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A REVIEW ON CARIPRAZINE AS AN ANTIPSYCHOTIC DRUG

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Abstract:-

Cariprazine is an antipsychotic medication and received approval by the U.S. Food and Drug Administration for the treatment of schizophrenia in September 2015. Cariprazine is a dopamine D3 and D2 receptor partial agonist, with a preference for the D3 receptor. Cariprazine is also a partial agonist at the serotonin 5-HT1A receptor and acts as an antagonist at 5-HT2B and 5-HT2A receptors. This comprehensive review of cariprazine summarizes its pharmacologic profile, clinical trial evidence, and post hoc investigations. Collective evidence suggests that the pharmacology of cariprazine may offer broad-spectrum efficacy advantages for patients with schizophrenia, including effects against difficult- to-treat negative and cognitive symptoms, as well as functional improvements.

Keywords: - Cariprazine, Drug Interaction, Pharmacokinetics.

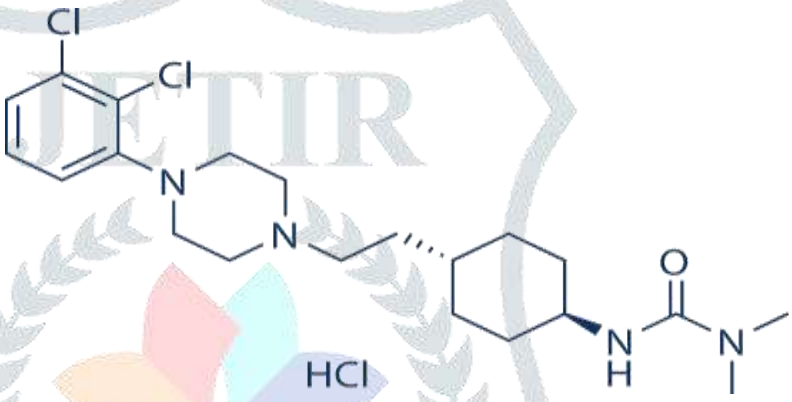
Introduction:-

Schizophrenia, a serious central nervous system disorder that affects approximately 1% of the world's population.[1] It is characterized by diverse symptom domains: positive symptoms (e.g., hallucinations, delusions), negative symptoms (e.g., social and emotional withdrawal, anhedonia), cognitive dysfunctions (e.g., attention deficit, executive function impairment), and comorbid affective symptoms (i.e., depression and anxiety) [2,3] Antipsychotics have different receptor binding properties, which result in different side effect profiles.[4]

Cariprazine differs from all other atypical antipsychotics in having a greater affinity for the D3 receptor than does dopamine itself, thereby exhibiting a functional D3 partial agonist in the human brain that other antipsychotics, such as aripiprazole, risperidone, and olanzapine, fail to exhibit. Since the D3 receptor is thought to play a role in moderating negative and cognitive symptoms, a compound that exhibits high affinity for D3 receptors may confer benefits in treating these symptoms in schizophrenia.[5-7]

Drug profile of Cariprazine Hydrochloride

Table Number 1:- Drug profile of Cariprazine Hydrochloride

Sr. no	Name	Cariprazine Hydrochloride
1	CAS number	1083076-69-0
2	Chemical Formula	$C_{21}H_{33}Cl_3N_4O$
3	Molecular weight	463.87
4	Structure	
	IUPAC Name	3,3-dimethyl-1-[(1r,4r)-4-{2-[4-(2,3-dichlorophenyl)piperazin-1-yl]ethyl}cyclohexyl]urea
5	Description	Cariprazine is an antipsychotic drug developed by Gedeon Richter and marketed by Actavis under the trade name Vraylar. Cariprazine acts as a D2 and D3 receptor partial agonist, with high selectivity towards the D3 receptor. This mechanism is relatively unique, since many other antipsychotics are D2 and 5-HT2A agonists. Cariprazine was approved by the FDA in September 2015 and is indicated in the
		treatment of schizophrenia and bipolar disorder. Action on the dopaminergic systems makes it also potentially useful as an add-on therapy in major depressive disorder.
6	Water Solubility	0.0279 mg/mL

7	logP	4.56
8	pKa	(Strongest Acidic) = 15.68 (Strongest Basic)= 7.91
9	Category	Cariprazine is an antipsychotic drug.
10	Indication	Cariprazine is an atypical antipsychotic indicated for the treatment of Schizophrenia and for the acute treatment of manic or mixed episodes associated with bipolar I disorder.

Table number 2:- Physical Properties of Cariprazine:-

Sr. No.	Physical Properties	Values
1	State	Solid
2	Water solubility	0.0279 mg/ml
3	pKa (strongest acidic)	15.68
4	pKa (strongest basic)	7.91
5	Refractivity	117.81m3. mol^{-1}
6	Hydrogen donor count	1
7	Hydrogen acceptor count	3
8	logP	4.56
9	logS	-4.2

Expert opinion:-

To characterize the overall safety profile of cariprazine within the recommended 1.5–6 mg/d dose range for schizophrenia, we conducted additional post hoc analyses of safety data from 8 studies in patients with short- or long-term cariprazine exposure.[8]

It I a dopamine D3- preferring D3/D4 receptor partial agonist. The efficacy
And safety of cariprazine is metabolized by CYP3A4 and to lesser extent by CYP2D6.
There does not appear to be clinically relevant adverse effect of cariprazine on metabolic relevant.

Pharmacokinetics study:-

Table no. 3: Pharmacokinetics parameter of Cariprazine

Sr. No.	Parameter	Values
1	Bioavailability	52 % oral
2	Half life	2 to 4 days
3	Volume of distribution	400 to 500 lit
4	Protein binding excretion	97%
5	Renal excretion	12.5 mg/day

The pharmacokinetics of cariprazine were characterized in a randomized, open-label, parallel-group, fixed-dose (3, 6, or 9 mg/day) study. Steady state was reached in 1–2 weeks for cariprazine and DCAR, 4 weeks for DDCAR, and 3 weeks for total active moieties. Levels of cariprazine and DCAR decreased by

more than 90% within 1 week after the last dose, while DDCARdecreased by ca. 50% at 1 week; the total active moieties decreased by ca. 90% within 4 weeks.[9]
Terminal half-lives ranged between 31.6 and 68.4 h for cariprazine, 29.7–37.5 h for
DCAR and 314–446 h for DDCAR. The effective half-life of the total active moieties, based on time to reach steady state, was ca. 1 week. Cariprazine is extensively metabolized by CYP3A4 and, to a lesser extent, by CYP2D6 to DCAR and DDCAR. The effect of CYP3A4 inducers on the exposure of cariprazine has not been evaluated, and the net effect is unclear. Tolerability and usability profile, the short- and Long-term safety data for cariprazine are also summarized across studies.

Mechanism of action:-

The discovery and characterization of the dopamine D3 receptor subtype advanced the
possibility of finding and developing new types of antipsychotic drugs that could provide a
more effective and better-tolerated target for the treatment of psychotic disorders than the previously used D2 receptor antagonists.[10,11]
Cariprazine is also a partial agonist at the serotonin 5-HT1A receptor (Ki value 2.6 nM). Cariprazine acts as an antagonist at 5-HT2B and 5-HT2A receptors, with high and moderate binding affinity (Ki values 0.58 nM and 18.8 nM, respectively). Moderate affinity is also observed at the histamine H1 receptor (Ki value 23.2 nM). Cariprazine has lower binding affinity to the serotonin 5-HT2C and α1A-adrenergic receptors (Ki values 134 nM and 155 nM, respectively) and has no appreciable affinity for cholinergic muscarinic receptors (IC50>1,000 nM). Serotonin 5-HT1A partial agonism, a property cariprazine also shares with aripiprazole, brexpiprazole, and lurasidone, is also thought to possibly benefit negative symptoms and cognitive deficits as evidenced in preclinical studies.[12, 13]

Usual dose and administration:-

Table no.: 4 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 2; 1.5 to 3 mg increased based on efficacy and tolerability.	3 to 6 mg orally once a day	6 mg per day

Comments:-

For Schizophrenia: - Due to long half-life, changes in dose will not be fully reflected in plasma for several weeks; monitor for adverse reaction and treatment response several weeks after beginning therapy and after each dose adjustment.

For Bipolar disorder:- Due to long half-life, changes in dose will not be fully reflected in plasma for several weeks; monitor for adverse reaction and treatment response several weeks after beginning therapy and after each dose adjustment.

Adverse effect:-

Table no.: 5 adverse effects

More Common	Less common	Rare
Blurred vision	Bladder pain	Dark urine
Chills	Confusion	Difficulty in speaking
Dizziness	Decrease urine output	Inability to speak
Fever	Sore throat	Indigestion
Headache	Swelling of face	Light coloured stool
Loss of balance control	Seizure	Slow speech

Drug-Drug Interaction:-

Table no.: 6 Drug-Drug Interactions

Drug	**Interaction**
Aceclofenac	The risk or severity of hypertension can be increased when carirprazine is combined with aceclofenac
Acetazolamide	The risk or severity of adverse effect can be increased when acetazolamide combined with cariprazine.
Aclidinium	Cariprazine may increase the several CNS system depressant activities of aclidinium

Various Method used for determination of quality, accuracy, of cariprazine:-

Table no.: 7 determination of quality, accuracy, of cariprazine

Sr. no.	**Sample**	**Method**	**Application**
1	Plasma	HPLC, UV spectroscopy	Used for quantitative study of drug
2	Plasma	HPLC, TLC	Used for Therapeutic dose monitoring.
3	Serum	UPLC, GC-MS	Used for Pharmacokinetics study
4	Plasma	Assay method LC-MS	Used for analytical purpose

Safety Assessments:-

Safety was assessed by adverse event (AE) recordings, clinical laboratory tests, vital sign parameters, weight changes, and electrocardiograms (ECGs). Events of akathisia were assessed through reports of AEs and by the Barnes Akathisia Rating Scale (BARS).[14] The Columbia-Suicide Severity Rating Scale (C-SSRS) was used to assess suicidality.[15]

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. Various method used for determination quality, accuracy safety of drug.

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Summary

Cariprazine is a new antipsychotic medication approved for the treatment of schizophrenia and for the acute treatment of manic or mixed episodes associated with bipolar I disorder. Further characterization of the comparative effectiveness of cariprazine with other antipsychotics for the treatment of schizophrenia awaits.

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