REVIEW

Cariprazine for Schizophrenia and Bipolar Disorder

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ABSTRACT

Schizophrenia and bipolar disorder are associated with significant morbidity and mortality. Although atypical antipsychotics reduce positive and negative symptoms of schizophrenia as well as manic or mixed episodes of bipolar disorder, they are associated with varying degrees of metabolic adverse effects. This necessitates continued development of efficacious yet metabolically favorable treatments. Cariprazine was recently approved to treat adult patients with schizophrenia and manic or mixed episodes. It was well-tolerated and adverse reactions included akathisia, extrapyramidal symptoms, nausea, or constipation. Cariprazine is taken once daily without regard to food. The dose should be adjusted in patients who receive CYP450 inhibitors, and it should not be given to patients with severe hepatic or renal disease. This article reviews mechanisms of action, efficacy, tolerability (including adverse effects), dosing, and contraindications of cariprazine.

INTRODUCTION

Schizophrenia is characterized by at least two of the following symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, or negative symptoms.[1] Bipolar disorder consists of manic, hypomanic, or mixed episodes alternating with depressive episodes.[2] Because second-generation or atypical antipsychotics reduce both positive and negative symptoms of schizophrenia as well as manic and mixed episodes of bipolar disorder, they are recommended treatments for both conditions.[3-5] However, they are associated with adverse effects such as weight gain, dyslipidemia, and hyperglycemia, which may worsen comorbid cardiovascular conditions.[6,7] This necessitates continued development of effective, tolerable, and metabolically favorable treatments. In September 2015, cariprazine was approved to treat schizophrenia and manic or mixed episodes in adults. This article reviews mechanisms of action, efficacy, tolerability (including adverse effects), dosing, and contraindications of cariprazine.

MECHANISMS OF ACTION

Cariprazine is a partial agonist at D_2 and D_3 receptors, with significantly greater affinity for D_3 receptors.[8] It exerts partial agonism at 5-HT_{1A} receptors, antagonism at 5-HT_{2A} and 5-HT_{2B} receptors, and minimal antagonism at 5-HT_{2C}, 5-HT_7, and H_1 receptors.[8] In contrast to full antagonism of dopamine receptors, partial agonism suggests lower risk of akathisia, tardive dyskinesia, extrapyramidal symptoms, and abnormal prolactin levels. Modulation of the D_3 receptor exerts a procognitive effect and may reduce negative symptoms.[9,10] Lack of significant histamine receptor antagonism decreases risk for sedation and weight gain.

TABLE 1. Studies of cariprazine

STUDY	ILLNESS	STUDY DESIGN	DURATION	*N*	DOSES
Phase 2 trial[13]	Schizophrenia	Randomized, double-blind, placebo-controlled, parallel-group, fixed dose	1 week washout, 6 weeks treatment, 2 week safety follow-up	732	1.5, 3, or 4.5mg/day; risperidone 4mg/day as active control for assay sensitivity
Phase 3 trial[14]	Schizophrenia	Randomized, double-blind, placebo-controlled, parallel-group, fixed dose	1 week washout, 6 weeks treatment, 2 week safety follow-up	617	3 or 6mg/day, or aripiprazole 10mg/day as active control for assay sensitivity
Phase 3 trial[15]	Schizophrenia	Randomized, double-blind, placebo-controlled, parallel-group	1 week washout, 6 weeks treatment, 2 week safety follow-up	446	3–6 or 6–9mg/day
Phase 2 trial[17]	Bipolar manic or mixed episode	Randomized, double-blind, placebo-controlled, flexible dose study	4 days washout, 3 weeks treatment, 2 week safety follow-up	238	3–12mg/day
Phase 3 trial[18]	Bipolar manic or mixed episode	Randomized, double-blind, placebo-controlled, parallel group, fixed/flexible dose study	1 week washout, 3 weeks treatment, 2 week safety follow-up	497	3–6 or 6–12mg/day
Phase 3 trial[19]	Bipolar manic or mixed episode	Randomized, single-blind, placebo-controlled	1 week washout, 3 weeks treatment, 2 week safety follow-up	312	3–12mg

EFFICACY

Schizophrenia. Cariprazine was evaluated for efficacy in three trials, which are detailed in Table 1. The primary endpoint was total change in the Positive and Negative Syndrome Scale (PANSS), and the main secondary endpoint was change in the Clinical Global Impressions – Severity scale (CGI-S).[11,12] All cariprazine doses demonstrated efficacy as evidenced by a reduction in PANSS total, PANSS subscales, and CGI scale.[13–15] Efficacy was noted starting at Week 1 for groups receiving higher doses and Weeks 2 or 3 for the lowest doses. Two studies used risperidone or aripiprazole as active controls to ensure assay sensitivity and did not compare their efficacy to cariprazine.[13,14]

Bipolar disorder. Cariprazine was evaluated in three studies of adults with manic or mixed episodes, which are detailed in Table 1. Efficacy was assessed using the Young Mania Rating Scale and the CGI-S.[12,16]] In the first study, cariprazine demonstrated efficacy within one week, and improvement on the CGI-S scale was noted as early as Day 2 of treatment; nearly twice as many patients achieved response and remission of symptoms with cariprazine.[17] In a second study, low and high doses of cariprazine reduced symptoms compared to placebo.[18] In a third study, cariprazine demonstrated significant reduction in symptoms, starting by Day 4 of treatment.[19] It was also associated with significant rates of response and remission.

TOLERABILITY

Cariprazine was generally well-tolerated. The most common adverse effects included akathisia, extrapyramidal symptoms, nausea, or constipation. Insomnia; headache; insignificant increases in alanine aminotransferase (ALT), heart rate, or glucose; and decreased prolactin were noted infrequently. There were no differences between treatment and placebo groups on other metabolic

parameters or electrocardiogram measures. However, all studies noted the short duration of treatment as a limitation, acknowledging that longer trials are needed to characterize the metabolic profile of cariprazine.

DOSING

Cariprazine is available in 1.5mg, 3mg, 4.5mg, and 6mg tablets given once daily without regard to food.[20] The recommended daily dose is 1.5- to 6mg for patients with schizophrenia and 3- to 6mg for patients with manic or mixed episodes. Dosing starts with 1mg for 1 day, then titration in 1.5- or 3mg increments as indicated. Patients taking cariprazine and starting a CYP3A4 inhibitor should decrease the dose of cariprazine by half (decrease to 1.5mg or 3mg daily if receiving 4.5mg, and take every other day if taking 1.5mg).[20] In patients receiving a stable dose of a CYP3A4 inhibitor, cariprazine is started at 1.5mg on Days 1 and 3, with a maximum dose of 3mg. Although no dosage adjustment is required in patients with mild or moderate hepatic or renal impairment, patients should not take cariprazine with a CYP3A4 inducer or if they have severe hepatic or renal disease.[20]

Following oral administration, cariprazine reaches peak concentration within 3 to 6 hours and steady-state within 1 to 2 weeks, with a half-life of 2 to 4 days. It has a high volume of distribution and is highly protein-bound in plasma.[20] It is metabolized into two active metabolites by CYP3A4 and to lesser extent by CYP2D6 isozymes. An inactive metabolite is excreted in urine.[20]

CONTRAINDICATIONS

Cariprazine is contraindicated in patients with known hypersensitivity to cariprazine. As with other atypical antipsychotics, cariprazine carries a "black box" warning for increased mortality and cerebrovascular events in elderly patients with dementia-related psychosis. It also includes warnings for neuroleptic malignant syndrome, tardive dyskinesia, metabolic abnormalities, low white blood cell count, orthostatic hypotension, seizures, cognitive and motor impairment, changes in body temperature, and dysphagia.[20] Prescribers are advised to monitor for delayed adverse reactions due to the long half-life of cariprazine.[20] Cariprazine is not yet assigned a pregnancy category, but neonates exposed to cariprazine in the third trimester are at risk for extrapyramidal and/or withdrawal symptoms.[20] While no data are available regarding safety in breastfeeding mothers, the manufacturer recommends that the benefits of breastfeeding should be considered along with the mother's need for cariprazine and potential adverse effects on the infant from the medication or the underlying mental illness.[20]

SUMMARY

Schizophrenia and bipolar disorder are debilitating conditions with significant morbidity and mortality. Many atypical antipsychotics improve functioning, but they carry risks for adverse effects. Cariprazine reduced symptoms of acute schizophrenia and manic or mixed episodes with minimal adverse effects. It is an additional option for clinicians who treat patients with schizophrenia and bipolar disorder. Further trials are warranted to evaluate its long-term efficacy and metabolic profile.

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