

Cariprazine Add-on in Inadequate Clozapine Response: A Report on Two Cases

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Cariprazine is a novel antipsychotic drug that exerts partial agonism of dopamine D₂/D₃ receptors with preferential binding to the D₃ receptor, antagonism of 5HT_{2B} receptors, and partial agonism of 5HT_{1A}. Currently, cariprazine has shown clinical efficacy in patients with schizophrenia and with bipolar disorder, as well as adjunctive treatment in patients with Major Depressive Disorder (MDD) and drug-resistant MDD. In the present case series, we report on two patients with treatment-resistant schizophrenia and partial response to clozapine who benefit from combination with cariprazine. The effects of cariprazine combination were remarkable also concerning the adverse metabolic effects of clozapine.

KEY WORDS: Cariprazine; Clozapine; Effectiveness; Efficacy; Schizophrenia; Tolerability.

INTRODUCTION

Schizophrenia is a chronic and devastating disease affecting around 0.5% of the population [1]. It is known that the complete remission or recovery of symptoms is relatively rare in schizophrenia, and the treatment resistance remains one of the most critical challenges in psychiatry [2]. The gold standard in the case of resistant schizophrenia is the clozapine treatment [3]. However, despite the greater efficacy of clozapine over other antipsychotics in the management of resistant schizophrenia, a significant number of patients fail to attain adequate response or develop clozapine-related adverse effects, and clozapine-resistant schizophrenia represents a challenge for

the clinician and a calamity for the patients [4,5].

Cariprazine, also named the "rip" [6], is a novel second-generation antipsychotic with antagonist-partial agonist properties at D₂ and D₃ receptors, with preferential binding to the D₃ receptors [7]. Cariprazine has been approved by the Food and Drug Administration for the treatment of adult patients with schizophrenia (Europe and USA) and acute treatment of manic/ and mixed episodes of bipolar disorder (only USA) [8,9].

Cariprazine acts as an antagonist or partial agonist at D₂/D₃ receptors, depending on the endogenous dopaminergic tone [10]. At high dopamine levels, it seems to act as an antagonist, while at lower dopamine levels, it exerts its agonist action, by increasing the dopamine receptor activity [11,12]. It preferentially has a 5- to 30-fold greater affinity for human D₃ receptors (K_i = 0.085 nM) than for the D_{2L} (K_i = 0.49 nM) and D_{2S} (K_i = 0.69 nM) [13]. Meanwhile, even though to a more limited extent, cariprazine also shows partial agonism at the 5HT_{1A} receptors (K_i = 2.46 nM), hence by exerting an anti-

Received: October 22, 2019 / **Revised:** November 19, 2019

Accepted: November 27, 2019

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depressant effect in addition to the antipsychotic effect [14,15]. Moreover, cariprazine also shows an antagonist at human 5HT_{2B} receptors (K_i = 0.58 nM), which has a crucial role in modulating dopamine release in the nucleus accumbens [16].

Interestingly, besides the positive effects on positive symptoms, cariprazine is associated with improvements in primary negative symptoms of schizophrenia and these improvements are unlikely to result from improved positive or overall symptoms [17].

In the present paper, we report on two cases of treatment-resistant schizophrenia with inadequate response to clozapine who were successfully treated with cariprazine combination in the outpatient facility of Hospital of Teramo, Italy.

CASE

Case 1

She is a 29-year-old unemployed and unmarried woman with a long history of schizophrenia diagnosed when she was 19-year-old with an acute episode characterized by mixed positive and negative symptoms with marked hostility. During the years, she underwent several treatments with both oral (haloperidol, olanzapine, and paliperidone) and long-acting antipsychotics (haloperidol decanoate and aripiprazole long-acting) with no effects on psychopathology. Then, from almost one year, she was switched to clozapine 450 mg/day with an inadequate response, despite a tentative to augment with amisulpride 800 mg/die that was reported ineffective. In fact, at the time of our observation (referred to us by her general practitioner) the patient was symptomatic, and the scores of Positive and Negative Symptoms Scale (PANSS) were still clinically significant (total score = 113, positive = 22, negative = 33, general = 58). Moreover, the patient developed weight gain during clozapine treatment (at the time of our first observation, her body weight was 84 kg, and body mass index [BMI] was 26.8 kg/m²).

Thus, considering the failure of previous treatment with aripiprazole (due to a non response, but without adverse effects), cariprazine combination was offered and introduced at the initial dosage of 1.5 mg in the morning. After a week, cariprazine was titrated to 3 mg/die without adverse effects. After 30 days of cariprazine combination we observed an improvement in PANSS scores (total

score = 89, positive = 18, negative = 27, general = 44). After other three months of therapy, the PANSS scores were remarkably improved (total score = 74, positive = 14, negative = 20, general = 40) without adverse effects reported. Moreover, we noted a significant improvement in weight (79 kg) and BMI (25.1 kg/m²).

The last observation was carried out in September 2019, after other four months of combination therapy, and the PANSS scores further improved (total score = 57, positive = 10, negative = 14, general = 33) as well as the BMI (24.6 kg/m²). The patient found a job as a part-time working in handbag manufacture with a reported good yield and performed a regular and moderate physical activity three times a week. No adverse effects were reported or observed, and the patient was taking 400 mg/day of clozapine and cariprazine 3 mg/day.

The subject gave us written informed consent for publication of this case report.

Case 2

He is a 35-year-old blue-collar unmarried man who was diagnosed with schizophrenia at the age of 24-year-old. His onset was accompanied by substance abuse (mainly cocaine and cannabis) and was characterized by positive symptoms, a marked impulse dyscontrol with great hostility and negative symptoms such as blunted affect, social withdrawal, and poor rapport. He was treated in the past with several antipsychotics (haloperidol, olanzapine, and paliperidone long-acting) without response and considerable problem in functioning (the patient lost his job). From almost one year and a half, he was taking clozapine 350 mg/day with a functional improvement only on hostility and uncooperativeness, without significant effects on other symptoms. He was also administered in the past clozapine 400 mg/day, but he developed marked sedation, and the dosage was reduced to 350 mg/day that was well tolerated. He willingly decided to consult us, and at the time of our observation, he was symptomatic, and the scores of PANSS were still clinically significant (total score = 121, positive = 27, negative = 34, general = 70).

Moreover, the patient was overweight even if he was unable to relate this to clozapine treatment (his body weight was 95 kg, and BMI was 28.4 kg/m²). He was offered to introduce aripiprazole, but he refused due to his friend, who was taking it and told him about unknown

“adverse effects.” Then, cariprazine was offered, and he agreed to introduce it at an initial dosage of 1.5 mg/day. After three weeks of therapy, a slight improvement on PANSS was seen (total score = 101, positive = 20, negative = 30, general = 61), and the patient reported that he “felt better” especially on functioning and cognitions without adverse effects. The patient agreed to titrate cariprazine up to 3 mg/day. After other two months we observed an improvement of both PANSS (total score = 77, positive = 13, negative = 15, general = 49) and BMI (26.9 kg/m²), and clozapine was reduced to 300 mg/day. The improvement was constant, and he was able to find a job as blue collar in a brick factory as “...my mind and thoughts are more clear...”.

The last observation was conducted in September 2019 after further three months of combination therapy, and the PANSS scores were also improved (total score = 57, positive = 9, negative = 12, general = 29) as well as the BMI (25.6 kg/m²). No adverse effects were reported or observed, and the patient was taking 300 mg/day of clozapine and cariprazine 3 mg/day.

The subject gave us written informed consent for publication of this case report.

DISCUSSION

To date, these were the first cases of cariprazine combination with clozapine in the occurrence of inadequate response to the latter. Cariprazine combination showed a remarkable effect, as demonstrated by a reduction in PANSS scores over time.

Even if the decrease in PANSS scores was observed for all subscales, a noticeable reduction was obtained concerning negative symptoms that are in line with the mechanism of action on D₃ of cariprazine [18]. The D₃ receptors, structurally similar to the D₂ receptor, are auto-receptors able to modulate the phasic dopaminergic activity and linked to cognition, mood, emotions and reward/substance abuse [19]. Therefore, some authors support its potential role as a pro-cognitive agent and effective treatment in the management of negative symptoms of schizophrenia and an enhancer of the working memory as well [20]. Several studies have suggested that cariprazine affinity and action on D₃ may explain its efficacy on negative symptoms, executive deficits, cognitive and mood impairment [21,22]. D₃ receptors are identified at

the asymmetric synapses at the head of dendritic spines, a localization that is in sharp contrast with D₁ and D₂ receptors, which are both pre-synaptic or spread all over dendrites and dendritic spines in neurons of the caudate putamen and NAc [20,23,24]. Moreover, the high concentration of the D₃ receptors in the ventral striatum, as compared to the dorsal part, increases the probability that D₃ antagonists may have an antipsychotic action with negligible adverse effects including extrapyramidal side effects and catalepsy [25-27].

Moreover, even though to a more limited extent, cariprazine also shows partial agonism at the 5HT_{1A} receptors, hence by exerting an antidepressant effect in addition to the antipsychotic effect [28]. These mechanisms may explain the positive impact of the cariprazine-clozapine combination seen in these cases.

It is also possible to hypothesize a pharmacokinetic interaction between cariprazine and clozapine to explain the positive outcome of this combination. Cariprazine primarily undergoes dealkylation, dihydroxylation, N-oxidation, and cleavage by CYP3A4 and, to a small degree, by CYP2D6 in hepatic microsomes [29]. Clozapine is mostly metabolized in the liver by the CYP1A2 and CYP1A2 activity is an essential determinant of clozapine dose [30]. Other liver enzymes involved in clozapine metabolism include CYP2D6 and CYP3A4 [31]. As the involvement of CYP3A4 in clozapine metabolism is secondary [32], one may hypothesize that a drug-drug interaction with cariprazine may be unlikely. Unluckily we did not evaluate clozapine blood levels, but none of patients reported symptoms of excessive clozapine dosage. Both patients were administered the maximum tolerated doses of clozapine, and no adverse events were reported.

Besides, we observed a good effect on weight and BMI with a reduction of both parameters with cariprazine combination. This effect may be explained by both cariprazine pro-cognitive action (both of patients started to perform a moderate physical activity) and by the decrease in negative symptoms through the action on D₃ receptors [22]. Moreover, cariprazine binds to the 5HT_{2A} (K_i = 19 nM) that may be involved in pro-cognitive activity [33] while it has a lower affinity for 5HT₇ (K_i = 111 nM), 5HT_{2C} (K_i = 134 nM) and α₁ receptors, by exerting an antagonist action. Its weak action on these receptors may further explain its good metabolic profile [34]. Concerning cariprazine adverse effects [12,35], post hoc analyses of safe-

ty data from cariprazine studies in schizophrenia showed a dose-response association for several treatment-emergent adverse events and clinical laboratory values including akathisia, extrapyramidal symptoms, creatine phosphokinase and transaminase elevations, increases in blood pressure, but none of these were observed in our cases.

In conclusion, cariprazine add-on to clozapine showed remarkable and relatively rapid efficacy in the treatment of subjects with inadequate response to clozapine. The tolerability of this association was excellent without reported adverse effects. However, future studies on larger samples are needed to elucidate this positive effect better.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

All the Authors contributed to this case series with equal efforts.

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