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Review Article

# A MINI REVIEW ON PROPERTIES, MECHANISM OF ACTION, PHARMACOKINETIC AND PHARMACODYNAMICS AND ANALYTICAL METHODS OF CARIPRAZINE

**ALANKAR SHRIVASTAVA[1], RADHIKA AGGARWAL[1*], RISHI PRATAP SINGH[2], RAKHI KHABIYA[3]**

**[1]Department of Pharmaceutical Quality Assurance, KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Ghaziabad-Meerut Road, Ghaziabad 201206, [2]IIHMR University, Prabhu Dayal Marg, Near Sanganer Airport, Maruti Nagar, Jaipur, Rajasthan 302029, [3]Acropolis Institute of Pharmaceutical Education and Research, Indore 453771, India**
**[*]Email: radhikagarg405@gmail.com**

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**ABSTRACT**

Cariprazine (CPZ) being a "D2/D3 receptor partial agonist" is used for schizophrenia treatment. CPZ illustrate different functional study at "dopamine receptors depending on the assay system". This study elaborate review summarizes the structure–activity relationship (SAR), Mechanism of action (MOA), pharmacokinetics, pharmacodynamics and analytical methods published. CPZ was found to be more effective than risperidone. It was analogus with a remarkably longer time to deteriorate than inactive drug in a long-term, phase III,-deteriorate prevention study. This study elaborate the activating and solemn or sedative properties of first-line oral second generation antipsychotics by explore the rates of adverse effect in product labelling for the indications of schizophrenia and ancillary treatment of major depressive disorder (MDD). The common adverse events reported were extrapyramidal disorder, insomnia, dizziness, solemn, anxiety, vomiting and constipation in "fixed dose study of tested 1.5, 3.0, and 4.5 mg/day". The presented review explains about biological properties, pharmacokinetics, pharmacodynamics, and analytical methods of CPZ.

**Keywords:** Method validation, Properties, Pharmacodynamics, Pharmacokinetics, Analytical methods, Green analytical method


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## INTRODUCTION

Schizophrenia is a clinical syndrome with diverse manifestations [1] both "genetic and environmental factors" likely play a significant role in the onset of symptoms [2]. One of the 15 most common causes of disability is schizophrenia, "a multisystem disorder with a global prevalence of 0.33-0.75%" [3]. Moreover, the suicide risk in schizophrenia is 4.9% [4]. There is currently no cure for it, which affects between 0.6 and 1.9 percent of people in the United States. Schizophrenia can be treated with a variety of medications at this time; however, many do not achieve their therapeutic objectives [5]. Schizophrenia is a complicated mental illness that presents a challenge for all medical professionals [6]. There have been numerous obstacles in the treatment of schizophrenia [7]. Schizophrenia is a progressive illness that reaches a plateau within a few years during the pre-psychotic and early course phases. Deterioration to this extent is observed [8].

CPZ is a novel atypical "antipsychotic" that is a "dopamine D3/D2 receptor partial agonist", was recently approved in the United States for "schizophrenia and bipolar mania/mixed disorder" [9]. There is a lot of overlap between schizophrenia and bipolar disorder in terms of "symptoms, familial patterns, risk genes, outcomes, and treatment responses". Treatment for acute schizophrenia patients initially focuses on reducing positive symptoms like suspicion and persuasion, hallucinations, and delusions [10]. However, negative cognitive and mood symptoms (such as depression and blunted affect, anhedonia, and avolition) can persist in clinically stable patients and have a significant impact on patient quality of life [11].

Manic-depressive illness, also known as "bipolar disorder (BD)", is a mental illness characterized by "episodes of mania and major depression" [14]. There are three types of BD: "Bipolar I, Bipolar II, and Cyclothymic Disorder" [12]. In 2001, the "World Health Organization (WHO)" stated that BD was the fifth cause of young adult life years spent with a disability [13]. BD I is characterized by "manic episodes lasting at least seven days or symptoms so severe that immediate hospitalization is required". Depressive episodes, which last at least two weeks, are common [15]. Adults with BD I account for 1% or 2% of the population. Both cyclothymia and bipolar I disorder affect men and women equally. Patients who suffer from BD have access to a variety of potent pharmacological treatment options [16].

Even though antipsychotics are the first-line treatment for bipolar mania, the disease's complicated pathophysiology poses a significant clinical challenge due to the fact that many patients do not fully recover from treatment [17]. CPZ is an "*N*-alkylpiperazine that is *N, N*-dimethyl-*N'*-{trans-4-[2-(piperazin-1-yl)ethyl]cyclohexyl}urea" substituted at position "4 on the piperazine" ring by a "2,3-dichlorophenyl" group (fig. 1) [18].

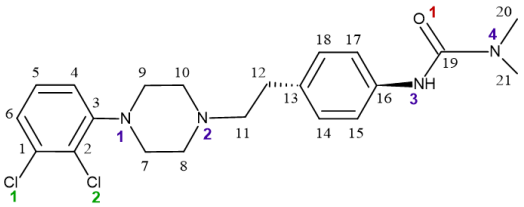

**Fig. 1: Chemical structure of CPZ**

For literature review, bentham, wiley, nature, springer, taylor and francis, oxford, hindawi databases were searched. Other than this, related articles were also searched in google. The keywords used were "Cariprazine", "determination of cariprazine", "analysis of cariprazine", "mechanism of action of cariprazine", and "green analytical methods" (if any), published till date.

Cariprazine (Vraylar) is an oral atypical antipsychotic. CPZ was granted its first worldwide approval in September 2015 in the United States for the acute treatment of "manic or mixed episodes associated with BD I and schizophrenia" [19, 20]. CPZ is covered by a composition-of-matter patent that will expire in 2029. Gedeon Richter Plc made the discovery of CPZ. Based in Budapest, Hungary) [21] and is licensed to Allergan (AbbVie) in the United States and Recordati SpA in Western European nations [22].

CPZ has therapeutic effects on negative symptoms, "antipsychotic-induced weight gain, and increased serum prolactin levels", and "Gedeon-Richter scientists were attempting to isolate a dopamine D2 and D3 antagonist when they ran into a problem: their

preparation had a persistent impurity" [23, 24]. Clinical studies suggest that CPZ has advantages over other antipsychotics in terms of therapeutic effects on "negative symptoms". They needed to identify the impurity before they could get rid of it. This compound, "trans-*N*-[4-[2-[4-(2,3-dichlorophenyl) piperazin-1-yl]ethyl] cyclohexyl]-*N*', *N*''-dimethylurea hydrochloride", was given the working name of "2m" and subsequently registered as "RGH-188" or CBZ [25].

The FDA likely approved the HCl salt due to the drug's higher solubility at the maximum recommended dose than at pH 6.0. The CPZ molecule in I and II is a chemical entity composed of "dichlorophenyl, piperazinyl, cyclohexyl, and *N,N*-dimethylurea" groups (fig. 2). The solubility profile of CPZ HCl is pH-dependent and decreases with pH "3.25 mg/ml at pH 1.0 versus 0.02 mg/ml at pH 6.0". The CPZ molecules have conformational flexibility thanks to the ethyl linkages. The anticipated proton transfer from the $N_2$ atom of the piperazine ring to the hydrochloric acid occurs; the electron density map clearly identified the H atom at the "piperazine $N_2$ atom". "$N_2$–$H_2$---$Cl_3$ charge-assisted hydrogen bonds" connect the CPZ molecules to the chlorine atoms, further stabilized by "weak intermolecular interactions". The "torsion angle $C_{11}$–$C_{12}$–$C_{13}$–$C_{14}$ is–70.8(3) °", indicating that the cyclohexane ring is also being rotated in relation to the piperazine ring. The hydrogen bond between the $N_2$ atom and II's Cl–counterion ($Cl_3$) can be seen in the structure. The increased solubility is made possible by II's ionized structure. The results of the DSC demonstrate that "II is more stable than I at room temperature when compared to the CPZ molecule" [26].

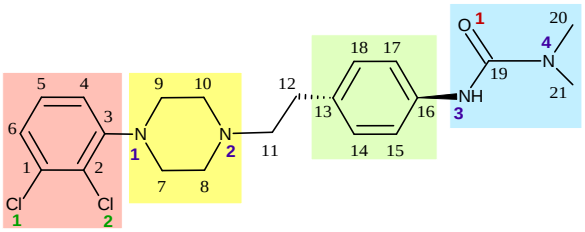


**Fig. 2: Dichlorophenyl (Pink), piperazinyl (Yellow), cyclohexyl (Green), and *N,N*-dimethylurea (Blue) groups in CPZ**

**Mechanism of action, PK and PD of CPZ**

Preclinical studies demonstrated unique pharmacological properties of CPZ, an oral "dopamine D3/D2 receptor partial agonist" with demonstrated *in vivo* binding to both "D3 and D2 receptors" and high brain penetration. In accordance with its "strong affinity for D3 and D2 receptors", CPZ prevented the "D3/D2 agonist [3H](+)-PHNO" from binding in the CB L9,10 and rat striatum, respectively. The D2-preferential partial agonist aripiprazole was active in the striatum, but it inhibited [3H](+)-PHNO binding in the CB L9,10 region much less than CPZ did; suggested that the pharmacologically active doses of aripiprazole only have a low level of D3 receptor affinity *in vivo* [27]. The interaction of CPZ with various receptors is shown in fig. 3.

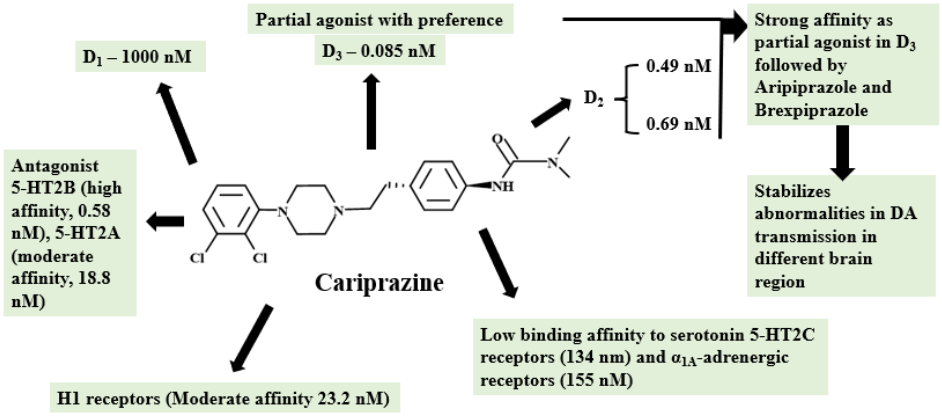


**Fig. 3: Receptor interactions of CPZ**

There are different doses of CPZ: 1.5, 3, and 6 mg tablets, taken once per day with or without food. Patients with BD who experience manic or mixed episodes should take 3 to 6 mg per day. CPZ has a half-life of two to six days. Within about a week, the steady state is reached. The isozymes CYP3A4 and, to a lesser extent, CYP2D6 break down CPZ into two active metabolites. Urine contains an inactive metabolite [3]. Since it takes approximately five half-lives to reach a steady state when starting CPZ, the effective dose rises for many weeks after starting a dose, even though the daily dose stays the same. On the other hand, once CPZ is stopped, it will take many weeks for the active drug to be eliminated. As a result, patients with poor compliance may benefit from the fact that "missing a dose would not have the same potentially devastating effects on relapse as half-life compounds" [28].

**Analytical methods**

The interpretation of data of analytical data is important to study the pharmacokinetics, bioavailability, and bioequivalence of any drug in drug development. Analytical methods provide justification of acceptable formulation of any drug [29, 30]. The valid analytical strategies are crucial before the release of formulations and, therefore, should be periodically modified and improved with change in matrix, technology, and scope of analysis [31].

The study of electromagnetic radiation's interaction with matter through either absorption, emission, or scattering by the system under investigation is known as spectroscopy [32-34]. This is one of the fundamental analytical techniques used for the analysis of many "inorganic and organic molecules" [35]. The "electromagnetic radiations" are traveling through space at the speed of light [32]. Therefore, "electromagnetic radiation consists of a stream of photons", which are considered to have "zero rest mass" [35]. The UV, IR and NMR spectrum of CPZ is shown under fig. 4 to 6 respectively.

The first developed and validated method for cariprazine (also known as RGH-188), published by Mészáros *et al.* [35]. Two LC-MS-

MS methods were developed for analysis in plasma and urine for CPR and its two active metabolites "desmethyl-and didesmethyl-RGH-188". The bioanalytical method for pharmacokinetic investigation in rats (LC-MS-MS method) was developed by Gyertyán *et al.* [36]. Extraction of drug from samples was performed using 1-chlorobutane.

The study published by Toth *et al.* [37], with an aim to determine brain uptake and *in vivo* binding to dopamine D3/D2 receptors. The researchers first converted CPR into carbon-11 radiolabelled CPR. The HPLC system was utilized with radio detector for the estimation. The CPR was found to cross the blood-brain barrier and entered the brain in large amounts ~7% of radioactivity observed in brain due to injected radiolabelled drug.

Various other chromatographic methods are also available [38-41]. The only stability indicating published method found CPZ to be susceptible to "acid hydrolysis, base hydrolysis, oxidation and thermal degradation". The wavelength selected for the study is 217 nm. The base hydrolysis and oxidative degradation were found to be 9.39% and 7.7%, respectively [39]. The summary of all published methods is provided under table 1.

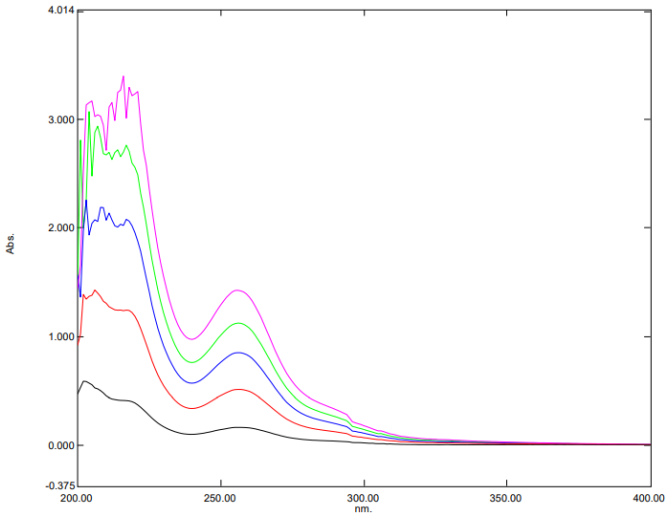


**Fig. 4: UV spectrum of CPZ (10,30,50,70,90 µg/ml)**

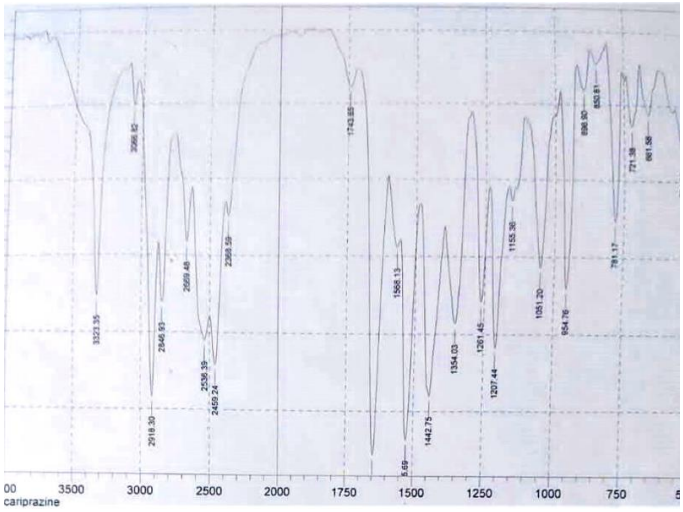


**Fig. 5: IR spectrum of CPZ**

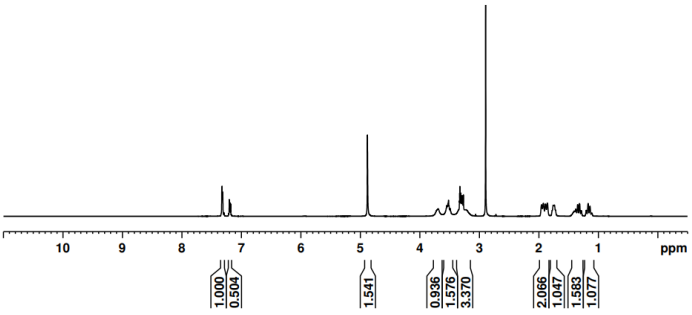


**Fig. 6: NMR spectrum of CPZ**

**Table 1: Summary of analytical methods**

| Method | Detector | Column | Chromatographic conditions | LOD | LOQ | Application | Reference |
|---|---|---|---|---|---|---|---|
| HPLC | MS/MS | $RP_{18}$, 150 mm × 4.6 mm, 5 µm | MeOH–$CH_3COONH_3$ (10 mmol) (90:10, v/v) | 0.05, 0.001 ng/ml | 0.1 ng/ml | Plasma and urine | [35] |
| HPLC | MS/MS | $C_{18}$ column (150×4.6 mm, 5 µm) | ACN-MeOH-0.2 M $CH_3OONH_3$-$H_2O$ (35:25:35:5, v/v/v/v) | 20 ng/ml | 80 ng/ml | Plasma | [36] |
| HPLC | UV (250 nm) | $C_{18}$ column (300 × 7.8 mm, 10 µm) | ACN: ammonium formaate (0.1 M) (40:60 v: v) | - | - | Brain uptake by injected dose | [37] |
| HPLC | MS/MS | - | - | - | - | Pharmacokinetic characterization | [38] |
| HPLC | PDA | $C_{18}$, 250 mm×4.6 mm×5µm) | 0.05 M $CH_3COONH_3$ Buffer (pH 4.8): ACN (50:50,v/v) | 0.2 µg/ml | 0.7 µg/ml | Stability indicating | [39] |
| UPLC | MS/MS | $C_{18}$, 1.6 µm, 100 Å, 2.1 × 50 mm | $H_2O$ (0.1% v/v $CH_3COOH$+ACN (0.1% v/v $CH_3COOH$) | - | - | Detection of drug and metabolites | [40] |
| LC | MS/MS/QTOF | $C_{18}$ 150×4.6 mm, 3.35 µm | MeOH: $H_3PO_4$ (0.1%), 50:50 (% v/v), | - | - | Stability indicating | [41] |

## DISCUSSION

One of the most severe brain diseases, schizophrenia presents with a variety of symptoms, including cognitive, negative, and positive ones. CPZ, an analogue of Ariprazole, an antipsychotic with a unique receptor binding profile (already discussed in MOA section). CPZ is metabolized by CYP3A4 (major) and CYP2D6 (minor) to produce two active metabolites didesmethyl cariprazine (DDCAR) and desmethyl cariprazine (DCAR). The overall pharmacological activity shown by this drug is due to the parent compound and its metabolite, which may also be a reason of its long half-life (2 to 4 d) [42]. The affinity towards receptors and medicinal effects are the basis of the classification of antipsychotic drugs. The initially developed drugs (first generation including chlorpromazine and haloperidol etc.) are mainly D2R antagonists with extrapyramidal effects and in higher doses showing negative and cognitive symptoms. The next (second) generation developed antipsychotics are multiple targeted receptors like 5-HT2AR (high preference) over D2R (e. g. ziprasidone), also targeting cholinergic, histamine (e. g. clozapine) and adrenergic causing less extrapyramidal side effects compared with former developed class of these drugs. But these also reported to cause some side effects like obesity, agranulocytosis and diabetes (e. g. clozapine). The third-generation developed antipsychotics reported preferential partial agonism at D2R (e. g. aripiprazole) and fewer side effects compared to the initial two classes discussed earlier in this paragraph. The higher occupancy of D2R (about 80%) shown by CPZ is reported to be more effective in bipolar disorder [43, 44].

There are limited analytical methods reported for CPZ till date. The treatment of schizophrenia is still a challenge for scientists [45,46]. The absence of any simple spectrophotometric and HPTLC methods is the gap of existing knowledge in this field. Since CBZ is a BCS class II drug, having less solubility and higher permeability. The reported solubility of CBZ in is organic solvents, as shown in the dilutions prepared in the analytical methods reported till date. Thus, the development of a green analytical method approach is another dimension of study in the future.

## CONCLUSION

Sadly, despite years of research into schizophrenia treatment, a significant number of patients do not experience sufficient improvement. A reduction in symptoms of less than 50% will be experienced by approximately two-thirds of those affected, with most of this improvement occurring in the positive symptoms. The need for more effective treatments and the utility of ERPs to objectively index brain-based treatment response are reflected in several of the papers assembled. Current treatment options are not ideal for improving negative and cognitive symptoms. One of the most difficult psychiatric disorders to manage is bipolar (affective) disorder, which was originally known as manic depressive illness. Despite the fact that it has been linked to creativity, it has a negative impact on the majority of patient's lives, and more than 6% commit suicide within two decades of being diagnosed. The presented review article explains the recent updates regarding pharmacodynamic, pharmacokinetic and analytical methods reported about this drug. The summary of reported analytical methods reported till date is presented under table 1.

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Nil

## AUTHORS CONTRIBUTIONS

First and corresponding authors have contributed equally, supported by the third and fourth authors.

## CONFLICT OF INTERESTS

Declared none

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