DRUG REVIEW

A Brief Review of Cariprazine

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Cariprazine has a unique pharmacological feature of being a partial agonist with high affinity for D_3 receptors, making it a potent and efficacious second-generation antipsychotic. The authors discuss its mechanism of action, administration and pharmacokinetics, and indications, as well as clinical studies and special populations regarding the use of this promising medication.

Cariprazine is a newer second-generation antipsychotic that was first approved in 2015 for the treatment of schizophrenia and bipolar disorder and recently approved (in December 2022) for adjunctive therapy in the treatment of unipolar depression. Given its side-effect profile, it is a promising new medication, especially in the treatment of unipolar depression, for which there are limited options for adjunctive therapy approved by the U.S. Food and Drug Administration (FDA).

MECHANISM OF ACTION

Cariprazine functions as a partial agonist of dopaminergic D_2 and D_3 receptors and serotonergic 5-HT_{1A} receptors (1). Cariprazine also has moderate antagonistic properties at serotonergic 5-HT_{2A} and 5-HT_{2B} receptors, as well as histaminergic H_1 receptors (2). Cariprazine's most salient feature is its preference for D_3 receptors; its D_3 binding affinity is higher than dopamine's affinity for this receptor (3). This means that at physiological doses, cariprazine can cause a unique D_3 blockade, unlike other second-generation antipsychotics whose D_3-binding properties are reversible by dopamine (4). D_3 receptors can be found in different areas of the brain, such as the hypothalamus, limbic areas, the ventral tegmental area, and the cerebral cortex (5). D_3 partial agonism in the cortex may improve negative symptoms and cognitive deficits among patients with schizophrenia (2). Although the mechanism is largely unclear, it has been hypothesized that there is an overexpression of D_3 receptors on dopaminergic neurons (autoreceptors) projecting from the ventral tegmental area to the prefrontal cortex leading to dopaminergic hypofunction (2). The partial agonism effect of cariprazine may therefore reverse this inhibition and thus lead to normalization of dopamine release within the prefrontal cortex. The activity of cariprazine on 5-HT_{1A} and 5-HT_{2A} receptors helps to improve psychotic or manic symptoms, as well as lower the occurrence of extrapyramidal symptoms (2). Cariprazine exhibits a greater binding affinity for D_2 receptors than dopamine; however, this is a pharmacological property shared with other commonly used antipsychotics (4).

ADMINISTRATION AND PHARMACOKINETICS

Cariprazine is available in four doses: 1.5 mg, 3 mg, 4.5 mg, and 6 mg. Cariprazine is extensively metabolized by the liver, mainly by CYP3A4 and to a lesser extent by CYP2D6. Administration of a single dose of cariprazine results in peak plasma concentration within 3–6 hours (6). After multiple doses of cariprazine, the mean systemic concentration reaches steady-state levels after 1–2 weeks. There is no effect of food on serum concentrations (6).

Given that cariprazine is metabolized by CYP3A4, specific considerations must be taken when patients are co-administered CYP3A4 inhibitors and inducers. If taken with a CYP3A4 inhibitor, cariprazine's active metabolite concentrations will be increased. For patients on a stable dose of cariprazine who are initiating a strong CYP3A4 inhibitor, the dose of cariprazine should be decreased by half (6). Because there has been little research on potential toxicity for patients who are concomitantly taking cariprazine and CYP3A4 inducers, taking them together is recommended against.

FDA INDICATIONS AND CLINICAL STUDIES

Acute and Maintenance Treatment of Schizophrenia

The efficacy of cariprazine in treating acutely decompensated schizophrenia was demonstrated in a 6-week clinical trial where cariprazine was shown to significantly reduce the Positive and Negative Syndrome Scale (PANSS) total score by a least-squares mean difference (LSMD) of –6.0 with cariprazine 3.0 mg and –8.8 with 6.0 mg when compared with placebo (7). FDA indications for the use of cariprazine for schizophrenia among adults are summarized in Box 1.

A study performed to evaluate the effect of cariprazine versus risperidone monotherapy on the negative symptoms of schizophrenia concluded that cariprazine led to a significantly greater LSMD in the PANSS scores compared with risperidone. The LSMD was –8.90 for cariprazine and –7.44 for risperidone, thus supporting the efficacy of cariprazine in treating predominant negative symptoms in schizophrenia (8).

In regard to maintenance treatment for schizophrenia, a 97-week multinational double-blind placebo-controlled

BOX 1. U.S. Food and Drug Administration indications for the use of cariprazine among adults

- Treatment for acute manic episodes and acute episodes with mixed features associated with bipolar I disorder among adults
- Treatment of depressive episodes associated with bipolar I disorder among adults (bipolar depression)
- Adjunctive therapy with an antidepressant for treatment of major depressive disorder among adults (unipolar depression)

randomized withdrawal study was completed in 2016 with the primary efficacy parameter being time to relapse (9). For patients taking cariprazine, there was a significantly longer time to relapse and significantly lower relapse rate compared with those in the placebo group (24.8% versus 47.5%) (9).

Manic and Mixed Episodes in Bipolar I Disorder

The efficacy of cariprazine in treating bipolar I disorder was exhibited in a 3-week double-blind placebo-controlled study comparing 3 mg–12 mg of cariprazine and placebo (10). Participants in this study had been experiencing acute manic or mixed episodes. Significant differences in scores on the Young Mania Rating Scale (YMRS) were observed by day 4 and maintained throughout the study (10). The YMRS score also reflected significantly improved manic symptoms by 58.9% with cariprazine, compared with 44.1% with placebo, and induced remission for 51.9% of patients, compared with 34.9% in the placebo group (10).

In addition, a 3-week, randomized double-blind placebo-controlled parallel-group multicenter phase-3 study with fixed and flexible doses demonstrated that cariprazine was significantly superior to placebo in the treatment of acute mania or mixed episodes among patients with bipolar I disorder. Patients were randomly assigned to placebo, cariprazine 3–6 mg/day, or cariprazine 6–12 mg/day, with the primary and secondary efficacy parameters being change from baseline on the YMRS total score and Clinical Global Impressions–severity of illness (CGI-S) scale score, respectively. Participants in both treatment groups scored significantly better on the YMRS and CGI-S than those in the placebo group (11).

Depression in Bipolar I Disorder

The efficacy of cariprazine in bipolar depression was exhibited in clinical trials demonstrating that cariprazine 1.5 mg/day significantly reduced depressive symptoms, shown by significant improvement in participants' scores from baseline on the Montgomery-Åsberg Depression Rating Scale (MADRS), with an LSMD of –2.5 (12). Although there was a reduction in depressive symptoms seen with cariprazine 3.0 mg/day, these data did not reach statistical significance (12, 13).

In a post-hoc analysis of bipolar I disorder with mixed features, patients were pooled from three studies comparing cariprazine with placebo. Depressive symptoms, measured as MADRS total scores, improved significantly among patients receiving cariprazine compared with those receiving placebo, with an LSMD of –1.59 (14).

Adjunctive Therapy of Unipolar Depression

The efficacy of cariprazine as an adjunctive therapy to antidepressants for the treatment of unipolar depression was established in a randomized double-blind placebo-controlled multicenter trial with 751 participants over a 6-week period, where participants were randomly assigned in a 1:1:1 ratio (15). The first group received antidepressant monotherapy plus placebo, the second group received antidepressant monotherapy plus cariprazine 1.5 mg/day, and the third received antidepressant monotherapy plus cariprazine 3.0 mg/day. After 6 weeks, it was concluded that adjunctive cariprazine resulted in clinically and statistically significant changes in MADRS scores among patients with major depressive disorder who received cariprazine 1.5 mg/day plus antidepressant monotherapy compared with those who received antidepressant monotherapy plus placebo, with a mean reduction in the MADRS baseline score of –14.1 versus –11.5 (15). In the group receiving cariprazine 3.0 mg/day plus antidepressant monotherapy, MADRS score reduction was not significantly different from that of the group receiving placebo (15). This may be, in part, a result of having two active treatment arms, which may have increased the placebo response and thus contributed to a lack of a statistically significant difference between the placebo group and the cariprazine 3.0 mg/day group (15).

ADVERSE REACTIONS AND WARNINGS

In clinical trials for patients with schizophrenia, the most frequent adverse reactions were extrapyramidal symptoms and akathisia (6). In clinical trials for patients with manic or mixed episodes associated with bipolar I disorder, the most frequent adverse reactions were extrapyramidal symptoms, headaches, and akathisia, where 2% of patients discontinued treatment because of akathisia (6). Extrapyramidal symptom events included parkinsonism, restlessness, dystonias, and musculoskeletal stiffness. Other adverse reactions noted were insomnia, weight gain, nausea, and constipation (10). A list of adverse reactions described in clinical trials is presented in Table 1.

During clinical trials, cariprazine caused no clinically meaningful changes in blood pressure (6). There was also a low incidence of cataracts as well as gastrointestinal, hepatobiliary, musculoskeletal, psychiatric, renal, and skin disorders (6). Despite reports of patient weight gain during these trials, no changes in lipid or metabolic serum chemistry were clinically meaningful, although there was a statistically significant increase in triglycerides with cariprazine in the 3–6 mg/day dose range (10). Overall, there were also no statistically significant changes in prolactin levels in all dose groups (10) and an increase in mean creatinine phosphokinase levels

TABLE 1. Adverse reactions and incidence described in clinical trials with cariprazine

Adverse reactions	Incidence (%)
Extrapyramidal symptoms (parkinsonism, restlessness, dystonia, and musculoskeletal stiffness)	15–29
Akathisia	9–21
Insomnia	8–13
Headaches	9–18
Weight gain	2–3
Nausea	5–13
Constipation	6–11

among 4% of patients, with no associated changes in renal function (6).

SPECIAL POPULATIONS

Special considerations must be taken for pregnant patients, because there are not enough available data regarding cariprazine-associated risks of birth defects or miscarriages among humans (6). Animal studies have shown that although cariprazine may be associated with malformations and developmental delays in rat models, it poses no teratogenic risk in rabbit models (6). Reported neonatal adverse reactions associated with the general use of antipsychotics include extrapyramidal or withdrawal symptoms during the third trimester of pregnancy. Data are insufficient to determine cariprazine's safety during breastfeeding and in the pediatric population. Previous studies have shown greater risk of death among elderly patients, and therefore the use of cariprazine for treatment of dementia-related psychosis is not approved at this time (16).

CONCLUSIONS

Cariprazine's unique pharmacological feature of being a partial agonist with an affinity for D_3 receptors that surpasses that of endogenous dopamine makes it a potent and efficacious second-generation antipsychotic. It has shown superior efficacy in the treatment of schizophrenia and manic and mixed episodes of bipolar I disorder. It is approved for the treatment of schizophrenia, manic and mixed episodes of bipolar I disorder, and bipolar depression and as adjunctive treatment for unipolar depression. Despite some side effects, such as akathisia and extrapyramidal symptoms, cariprazine has shown a positive safety and tolerance profile that may contribute to treatment adherence among patients with the aforementioned psychiatric conditions.

KEY POINTS/CLINICAL PEARLS:

- Cariprazine has unique pharmacologic properties due to high affinity for D_3 receptors, as well as upregulation of D_2 and D_4 receptors.
- Cariprazine has shown efficacy among adults with schizophrenia, acute manic and mixed episodes, bipolar depression, and unipolar depression.
- The most common side effects of cariprazine are akathisia and extrapyramidal symptoms, with relatively less risk than many other antipsychotics.

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