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ORIGINAL RESEARCH

Using Cariprazine to Ameliorate Negative Symptoms and Metabolic Side Effects of Clozapine and Paliperidone – Clinical Cases

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Introduction: Cariprazine is a third-generation antipsychotic approved in Europe in 2017 for the treatment of schizophrenia. It presents distinct pharmacodynamic properties, such as D3/D2 partial agonism, preferential binding to D3 receptors, antagonism at the serotonin 5-HT2A and 5-HT2B receptors, partial agonism at 5-HT1A receptors, and low affinity to other receptors (including noradrenergic, histaminergic, and cholinergic). It has demonstrated efficacy in the treatment of positive and negative symptoms of schizophrenia with a safe side effect and metabolic profile.

Methods: Here, we describe one clinical case of a patient that benefited from an add-on of cariprazine to a regimen of clozapine; and two clinical cases of patients that benefited from the switch from clozapine and paliperidone long-acting injectable to cariprazine.

Results and Discussion: Those cases illustrate how cariprazine can be used in patients with schizophrenia in the treatment of both positive and negative symptoms, and when aiming to ameliorate the metabolic burden associated with other treatments. However, further studies are needed to consubstantiate those findings.

Keywords: cariprazine, clozapine, paliperidone, schizophrenia, negative symptoms

Introduction

Schizophrenia is a chronic and disabling disease, affecting mental and social functions.[1,2] Typically, the symptoms can be classified in the following domains: positive symptoms (such as delusions and hallucinations), negative symptoms (alogia, anhedonia, asociality, avolition, and blunted affect), and cognitive symptoms (such as impaired learning, thinking, memorizing, among others).[1,3] Patients with schizophrenia vary broadly with regard to the symptoms and these may change with time, with different symptoms becoming the predominant symptoms at different times.[4]

Antipsychotics are a central part of schizophrenia management, although complete remission or recovery of symptoms is relatively rare and some patients have a resistant disease (treatment-refractory schizophrenia is defined as failure of two attempts of adequate antipsychotic medical treatment).[1–3] Despite the greater efficacy of clozapine over other antipsychotics in the management of resistant schizophrenia, this drug has a high propensity for weight gain and general metabolic dysregulation, and a noteworthy number of patients still do not attain an adequate response.[2,5]

Cariprazine is a third-generation antipsychotic approved in Europe in 2017 for the treatment of schizophrenia, with D3/D2 partial agonist properties and preferential binding to D3 receptors, and has the potential to be of additional value, because of its exceptional receptor profile and tolerability.[1,2,6] In addition to partial agonist activity at D3 and D2 receptors, it is also an antagonist at the serotonin 5-HT2A and 5-HT2B receptors, a partial agonist at 5-HT1A receptors, and has a low affinity at other receptors, including noradrenergic, histaminergic, and cholinergic receptors.[1]

Studies suggest that cariprazine may be of particular interest regarding the treatment of negative symptoms, and some reports additionally suggest its usefulness in treatment-refractory schizophrenia. It is also a useful alternative to patients with serious metabolic side effects from antipsychotic medication.[1,2,6]

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Here, we report a case of a patient with clozapine-resistant schizophrenia who responded to cariprazine combination, a case of a clozapine-resistant schizophrenia who responded to cariprazine monotherapy, and a case of a patient with serious metabolic side effects related to paliperidone long acting injectable (LAI) that benefited from a switch to cariprazine. Written informed consent for publication of patients' details was obtained.

Case Description

Case 1

He is a 29-year-old, unemployed and unmarried man, with a long history of schizophrenia. At the age of 22, he was admitted to a psychiatric ward with a one-year history of persecutory delusional ideas, running commentary hallucinations, and behavioral changes with marked agitation. At the psychiatry ward, risperidone was tried for up to 8 mg/day, but clinical remission was not seen, so a switch to olanzapine was made. He was discharged with olanzapine 30 mg daily and flurazepam 30 mg but maintained hallucinations, abulia, hypersomnia and psychomotor retardation with significant compromise in functionality. He did not adhere to the proposed socio-occupational projects, preserving hallucinatory activity and negative symptoms. In ambulatory, a switch was made from olanzapine to clozapine, which was titrated up to 500 mg per day over a year. He maintained hallucinations in the form of derogatory comments, as well as negative symptoms (alogia, anhedonia, and asociality) and depressed mood. Concomitantly, he started amisulpride 50 mg/day. Due to lack of clinical improvement, clozapine continued to be titrated up to 800 mg/day, with blood counts showing no alterations, and amisulpride was discontinued. Clozapine dosing was requested, but the patient did not accept doing it. However, family members confirm therapeutic compliance, since they supervise the medication.

Because he maintained hallucinatory activity and negative symptoms, with high impact on functionality, cariprazine 1.5 mg/day was added for 3 days and then increased up to 3 mg/day without adverse effects. After 30 days of cariprazine in combination with clozapine, we observed an improvement in his psychomotor drive and mood. After three months, he was more communicative and sociable (referring he had meeting friends from the past and joined them in recreational activities) and hallucinations were gone. His family members also noted a major improvement in the negative symptoms, and alertness. He was more helpful at chores in his house. After six months, the clinical improvement is still observed (subjectively and objectively) and the patient will start an occupation project in a rehabilitation structure.

Case 2

He is a 21-year-old college student who develops polythematic delusional ideas (persecutory and messianic), with marked social isolation, aggression toward family members, and academic withdrawal. During psychiatric admission, risperidone was tried on a slow titration of up to 3 mg/day but had to be discontinued due to marked extrapyramidal symptoms. In this sequence, olanzapine was tried and titrated up to 10 mg/day, but he again developed severe extrapyramidal symptoms (marked tremor and rigidity with acute dystonia), maintaining delusional ideas. Later on, a switch was made to clozapine, slowly titrated up to 200 mg/day, with apparent remission of the positive symptoms and no evidence of extrapyramidal symptoms.

After discharge, the patient complained of considerable weight gain (20 kg in two months; body mass index [BMI] of 29.3 kg/m2), maintaining social isolation, amotivation, abulia, and anhedonia. Although more distant from the ideas that motivated his hospitalization, he still had the conviction he had a special mission, spending most of his time in his bedroom. Thus, cariprazine was considered and started at a dose of 1.5 mg/day, increasing up to 3 mg/day one week later, and then (also one week later) to 4.5 mg daily. Simultaneously, clozapine was discontinued over three weeks because of his weight and cardiovascular risk.

After one month with cariprazine 4.5 mg/day, the patient still presented no extrapyramidal symptoms and was more alert in consultation. In the second month, he began to objectify progressive weight loss, denied the delusional ideas (although with no insight into them), was more communicative and had plans to resume training in his area of interest. Family members corroborated the improvement, stating that the patient was more participative at home and was willing to spend time with former colleagues. After 8 months of monotherapy with cariprazine 4.5 mg/day, the patient remained

compensated, with no evidence of recrudescence of positive symptoms, a normalized BMI of 24.7 kg/m2 and attending vocational training with hedonic feedback and good performance.

Case 3

He was a 32-year-old patient, with the first psychotic episode at the age of 25, characterized by delusional persecutory ideas and auditory-verbal hallucinations, which led to his first admission in 2014. There was a clinical improvement under risperidone LAI 37.5 mg fortnightly. The patient abandoned therapy after 12 months, leading to relapse of symptoms with a new admission in 2016. He was discharged under paliperidone 150 mg IM monthly. During follow-up, due to side effects (hyperprolactinemia with altered sexual function, weight gain and changes in liver function tests) and negative symptomatology, a reduction in paliperidone to 75 mg monthly and an add-on with aripiprazole 7.5 mg oral were tried. In early 2020, partly motivated by the COVID-19 pandemic, his medication was changed to paliperidone 263 mg IM quarterly.

Around June 2020, faced with a marked worsening of metabolic parameters – obesity (BMI of 43.7 kg/m2), dyslipidemia and diabetes – and pronounced negative symptoms (affective flattening, anhedonia, asociality, and avolition), it was decided to switch from paliperidone to cariprazine. In the beginning, the patient had regular appointments with the nurse in the community outpatient team to help him during the transition, to promote a therapeutic alliance with the patient and family and to monitor his clinical state. In early September, he took 75 mg injectable paliperidone and started cariprazine up to 3 mg daily. He received the last administration of paliperidone (50 mg) in October. At the same time, cariprazine was titrated according to clinical response, increasing to 4.5 mg in October and 6 mg in late November, with good tolerability and no reported side effects.

In August 2021 (9 months after stopping the long-acting injectable), the patient had no psychotic symptoms (such as delusions or hallucinations) and showed some improvement in negative symptoms: he reported more pleasure in tasks, having restarted activities he enjoyed such as drawing; greater socialization, having resumed contact with friends; and some investment in physical activity. His BMI at that time was 38 kg/m2 - although it is important to mention that he started metformin in Dec/2020 and liraglutide in June/2021, whose effect cannot be despised. Furthermore, there was resolution of the sexual dysfunction.

Discussion

In case number 1, there is a situation of a treatment-resistant schizophrenia under a high clozapine dosage, where positive symptoms persisted, and functionality was seriously affected. In case number 2, the patient did not tolerate risperidone and olanzapine, and developed marked extrapyramidal effects with this medication. Under clozapine, the patient maintained residual delusional ideas and presented marked weight gain.

At the time when it was decided to add cariprazine to our patients' treatment, they had previously been treated with a range of antipsychotic drugs. None of them had led to complete symptom relief, and the suffering of negative and cognitive symptoms persisted. Cariprazine has demonstrated wide-spectrum efficacy in the treatment of positive and negative symptoms of schizophrenia (the improvements in negative symptoms being unlikely to result from improved positive symptoms).[1,3,4] The D3 receptors, where cariprazine has a high affinity, are auto-receptors that modulate the phasic dopaminergic activity linked to cognition, mood, emotions and reward, so cariprazine is considered by some authors as a pro-cognitive agent, effective in the management of negative symptoms of schizophrenia.[2,4,7] Cariprazine also demonstrates, to a lesser extent, partial agonism at the 5HT1A receptors, exerting also an antidepressant effect. This, combined with clozapine effects and cariprazine effects in D3 receptors, may explain the positive impact of the cariprazine–clozapine combination in case number.[1,4,7] As described above, both patients improved their negative symptoms after the introduction of cariprazine. According to some authors, patients receiving cariprazine have a greater improvement in functioning, suggesting that improvement in negative symptoms translates to improved community functioning.[1] In both cases, positive symptoms also yielded with cariprazine. As shown in clinical trials, cariprazine efficaciously reduces psychotic symptoms and is effective for the maintenance treatment of schizophrenia by delaying time to relapse when compared with placebo.[4,7]

In case 3, besides problems related to negative symptoms, there were some serious metabolic effects that could impair the patient health and functionality. Cariprazine shows a safe side effect and metabolic profile, being a reasonable choice in those with the first episode of psychosis, and significant side effects (metabolic side effects, sedation) with other antipsychotics.[2,4,7,8] D3 receptors are highly concentrated in the ventral striatum, so its antagonists may have an antipsychotic action with negligible adverse effects including extrapyramidal side effects, in contrast to other dopamine receptors.[2,7] In cases number 2 and 3, we observed a positive effect on BMI with cariprazine monotherapy and switch from paliperidone, respectively. This effect may be explained by cariprazine pro-cognitive action (the patient started to be more active), by the decrease in negative symptoms through the action on D3 receptors and because of clozapine/paliperidone suspension.

When the long-term treatment of a chronic illness is weighted, cariprazine might become one of the first-line medications, not only for patients with predominant negative symptoms but also for those with refractory positive symptoms and vulnerability to side effects of other antipsychotics.[8] Cariprazine may be prescribed as an add-on to other antipsychotics, such as clozapine, when that medication is ineffective (such as in case number 1), and in some cases, a switch to cariprazine may be considered, after a period of stability, leaving the patient on a metabolically friendly antipsychotic regimen, such as cases number 2 and 3.[8]

Conclusion

In summary, cariprazine add-on to clozapine showed notable efficacy in the treatment of patients with inadequate response to clozapine and predominant negative symptoms and this combination did not cause adverse effects. However, future studies on larger samples are needed. To our knowledge, no randomized controlled trials studying the combination of cariprazine and clozapine have been conducted to date and the results from metaanalyses of antipsychotic combinations indicate that data are scarce. Although it is not possible to generalize the observations and findings of the first two cases, they have the novelty of detecting a potential effect of cariprazine in treatment-resistant schizophrenia under clozapine with predominant negative symptoms.

Concerning the third clinical case, switching from LAI to oral cariprazine could be a challenge, especially because of adherence issues, but with a concomitant multidisciplinary team-based psychoeducation and if the patient finds benefit in the medication, it could be worth considering in selected cases.

We are aware of the limited evidence of case studies; however, the results seen with these patients are promising.

Consent for Publication

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for publication of their details was obtained from the patients.

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Disclosure

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