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Cariprazine in Bipolar Disorders

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This issue of *JCP* includes a report on the efficacy and safety of cariprazine for the treatment of bipolar mania from Calabrese and colleagues.[1]

Key Study Findings

The authors report a multicenter (N = 497), randomized, double-blind, placebo-controlled study (NCT01058668). Patients were randomly assigned to placebo, cariprazine 3–6 mg/d, or cariprazine 6–12 mg/d for 3 weeks. The primary outcome was change from baseline to week 3 utilizing the Young Mania Rating Scale (YMRS). Both cariprazine groups were statistically significantly superior to placebo on the primary outcome, all 11 YMRS single items, and Clinical Global Impressions-Severity of Illness scores. The most common (≥ 5% and twice the rate of placebo) treatment-related adverse events for cariprazine were akathisia (both groups) and nausea, constipation, and tremor (6–12 mg/d only).

Other Controlled Studies of Cariprazine for Acute Mania

Including the current study, 3 placebo-controlled studies utilizing cariprazine in the treatment of acute mania have been conducted (NCT01058668, NCT00488618, NCT01058096),[1–3] and all show significantly higher efficacy for cariprazine compared to placebo. Pooled analysis of the 3 trials (N = 1,037) on the primary outcome scale (YMRS), recently presented at a scientific meeting,[4] showed significance in all items favoring cariprazine, with moderate effect sizes (Cohen *d*) on YMRS items ranging from −0.31 (increased motor activity) to −0.55 (irritability). Pooled safety and tolerability analyses of the 3 trials (N = 1,065), also presented at a scientific meeting,[5] reported treatment-emergent adverse events (5% and twice placebo) including akathisia (placebo, 5%; cariprazine, 20%), extrapyramidal symptoms (5%/13%), restlessness (2%/6%), and vomiting (4%/9%), with a small amount of weight gain (placebo, 0.17 kg; cariprazine, 0.54 kg).

How Does Cariprazine Efficacy Compare to That of Other Agents?

The design of Calabrese and colleagues' study[1] is similar to those of previous clinical trials with other compounds explored for the treatment of mania. This includes the duration (3 weeks) and the minimum YMRS severity score (> 20), although a minimum severity score for the Montgomery-Asberg Depression Rating Scale total score < 18 may limit the generalizability of findings in patients with mixed features. Exclusion criteria were similar to those of previous clinical trials as well.[6]

Yildiz et al[7] recently published a network meta-analysis, with a Bayesian framework, comparing 18 active treatments against placebo including the current cariprazine study (NCT01058668)[1] from data available from meeting abstracts.[8] Cariprazine appears to compare well with other treatments, with an effect size of 0.62 and a number needed to treat (NNT) of 5 for response and 7 for remission. Yildiz and colleagues'[7] effect size estimations put cariprazine toward the top: only topiramate, risperidone, and olanzapine had larger effect size estimations. A limitation of these comparisons across studies is of course that their populations may be quite diverse in terms of demographics and inclusion and exclusion criteria. In addition, the NNT of 5 for remission in this study[1] compares favorably to a pooled NNT of 8 for all atypical agents estimated by another meta-analysis conducted by Tamayo et al.[9]

Furthermore, Citrome[10] recently reported effect size metrics of different atypical antipsychotics compared to cariprazine with NNT values versus placebo for response and remission. The NNTs for response of 5 in this trial and 7 in a phase 2 study[3] are similar to those observed with other compounds including lithium (NNT = 4), divalproex extended release (NNT = 7), carbamazepine extended release (NNT = 4), olanzapine (NNT = 5), risperidone (NNT = 4), quetiapine extended release (NNT = 6), ziprasidone (NNT = 7), aripiprazole (NNT = 5), and asenapine (NNT = 8).[10] Citrome also noted that number needed to harm values regarding akathisia for cariprazine versus placebo are approximately the same as the NNT for response. A remission NNT of 5 appears good. However, Calabrese et al[1] also estimated remission rates using a definition recommended by the International Society for Bipolar Disorders[11] of YMRS score < 8, and the results were quite modest, with only 25% of patients achieving remission. In other words, the vast majority of patients in this study either did not remit or achieved only partial remission and remained in a subsyndromic manic state. Data have shown that when patients achieve only partial remission, the risk of relapse is higher compared to those who achieve full remission.[12]

Other Studies of Cariprazine in Mood Disorders

Positive results have been presented at scientific meetings on the efficacy of cariprazine in phase 2 studies (NCT01396447) for bipolar depression[13] and as an

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adjunctive treatment in patients with inadequate response to standard antidepressant therapy (NCT01469377).[14]

Do We Need Another Molecule to Treat Mania?

I wish the answer were no. However, the available treatments including mood stabilizers are effective and tolerable to only some patients, and in many cases the efficacy is only partial. Currently, we have 11 US Food and Drug Administration (FDA)–approved treatments for acute mania (lithium, valproate, chlorpromazine, and 7 atypical antipsychotics including risperidone, olanzapine, paliperidone, aripiprazole, asenapine, quetiapine, and ziprasidone). Cariprazine appears to be novel: it is a dopamine D_3 and D_2 receptor partial agonist with preferential binding to D_3 receptors, which have been reported to regulate both mood and cognition.[15] The unique pharmacologic profile of cariprazine may provide added value to the existing armamentarium for treatment options of acute mania. However, it has not yet been approved by the FDA; according to the manufacturer[16] and sources publicly available on the Internet,[17] it appears that the agency has requested more clinical data to better define the optimal dosing for its use in schizophrenia and bipolar mania. Assuming regulatory approval is met, cariprazine for the treatment of acute mania may be an additional option. With a number of atypical antipsychotics already available as generic, cost will be a major challenge unless, of course, further studies demonstrate an advantage of cariprazine in head-to-head studies and/or focus on other outcomes such as cognition or functioning.

Areas of Unmet Medical Need in Bipolar Disorder

Our patients have a larger need for more options for bipolar depression and maintenance treatment. As mentioned, 1 trial for bipolar depression has been completed.[13] For bipolar depression, the only products approved by the FDA are quetiapine, lurasidone as monotherapy and in combination with lithium or valproate, and the combination of olanzapine and fluoxetine. FDA-approved maintenance treatment for bipolar disorder includes lithium, lamotrigine, olanzapine, quetiapine as monotherapy and in combination with lithium or valproate, aripiprazole, risperidone depot intramuscular, and ziprasidone in combination with lithium or valproate. No controlled maintenance studies for cariprazine are currently listed on the ClinicalTrials.gov website.

Psychopharmacology has not yet reached the state of personalized medicine.[18] Currently, we do not even tailor treatment for individual patients on the basis of their clinical characteristics. Even if we did tailor to symptoms, this does not guarantee success. Tailoring to biomarkers, already a reality in oncology, is hopefully coming soon to psychiatry. We also need to "personalize" our outcomes. We currently focus on symptomatic remission, which has been shown in observational studies[19,20] to always exceed functional recovery.

To summarize, the additional value of cariprazine to our current treatment armamentarium in bipolar disorder remains to be determined. My hope is that our field will move into personalized medicine with an emphasis in patient-based functional outcomes.

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Potential conflicts of interest: **Dr Tohen** was a full-time employee at Eli Lilly (1997–2008). In the past 2 years, he has received grant/research support from American Psychiatric Association, Baptist Health Foundation, Pfizer, Johnson & Johnson, Forest, National Institute of Mental Health, and the Atlas Foundation. He has received honoraria from or consulted for Abbott, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Johnson & Johnson, Otsuka, Merck, Sunovion, Forest, Gedeon Richter, Roche, Elan, Alkermes, Lundbeck, Teva, Pamlab, Wyeth, and Wiley Publishing. His spouse was also a full-time employee at Eli Lilly (1998–2013).
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