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Role Of Cariprazine In Schizophrenia: A Review

Mohit Goyal[1*], Srishti Gosain[2], Sakshi Garg[3], Shaffi K. Tangri[4], Saumya Goyal[5], Ayush Kumar[6]

[1,2,5]Intern, Department of Pharmacy Practice, Shri Guru Ram Rai University, Dehradun, Uttarakhand*
[3]Assistant professor, Department of pharmaceutics, KIET group of institutions, Muradnagar, Ghaziabad
[4]Assistant Professor, Department of Pharmaceutics, Shri Guru Ram Rai University, Dehradun, Uttarakhand.
[6]Research Scholar, Department of Pharmacy Practice, Shri Guru Ram Rai University, Dehradun, Uttarakhand.

***Corresponding Author:** Mohit Goyal*
**Intern, School of Pharmaceutical sciences, SGRR University, Dehradun, India.*
Email: mohitgoyal23102000@gmail.com

Abstract

Schizophrenia is a severe mental illness and is most commonly observed/ encountered by the majority of clinicians during their clinical practice Among numerous treatment methods, Cariprazine, and its related drugs have shown their clinical efficacy in the treatment of Schizophrenia. Cariprazine is one of the dopamine D3 – preferring the D3/D2 receptor partial agonist, which is indicated for the treatment of individuals suffering from Schizophrenia. It is a partial agonist of the dopamine receptors which has turned out to show efficacious results for the treatment of Schizophrenia, Bipolar Disorder, Mixed and Manic Disorders, and Major Depressive Disorders. This narrative summarises the pharmacological action of the Cariprazine treatment of Schizophrenia**.**

Key Words: Schizophrenia, Cariprazine, Dopamine, Cognitive Impairment, Disorders.

INTRODUCTION:

Schizophrenia is a stigmatized, complex, and heterogenous mental disorder with numerous domains of presentation. Out of the total world population, merely 1% of the population is affected by Schizophrenia which comprises an estimation of 20 million cases globally. Recalling the past, it is worth noting that the Nobel Laureate and King Henry VI shared something in common: they were both believed to have had Schizophrenia. The term Schizophrenia was first identified in 1887 and termed as a Mental Illness which is derived from the Greek 'Schizo' (splitting) and 'Phren' (mind), the term was first coined by Eugen Bleuler in 1908 [1,2.3,4]. It is characterized by multiple symptoms, including cognitive deficits (for example impaired/defective memory), positive symptoms (including hallucinations, and delusions), and negative symptoms (For example: lack of drive). It is a progressive disorder that can reoccur and the symptoms may vary from time to time [5].

Highlighting the key theory of symptoms, they are divided into three major categories including Positive', 'Negative' and 'Cognitive' categories. Positive symptoms include hallucinations and delusions which is the primary reason to go to the physician. The negative symptoms include social withdrawal, including discrepancies in working memory and processing cognitive speed [6,7,8]. However, Crow in one of his

influential works published in 1980, classified Schizophrenia into two types mainly Type I and Type II. Type I Schizophrenia is characterized by prominent positive symptoms which included an acute onset, good premorbid adjustment, a good response to treatment, intact cognition, intact brain structure, and an underlying mechanism that was neurochemical (Dopaminergic) and therefore reversible [9]. Furthermore, Jackson explained positive symptoms as "Release Phenomena" occurring in healthy tissue acting at a "lower level of evolution," while negative symptoms represent neuronal loss (dissolution). Type II Schizophrenia was characterized by prominent negative symptoms, an insidious onset, poor premorbid adjustment, a poor response to treatment, impaired cognition, structural brain abnormalities (i.e., ventricular enlargement as visualized by computerized tomography (CT)), and an underlying mechanism that was characterized by neuronal loss and therefore irreversible [10,11].

Over the years, vast development has been observed in the sector with better treatment modalities. In earlier times, patients were confined to the asylum for their treatment but with recent changes and advancements, a wide range of rehabilitation strategies and psychotic agents are developed which are known for their proven efficiency [12,13]. The major concern arising is patient compliance. There are underlying gaps and one of the major sources identified is that only half of the patients suffering from Schizophrenia receive their treatment [11,14].
On deeply analysing things it is observed that patients suffering from Schizophrenia experiences negative symptoms, which makes it challenging for developing treatment strategies. Negative symptoms are correlated with poor treatment response, thereby leading to worst functional outcomes. One of the major challenges that physicians face is the heterogeneity of the anti-psychotic response (including its efficacy and tolerability towards the disease) [15]. As the saying goes, "One size fit all" doesn't apply to this chronic disorder. With new drugs getting available in the market, a patient will have numerous options to opt for the newer drugs that may be more beneficial for reducing the symptoms. While contemplating the medications, novel antipsychotic medications have turned out to be effective for the treatment and prevention of relapse in patients suffering from Schizophrenia [15, 16].

Second-generation drugs are referred to as "Metabolically-Friendlier" drugs and are more efficient in terms of titration requirement, meal requirement, availability of supplementary formulations, and related indications. Cariprazine is one such second-generation antipsychotic that is a D3/D2 receptor agonist which is mainly used for the treatment of Schizophrenia. Cariprazine belongs to the distinct group of antipsychotics which is characterized by its unique receptor profile [17]. It shows and exerts its mechanism of action by acting as a D3-preferring D3/D2 agonist. Also, it acts as a partial 5-HT1A partial agonist. Cariprazine is selective for D3 receptors majorly as when compared to D2 receptors [18,19].

MATERIALS AND METHODS:

This literature review provides a comprehensive understanding of Cariprazine, its unique pharmacological action, and evidence base studies that clinically prove its action in patients with Schizophrenia.

1. Pathophysiology of Schizophrenia

Majorly the monoamines (including Serotonin, Dopamine, and Adrenaline] have their major role in maintaining the normal pathology and behaviour of the human brain, and fluctuations or distortions in their level can be an underlying issue for a number of psychiatric conditions. Out the three monoamines, the dopaminergic system is mainly responsible for the process of cognition and locomotion and is known to be laid down during Ontogeny [20,21]. This process signified its important aspect in stabilizing the brain circuits and thus its disruption can lead to numerous disorders. In contrast, Serotonin and Nor-Adrenaline neurons serve their major role in innervating the numerous regions of the brain and are thus responsible for the aspect of behavioural changes [including Fight, Flight or Approach]. Concentrating on the dopaminergic neurons, which are mainly covering the midbrain are further divided with regards to their Location, Function, and Sites. In rats, the dopamine neuron system is known as the Ventral Tegmental Area [VTA], whereas in primates, the Dopamine neurons are more towards the substantia nigra [22,23,24]

The dopamine system mainly comprises dopaminergic neurons that implicate several functions. To mention the functioning, it acts as a pacemaker conductance that can be spontaneous in nature. Further, the action of dopamine neurons can be affected by the striated uptake of Radiotracer Fluorodopa. Numerous evidences justify that hyper-responsive functioning of dopamine system is observed in patients with Schizophrenia.

Majority of the antipsychotic drugs used clinically acts at D2 receptors. Additionally, the use of 3,4-dihydroxyphenylalanine [L-dopa], and amphetamine will exacerbate the process of psychosis and thus will induce Schizophrenia-like symptoms if given at higher doses. Thus, this has led to enhanced research on how amplified and augmented levels are correlated with the aspects of Schizophrenia, Delusions, and Hallucinations. The focus of the research is now shifted more towards the aspects of dysregulation of dopamine system mainly due to afferent structures [25,26,27].

1.1.Hippocampal Hyperactivity:

Evidentiary post-mortem studies have concluded that the size of hippocampus is smaller in patients suffering from Schizophrenia. Also, it can be concluded through the imaging studies that the anterior hippocampus is majorly hyperactive in patients suffering from Schizophrenia, which is directly correlated with the aspects of psychosis. This hyperactivity can significantly result in reducing and inhibiting the parvalbumin-expressing GABAergic interneurons in hippocampus which are in turn crucial for developing gamma-rhythms that too gets disrupted during the process of Schizophrenia. Enhanced fluorodopa uptake in the dopaminergic terms is associated with enhanced functioning of glutamate functioning, which thus leads to a hippocampal overdrive and can lead to hyper-responsive state. In a study it was evaluated that administration of mitotoxin methyl azoxymethanol acetate [MAM] in a pregnant rat daily could result in developing an offspring which shows characteristic features of Schizophrenia including enhanced cell density, shrinked limbic cords, and altered levels of amphetamine and phencyclidine. Various data further suggests that the positive symptoms of Schizophrenia are mainly correlated with the loss of parvalbumin interneurons present in the limbic hippocampus. Whenever a dopamine system gets hyper-response, it would lead to the generation of a stimulus which in turn can lead to generation of a maximal dopamine signal thereby making it difficult to individual to differentiate between the relevant and irrelevant stimulus and leading to salience, which is one of the conditions that is termed as Aberrant Salience of Psychosis. Hippocampus and amygdala are known for their important functioning in emotion and cognition, and exerts their action in negative deficits [28,29,30].

1.2.The Stress and Hippocampal Pathology

Stress is one of the major underlying factors which is known to aggravate psychosis in individuals with Schizophrenia, followed by relapse in the patients suffering from it. Stress is majorly responsible for activating the hippocampus and results in heightening responses. Studies have concluded that stress results in loss of parvalbumin interneurons and it also activates amygdala, which is majorly known for its glutamatergic projects. Knowingly, the potent activation of the amygdala via a picrotoxin injection results in loss of the parvalbumin interneurons, which proves that stress-induced hyperactivity can be responsible for Schizophrenia. Majorly the Pre-frontal cortex [PFC] regulates the responses of amygdala and serves its role in the aetiology of Schizophrenia. Extreme stress could be fatal and can lead to failure of the PFC to reduce the impact of stress, thereby leading to sudden loss of parvalbumin interneurons, causing hippocampus hyperactivity and dopamine overdrive [31, 32]

Therefore, controlling stress is one of the crucial factors that needs to be taken care of in preventing the emergence of psychosis like behaviour. The individuals having a family history and with an abnormal response towards stressors, need to focus on the mitigating strategies of stress [33, 34].

2.Treatment Strategies

It has taken a long time to find effective psychotherapeutic initiatives for Schizophrenia. Recent advancements in psychological treatments have brought us to the juncture in which optimism is warranted. As evidence for the benefits of psycho - social Schizophrenia treatment has gathered, so has the recognition that the advantages may be transient and that numerous patients requires constant intervention to sustain their therapeutic outcomes. This understanding is consistent with the need to recognise Schizophrenia as a long-term illness, and it needs to be taken care of through a regular treatment. The ultimate diagnostic and therapeutic gains from individual and family psychosocial treatment are typically modest. Nevertheless, due to the rapidity of advancement over the last 20 years, those who work in the field must take these positive outcomes as encouraging words. Prior to the 1990s, there was not much proof from governed studies that any framework of psychotherapy [whether cognitive behavioural therapy or some other methods] that could have been helpful to individuals with Schizophrenia. There is currently evidence, reproduced across research, assisting the effectiveness of a wide range of intervention models, as well as training in social skills; other cognitive behavioural therapy strategies [e.g., cognitive restructuring, coping skill teaching] are still being researched and developed, tabulated in the below mentioned table [35,36,37].

Table no.1 first and second line treatments of various Psychiatric Disorders [35,36,37]

Syndrome	First-line drug	Second-line drug
Anxiety	Benzodiazepine, Antidepressant, and Propranolol will help in ruling out akathisia and manic symptoms	Switch to clozapine
Bipolar/Maniac Symptoms	Mood Stabilizers	Cariprazine, Risperidone, or olanzapine
Catatonia	Can be treated using lorazepam	ECT can be the second line of treatment.
Depressive Symptoms	Clozapine can be administered in suicidal symptoms, further coupled with Selective Serotonin Reuptake Inhibitors [SSRI]	Reduce the dose of antipsychotics. Further Second line drug can include Clozapine.

Antipsychotic drugs differ in terms of their pharmacodynamic properties, whereas the differences can be observed in efficacy, and tolerability of the drug. As a result of these differences, every antipsychotic drug has its own pharmacokinetic and pharmacodynamic profile comprising of their Absorption, Distribution, Metabolism, Excretion, related Adverse Events, and Reactions. Highlighting upon the available options, there are several first and second-line generation antipsychotic medications which are available including Risperidone, Quetiapine, Ziprasidone, and olanzapine. Apart from these, there are several second-line drugs including Cariprazine, Iloperidone, Lurasidone, and Asenapine amongst others that is administered with Ziprasidone [38, 39, 40].

3. Cariprazine Profile

3.1. Pharmacodynamics and Functional Effects of Cariprazine

The Cariprazine is chemically termed as [RGH-188; N′-[trans-4-[2-[4- [2,3-dichlorophenyl]-1-piperazinyl]ethyl]cyclohexyl]-N, Ndimethylurea] which belongs to a series of piperidine/piperazine derivatives and mainly targets DA-receptor subtypes D2 and D3. Further, it is assumed that Cariprazine acts via blocking D2-receptor which in turn is required for its antipsychotic efficacy [41, 42]. Moreover, the D3 receptor partial agonism/antagonism is responsible for plummeting the side effects which are caused as a result of D2-receptor antagonism. Various in-vitro studies have shown that Cariprazine exerts its refined safety profile. Considering the aspects of affinity, Cariprazine exerts lower affinity towards recombinant D3 and D receptors in an experimental study in rat striatal membranes but due to this protein Ser9Gly polymorphed, Cariprazine has no effect on the human D3 receptor. It strongly bounds and shows its action for a range of D receptors and 5-HT2B receptors inside CHO-K1 cells. With a higher affinity towards 5-HT1A, it is less selective for D2 receptors. In another study, it was observed that it binds to different receptors with different affinity level. For example, it binds to human histamine H1, 5-HT2A, and human σ1 receptors with moderate affinity while on interacting with α1A, 5-HT7, and 5-HT2C it shows a lesser affinity. As per the study conducted by Kiss et al, it was evaluated that Cariprazine has a lesser in-vitro affinity for numerous ion channels, transporters, neurotransmitter including that of Cannabinoid [CB1 and CB2], Dopamine [D1, D4, and D5], Adenosine [A1, A2, and A3], Galanin, Glucocorticoid, Histamine, Nicotine, Opiates, Norepinephrine, and others (which is less than 20 percent displacement at 1Mm) [43,44,45].

Various assays and studies are carried out in order to investigate the stimulating or inhibitory activity of D2 and D3 receptors. Assays like independent signalling and G-Protein dependent signalling are carried out where guanosine 5′-O-[gamma-thio] triphosphate [GTPγS]-binding assay, Cariprazine served as a silent antagonist of the human D2 and D3 receptors, thereby resulting in DA-induced simulations of striatal membranes and CHO-HD3 cells of rats. It acts as a D3-receptor partial agonist under certain regulatory circumstances where it inhibits the production of Forskolin stimulated cAMP production in CHO-HD3 cells that exerts higher intrinsic activity. It partially exerts its inhibitory action on Forskolin-induced accumulation of cAMP by the D2/D3 agonist 7-OH-DPAT [dipropylamino-7-hydroxy-1,2,3,4 tetrahydronaphtalene], whereas in the D2 receptors/ β-arrestin assay, it exerted its weak agonist activity but a potent Antagonist Effect. Cariprazine doesn't exert any action of its own but its potentially acts as a 5-HT-induced contraction inhibitor at its half-maximal concentration which suggests that it is a pure antagonist of the rat 5-HT2B receptors. As when compared with other drugs of the same class including that of Brexpiprazole and Aripiprazole, its exert its similar intrinsic activity to that of Brexpiprazole but lesser than that of aripiprazole. Majority of the antipsychotics acts as silent antagonists [46,47,48,49,50].

Many in-vivo studies are carried out that are mainly emphasized on the Serotonergic and Dopaminergic neuronal and Behavioural Characterisation. It is believed that Cariprazine can lead to enhanced turnover and metabolism of DA preferably in the olfactory tubercle of mouse as compared to the frontal and striatum cortex [51]. It is assumed and stated well through the case studies that long-term administration of Cariprazine can lead to suppression of the spontaneous activity of mesolimbic DA neurons, but exerts no action on the mesostriatal DA neurons. Intraperitoneal administration of Cariprazine [in a dose concentration of 0.06-0.6 mg/kg] for a longer time duration can result in adaptive changes in the Serotonergic, Dopaminergic, and Glutamatergic Receptors. Augmented levels of D2 receptors were observed in the nucleus accumbens, prefrontal cortex, and medial prefrontal cortex. The D3 receptor density was further enhanced in the islands of Calleja and olfactory tubercle but no significant effect was observed on D1 receptor [52,53].

Cariprazine leads to augmented density of 5-HT1A-receptor in the rat hippocampus in the dorsal and medical prefrontal cortex. Further glutamate receptors including that of AMPA and NMDA acts in an opposite direction. Cariprazine acts as a D2-autoreceptor that acts by blocking and suppressing the synthesis of DA which is induced by apomorphine. Cariprazine acts as a behavioural model in antipsychotic drugs and can lead to inhibition of amphetamine, MK -801, and phencyclidine. When administered in a dose of 0.005-0.01mg/kg in mice, it improved the phencyclidine-induced deficit recognition memory, reversal-learning paragdim, and social avoidance. Cariprazine exerted its antidepressant effect in a model where 0.2 mg/kg was administered daily for a time period of 21 days. Cariprazine also shows its antimanic like activity in amphetamine/ chlordiazepoxide induced mice models [54,55].

3.2. Pharmacokinetics

Taking into consideration the pharmacokinetics, it is rapidly absorbed and reaches its peak concentration within 3-4hours of oral administration in health patients. It shows a linear concentration-time graph within a dose range of 3 to 5 mg. Absorption of food is delayed as a result of absorption of Cariprazine. Continuous administration of Cariprazine can lead to its accumulation in plasma within the dose range of 1.5 – 12.5 mg/day. The mean half-life [t ½] is 2-5 days. Once absorbed, it behaves like that of a lipophilic antipsychotic that significantly distributes to the tissues with its major proportion. Primary it follows hepatic metabolism where it undergoes numerous processes including that of Oxidation, Dealkylation, Hydroxylation, and Cleavage by cytochromes [including CYP2D6.38 and P450 [CYP] 3A4] [55,56,57,58].

There is no related information available on these metabolites exert their action towards the pharmacological activity. There is no significant report on how these metabolites and their concentrates are taken up by brain. In patients suffering from Schizophrenia, a significant amount of information is lacking related to how potential interactions occurs involving Cariprazine. In human hepatocytes, it acts as a weak and competitive inhibitor of CYP3A4 and CYPD26. Further it is not known whether the metabolites of Cariprazine acts as inhibitors or substrates for p-glycoprotein. They have their major potential in influencing and affecting the pharmacokinetics as well as pharmacodynamics of the co-administered drugs via inhibiting the p-glycoprotein mediated efflux procedure [59,60].

Many abstracts, scientific journals and publications have stressed over the clinical studies and efficacy on how Cariprazine serve its action in Schizophrenia. Various studies have shown and evaluated the short-term efficacy and safety profile of Cariprazine in schizophrenic patients. In a study conducted by Citrome L and his co-workers where a randomized efficacy trial was carried out [phase II and phase III trials of six weeks duration] wherein the inclusion criteria was patients suffering from Schizophrenia [61]. A total of 1880 patients participated belonging to an age group of 18-65 years were selected for the controlled trials which included test period of around 3-8 weeks. An NDA [New drug application has been submitted which can be useful for the treatment of Schizophrenia and acute manic symptoms associated with the same]. The data was collected from the trials of around 1795 patients wherein two fixed-dose studies [with active and fixed-dose controls, a phase II trial where Risperidone [4.0mg/day], a phase 3 study with Aripiprazole [10mg/day], and phase III fixed placebo trial. In the clinical trials where active control was there, the Risperidone turned out to be superior to placebo on the total score of the Positive and Negative Syndrome Scale [PANSS]. Further, an improvement was observed after 6 weeks of administering Cariprazine and risperidone as when compared to the placebo sample. This was further observed on the Clinical Global Impressions – Severity and Clinical Global Impressions – Improvement scales. Dose-specific response and efficacy outcomes were evaluated for Cariprazine. In Phase II trial, around 392 patients were there, wherein around 46 percent discontinued at premature stage and thus lead to worsening of Schizophrenia [61,62,63,64,65].

Considering the aspects of safety, no clinical trials are available on the safety and tolerability aspects. Citrome L has mentioned in his review article on the short-term safety profile of Cariprazine. The most significant adverse events related includes insomnia, sedation, dizziness, anxiety, constipation, and extrapyramidal disorders. Weight gain was observed in patients, the one administering Risperidone showed a significant increase of about 16.7 percent, whereas in Cariprazine the result turned out to be dose-specific [8.5%10.7%, and 4.9% for 1.5, 3.0, and 4.5 mg/day] or placebo [2%]. Highlighting about the long-term stability, the major adverse events related are headache, akathisia, weight gain, and restlessness [61, 66, 67, 68, 69,70] .

RESULT & DISCUSSIONS:

Cariprazine acts as a dopamine partial agonist receptor which is distinguished from all other second-generation Antipsychotic drugs majorly because of its partial agonism action at D3 and D2 receptors. It is one of the first-line drug which is preferred for the treatment of Schizophrenia. It serves its unique mechanism via acting as a partial agonist that binds with the highest affinity at the dopamine D3 receptors. It has its longest duration, is broad spectrum and thus effectively work against the various domains of Schizophrenia. The D2 receptors majorly accounts for reducing the activity and positive symptoms. Furthermore, it has its role in preventing the relapse conditions which majorly occurs during Schizophrenia. D3 receptors have much greater affinity as compared to D2 receptors and thus are known for promoting efficacy against the persistent cognitive as well as negative symptoms. Further, antipsychotics are known to be the gold treatment for Schizophrenia. As when compared to other drugs, Cariprazine is known to have better effects. Furthermore, when it comes of side effects, it is far better than other agents that have their major side effects as weight gain, QTc prolongation, prolactin elevation and sedation. Cariprazine is one of the drugs which is useful in the treatment of Schizophrenia in patients with predominantly negative symptoms, first episode psychosis. Initially, it is administered in order to treat the acute symptoms and later on prescribed in order to prevent the relapse. The long-term efficacy for Cariprazine has been evaluated during a relapse prevention trial wherein individuals with stable symptoms were treated with Cariprazine and a placebo. In various treatment studies Cariprazine is considered as the first-line treatment drug for treating the patients with Schizophrenia followed by other drugs including that of Olanzapine, Amisulpride, and Quetiapine. Clinical trials have shown that Cariprazine is safe and well tolerated by patients within a dose range of 1.5-2.0mg/day and the most common side effects included headache, insomnia, and akathisia. Greater incidences of mild of moderate headache is observed in patients and on further discontinuation of the drugs no major adverse events were observed. Cariprazine is known to be the safest and most well-tolerated drug in patients suffering from Schizophrenia. Further, it possesses a neutral metabolic profile with no increase in prolactin level and no cardiac changes. It is known to be advantageous for the treatment and its adverse event [if occurs] can be reduced by altering dose levels (70,71,72,73).

4. CONCLUSION

To summarise, Cariprazine is an effective and very well tolerated drug for Schizophrenia. It is an invaluable complement to the possible treatments for this disorder, and it could prove particularly helpful for people who do have primarily negative symptoms. For decades, Antipsychotic Medications has been the cornerstone of efficient treatment of patients suffering from Schizophrenia. Even though all representatives rely on d2 Dopamine receptor blockade for Anti - Psychotic efficacy, Cariprazine has a distinct pharmacological activity that endorses well-defined effectiveness benefits as well as a favourable tolerability and safety profile. The half-lives of Cariprazine and its major active metabolites are extremely long. This could be advantageous because patients with Schizophrenia frequently fail to comply with treatment. A skipped dose may be linked to a decreased risk of recurrence than a drug with a shortened half-life. Cariprazine has demonstrated broad-spectrum effectiveness across the various disciplines of psychosis in both short- and long-term clinical studies, as well as in countless post-hoc inquests, establishing its spot as a useful therapeutic remedy for the Schizophrenia treatment in everyday practice.

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