

Switching Clozapine to Cariprazine in Three Patients with Persistent Symptoms of Schizophrenia: A Case Series

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Abstract: Despite many available treatments for schizophrenia, several unmet needs persist in treating individuals with this disorder, and the response rate to first-line antipsychotics remains relatively low. Clozapine has shown efficacy in treating schizophrenia patients who failed to respond to previous antipsychotics. However, side effects and the need for routine blood tests have limited its use as a first-line treatment. Cariprazine is a D₂/D₃ partial agonist antipsychotic with a mechanism of action that differs from other antipsychotics due to its higher affinity for D₃ receptors. Several trials have demonstrated the efficacy of cariprazine on positive and negative symptoms of schizophrenia and have shown that it is a well-tolerated treatment. In this series, we present 3 cases of patients diagnosed with schizophrenia who were initially under treatment with clozapine. Despite some initial improvement, the patients showed persisting positive and negative symptoms or developed limiting side effects while in treatment with clozapine. Cariprazine treatment was titrated concurrently with clozapine tapering until its discontinuation. Significant improvement in both positive and negative symptoms was observed up to 14 months after starting cariprazine, and resolution of side effects was reported in all cases. Our case series supports cariprazine as an effective treatment for positive and negative symptoms in patients who failed to adequately respond or poorly tolerated treatment with clozapine, as well as a potential treatment in dual disorders, specifically psychotic disorders and cocaine use disorder.

Keywords: schizophrenia, cariprazine, atypical antipsychotics, clozapine, resistant schizophrenia

Introduction

Schizophrenia is a chronic and severely disabling disorder with a prevalence of 0.5–1.5%, globally.^{1,2} Typical symptoms of schizophrenia can be divided into positive, negative, and cognitive domains. Positive symptoms include abnormal thoughts and behaviors such as formal thought disorder, delusions, hallucinations, and disorganized speech and behavior.^{1–4} Negative symptoms include social withdrawal, affective blunting, anhedonia, diminished initiative (avolition), and anergy.^{1,2,4} Cognitive symptoms are expressed in a wide variety of cognitive dysfunctions, predominantly in attention, memory, and judgment.^{1,2,4} The clinical course is typically progressive and deteriorating, with onset usually during late adolescence.^{1,2,4}

Antipsychotics are the treatment of choice in acute and chronic phases of schizophrenia, which are frequently effective in controlling positive symptoms, with mild-to-moderate efficacy in treating negative symptoms.^{5–8} Although all antipsychotics exert their effect by their actions at receptors of the dopamine or serotonin pathway, different drugs have been developed and classified into typical (first-generation) antipsychotics (FGA) and atypical (second-generation) antipsychotics (SGA).^{1,7,9} The main differences between FGA and SGA are their target receptors and side effect profile.^{9,10} FGA antipsychotics act predominantly via antagonism of D₂ receptors. Both their antipsychotic efficacy and extrapyramidal side effects are thought to be mediated through this mechanism of action.^{9,10} SGAs were developed to improve tolerability and enhance their effectiveness in treating negative symptoms of schizophrenia.¹⁰ SGA also act as

D₂ receptor antagonists, although their clinical efficacy in positive and negative symptoms and the lower frequency of extrapyramidal side effects are attributable to their 5-HT_{2A} receptor antagonism.¹⁰ SGAs not only have an affinity for these two receptors but also on other serotonin and dopamine receptors, as well as histaminergic, cholinergic, and adrenergic receptors.^{7,10,11}

Clozapine was the first atypical antipsychotic developed to treat schizophrenia with the promise of better tolerability, given the absence of extrapyramidal side effects that afflicted patients under treatment with typical antipsychotics.^{12,13} This gave people with treatment-refractory schizophrenia a new alternative for a better quality of life.¹² Pharmacodynamic studies indicate that clozapine has a high binding affinity for D₄, M₁-M₅, α_1 , H₁, H₃, 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, 5-HT₆, and 5-HT₇ receptors. In contrast, clozapine has a relatively low affinity for GABA, sigma, α_2 and β -adrenoreceptors, NMDA, D₂, D₃, and neuropeptide receptors.¹⁴ Even though clozapine produces minimal to no extrapyramidal symptoms (EPS), its main handicap is the high incidence of metabolic alterations, weight gain, sedation, and sialorrhea. Besides, the risk of developing clozapine-induced agranulocytosis has warranted the use of routine blood tests, which has limited its widespread use.¹²

Cariprazine, one of the most recently developed antipsychotics, was approved by the Food and Drug Administration (FDA) in the United States (US) and by the European Medicines Agency (EMA) in the European Union (EU) for acute exacerbation and maintenance treatment of schizophrenia in adults.¹⁵⁻¹⁷ It has a unique receptor profile characterized by a preferentially D₃ receptor partial agonism.^{15,16,18} Compared to other similar drugs, such as aripiprazole or brexpiprazole, Cariprazine shows a preference for D₃ receptors. Besides its partial agonist activity at D₂/D₃ receptors, cariprazine has a high affinity with partial agonist activity for the 5HT_{1A} receptor, high affinity with antagonist activity for the 5HT_{2B} receptor, and moderate affinity with antagonist activity at 5HT_{2A} and some of the histaminergic, adrenergic, and cholinergic receptors.^{15,16,18}

Given its unique affinity profile for different neurotransmitter receptors, it has also been approved for treating manic, mixed, and depressive episodes associated with Type I Bipolar Disorder¹⁹ in the US and is currently being tested in clinical trials as an adjunctive treatment for major depressive disorder.^{20,21}

The most common adverse events reported by patients include akathisia, insomnia, and headache.^{15,17} Metabolic parameters (weight, blood glucose, cholesterol, and triglyceride levels) with cariprazine were like those of patients taking placebo, and no prolactin elevation or QTc prolongation over 500 ms was observed relative to placebo.^{15,17} The emergence of EPS was noted with high doses of cariprazine. However, they were less frequent than with other SGA, or FGA.^{15,17} Pooled analysis demonstrated that cariprazine was generally safe and well tolerated in patients with schizophrenia, with a dose-response relation observed in the incidence of adverse effects.^{15,17}

Here, we present a case series of three patients diagnosed with schizophrenia selected from a psychiatry outpatient service at the Public Mental Health network in Catalonia, Spain, who were being treated with clozapine and later switched to cariprazine. In each of these cases, clozapine was changed to cariprazine due to poor tolerability, partial response, or both.

Description of the Cases

Case I

A 29-year-old Algerian woman with a history of schizophrenia was referred to our Mental Health Center (MHC) by her primary care physician because of severe behavioral alterations and positive psychotic symptoms consisting of delusions and verbal hallucinations.

She was diagnosed with schizophrenia at age 19 in her home country due to auditory hallucinations, incoherent speech, and bizarre behavior. Haloperidol was prescribed and self-discontinued after several months of poor compliance due to non-specific adverse effects reported by the patient. No further treatments were attempted at that time. Notably, she was never admitted to a psychiatric inpatient unit. Family psychiatric history includes schizophrenia in her father. No personal or family history of substance or alcohol use was reported.

Shortly after arriving in Spain, the patient developed referential and persecutory delusions, secluding herself at home and partly destroying the furniture for fear of being watched or controlled. Subsequently, she required forced inpatient

psychiatric hospitalization, and pharmacological therapy with risperidone was introduced. Due to the early appearance of EPS (muscle stiffness and distal tremor) associated with risperidone, she was switched to olanzapine up to 30mg daily with persistent symptoms of hallucinations, disorganized speech and behavior, apathy, and anhedonia, although no EPS were reported. Owing to the lack of response to olanzapine after a 14-day trial, clozapine was initiated, and the dose was uptitrated to 400 milligrams daily, achieving adequate control of her psychiatric symptoms, although she complained of drowsiness and sialorrhea. Given the improvement, the patient was discharged to the community to stay with her sister.

Approximately eight months after discharge, the patient developed intermittent episodes of mutism, isolated herself in her room, and refused to leave her apartment to attend follow-up appointments with her psychiatrist. Eventually, a year after being discharged, her sister persuaded her to go to the Mental Health Center. Psychopathological exploration revealed she was exhibiting soliloquies, incoherent speech, auditory hallucinations, and mannerisms. Additionally, during the interview, the patient appeared drowsy and slowed down, which she and her sister attributed to clozapine. On collateral information obtained from her sister, she presented bizarre behaviors at home, accompanied by social withdrawal, distrust, hostility, and aggressive outbursts.

After a year of treatment with clozapine, only partial remission of psychotic symptoms was accomplished. Additionally, the patient complained that clozapine caused her to be sedated, cognitively blunted, and apathetic. Adequate adherence was confirmed by plasma clozapine levels, ranging 375–415 ng/mL throughout the year of treatment.

In light of the recent worsening of the symptoms and limiting side effects, alternative treatment approaches were considered, and treatment with cariprazine was proposed. Switching from clozapine to cariprazine was conducted through a five-week cross-titration process. In the first week, cariprazine was started at a dose of 1.5 mg per day without any dose reduction of clozapine. Subsequently, weekly increases of 1.5 mg of cariprazine were made until reaching a dose of 6 mg daily. Simultaneously, starting on week 2, clozapine was reduced at a weekly rate of 100mg until discontinued. During the five weeks of the titration process, the patient did not exhibit worsening psychotic symptoms and experienced improvement in sedation and cognitive blunting. The only side effect reported was a mild self-limited headache during the first week after introducing cariprazine. She denied any EPS.

Four months after having completed the titration process, the patient showed a significant decrease in verbal hallucinations and mannerisms and a reduction in language and thought disorganization. Additionally, her sister described a marked improvement in functionality that could be seen in a greater tendency to relate to her relatives, frequent outdoor activities, and a better ability to collaborate with household chores. The patient also reported feeling less apathetic, and more motivated, and that she had recovered some capacity to enjoy daily activities.

In the follow-up after one year of the introduction of cariprazine, the patient reported adequate adherence to treatment as she continued to be in remission and displayed a stable functional status, which her sister corroborated.

Case 2

A 45-year-old white male diagnosed with paranoid schizophrenia 25 years earlier was referred to our MHC at his request after ten years of irregular follow-up at another specialized facility. No family history of psychiatric disorder, substance, alcohol, or tobacco use was reported.

His psychotic symptoms first appeared at age 20, which required forced psychiatric admission due to an assault on a public street committed by the patient in the context of delusions of persecution and auditory hallucinations of imperative content. Multiple antipsychotic drugs (haloperidol, risperidone, paliperidone, olanzapine, and aripiprazole) were tried without much success in controlling his psychiatric symptoms. Lastly, clozapine at 500 mg per day was prescribed, achieving significant improvement in his symptoms. The patient suffered three other acute psychotic episodes in the following ten years attributed to poor adherence and abandonment of outpatient follow-up. His reluctance to take the medication was due to drowsiness and psychomotor retardation. Despite the side effects, adherence to clozapine for the past week was confirmed by plasma levels of clozapine at 387 ng/mL.

Throughout the first interview at our center, the patient complained of generalized weakness, drowsiness, apathy, anhedonia, and absence of life goals. His family reported poor hygiene, a lack of social relations, and no interest in activities outside the home. On exploration, psychomotor retardation, persisting auditory hallucinations, persecutory

delusions, blunted affect, and disorganized speech were observed. There was a lack of insight and the patient did not consider the treatment necessary, although eventually he was persuaded to take the medication, and he had been taking it regularly over the last year.

Due to the persistence of psychotic symptoms, side effects, and attending to the patient's request, it was decided to discontinue clozapine. Given its good tolerability profile and previously unsuccessful trials with other typical and atypical antipsychotics, treatment with cariprazine was offered and accepted by him.

The cross-titration process lasted six weeks and was started by progressively increasing the dose of cariprazine and simultaneously reducing the amount of clozapine. During the first week, cariprazine 1.5 mg per day was prescribed without modifying the dose of clozapine. The dose was increased to 3 mg per day during the second week, and clozapine was decreased to 400 mg per day. Cariprazine dose was increased at a weekly rate of 1.5 mg until 6mg per day was reached, and clozapine was tapered-off by 100 mg each week until it was discontinued. A progressive decrease in drowsiness and psychomotor retardation was observed. In parallel, there was no worsening of the psychotic symptoms, and a gradual reduction of hallucinations, delusional ideas, and improvement in content and quality of the speech throughout the following six months were observed. The patient also reported feeling less apathetic and having recovered some capacity to enjoy daily activities.

One year follow-up after initiating cariprazine, the family and the patient reported improved hygiene, emotional expression, ability to relate to other people, and a greater initiative to perform activities outside his home. Additionally, minimal sedation and adequate adherence to the treatment were confirmed by his family. No further admissions to inpatient psychiatric wards during the follow-up period were required.

Case 3

A 25-year-old white male was referred to our MHC by his primary care physician due to psychotic symptoms consisting of auditory and somatic hallucinations, soliloquies, incoherent speech, hostility, and delusions. Previously, he had received treatment at another mental health center but did not continue to attend his appointments for the last year.

His mother had a history of major depressive disorder and was in remission. The patient reported tobacco, cannabis, and cocaine use since 16 years of age. He denied alcohol use. Although substance use had been persistent throughout the years, he reported short intermittent periods of temporal discontinuation. Nevertheless, the use of cannabis and cocaine has increased and remained constant for the last year.

At the age of 16, the patient presented a psychotic episode consisting of persecutory delusions and auditory hallucinations attributed to cocaine use, for which a substance-induced psychotic disorder was diagnosed. On that occasion, treatment with risperidone was implemented and well tolerated, achieving a complete remission of the psychotic symptoms. After several months of taking risperidone, the patient stopped going to the psychiatrist and abandoned the treatment because he did not consider it necessary. At age 22, he developed another acute psychotic episode consisting of somatic hallucinations, bizarre behavior, incoherent speech, mannerisms, self-abandonment, anhedonia, social withdrawal, and self-isolation at home. No drug use was reported at that time, and forced inpatient hospitalization was required. In the ward, treatment with oral paliperidone was started up to a dose of 12 mg per day, with some improvement regarding the hallucinations, delusions, and mannerisms. However, self-abandonment, anhedonia, social withdrawal, and the tendency to isolate himself remained. Given the persistence of these symptoms, it was decided to augment treatment with clozapine until a dose of 400 mg per day was reached, which achieved a partial improvement in self-care and a reduction in anhedonia, social withdrawal, and isolation. During this hospitalization, a diagnosis of schizophrenia was made, and paliperidone and clozapine were prescribed upon discharge. Unfortunately, after discharge, the patient resumed substance use, and his family reported poor adherence due to lack of insight (patient persistently denied having a psychiatric disorder), reluctance to take medication because of side effects (drowsiness, sexual dysfunction, slurred speech, and drooling), and continued use of cocaine and cannabis. Lack of adherence was confirmed on routine blood tests, showing subtherapeutic plasma levels of clozapine. A decision was made to switch from oral paliperidone to 150 mg of long-acting intramuscular paliperidone administered every 28 days at his primary care center. Although the monthly administration of injectable paliperidone could be guaranteed, the patient continued to refuse to

take clozapine due to reported side effects of sexual dysfunction, slurred speech, excessive salivation, and drowsiness. Thus, the patient stopped attending his psychiatrist appointments and only took the clozapine irregularly.

Probably due to poor adherence to clozapine treatment, the patient developed psychotic symptoms again, for which he was referred to our center by his family physician. Plasma levels of clozapine were taken at his primary care center one month prior to consulting at our MHC and were in the range of 75 ng/mL.

Upon evaluation at our MHC, the patient presented a hostile attitude, auditory and cenestopathic hallucinations, soliloquies, delusional ideas of persecution and reference, significant psychomotor retardation, and affective blunting. Similarly, distal tremors and muscle rigidity in the upper extremities were observed. He stated that the onset of these last symptoms coincided with the initiation of IM paliperidone. Still, since he stopped attending outpatient follow-ups, he did not report these side effects to his psychiatrist.

In light of persistent psychotic symptoms and reported side effects of IM paliperidone, he was offered to stop paliperidone injections and resume clozapine monotherapy. Still, he refused due to fear of previously reported side effects when taking clozapine. Considering this, cariprazine was suggested, and after reviewing the benefits and side effects, the patient agreed to start the medication. No tapering of clozapine was needed because the patient had not been taking it for the last month. Cariprazine was started at a dose of 1,5 mg per day, and after two days, the dose was raised to 3 mg per day. The patient showed good tolerability to the medication, and the dose was increased by 1.5 mg every two days until 6 mg per day was reached after one week. The patient did not report any side effects, and the medication was kept at this dose. After two weeks of receiving cariprazine 6mg daily, a marked reduction of the hallucinations (both auditory and cenestopathic), delusions, and speech disturbances was observed. Additionally, five weeks after the last administration of paliperidone, the patient stated that the stiffness, drowsiness, tremor, and psychomotor retardation significantly improved and were no longer present.

Clinical improvement has been maintained up to fourteen months follow-up, and his family has confirmed adequate adherence. In addition, the patient has begun to study and has significantly increased his daily outdoor activities.

Interestingly, on follow-up, the patient expressed he was no longer using cocaine, which he attributed to cariprazine, given that his urge to use cocaine had markedly decreased since he started taking the medication. He has reported that he has continued to use cannabis occasionally, although less frequently and in smaller amounts than before.

Discussion

Here, we present a case series of three patients with significant positive (delusions, disorganized speech and behavior, and auditory hallucinations) and negative (apathy, social withdrawal, avolition, blunted affect) symptoms that were successfully treated with cariprazine after other antipsychotics, including clozapine, failed to show a clinically meaningful and sustained response. All three patients reported at least one adverse effect (EPS in the patient under treatment with paliperidone; sedation and psychomotor retardation in all cases related to clozapine treatment) to their previous treatments before starting cariprazine. In all three cases, it was decided to discontinue or avoid resuming clozapine because, at the prescribed doses, the improvement was partial and unsatisfactory; the patients complained of limiting and intolerable side effects; or were refusing to take the medication. A good alternative would have been to increase the dose of clozapine or to augment treatment with another antipsychotic. Still, these two options were ruled out because the patients reported limiting side effects at the doses of clozapine they were taking. Given the above, it was decided that the best course of action would be to discontinue clozapine and prescribe a different antipsychotic. In this sense, and with the simultaneous objective of reducing adverse effects and seeking clinical improvement, it was decided to introduce an antipsychotic with a better tolerability profile and proven antipsychotic efficacy, as is the case for cariprazine.¹⁵⁻¹⁷

Switching clozapine to cariprazine was achieved through a cross-titration process that lasted five weeks in the first case and six weeks in the second case. In the third case, no tapering was needed since the patient had stopped taking clozapine on his own account weeks before starting cariprazine. In all three cases, treatment switching was carried out on an outpatient basis in a mental health day center. Careful titration is recommended when switching from clozapine^{22,23} due to the risk of cholinergic rebound or worsening psychotic symptoms, as exemplified in the third case. There are two titration strategies for initiating treatment with cariprazine: one slow and one fast.²³⁻²⁵ The slow method consists of weekly increases of 1.5 mg, while the fast method consists of daily or every second-day increases of 1.5 mg until

reaching a dose that is effective and produces minimal adverse effects. The maximum recommended dose for schizophrenia is 6 mg per day.^{24,25} Above this dose, the benefits are minimal, and the risk of adverse effects increases significantly.^{23,24,26} In the first two cases, the slow method was used, while in the third case, the fast method was implemented, although increases were made every other day and not every day. In all cases, the implementation of the treatment was well tolerated.

After having completed the titration process, a reduction of auditory hallucinations, delusions, disorganized behavior, and speech disturbances was observed during follow-up appointments. We similarly noted a significant improvement in negative symptoms as evidenced by an increase in daily activity, sociability, a wider range of emotional experiences, and a decrease in the levels of anhedonia, apathy, and avolition. Importantly, complete resolution of side effects from clozapine or paliperidone was achieved after discontinuation. No significant adverse effects were reported with cariprazine, except for a mild self-limited headache in the first case. Additionally, none of the patients had worsening psychotic symptoms during the titration period.

An essential aspect in the treatment of schizophrenia is adequate adherence, which is partially modulated by the perceived efficacy and tolerability of the medication. The patients' understanding of their illness, or insight, is another important variable to ensure adequate compliance and should be a primary focus in treating patients with schizophrenia.²⁷ In our series, cariprazine has shown to be an effective and well-tolerated treatment for schizophrenia, and good compliance was observed in all three cases up to 14-month follow-up. Likewise, cariprazine may be a good pharmacological alternative in patients who fail to take the medication on a daily basis since the half-life of one of its active metabolites (di-desmethyl-cariprazine) is longer than a week after reaching steady-state plasma drug levels, although this might take up to three weeks.^{15,16,19}

Other case reports have been published where clozapine had been successfully augmented with cariprazine in patients who only partially responded to clozapine monotherapy.^{28–31} Still, to this date, few cases have been published in which clozapine was effectively switched to cariprazine due to an unsatisfactory clinical response or development of adverse effects.²⁸ Furthermore, in contrast to available evidence supporting the use of cariprazine as first-line treatment for patients with first-episode psychosis,³² in schizophrenia patients with predominantly negative symptoms,³³ or in patients with acute exacerbations,³⁴ our series suggests that cariprazine can be a good treatment option for patients suffering from both positive and negative symptoms of schizophrenia for many years and who have insufficiently responded to previous antipsychotic treatments. In addition, one of the main advantages of our series is that it provides clinical observations on the need to change antipsychotic treatment in the not rare cases of clozapine-resistant schizophrenia.

An exciting finding observed in the third case that presented comorbidity of schizophrenia with substance use disorder (cocaine and cannabis) was the reduction in the frequency, quantity, and craving of cocaine use, to the point that the patient discontinued its use. In the same case, cannabis use was markedly reduced, although he kept using it fourteen months after starting cariprazine. Even though changes in the craving and use of cocaine were not objectively assessed in this patient, some published case reports support the hypothesis that the pharmacological profile of cariprazine could be beneficial in patients with psychosis and Substance Use Disorder (SUD).^{35–40} As previously described, cariprazine is a dopamine D3- preferring D3/D2 receptor partial agonist. While other atypical antipsychotics may have significant activity at the D3 receptor (D3R), its high potency as an antagonist/partial agonist at the D3R highlights its unique pharmacological profile among other antipsychotics.^{18,39} In addition to its clinical implications, the D3R is known to mediate reward-related behaviors.⁴¹ Preclinical evidence from several animal models of addiction supports the D3R as a viable target for SUD treatment development and predicts that D3R selective antagonists and partial agonists may be effective in addiction treatment by regulating the motivation to self-administer drugs and disrupting drug-associated cue-induced craving.^{42,43} Furthermore, a randomized clinical trial assessing the effects of cariprazine on the brain and behavior in patients with Cocaine Use Disorder has recently been completed, although results are yet to be published.⁴⁴ Despite the above, we want to clarify that this is an incidental finding in one of the three cases we have described from which no conclusions can be drawn for clinical practice, so it would be advisable to conduct randomized controlled studies to assess the efficacy of cariprazine in this population.

Our series has some limitations. The generalization of our conclusions to a broader population might be limited given the case-report nature of our series. The fact that no evaluation measures to assess symptomatology, adverse events, or

compliance were administered limits our capacity to accurately evaluate the efficacy and side effects of cariprazine in the long term. Besides, an observation period of one year, as in our cases, is not sufficient to assess the efficacy of cariprazine in preventing relapses, hospitalizations, and worsening negative and cognitive symptoms. Therefore, in future publications it is important to include cases with longer follow-up periods in order to adequately assess the efficacy of cariprazine in these settings. Moreover, some relevant clinical data might have been missed because the patients were previously treated in other countries or health centers, making it difficult to gather some historical information that could have been valuable in understanding their previous clinical trajectory.

Conclusion

Our case series supports the evidence that cariprazine can be an effective and well-tolerated antipsychotic treatment for both positive and negative symptoms of schizophrenia in patients who failed to adequately respond to or poorly tolerated treatment with clozapine. Cariprazine might also be a broad-spectrum treatment in dual disorders, specifically psychotic disorders and concomitant cocaine use disorder, although more robust empirical and clinical data are required. Finally, treatment adherence appears to improve with cariprazine due to its efficacy and good tolerability.

Consent for Publication

Written informed consent were signed and obtained from all patients prior to writing and submission for publication. Institutional approval was not required for publication. Sociodemographic and clinical data have been de-identified to protect patients' privacy.

Disclosure

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