS: In the bipolar mania studies (N=1065), TEAEs of akathisia occurred in 20.2% of cariprazine-treated patients and 4.8% of placebo-treated patients; 2.4% of cariprazine-treated patients discontinued due to akathisia. TEAEs of restlessness occurred in 6.7% and 2.3% of cariprazine- and placebo-treated patients, respectively, and caused discontinuation of 0.3% of cariprazine-treated patients. In the bipolar depression studies (N=1407), akathisia occurred in 2.1%, 5.5%, and 9.6% of patients in the placebo, cariprazine 1.5 mg/d, and cariprazine 3 mg/d groups, respectively; <2% of patients in each group discontinued due to akathisia. Restlessness occurred in 3.2% of placebo-treated patients and 2.1% and 6.6% of patients in the 1.5 and 3 mg/d groups, respectively; discontinuations due to restlessness occurred in 0.2% and 1.1% of patients in the 1.5 and 3 mg/d groups. Akathisia and restlessness in cariprazine-treated patients was generally mild or moderate in severity (>92% in both populations). Most akathisia events in the bipolar mania studies were reported for the first time within the first 2-3 weeks of treatment.

CONCLUSIONS: In these post hoc analyses, the incidence of akathisia and restlessness were generally higher with cariprazine than with placebo. However, most incidences were mild or moderate in severity, and infrequently led to discontinuation. Akathisia appears to be dose related in both mania and depression, suggesting lower doses and slower titration may reduce occurrence.

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