Case Series

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Cariprazine Augmentation in Inadequate Clozapine Response: A Case Series

Psychiatry/Mental Health Section

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ABSTRACT

Managing patients with treatment-resistant schizophrenia who do not respond adequately to Clozapine poses a challenge. Cariprazine, with its unique mechanism of action, may be an option for such patients. The additional benefits of using Cariprazine as an augmentation strategy include once-daily dosing, ease of titration, and a favourable side-effect profile. The report outlines the authors' experience of six patients with treatment-resistant schizophrenia who did not respond to Clozapine. The addition of Cariprazine was tolerated by all the patients. The majority showed improvement with symptom reduction, and in some cases, the dose of Clozapine could be reduced, thereby decreasing the side-effects of Clozapine.

Keywords: Anti-psychotic agents, Clozapine related side-effects, Ultra-resistant schizophrenia

INTRODUCTION

Cariprazine is a novel third-generation antipsychotic with a unique receptor profile. It exhibits partial agonism at Dopamine (D2/D3) receptors, with preferential binding to the D3 receptor, as well as partial agonism at the Serotonin- 5HT1A receptor and antagonistic actions at 5HT2A and 5HT2B receptors. Its low affinity for histaminergic, cholinergic, and adrenergic receptors contributes to its favourable side-effect profile. The active metabolites of Cariprazine- desmethyl Cariprazine and didesmethyl Cariprazine- have long half-lives, enabling a once-daily dosing schedule [1].

The concept of treatment resistance has evolved over the years as it became evident that many patients did not respond to antipsychotic medications and psychosocial interventions. The modified Kane's criteria is the most widely accepted among the various criteria used to describe this concept. It defines treatment resistance as a lack of significant improvement in positive symptoms after treatment with two or more different non-clozapine antipsychotic medications at adequate doses (at least 600 mg Chlorpromazine equivalents), duration (6-8 weeks), and ensured medication adherence [2]. With a reported prevalence of 20-33%, it is one of the most challenging psychiatric diagnoses [3]. Clozapine is considered to be the drug of choice for its treatment. However, about 60% of individuals with Treatment Resistant Schizopenia (TRS) do not respond adequately to Clozapine. While definitions of Clozapine Resistant Schizophrenia (CRS) have been formulated, these are excessively reliant on positive symptoms [4]. The utilisation of these criteria in clinical practice is hindered by practical difficulties in determining the adequacy of dose, estimating blood levels, judging adherence, and conducting prospective observation of patients during treatment with Clozapine.

In patients with CRS, strategies that have been attempted to manage persistent symptoms include giving higher doses of Clozapine or augmenting Clozapine with an antipsychotic, mood stabiliser, electroconvulsive therapy, or antidepressant. However, evidence supporting these strategies is inadequate. Psychotherapeutic interventions have also been reported to be beneficial in Clozapine-refractory psychotic symptoms [5].

Cariprazine, with its unique mechanism of action and favourable side-effect profile, would be an ideal augmentation agent in patients who do not respond to or are unable to tolerate Clozapine. However, evidence for its use and safety is limited as the drug has only recently been approved for use by regulatory agencies [6]. There are reports of Cariprazine being successfully used as a substitute for Clozapine in patients who did not respond adequately or developed intolerable side-effects with it [7]. Some reports show encouraging outcomes with Cariprazine as an augmentation agent in patients with Clozapine resistance; however, there is a lack of data from Asia in this regard [1,6,8-12]. This case series details the authors' experience with six patients with treatment-resistant schizophrenia who were augmented with Cariprazine due to inadequate response to Clozapine.

Case 1

A 31-year-old unmarried male presented to the Department of Psychiatry with an 18-month history of a continuous illness characterised by anger, irritability, auditory hallucinations, hallucinatory behaviour, delusions of persecution and reference, disorganised behaviour, and disturbed sleep and appetite. He was socially withdrawn, and his personal care and occupational functioning had declined. There was no history of any medical illness or substance use. A diagnosis of schizophrenia was made, and the patient was initially treated with Olanzapine (25 mg/day for 7 months), followed by Risperidone (8 mg/day for six months). Despite the addition of Fluphenazine Decanoate (50 mg/month), he continued to experience persistent persecutory delusions and disorganised behaviour. Therefore, treatment resistance was considered, and Clozapine was initiated up to a dose of 400 mg/day. Following an episode of viral hepatitis, Clozapine had to be discontinued, and Amisulpride was started (700 mg per day). However, due to an exacerbation of symptoms and the onset of tardive dyskinetic movements, Clozapine was restarted with serial monitoring of liver function tests as advised by the Department of Hepatology. During the Coronavirus Disease-2019 (COVID-19) pandemic, he was lost to follow-up but continued Clozapine in the post-COVID-19 period. After reviewing his case, persistent positive, negative, and cognitive symptoms were noted post-COVID-19. In light of resistance to Clozapine, Cariprazine was added, and the dose was increased to 3 mg/day. Within five weeks, there was a clinically significant reduction in positive symptoms. These improvements were maintained, along with a reduction in negative symptoms, at the one-year follow-up. No adverse effects were reported following the addition of Cariprazine.

Case 2

A 48-year-old unmarried male presented to the Psychiatry Department in 2004 with a 15-year history of auditory hallucinations, delusions of persecution and reference, and thought broadcasting. Negative symptoms of affective blunting, anhedonia, poor socialisation, and cognitive symptoms of impaired attention and forgetfulness were also present. A diagnosis of schizophrenia was made. He was found to have hypothyroidism and was on Thyroxine replacement with normal thyroid stimulating hormone levels. A Psychiatrist in his hometown had initiated Clozapine due to poor response to Olanzapine, Risperidone, and Loxapine. Upon his visit to this centre, he was on Clozapine 75 mg/day, which was gradually increased to 550 mg/day. Despite the dose escalation, he remained symptomatic with auditory hallucinations, delusions of reference and persecution, and thought broadcasting. Negative and cognitive symptoms persisted. The patient reported side-effects of giddiness, sialorrhoea and a pulling sensation in the lower limbs, especially at night. Given the poor response to Clozapine, sequential augmentations with Amisulpride (500 mg per day), Aripiprazole (30 mg per day), Risperidone (5 mg per day), and repetitive transcranial magnetic stimulation (7 sessions) were attempted with inadequate response. Therefore, Cariprazine augmentation was considered. Within four weeks of initiating Cariprazine, there was a significant improvement in symptoms, including a reduction in delusions, hallucinations, and thought broadcasting. The dose of Clozapine could also be gradually reduced, thereby alleviating the distressing side-effects [13]. These improvements were sustained at his last review, and the patient had successfully returned to his job.

Case 3

A 36-year-old unmarried male presented to the outpatient clinic of the Department of Psychiatry in 2014 with a 10-year illness characterised by delusions of persecution and reference, auditory hallucinations, disinhibited behaviour, disturbed biological functions, and poor socialisation. A diagnosis of schizophrenia was confirmed. His previous psychiatrist had diagnosed treatment resistance, and he was on Clozapine at the initial visit to this centre. He continued to take Clozapine but did not follow-up at centre for the next six years. During the next review in 2020, psychotic symptoms persisted (auditory hallucinations, delusions of persecution, reference, and aggression). Therefore, the dose of Clozapine was increased from 300 mg to 600 mg per day, with the addition of Sodium Valproate at 1 gm/day. Despite being on this dose of Clozapine for the following two years, he continued to experience psychotic symptoms and also developed side-effects such as sedation, sialorrhoea and constipation. Therefore, augmentation with Cariprazine was initiated, and the dose was increased to 3 mg/day in December 2022. A clinically significant reduction in psychotic symptoms was observed within four weeks, leading to a 25 mg reduction in the dose of Clozapine.

Case 4

A 36-year-old male, who is an engineer, presented to outpaient clinic in 2011 with a one-year history of an insidious onset, gradually progressive illness initially characterised by disorganised behaviour and ambivalence, followed by delusions of persecution and reference, along with amotivation, avolition, flattening of affect, impaired attention, and executive dysfunction. He was socially withdrawn and unable to sustain a job. A diagnosis of schizophrenia was made. Sequential trials of Risperidone (8 mg/day for 11 months), Amisulpride (800 mg/day for 9 months), and depot Fluphenazine decanoate (50 mg/month for 7 months) did not show any benefit. There was minimal response to Olanzapine (25 mg/day for 13 months); however, it had to be discontinued due to poor glycaemic control necessitating insulin injections. In 2019, treatment resistance was considered, and he was started on Clozapine. He remained stable on 400 mg per day of Clozapine for two years with no positive symptoms and good work functioning, after which the dose was gradually reduced to 350 mg. However, following the dose reduction, the patient experienced a relapse of symptoms characterised by wandering behaviour, irritability, irrelevant speech, hallucinatory behaviour, and difficulty with work. Despite increasing the dose back to 400 mg per day, with adequate serum Clozapine levels, there was no improvement noted. Therefore, augmentation with Cariprazine was initiated in February 2023. Within six weeks of starting Cariprazine (upto 3 mg/day), he returned to his premorbid level of functioning and rejoined work, remaining stable at follow-up after nine months. He has not reported any emergent side-effects following the addition of Cariprazine.

Case 5

A 34-year-old unmarried male presented to the Psychiatry Outpatient Department in 2010 with a two-month history of poor sleep, irritability, hearing non existent voices, disorganised behaviour, poor socialisation, and decreased personal care. In the absence of organic causes and substance use, a diagnosis of schizophrenia was made. He later reported delusions of erotomania, persecution, and reference and made several attempts of self-harm secondary to the psychotic symptoms. Negative symptoms of poor socialisation, decreased motivation, and poor personal care were also present. He had medical co-morbidities of iron deficiency anaemia, hiatus hernia, haemorrhoids, and reactive airway disease for which he was treated with hematinics, prokinetic agents, and bronchodilators. He was lost to follow-up but continued to be symptomatic despite adequate trials of Risperidone (5 mg per day), Aripiprazole (30 mg/day), and Olanzapine (25 mg/day) from elsewhere. There is a history of laryngeal dystonia and tardive dyskinesia while on Risperidone. The diagnosis was revised to treatment-resistant schizophrenia, and he was started on Clozapine in September 2021. He continued to remain symptomatic on Clozapine (425 mg/day). The addition of Olanzapine (25 mg/day) did not benefit the patient; therefore, Cariprazine augmentation was initiated in 2023, and the dose was increased to 4.5 mg per day. Even three months after the initiation of Cariprazine, he continued to have positive symptoms of auditory hallucinations, delusions of persecution, reference, and erotomania, disorganised behaviour, and significant socio-occupational decline, along with gestures of intentional self-harm. Consequently, Cariprazine was discontinued, and Amisulpride was started. He continues to remain symptomatic and at risk of self-harm at follow-up.

Case 6

A 25-year-old unmarried female was diagnosed with schizophrenia during her initial presentation to the department in 2021 based on a five-year history of hallucinatory behaviour, delusions of persecution, reference, somatic passivity, irritability, and progressive decline in social and occupational functioning. Medical co-morbidities of hypothyroidism and anaemia were present, which were well controlled with medication. Treatment resistance was diagnosed elsewhere due to failed trials of Lurasidone (80 mg/day) and Amisulpride (800 mg/day), and she had been started on Clozapine (250 mg/day) in 2018. Given the persistence of symptoms, the dose of Clozapine was increased to 450 mg per day. However, she remained symptomatic. Augmentation with Risperidone (4 mg/day) and Amisulpride (700 mg/day) did not provide much benefit, so Cariprazine was added, and the dose was increased to 4.5 mg/day. After four weeks of Cariprazine with no reduction in symptoms, it was tapered and stopped. Haloperidol and Olanzapine were added to Clozapine; however, the patient continues to have poor functioning and persistent psychotic symptoms at follow-up.

The sociodemographic and clinical details of the patients are described in [Table/Fig-1].

DISCUSSION

Managing patients with Clozapine-resistant schizophrenia is one of the most challenging situations faced by a psychiatrist. While augmentation is a common strategy used in this situation, new side-effects associated with the add-on antipsychotic or the drug combination may emerge. Evidence for augmentation strategies is limited to anecdotal studies and small uncontrolled trials. Literature on the augmentation of Clozapine with Cariprazine is sparse [Table/Fig-2] [1,6,8,11,12,16].

Clinical variables	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (in years)	31	48	36	36	34	25
Gender	Male	Male	Male	Male	Male	Female
Duration of illness in years	13	32	23	23	13	6
Medical co-morbidities	Past viral hepatitis	Hypothyroidism	-	Diabetes mellitus	Iron deficiency anaemia, hiatus hernia, haemorrhoids, reactive airway disease	Hypothyroidism Anaemia
Past medication trials	Olanzapine, Risperidone, Fluphenazine decanoate, Amisulpride*	Olanzapine, Risperidone, Loxapine	Diagnosed TR elsewhere, past treatment details not available Risperidone* Amisulpride*	Risperidone, Amisulpride, Fluphenazine decanoate	Aripiprazole, Olanzapine, Risperidone*	Lurasidone Amisulpride
Tardive dyskinesia	Yes	No	No	No	Yes	No
Maximum dose of Clozapine (mg/day)	400	550	600	400	425	400
Duration of Clozapine treatment in years	10	18	18	4	1.5	2.5
Compliance to medications	Good	Good	Good	Good	Good	Good
Clozapine level (ng/mL)	560.94	1031	NA	745.15	NA	506
Past augmentation trials- poor response (mg/day)	Nil	Amisulpride (700), Aripiprazole (30), Risperidone (4), rTMS (7 sessions)	Nil	Nil	Olanzapine (20)	Risperidone (5), Amisulpride (800)
Non pharmacological Interventions	Cognitive techniques and behavioural interventions	Cognitive techniques, behaviour interventions, social skills training, and vocational training	Cognitive techniques	Cognitive techniques	Cognitive techniques, behavioural interventions, social skills training, and vocational training	Cognitive techniques
Side-effect reduction	Nil	Giddiness, sialorrhoea, pulling sensation	Sedation, sialorrhoea	Nil	Nil	Nil
PANSS score before Cariprazine	41 (P9, N14, G18)	78 (P14, N28, G36)	64 (P18, N22, G24).	-	-	107 (P25, N20, G62)
Cariprazine dose (mg)	3	3	3	3	4.5	4.5
Number of weeks after observable therapeutic effects was noticed	5	4	4	6	-	-
Duration of combined treatment with Clozapine and Cariprazine	12 months	1 month	1 month	1.5-3 months	4 months	1 month
PANSS score after Cariprazine	35 (P7, N10, G18)	40 (P8, N10, G22),	54 (P14, N18, G22)	-	-	90 (P20, N20, G50)

[Table/Fig-1]: Sociodemographic and clinical details of the patients.
*Severe side-effects necessitated discontinuation; PANSS: Positive and negative syndrome scale

Author	Type of study	Number of patients	Cariprazine dose (mg/day)	Duration of Cariprazine treatment	Patient profile for recruitment to the study	Response
Oloyede E et al., [1]	Case series	5	1.5	6-12 months	Treatment resistant negative symptoms on Clozapine Assessment measure-SANS	Reduction in negative symptoms at six months
Siwek M et al., [16]	Retrospective chart review	12	1.5-4.5	10-40 weeks	Treatment resistant schizophrenia-poor response to Clozapine Assessment measure-Clinical Global Information (Improvement)	Nine out of twelve patients had a positive therapeutic effect (CGI-I=2) after 4-12 weeks
De Berardis D et al., [6]	Case report	2	3	4-6 months	Treatment resistant schizophrenia-Clozapine resistant positive symptoms Assessment measure: PANSS	Overall reduction in PANSS score
Aubel T [12]	Case series	3	4.5	More than 2 months	Treatment resistant schizophrenia with poor response to Clozapine Assessment measure: clinical response	Improvement in positive and negative symptoms and functioning
Pappa S et al., [8]	Open label study	10	1.5-6	More than 6 weeks	Predominantly TRS- inadequate treatment response, persistent negative symptoms and/or tolerability issues with Clozapine or previous augmentation options. Assessment measure: PANSS	Reduction in the median total PANSS score from baseline
Bogren M et al., [11]	Case report	1	6	24 months	Negative symptoms Assessment measure: CGI-S	CGI-S score reduction and reduction in dose of Clozapine

[Table/Fig-2]: Previous studies on Cariprazine augmentation in patients with Clozapine [1,6,8,11,12,16].
SANS: Scale for the assessment of negative symptoms; CGI-S: Clinical global impression-severity

The present case series documents naturalistic observations on a small group of patients with schizophrenia with inadequate response to treatment with Clozapine. Four out of the six patients showed clinical improvement with the addition of Cariprazine, which allowed for a reduction in the dose of Clozapine and its associated side-effects such as sedation, sialorrhoea and weight gain. As with any antipsychotic, it appears that some (n=4; 66.6%) patients respond to Cariprazine, while others do not. While the clinical response

was mixed, Cariprazine was found to be safe in all patients as no significant side-effects emerged with the addition of this drug. The advantages of using Cariprazine as an augmenting agent are its unique pharmacokinetic and pharmacodynamic properties that contribute to its efficacy and tolerability. Once-daily dosing, ease of titration, and a safer side-effect profile are the added benefits. The likelihood of weight gain and sedation is less with Cariprazine compared to other antipsychotic drugs due to its lower affinity to adrenergic, histaminergic, and cholinergic receptors [13,14]. Based on the mechanism of action, both Clozapine and Cariprazine are thought to be beneficial in treating negative and cognitive symptoms of schizophrenia [14,15]. The synergistic effect of this combination needs to be explored in well-designed studies in the future.

Another benefit of adding Cariprazine is its weak competitive inhibition of CYP1A2, which metabolises Clozapine; thus, unlike other antipsychotics, it may not increase the plasma Clozapine levels and accentuate the adverse effects [9]. As Cariprazine has only been introduced recently, its long-term effectiveness and side-effects are not clearly understood.

One could argue that pseudo-resistance to Clozapine was present in some of the patients in this series. The common causes of pseudo-resistance to Clozapine include inaccurate diagnosis, inadequate dose or treatment duration, insufficient serum Clozapine levels, limited compliance, and/or medical or psychiatric comorbidities [3]. These factors were excluded by reclarifying history, including adherence to treatment, serial mental state examinations, and appropriate blood tests.

Recent evidence has suggested that patients who do not respond to a trial of Clozapine monotherapy are among the most severely ill of all patients with schizophrenia [15,16]. Two patients did not respond to Cariprazine or other augmentation strategies. This is in keeping with some researchers who suggest that the addition of a second antipsychotic to Clozapine may not have a significant impact on clinical response or symptom severity. Neurobiological postulates to this phenomenon have also been described. PANSS scoring was not available in two patients who had been initiated on Cariprazine on an outpatient basis. For patients from geographically distant places, both within and outside India, follow-up visits were limited by the COVID-19 pandemic, financial constraints, and travel constraints. For some patients in this series, this led to long delays in introducing augmentation agents. Patient and caregiver reluctance to consider augmentation strategies earlier in the course of treatment also contributed to the delay. The present case series report adds to existing knowledge and suggests the need for further studies on Cariprazine as an augmenting agent for Clozapine in treatment-resistant schizophrenia.

CONCLUSION(S)

Cariprazine can be a useful augmenting agent in some patients with Clozapine-resistant schizophrenia. No adverse effects were reported among the patients in this series. Further research and randomised controlled trials are necessary to ascertain the efficacy and tolerability of this combination.

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