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# A REVIEW ON ANALYTICAL METHOD OF CARIPRAZINE AS AN ANTIPSYCHOTIC DRUG

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## ABSTRACT

Cariprazine is one of the newest dopamine-serotonin partial agonists, also known as 'atypical' second generation antipsychotics. Originally approved for acute and maintenance treatment of schizophrenia as well as for acute mania and mixed mania/depression, cariprazine has now been approved for bipolar I depression. Maintenance studies are in progress in bipolar disorder, as are studies to augment antidepressants in unipolar major depressive episodes insufficiently responsive to treatment. Here, we review specifically the efficacy and safety data of cariprazine in bipolar I disorder and discuss the hypothesized mechanism of action of cariprazine and how it could theoretically be linked to Cariprazine's broad therapeutic actions across the mood disorder spectrum.

**KEYWORDS:** Cariprazine**,** Bipolar depression, Bipolar disorder, Cariprazine, Schizophrenia.

## INTRODUCTION

### Introduction of Cariprazine HCl

Schizophrenia is a mental illness that can be treated with the medication cariprazine. It causes intense or inappropriate emotions, loss of interest in life, and weird or abnormal thinking. Manic episodes, depressive periods, and other abnormal moods are treated with cariprazine.

Additionally, It is used as a short-term treatment for manic episodes or mixed episodes (manic-depressive symptoms that co-occur) in patients with bipolar I disorder. Cariprazine belongs to the group of drugs known as atypical antipsychotics. It works by changing the

activity of certain natural substances in the brain.[1-5]

**History of Cariprazine HCl**

Cariprazine was initially developed in Hungary and has been studied in a number of psychiatric disorders, including schizophrenia, bipolar disorders, and major depressive disorder. Cariprazine received its first global approval in the US in September 2015 and was later approved by Health Canada in April 2022.[6]

**General Introduction of Atypical Antipsychotics**

Atypical antipsychotics (AAP), often referred to as second generation antipsychotics (SGAs) and serotonin-dopamine antagonists (SDAs), are a class of antipsychotic drugs used to treat mental health issues. Regulatory approval has been granted to some atypical antipsychotics for the treatment of schizophrenia, bipolar disorder, irritability in autism, and major depressive disorder. There is a tendency for both generations of medications to interfere with brain dopamine receptors.

Atypical are less likely than haloperidol the most widely used typical antipsychotic to cause extrapyramidal motor control disabilities in patients such as unsteady Parkinson's disease.

There are 6 atypical antipsychotics commercially available in the United States: clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole. He atypical is more likely to have weight gain, hyperprolactinemia, drowsiness, dysfunctional sexual function, and negative metabolic and anticholinergic consequences. It is gradually becoming clearer how antipsychotic medication affects the onset of metabolic issues.[7]

**Introduction of Schizophrenia**

Schizophrenia is a serious mental disorder in which people interpret reality abnormally. Schizophrenia may result in some combination of hallucinations, delusions, and extremely disordered thinking and behavior that impairs daily functioning, and can be disabling.

**Symptoms may include**

- **Delusions.** These are false beliefs that are not based in reality. For example, you think that you're being harmed or harassed; certain gestures or comments are directed at you; you have exceptional ability or fame; another person is in love with you; or a major catastrophe is about to occur. Delusions occur in most people with schizophrenia.

- **Hallucinations.** These usually involve seeing or hearing things that don't exist. Yet for the person with schizophrenia, they have the full force and impact of a normal experience. Hallucinations can be in any of the senses, but hearing voices is the most common hallucination.
- **Disorganized thinking (speech).** Disorganized thinking is inferred from disorganized speech. Effective communication can be impaired, and answers to questions may be partially or completely unrelated. Rarely, speech may include putting together meaningless words that can't be understood, sometimes known as word salad.
- **Extremely disorganized or abnormal motor behavior.** This may show in a number of ways, from childlike silliness to unpredictable agitation. Behavior isn't focused on a goal, so it's hard to do tasks. Behavior can include resistance to instructions, inappropriate or bizarre posture, a complete lack of response, or useless and excessive movement.
- **Negative symptoms.** This refers to reduced or lack of ability to function normally. For example, the person may neglect personal hygiene or appear to lack emotion (doesn't make eye contact, doesn't change facial expressions or speaks in a monotone). Also, the person may lose interest in everyday activities, socially withdraw or lack the ability to experience pleasure.[8]

**Mechanism of Action**

Cariprazine is a brand-new atypical antipsychotic drug (APD) with a unique pharmacodynamics profile that sets it apart from other atypical and conventional APDs. Specifically, cariprazine acts as an antagonist at the serotonin 5-HT1A and 5-HT2B receptors and a partial agonist at the dopamine (DA) D2 and D3 receptors.(fig:1).[9,10]

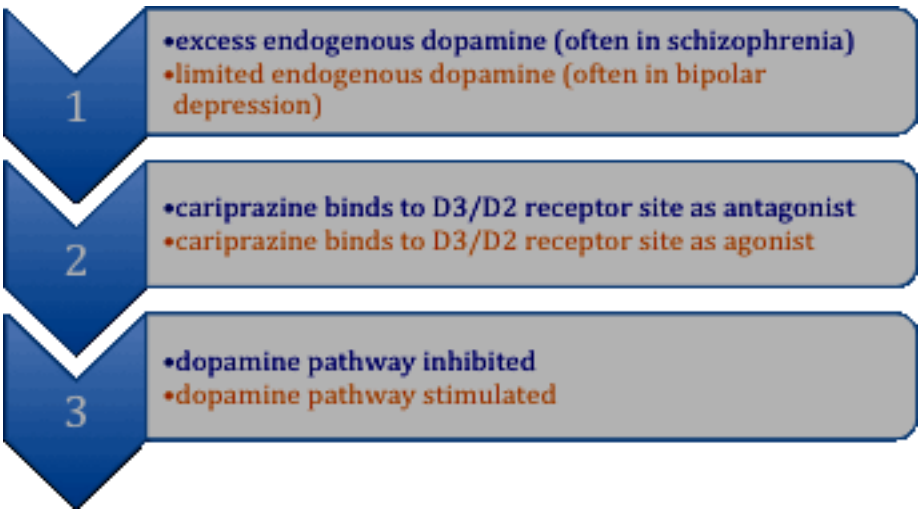


**Figure 1: Mechanism Of Action.**

**Chemistry of Cariprazine**

Cariprazine HCL (CAS Number: 1083076-9-0).

Cariprazine, or *N'*-[Trans-4-(2, 3-Dichlorophenyl)-1-Piperazinyl] Ethyl] Cyclohexyl]-N, N-diethyl urea.

**Pharmacology**

Cariprazine is an antipsychotic agent. In clinical trials, it reduced positive and negative symptoms in patients with schizophrenia and acute mania in patients with bipolar I disorder. In animal models, cariprazine showed therapeutic benefits against cognitive deficits, mania, and catalepsy. In a meta-analysis study, cariprazine was shown to improve anxiety and depressed mood in patients with psychosis.

As cariprazine is a partial agonist at dopamine D2 and D3 receptors, it produces an apparent lower blockade level than other antipsychotic agents that block dopamine receptors. This receptor binding profile is advantageous as dopamine receptor blockade is associated with extrapyramidal symptoms as side effects. Partial agonism would allow the dopamine receptor to be stimulated even at maximal receptor occupancy by the drug. Antagonism at 5-HT1A and 5-HT2A receptors by cariprazine can increase dopaminergic neurotransmission in the nigrostriatal pathway, thereby further reducing the risk of extrapyramidal symptoms. However, cariprazine is still associated with a risk of akathisia, extrapyramidal disorder, restlessness, and tremor.

**Pharmacokinetics**

**Absorption:** Peak plasma time: 3-6 hr. (cariprazine) Mean concentrations of DCAR and DDCAR are ~30% and 400%, respectively, ofcariprazine concentrations by the end of 12-week treatment.

**Distribution:** Protein bound: 91-97% (parent drug and metabolites).

**Metabolism:** Active metabolites: Desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR) are pharmacologically equipotent to cariprazine extensively metabolized by CYP3A4 to DCAR and DDCAR metabolized to a lesser extent by CYP2D6 to DCAR and DDCAR is metabolized by CYP3A4 to a hydroxylated metabolite.

**Elimination:** Half-life: 2-4 days (cariprazine); 1-3 weeks (DDCAR) Excretion, cariprazine 12.5 mg/day: Urine (21%); [1.2% unchanged].

**Dosing:** Simply take 1.5–6 mg of cariprazine hydrochloride once a day at the same time, with or without food.

**Adverse drug effects**

**Most common:** Extreme tiredness, Restlessness, Anxiety, Agitation, Difficulty falling asleep or staying asleep, Dizziness, feeling unsteady, or having trouble keeping your balance, Increased appetite, Weight gain, Constipation, Indigestion, Nausea, Increased saliva or drooling, Blurred vision.

**Indications:** Cariprazine is indicated for the treatment of schizophrenia in adults to manage both positive and negative symptoms. It is also indicated to monotherapy for acute management of manic or mixed episodes associated with bipolar I disorder (bipolar mania) in adults, and acute management of depressive episodes associated with bipolar I disorder (bipolar depression) in adults.

**Contraindications:** Cariprazine is contraindicating in patients with history of a hypersensitivity reaction to cariprazine. Reactions have ranged from rash, pruritus, urticaria, and events suggestive of angioedema (e.g., swollen tongue, lip swelling, face edema, pharyngeal edema, and swelling face).

**Medical uses:** Cariprazine is used to treat patients with schizophrenia and manic, depressive, or mixed episodes associated with bipolar I disorder. In the United States it is approved for schizophrenia in adults, acute treatment of manic or mixed episodes associated with bipolar I disorder in adults and treatment of depressive episodes associated with bipolar I disorder (bipolar depression).

Cariprazine consistently improved depressive symptoms across a spectrum of patients with bipolar I depression.[11]

**Usual dose and administration[12]**

**Table: usual dose and administration.**

| Usual Dose | Initial Dose | Titration Regimen | Maintenance Dose | Maximum dose |
|---|---|---|---|---|
| Adult dose for Schizophrenia | 1.5 mg orally once a day | Increased to 3 mg once a day | 1.5 to 6 mg orally once a day | 6 mg per day |
| Adult dose for Bipolar disorder | 1.5 mg orally once a day | Increased to 3 mg once a day. On Day | 3 to 6 mg orally once a day | 6 mg per day |

| | | | | |
|---|---|---|---|---|
| | | 2; 1.5 to 3 mg increased based on efficacy and tolerability | | |

**Literature Review**

**Literature review of Cariprazine HCl**

- Cariprazine HCl is not official in any pharmacopeia.
- Only non- official reported methods are available.

**Reported method for assessment of Cariprazine HCl**

**Table Reported methods for Cariprazine HCl.**

| Sr. no. | Title | Description | Ref. no. |
|---|---|---|---|
| **HPTLC(High Performance Thin Layer Chromatographic Method)** | | | |
| 1 | **HPTLC Method** Development of Cariprazine Hydrochloride for Applicative Quantification of Nanostructured Lipid Carriers | **Stationary phase**: Silica gel 60$F_{254}$ plates<br>**Mobile phase**: Toluene: Methanol (7:3 % v/v)<br>**Detection**: 253 nm<br>**Flow rate**: 1 mL/min | [13] |
| **RP-HPLC (Reverse Phase – High Performance Liquid Chromatographic) Method** | | | |
| 2 | Development and validation of a stability-indicating **high performance liquid chromatographic** assay for determination of cariprazine in bulk from and in drug product. | **Stationary phase**: Phenomenex kinetex® $C_{18}$ column(250 x 4.6 mm, 5 µm)<br>**Mobile phase**: Acetonitrile : Potassium dihydrogen orthophosphate buffer, pH 4 (30:70 % v/v)<br>**Detection**: 248 nm<br>**Flow rate**: 1 mL/min | [14] |
| 3 | Development and Validation of stability **RP-HPLC** method for determination of Cariprazine in bulk Drug. | **Stationary phase**: $C_{18}$ Inertsil ODS column (250 x 4.6 mm, 5 µm)<br>**Mobile phase**: 0.05M Ammonium Acetate Buffer : Acetonitrile (50:50 % v/v), pH 4.8<br>**Linearity**: 1-3 µg/mL<br>**Detection**: 248 nm<br>**Flow rate**: 1 mL/min | [15] |
| 4 | Specific and sensitive **RP-HPLC**method development and validation for the determination of aripiprazole: Application inpreformulation screening of Nano emulsion. | **Stationary phase:** HIQ SIC $C_{18}$ column (250x 4.6mm, 5µm)<br>**Mobile phase:** Methanol: Acetonitrile (80:20 % v/v)<br>**Detection:** 218nm<br>**Flow rate:** 1.0 mL/min | [16] |
| 5 | Validated **RP-HPLC** method for analysis of Aripiprazole in a formulation. | **Stationary phase:** $C_{18}$ column (150 x 4.6 mm, 5µm)<br>**Mobile phase:** Acetonitrile : Tri ethanolamine buffer,pH 3.5 (40 :60 % v/v)<br>**Detection:** 254 nm<br>**Linearity:** 20-60 µg/mL | [17] |

| | | | |
|---|---|---|---|
| **UV Spectroscopy Method** | | | |
| 6 | Method development and validation of Cariprazine HCl in bulk by **UV spectrophotometry method**. | **Wavelength:** 252nm<br>**Solvent:** Methanol<br>**Linearity**: 10 µg/mL- 50 µg/mL | [18] |
| 7 | Development and validation of **spectrophotometric method** for the estimation of Aripiprazole in tablet dosage forms. | **Wavelength:** 218nm<br>**Solvent:** 0.05M Phosphoric acidand Acetonitrile ( 40:60 % v/v)<br>**Linearity**: 2.5 µg/mL- 20 µg/mL | [19] |
| **LC- MS/MS Method** | | | |
| 8 | Identification, separation and mass spectral characterization of degradants in Cariprazine HCl by **LC-MS/MS/QTOF** | **Stationary phase:** Symmetry $C_{18}$ column (150 x 4.60 mm, 3.35 µm)<br>**Mobile phase:** Methanol: Orthophosphoric acid proportion of ( 50:50% v/v) **Linearity:** 5-75 mg/mL<br>**Flow rate:** 1 mL/min | [20] |
| 9 | **LC- MS/MS** determination and pharmacokinetic study of clozapine in human plasma. | **Stationary phase**: Hanbon kromail $C_{18}$ column(250 x 4.60mm, 5 µm)<br>**Mobile phase**: Methanol : Water (70:30)<br>**Linearity**: 0.10- 200 mg/mL<br>**Flow Rate**: 1 mL/min | [21] |

## CONCLUSION

In this review article we have discussed the pharmacokinetics, adverse drug interaction, history of cariprazine. Cariprazine was safe and generally well tolerated in patients with acute and long-term exposure in the recommended dose range. Cariprazine expands the antipsychotic armamentarium for management of acute schizophrenia exacerbations and acute manic and mixed bipolar disorder episodes. It is still under investigation for use in bipolar and unipolar depression. Advantages to its use include minimal anticholinergic, adrenergic, histaminergic, metabolic, and prolactin-related side effects; once daily dosing; absence of prolonged titration periods; and absence of CYP2D6 drug-drug interactions. Various method used for determination quality, accuracy, safety of drug.

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## REFERENCES

1. Medline plus, *Cariprazine*, November 2023. https://medlineplus.gov/druginfo/meds/a615050.html#:~:text=Cariprazine%20is%20also%20used%20to,depression%20and%20other%20abnormal%20moods

2. Gerhard Gross, Mark A. Geyer, Current Antipsychotics, 2022; 212: 147.
3. Wikipedia, Atypical antipsychotics, November 2023. https://en.wikipedia.org/wiki/Atypical_antipsychotic#:~:text=Atypical%20antipsychotics%20are%20typically%20used,an%20off%2Dlabel%20 use).
4. Farah A. A typicality of atypical antipsychotic. Prim Care Companion J ClinPsychiatry, 2005; 7: 268-274.
5. Calabrese F, Tarazi FI, Racagni G, Riva MA. The role of dopamine D3 receptorsin the mechanism of action of cariprazine. CNS Spectr, 2020; 25: 343-351.
6. Wikipedia, Cariprazine, November 2023.
7. https://en.wikipedia.org/wiki/Cariprazine
8. PubChem, Cariprazine hydrochloride, November 2023. https://pubchem.ncbi.nlm.nih.gov/compound/Cariprazine-hydrochloride
9. Robert A. McCuutcheon, Tiago Reis Marques, Schizophrenia—An Overview. JAMA Psychiatry, 2020; 77: 201-210.
10. Medscape, Cariprazine, November 2023.
11. https://reference.medscape.com/drug/vraylar-cariprazine-999874#10
12. VRAYLAR, Cariprazine, November 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204370lbl.pdf
13. Drug bank (DB06016), Cariprazine, November 2023,
14. https://go.drugbank.com/drugs/DB06016
15. Mr. Ghumare Vaibhav, Mr. Lahu Hingane, Mr. Mhaske Mahesh, Mr. Dhonde Pritam. A review on cariprazine as an antipsychotic drug. JETIR, July 2022; 9: 445.
16. Chiprikar, P., Mastiholimath, V. & Balekundri, A. HPTLC Method Development of Cariprazine Hydrochloride for Applicative Quantification of Nanostructured Lipid Carriers. Chem Africa, 2023; 25-28.
17. E. Toujani, W. Mejri, H.E. Lassoued, S. Toujani, O. Fliss, M.H.B.cheikh and F.Safta. Development and validation of a stability-indicating high performance liquid chromatographic J assay for determination of cariprazine in bulk form and in drug product. Annales. Pharm. Françaises, 2022; 80: 76-994.
18. Pooja T and Purmia DH. Development and validation of a stability indicating RP-HPLC method for determination of cariprazine in bulk drug. World J. Pharm. Res, 2020; 9: 23-26.
19. S. Kumar, C. Kokare, B. Shrivastava and H. Choudhury. Specific and sensitive RP-HPLC method development and validation for the determination of aripiprazole: Application in

preformulation screening of Nano emulsion. Int. J. Pharm. Sci, 2020; 2: 76-86.

20. R. Kalaichelvi, B. Thangbalan and D. Srinivasarao. Validated RP-HPLC method for analysis of Aripiprazole in a formulation. E. J. Chem, 2010; 3: 827-832.
21. P. Chiprikar and V. Mastiholimath, Method development and validation of Cariprazine HCl in bulk by UV spectrophotometry method. Ind. J. Novel. D. D., 2022; 1: 52-57.
22. J. Nagamallika and A. Mahesh. Development and validation of spectrophotometric method for the estimation of Aripiprazole in tablet dosage forms. A. J. Pharm. Anal, 2011; 3: 46-49.
23. Pallekona S and A. Krishnamanjari P. Identification, separation and mass spectral characterization of degradants in Cariprazine HCl by LC-MS/MS/QTOF. J. Chem. Metrol, 2022; 7: 26.
24. S. Min, Y. Xiaorong, Z. Hua, H. Taijun, Y. Lin and X. wei. LC- MS/MS determination and pharmacokinetic study of clozapine in human plasma. Chroma, 2009; 69: 1049-1054.