Cariprazine Demonstrates Greater Potency Than Aripiprazole in Animal Models of Psychosis, Cognitive Impairment, and Negative Symptoms

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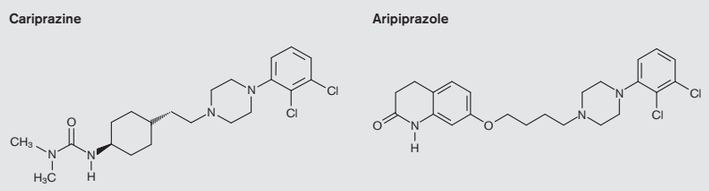
INTRODUCTION

Antipsychotics have shown strong efficacy in treating the positive symptoms of schizophrenia but limited efficacy in treating cognitive impairment and negative and mood symptoms. Although antipsychotics are thought to primarily exert their actions by blockade of dopamine D_2 receptors, affinity for other neuroreceptors may provide benefits in the treatment of schizophrenia and mood disorders. These antipsychotics display variable affinity for dopamine D_3 receptors in vitro but under *in vivo* conditions they show no or only negligible D_3 receptor occupancy. The D_3 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.

Cariprazine is an orally active and potent dopamine D_3 and D_2 receptor partial agonist with preferential binding to D_3 receptors in clinical development for the treatment of schizophrenia, bipolar mania, bipolar depression, and the adjunctive treatment of major depressive disorder (MDD). Aripiprazole is also a D_2 receptor partial agonist with affinity for D_3 receptors and the only D_2 partial agonist currently approved for the treatment of schizophrenia and bipolar mania. Compared with aripiprazole, cariprazine shows markedly greater affinity and selectivity for D_3 receptors. Here we compared the pharmacological profiles of cariprazine and aripiprazole and evaluated the comparative efficacy and potency of both compounds across a number of animal paradigms that model different symptom domains of schizophrenia and bipolar disorder.

Figure 1. Structure of Cariprazine and Aripiprazole

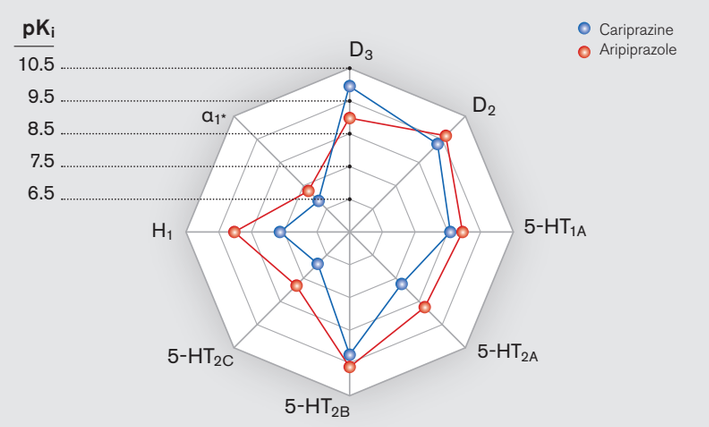


RESULTS

In Vitro Receptor Binding Profile of Cariprazine and Aripiprazole[1]

- Cariprazine and aripiprazole show subnanomolar affinity for dopamine D_2 receptors, (K_i [nM]: cariprazine: 0.49; aripiprazole: 0.21) (Figure 2)
- Cariprazine shows greater D_3 receptor selectivity with almost 10-fold higher affinity than aripiprazole for D_3 receptors (K_i [nM]: cariprazine: 0.085, aripiprazole 0.94)
- Both compounds also display subnanomolar affinity for 5-HT_{2B} receptors (K_i [nM]: cariprazine, 0.58; aripiprazole, 0.25)
- Affinities for the 5-HT_{1A} receptors were in the nanomolar range for both compounds (K_i [nM]: cariprazine: 2.6; aripiprazole: 1.1)
- Cariprazine displayed only moderate or weak affinity for 5-HT_{2A} and histaminergic H_1 receptors; in contrast, aripiprazole showed nanomolar affinity for the 5-HT_{2A} receptor and subnanomolar affinity for the H_1 receptor
  - Weak to negligible affinity was seen at other receptors with both compounds

Figure 2. *In Vitro* Affinity of Cariprazine and Aripiprazole for Human Neurotransmitter Receptors

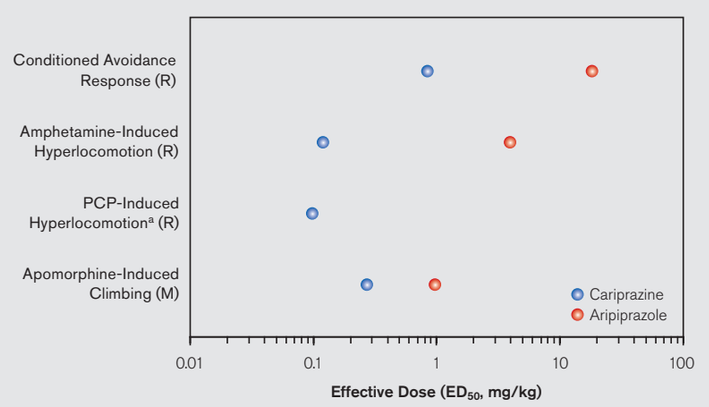


*Based on rat α_{1A} receptors.
Cariprazine and aripiprazole were further tested for 59 other targets (receptors, enzymes, transporters and channels) but the compounds produced negligible (ie, <50 %) displacement at 1 µM concentrations.

Potency of Cariprazine in Rat Models Predictive of Antipsychotic Efficacy[2]

- Cariprazine significantly inhibited conditioned avoidance response and amphetamine-induced hyperactivity in rats with ≥20-fold higher potency than aripiprazole (Figure 3)
  - Cariprazine but not aripiprazole demonstrated significant activity in the PCP-induced hyperlocomotion model
- In mice, cariprazine was also more potent than aripiprazole in the apomorphine-induced climbing model

Figure 3. Potency of Cariprazine and Aripiprazole in Models Predictive of Antipsychotic Efficacy

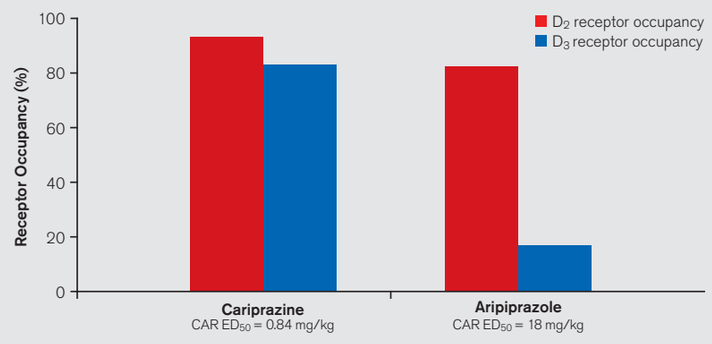


[a]In PCP-induced hyperlocomotion model, only cariprazine demonstrated significant activity.
R indicates rat; M, mouse.
Behavioral tests in animal models screening for antipsychotic-like activity were performed as previously described in Gyertyán et al.[2]

In Vivo Occupancy of D_2 and D_3 Receptor at Antipsychotic-Like Effective Doses

- At a dose equivalent to the ED_{50} for antipsychotic-like activity in the conditioned avoidance response (CAR) behavioral model, cariprazine showed high levels of both D_2 and D_3 receptor occupancy (Figure 4)
- Aripiprazole showed high occupancy of D_2 receptors but only low occupancy of D_3 receptors
- The conditioned avoidance response model of antipsychotic-like efficacy shows high construct validity with respect to efficacy and potency on the positive symptoms of schizophrenia[3]
  - This model also has predictive validity since antipsychotics inhibit conditioned avoidance response at a striatal D_2 receptor occupancy level that correlate with the human D_2 receptor occupancy threshold of clinical efficacy[4,5]

Figure 4. D_2 and D_3 Receptor Occupancy in Rats at ED_{50} for Inhibition of Conditioned Avoidance Response

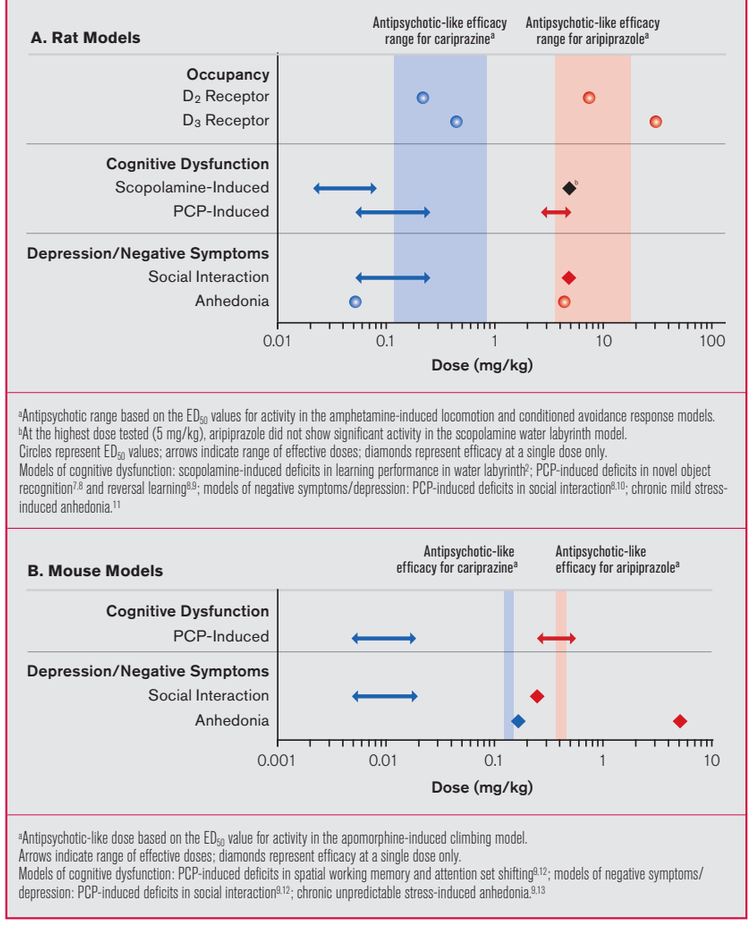


CAR indicates conditioned avoidance response.
For *in vivo* occupancy determination, Wistar rats were administered vehicle or drug (0.5 mL/100 g body weight) followed by intravenous (IV) injection of [^{3}H] (+)-PHNO. Percent radioactivity bound (bound %) in the D_2-rich striatum and in the D_3-rich L9,10 lobe of cerebellum was calculated. Receptor occupancy at the CAR ED_{50} was estimated from occupancy dose response curves as determined by [^{3}H] (+)-PHNO uptake in striatal (D_2) and cerebellar (D_3) regions.[6] CAR ED_{50} values for cariprazine and aripiprazole were obtained from Gyertyán et al.[2]

Relationship Between Antipsychotic-Like Effective Doses, Receptor Occupancy, and Efficacy in Other Behavioral Models

- For cariprazine, the ED_{50} for occupying both D_2 and D_3 receptors was in the range that cariprazine showed efficacy in models predictive of antipsychotic efficacy (Figure 5A; Table 1)
- In models of cognitive impairment and depression/negative symptoms, cariprazine was effective at much lower doses than its antipsychotic-like effective dose (over 6-fold lower in rats; nearly 50-fold lower in mice)
- Aripiprazole was only effective in rat models of cognitive impairment and depression/negative symptoms at doses similar to or higher than its antipsychotic-like effective dose
  - The ED_{50} of aripiprazole for occupying D_2 receptors was in the range of its antipsychotic-like effective dose; conversely, the ED_{50} for occupying D_3 receptors was higher than the antipsychotic-like effective dose

Figure 5. Potency of Cariprazine and Aripiprazole in Rodent Behavioral Models and Their Affinities for D_2/D_3 Receptor Occupancy *in Vivo*



[a]Antipsychotic range based on the ED_{50} values for activity in the amphetamine-induced locomotion and conditioned avoidance response models.
[b]At the highest dose tested (5 mg/kg), aripiprazole did not show significant activity in the scopolamine water labyrinth model.
Circles represent ED_{50} values; arrows indicate range of effective doses; diamonds represent efficacy at a single dose only.
Models of cognitive dysfunction: scopolamine-induced deficits in learning performance in water labyrinth[2]; PCP-induced deficits in novel object recognition[7,8] and reversal learning[8,9]; models of negative symptoms/depression: PCP-induced deficits in social interaction[8,10]; chronic mild stress-induced anhedonia.[11]

[a]Antipsychotic-like dose based on the ED_{50} value for activity in the apomorphine-induced climbing model.
Arrows indicate range of effective doses; diamonds represent efficacy at a single dose only.
Models of cognitive dysfunction: PCP-induced deficits in spatial working memory and attention set shifting[9,12]; models of negative symptoms/depression: PCP-induced deficits in social interaction[9,12]; chronic unpredictable stress-induced anhedonia.[9,13]

Comparison of Cariprazine and Aripiprazole Affinity/Potency

- Cariprazine was approximately 30 times more potent than aripiprazole in occupying D_2 receptors in rats (Table 1; Figure 6)
  - Interestingly, the potency difference between cariprazine and aripiprazole in assays of antipsychotic-like activity in rats (20-30 times more potent) aligned with affinities for occupying D_2 receptors
- The affinity difference between cariprazine and aripiprazole was even greater for D_3 receptor occupancy (cariprazine was >70-fold more potent than aripiprazole in rats)
- In models of cognitive impairment and depression/negative symptoms, the potency differences between cariprazine and aripiprazole (cariprazine was 25 to >250-fold more potent than aripiprazole) were much higher than for models of antipsychotic-like activity
- Similar trends were observed in mice, with cariprazine demonstrating an approximate 4-fold greater potency than aripiprazole for antipsychotic-like activity but up to 100-fold greater potency in cognitive impairment models and up to 50-fold greater potency in models of negative symptoms/depression

Table 1. Comparison of Affinities of Cariprazine and Aripiprazole for D_2 and D_3 Receptor Occupancy and Their Potencies Across Different Behavioral Models

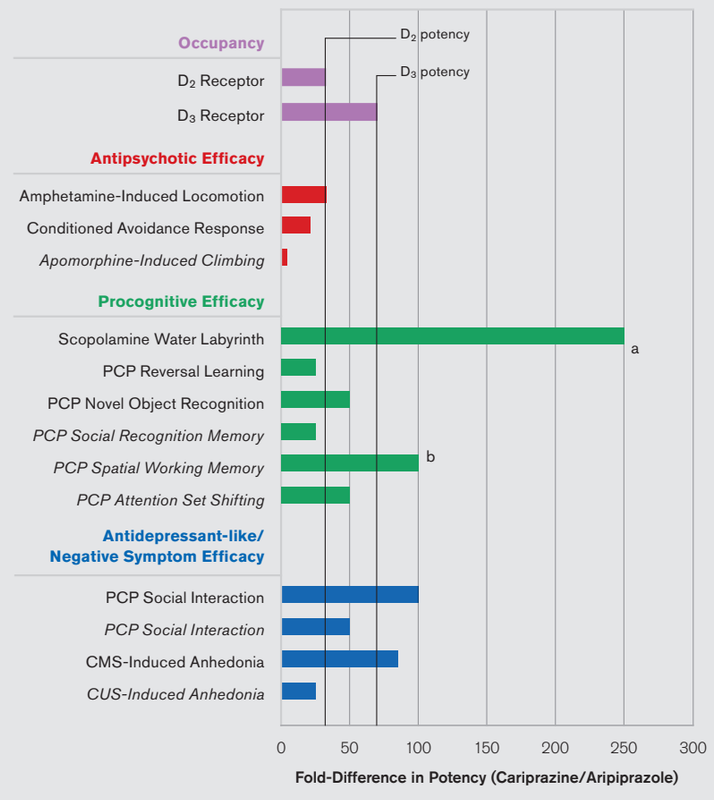
Characteristics	Model Tested	Cariprazine ED_{50}, mg/kg	Aripiprazole ED_{50}, mg/kg	Potency Difference
Rat				
Receptor Occupancy	D_2 receptor[6]	0.23	7.65	33
	D_3 receptor[6]	0.43	>30	>70
Antipsychotic Efficacy	Amphetamine-induced locomotion[2]	0.12	3.9	33
	Conditioned avoidance response[2]	0.84	18	21
Procognitive Efficacy	Scopolamine water labyrinth[2]	0.02[a]	>5[a]	>250
	PCP reversal learning[8,9]	0.1[a]	2.5[a]	25
	PCP novel object recognition[7,8]	0.05[a]	2.5[a]	50
Antidepressant-like/ Negative Symptom Efficacy	CMS-induced anhedonia[11]	0.052	4.4	85
	PCP social interaction[8,10]	0.05[a]	5[a]	100
Mouse				
Antipsychotic Efficacy	Apomorphine-induced climbing[2]	0.27	0.97	4
Procognitive Efficacy	PCP social recognition memory[9,12]	0.01[a]	0.25[a]	25
	PCP spatial working memory[9,12]	0.005[a]	0.5[a]	100
	PCP attention set shifting[9,12]	0.01[a]	>0.5[a]	>50
Antidepressant-like/ Negative Symptom Efficacy	CUS anhedonia[9,13]	0.2[a]	5[a]	25
	PCP social interaction[9,12]	0.005[a]	0.25[a]	50

[a]Doses represent the minimally effective doses (MED) rather than ED_{50} values. CMS indicates chronic mild stress; CUS, chronic unpredictable stress.

CONCLUSIONS

- Cariprazine is a potent dopamine D_3 and D_2 receptor partial agonist with preferential binding to D_3 receptors
  - Unlike aripiprazole, cariprazine demonstrated high and balanced occupancy of D_2 and D_3 receptors at 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 in models of antipsychotic activity (~20-30 fold) was similar in magnitude to the affinity differences for D_2 receptor occupancy (~30 fold)
- The greatest differences in potency between cariprazine and aripiprazole were seen in rat models of cognitive impairment (cariprazine was 25 to >250-fold more potent than aripiprazole) and depression/negative symptoms (cariprazine was 85 to 100 fold more potent than aripiprazole)
  - The magnitude of these potency differences were comparable to the affinity difference between cariprazine and aripiprazole for D_3 receptor occupancy (>70 fold)
- Studies in D_3 receptor knockout mice supported the hypothesis that the procognitive and antidepressant-like activity of cariprazine is at least partly mediated by activity at the D_3 receptor
- These results suggest that the high affinity and brain occupancy of cariprazine at D_3 receptors may underlie 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

Figure 6. Potency Differences of Cariprazine and Aripiprazole Across Behavioral Models



Italicized models were experiments conducted in mice.
[a]At the highest dose tested (5 mg/kg), aripiprazole did not show significant activity in the scopolamine water labyrinth model.
[b]At the highest dose tested (0.5 mg/kg), aripiprazole did not show significant activity in the PCP attention set shifting model.

D_3 Receptor-Mediated Effects of Cariprazine in D_3 Receptor Knockout Mice[12,13]

- Cariprazine reversed PCP-induced cognitive impairment in wild-type mice but not in D_3 knockout mice suggesting that the procognitive effects of cariprazine are at least partly mediated by the D_3 receptor (Zimniski et al, 2013)[12]
- In the chronic unpredictable stress (CUS)-induced anhedonia model, cariprazine showed significant antidepressant-like effects in wild type mice, but not in D_3 receptor knockout mice, indicating that effects in these models were also at least partly mediated by the D_3 receptor (Duman et al, 2012)[13]

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Presented at the 27th Congress of the European College of Neuropsychopharmacology
October 18-21, 2014 | Berlin, Germany

This poster is financially supported by Forest Laboratories, LLC, a subsidiary of Actavis plc, and Gedeon Richter Plc. Editorial support was provided by Prescott Medical Communications Group, Chicago, Illinois.

N. Adham is an employee of Forest Research Institute, a subsidiary of Actavisc plc. I. Gyertyán and B. Kiss are employees of Gedeon Richter Plc.

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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 D_2 receptor partial agonist currently approved for the treatment of schizophrenia. Cariprazine is also a D_2 receptor partial agonist currently in clinical development for the treatment of schizophrenia. Cariprazine differs from aripiprazole in that it has relatively higher dopamine D_3 receptor affinity and selectivity. The D_3 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 D_3 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 ED_{50} values or minimal effective doses (MED) for each behavioral model. Striatal D_2 and cerebellar D_3 receptor *in vivo* occupancy in rats was determined using the high affinity agonist radioligand [^{3}H](+)-PHNO.

Results: Cariprazine occupied D_2 receptors in rats with approximately 30-fold greater potency than aripiprazole (ED_{50}: cariprazine, 0.23mg/kg; aripiprazole, 7.7mg/kg); potency for D_3 receptor occupancy in rats was >70-fold higher for cariprazine vs aripiprazole (ED_{50}: cariprazine, 0.43mg/kg; aripiprazole, >30mg/kg). In rat models of antipsychotic-like activity, cariprazine demonstrated 20 to 30-fold greater potency than aripiprazole (ED_{50} for conditioned avoidance response: cariprazine, 0.8mg/kg, aripiprazole, 18mg/kg; ED_{50} 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 (ED_{50}: 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 D_3 receptors may underlie the greater potency relative to aripiprazole in models of cognitive impairment and negative symptoms.

Disclosure statement: This abstract is financially supported by Forest Laboratories, Inc. and Gedeon Richter Plc. N. Adham is an employee of Forest Research Institute.

Citation: Eur Neuropsychopharmacol. 2014;24(Suppl 2):S233

Keywords

Neuroleptics & antipsychotics: basic

Schizophrenia: basic

Animal models