**INTRODUCTION**

Antipsychotics have shown strong efficacy in treating the positive symptoms of schizophrenia but limited efficacy in treating negative symptoms and cognitive impairments. Although antipsychotics are thought to primarily act on receptors of dopamine D2 receptors, affinity for other receptors may provide benefits in the treatment of schizophrenia and mood disorders. This article highlights the use of cariprazine for treating schizophrenia and cognitive impairments.

**RESULTS**

- Cariprazine has high affinity for dopamine D2 receptors, as evidenced by the ED50 of 3 mg/kg in the conditioned avoidance response (CAR) model.
- Cariprazine has lower affinity for other receptors such as 5-HT1A, 5-HT2A, 5-HT2C, 5-HT3, 5-HT6, 5-HT7, and histaminergic H1 receptors.
- Cariprazine shows efficacy in models of antipsychotic activity, such as the PCP social interaction and PCP social recognition memory models.
- Cariprazine demonstrates greater potency than aripiprazole for antipsychotic-like activity. Cariprazine was 25- to 100-fold more potent than aripiprazole in animal models of antipsychotic activity.
- Cariprazine showed improved efficacy in models of emotional and cognitive impairments compared to aripiprazole.

**CONCLUSIONS**

- Cariprazine is a potential dopamine D2/D3 receptor partial agonist with potential benefits for both positive and negative symptoms of schizophrenia.
- Unlike aripiprazole, cariprazine demonstrated high and balanced occupancy at D2 and D3 receptors with antipsychotic-like effective doses.
- Cariprazine showed greater potency than aripiprazole across a number of animal models that represent different aspects of schizophrenia.
- The potency difference between cariprazine and aripiprazole was seen across the range of cognitive impairments (cariprazine was 25 to 100-fold more potent than aripiprazole) and depression/negative symptoms (cariprazine was 80 to 100-fold more potent than aripiprazole).
- The magnitude of the potency differences were comparable to the affinity differences between cariprazine and aripiprazole for D3 receptor occupancy (> 70-fold).
- Studies in D2 receptor knockout mice supported the hypothesis that the procognitive and antidepressant-like activity of cariprazine is at least partly mediated by the D3 receptor.
- These results suggest that the high affinity and brain exposure of cariprazine at D3 receptors may explain the greater relative potency of cariprazine versus aripiprazole in models of cognitive impairment and negative symptoms.

With its distinct pharmacological profile, cariprazine may provide a new option for the treatment of schizophrenia, bipolar disorder, and MDD.
Cariprazine demonstrates greater potency than aripiprazole in animal models of psychosis, cognitive impairment, and negative symptoms

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Background: Antipsychotics have shown strong efficacy in treating the positive symptoms of schizophrenia but limited efficacy in treating negative symptoms, cognitive impairment, and depressed mood. Aripiprazole is the only dopamine D2 receptor partial agonist currently approved for the treatment of schizophrenia. Cariprazine is also a D2 receptor partial agonist currently in clinical development for the treatment of schizophrenia. Cariprazine differs from aripiprazole in that it has relatively higher dopamine D3 receptor affinity and selectivity. The D3 receptor is preferentially expressed in areas of the brain known to modulate cognitive and emotional functions, which has led to targeting of this receptor for new antipsychotic drugs. Functional blockade of D3 receptors may be beneficial in treating the negative, cognitive, and mood symptoms associated with schizophrenia. In this analysis, we compared the potencies of cariprazine and aripiprazole across a number of animal paradigms that model the different symptom domains of schizophrenia.

Methods: Established rodent models of psychosis, cognitive impairment, and negative symptoms/depression were used to evaluate the effects of cariprazine and aripiprazole at various doses in rats and mice. Differences in potency between the 2 compounds were estimated using ED50 values or minimal effective doses (MED) for each behavioral model. Striatal D2 and cerebellar D3 receptor in vivo occupancy in rats was determined using the high affinity agonist radioligand [3H](+)-PHNO.

Results: Cariprazine occupied D2 receptors in rats with approximately 30-fold greater potency than aripiprazole (ED50: cariprazine, 0.23mg/kg; aripiprazole, 7.7mg/kg); potency for D3 receptor occupancy in rats was >70-fold higher for cariprazine vs aripiprazole (ED50: cariprazine, 0.43mg/kg; aripiprazole, >30mg/kg). In rat models of antipsychotic-like activity, cariprazine demonstrated 20 to 30-fold greater potency than aripiprazole (ED50 for conditioned avoidance response: cariprazine, 0.8mg/kg; aripiprazole, 18mg/kg; ED50 for amphetamine-induced motor activity: cariprazine, 0.12mg/kg; aripiprazole, 3.9mg/kg). In comparison, cariprazine showed much greater differences in potency relative to aripiprazole in the models of cognitive impairment (cariprazine was 25 to >250-fold more potent than aripiprazole) and negative symptoms/depression (cariprazine was 85 to 100-fold more potent than aripiprazole).

In mice, cariprazine was approximately 4-fold more potent than aripiprazole in the apomorphine-induced climbing model of antipsychotic-like activity (ED50: cariprazine, 0.27mg/kg; aripiprazole, 0.97mg/kg) but it was 100-fold more potent than aripiprazole in cognitive impairment models and 25 to 50-fold more potent than aripiprazole in models of negative symptoms/depression.

Conclusion: Cariprazine showed greater potency than aripiprazole across a number of animal models that represent different aspects of schizophrenia. Interestingly, the potency differences between cariprazine and aripiprazole varied widely across models. The greatest differences in potency between cariprazine and aripiprazole were seen in models of cognitive impairment and negative symptoms/depression. The high affinity of cariprazine at D3 receptors may underlie the greater potency relative to aripiprazole in models of cognitive impairment and negative symptoms.

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