



## An Overview on Cariprazine

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### Abstract

*Schizophrenia is a serious mental disorder with a long and painful course. It contributes significantly to the worldwide burden of disease caused by mental health conditions. Relapses are common in schizophrenia, and each one worsens clinical symptoms, cognitive impairment, social and vocational performance, and overall quality of life. Cariprazine is a new antipsychotic that acts as a partial D2, D3 receptor agonist with a preference for the D3 receptor over the D2 receptor, whereas many existing antipsychotics favor the D2. The dopamine D3 receptor, in particular, has been proposed as a potential target for the treatment of unipolar depression. When flexibly dosed at 3–9 mg/day for up to 48 weeks, cariprazine was typically safe and well tolerated in patients with schizophrenia. Cariprazine binds with high potency to D3 dopamine, D2 dopamine, and 5HT2B serotonin receptors, but only moderately to 5HT1A and 5HT2A serotonin receptors, a profile that differs from brexpiprazole and aripiprazole.*

**Keywords:** schizophrenia, Cariprazine, dopamine D3 receptor, mental health disorders.

### Introduction:

Cariprazine is a novel antipsychotic that works as a partial D2, D3 receptor agonist, preferring the D3 receptor over the D2 receptor, although many existing antipsychotics prefer the D2. Unipolar depression has been linked to the dopamine D3 receptor, which has been considered as a potential therapeutic target<sup>[1]</sup>. The administration of a selective D3 receptor antagonist raises dopamine, norepinephrine, and acetylcholine concentrations in the anterior cingulate cortex (ACC) without boosting serotonin levels, according to preclinical studies<sup>[2]</sup>. Indeed, disruption of the ACC has been linked to the pathophysiology of bipolar disorder's multiple mood states (BD)<sup>[3]</sup>. Cariprazine has been shown to have antidepressant, antianhedonic,

antipsychotic, and pro-cognitive effects in preclinical trials.<sup>[4,5]</sup>

### Chemical Name

Cariprazine (IUPAC name: 3-[4-[2-[4-(2,3-dichlorophenyl)piperazin-1-yl]ethyl]cyclohexyl]-1,1-dimethylurea) is a D3 preferring partial D2, D3 receptor agonist and has the molecular formula C<sub>21</sub>H<sub>32</sub>Cl<sub>2</sub>N<sub>4</sub>O with a molecular weight of 427.41 g/mol.

### Dosage

Cariprazine was typically safe and well tolerated in schizophrenic patients when dosed flexibly at 3–9 mg/d for up to 48 weeks<sup>[6]</sup>. Patients had been randomized to either cariprazine or risperidone and after a fixed dose period of 2–4 weeks patients

continued up to 48 weeks on the respective treatment arm with a flexible dosing of 1.5–9 mg/day (1.5 mg, 3 mg, 6 mg, or 9 mg) of cariprazine or 2–12 mg/day (2 mg, 4 mg, 6 mg, 8 mg, 10 mg, or 12 mg) of risperidone. However, while risperidone doses were allowed to be changed after two weeks of treatment, for the cariprazine treated patients this was only allowed after week 4 due to the pharmacokinetics of the compound<sup>[7]</sup>.

### Mechanism of Action

Cariprazine is a dopamine-serotonin partial agonist in the same pharmacologic class with brexpiprazole and aripiprazole.<sup>[5,6]</sup> More specifically, cariprazine binds to D3 dopamine, D2 dopamine, and 5HT2B serotonin receptors with high potency, and to 5HT1A serotonin and 5HT2A serotonin receptors with moderate potency, a profile that differs from both brexpiprazole and aripiprazole.<sup>[6,7]</sup> In animal models, cariprazine has antipsychotic effect not surprising for an agent with D2 partial agonist actions, and indeed cariprazine is approved for the acute and maintenance treatment of schizophrenia.

### Discussion

Dopamine receptor partial agonists, such as cariprazine, differ from all other second-generation antipsychotics in that they cause partial agonism at the dopamine D2 and D3 receptors. Because of their generally favorable tolerability profiles, these agents are considered first-line options for the treatment of schizophrenia.<sup>[11]</sup> Cariprazine's unique mode of action, as a partial agonist with the highest affinity and longest half-life for the dopamine D3 receptor, supports broad-spectrum efficacy across the symptom domains of schizophrenia<sup>[12]</sup>. Efficacy in lowering positive symptoms and delaying relapse of schizophrenia during long-term therapy is attributed to high dopamine D2 receptor affinity. High in vivo occupancy at both D3 and D2 receptors, as well as greater affinity for D3 receptors than D2 receptors, are likely to increase efficacy against

difficult-to-treat predominant and persistent negative symptoms and cognitive symptoms<sup>[13]</sup>. When the findings of a cariprazine proof-of-concept research suggested an efficacy signal for cariprazine in the treatment of acute exacerbations of schizophrenia, the drug's efficacy was further investigated<sup>[14]</sup>.

### Pharmacodynamic Properties of Cariprazine

While the exact mechanism of action for cariprazine in schizophrenia patients is uncertain, it appears to work by acting as a partial agonist at central dopamine D2 and serotonin 5-HT1A receptors while acting as an antagonist at 5-HT2A receptors<sup>[8]</sup>. Cariprazine also acts as a partial agonist at the D3 receptor and as an antagonist at the 5-HT2B receptor.

### Pharmacokinetic Properties of Cariprazine:

According to a population pharmacokinetic analysis, the pharmacokinetics of oral cariprazine can be described by a three-compartment model with first-order absorption and elimination; those of its major metabolites (desmethyl cariprazine and didesmethyl cariprazine) by a two-compartment model with linear elimination<sup>[9]</sup>.

### Safety Measures

In patients with schizophrenia, acute and long-term exposure to cariprazine was typically safe and well tolerated. During long-term treatment, no new safety concerns emerged, and adverse events (AEs) were similar to those seen with atypical antipsychotics. In cariprazine clinical studies, one serious and unintentional overdose was documented. With cariprazine 48 mg/day, orthostasis and sedation were reported in a patient with schizophrenia, which resolved on the day of overdose<sup>[10]</sup>.

### Abbreviations

anterior cingulate cortex (ACC)  
adverse events (AEs)  
bipolar disorder (BD)  
dopamine 2 receptor(d2 receptor)

dopamine 3 receptor(D3 receptor)  
 serotoninine (5HT1A receptor)  
 serotoninine (5HT2 A receptor)

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