Case Report
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Cariprazine — an Alternative Treatment for Clozapine-resistant Schizophrenia?

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Treatment-resistant schizophrenia (TRS) poses a significant therapeutic challenge in psychiatric practice. Clozapine is recognized as a treatment of choice in TRS but is not always effective in alleviating patients' symptoms. Additionally, clozapine therapy is associated with multiple side effects and monitoring requirements that often limit its use and negatively affect patients' compliance with the treatment. Although clozapine augmentation options are available, there is currently no alternative monotherapy proven to be effective in TRS. We present a case of a young man with TRS who failed to respond to appropriate trials of risperidone, aripiprazole and also clozapine, and who experienced impairing adverse effects of clozapine that made further clozapine treatment not only futile but also detrimental to his health. He was successfully treated with cariprazine monotherapy, which culminated in the remission of his both positive and negative symptoms of psychosis as well as in the marked improvement in social functioning. Cariprazine, a newer atypical antipsychotic endowed with a D3-preferring mode of action, may offer a better tolerated and more acceptable treatment option for patients with difficult-to-treat psychotic symptoms.

KEY WORDS: Antipsychotics; Cariprazine; Clozapine; Schizophrenia; Treatment-resistant schizophrenia; Psychotic disorders.

INTRODUCTION

Treatment-resistant schizophrenia (TRS) is defined as persistence of psychotic symptoms and functional impairment in patients with a diagnosis of schizophrenia despite two adequate trials of different antipsychotics with appropriate adherence monitoring [1]. TRS affects up to 33% of patients [1] and outcomes of pharmacological treatment are less favorable in those with predominantly negative symptoms [2]. The antipsychotic of choice for TRS is clozapine [3]. However, only up to 40% of patients with TRS may respond to clozapine, whereby 12−20% of patients may be ultra-resistant [1]. Barriers to successful clozapine use include intolerability to its side-effects, poor adherence to treatment and the burden of the monitoring regimen, as well as clinician and health system-related factors [4,5]. Pharmacotherapy options for ultra-resistant patients are limited and mostly based on augmentation of clozapine with other medication.

Cariprazine is a novel atypical antipsychotic, the pharmacological profile of which is similar to that of brexpiprazole and aripiprazole, and which acts as a dopamine D2/D3 receptor partial agonist, with a high affinity for D3 receptors [6,7]. Its safety and efficacy in treating patients with schizophrenia has been well documented [8-11], and in a head-to-head comparison with risperidone, cariprazine has been shown to be more effective in reduction of negative symptoms of schizophrenia, improvement in executive functioning and cognitive ability [7,12,13]. Cariprazine has also been used to augment clozapine treatment in TRS [12,14]. However, the benefits of cariprazine monotherapy in TRS remain unclear.

We describe a young adult man who was compulsorily admitted to our acute in-patient unit for treatment of schizophrenia with predominantly negative symptoms, who failed to respond to adequate trials of aripiprazole and risperidone, and who subsequently also failed to respond to clozapine. He responded successfully to car-

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iprazine treatment after his clozapine was discontinued.

The patient provided full informed consent for the use of this anonymised case for publication.

CASE

A 25-year-old Black British male was compulsory admitted to our unit with features of first-episode psychosis. He held a complex delusional belief system involving the British royal family, associated with plans to acquire firearms to seek revenge on a stranger who allegedly stole his bicycle. Upon admission, he presented with a range of positive and negative symptoms of schizophrenia, including paranoid delusions, ideas of reference, conceptual disorganisation and generalised suspiciousness. These were accompanied by severe perplexity, blunted affect and social withdrawal, as well as avolition and alogia.

Eleven days prior to admission, his community mental health team had begun prescribing risperidone 2 mg daily orally, but this had proved ineffective. In hospital, his dose of risperidone was increased to 4 mg and then 6 mg daily on day 11 of admission, but he failed to respond after complying with treatment for 21 days. On day 22, his risperidone was discontinued and he was commenced on aripiprazole 10 mg daily orally, the dose of which was increased to 20 mg daily on day 25 of his admission. In the absence of any symptom amelioration after a 30-day trial, his aripiprazole was discontinued. On day 51, he was started on clozapine treatment. By day 65, his dose had been increased to 150 mg twice daily, at which point his point of care clozapine blood test demonstrated a level of 265 ng/ml (range 300−500 ng/ml). The dose was gradually increased up to 200 mg twice daily by day 70.

During clozapine treatment, his negative symptoms worsened further. He presented with progressive social withdrawal and marked passivity and flatness of affect, while his positive symptoms remained as florid as before. Moreover, he did not tolerate clozapine titration well. Previously an athletic man, he gained 5.3 kg after 26 days on clozapine and also developed hypertension (mean systolic blood pressure before clozapine: 135 mmHg, on clozapine: 147 mmHg) and tachycardia (mean heart rate before clozapine 80 beats/min, on clozapine: 110 beats/min). His lipid profile deteriorated (total cholesterol/HDL ratio increased from 3.3 to 4.0) and he started to experience hypersalivation. His clozapine treatment was terminated.

On day 76, he was commenced on daily doses of cariprazine 1.5 mg orally, which was increased to 3 mg daily after one week. After a few days on this dose, his affect gradually became more responsive, he became more spontaneous in conversation and started to engage socially with the clinical team, and also to participate in therapeutic activities, including sports. After 14 days on cariprazine 3 mg daily, he was noted to interact actively with other patients and to safely and constructively utilise his leaves off the ward. Although his insight into his clinical circumstances remained limited, his speech had become coherent and spontaneous, and he seemed far less preoccupied with his delusional beliefs.

We used the Scale for Assessment of Negative Symptoms to monitor his progress. The patient's initial score was 85 out of 120 (reduced overall score, as one category could not be assessed), indicating severe illness [15]. After 50 days on cariprazine, his score reduced to 30 (Table 1), indicating mild/borderline negative symptoms. Significant improvement of his psychotic symptoms and level of functioning was confirmed by his nearest relative, who felt he had recovered to his pre-illness level of functioning. He

Table 1. SANS score changes following cariprazine treatment in a patient with treatment-resistant schizophrenia

SANS sections	Maximal score	Score on the day of cariprazine initiation	Score after 50 days of treatment with cariprazine	Change (%)
Affective flattening or blunting	40	31	14	−54.8
Alogia	25	12	2	−83.3
Avolition/apathy	20	12	4	−66.7
Anhedonia/asociality	20[a]	17	7	−58.8
Attention	15	13	3	−76.9
Total	120	85	30	−64.7

SANS, Scale for Assessment of Negative Symptoms.

[a]Anhedonia/asociality score in the original SANS is 25, however, the patient's sexual activity could not be assessed due to the artificial environment of the ward and his initially poor engagement in personal conversations; we have therefore, reduced the maximum score in this section.

was discharged from hospital on cariprazine 3 mg daily to supported accommodation under the care of community services. He subsequently managed to find employment and joined a fitness centre. Over one year after his discharge from hospital, he remains clinically well, compliant with his antipsychotic medication and fully engaged with community services.

DISCUSSION

Clozapine, the gold standard for the pharmacological treatment of TRS patients [3], can be highly effective for some, but treatment options for patients who do not respond or cannot tolerate clozapine are few [16], and their prospect of remaining partially or totally untreated is real. Cariprazine, a novel treatment option for schizophrenia [17,18], is the only currently licensed antipsychotic to demonstrate increased effectiveness in treating negative symptoms as compared to other drugs of its class [13]. It has also been described as a potential adjunct to clozapine, particularly in patients whose negative symptoms persist while on clozapine monotherapy [12,14,19]. Reports on cariprazine monotherapy in TRS are scarce [20,21].

Clozapine is a potent antagonist of serotonin 5-HT 2A/2C and D4 receptors and weak antagonist of D2 receptors [22]. It is also a potent muscarinic receptor antagonist. Clozapine is associated with a wide range of adverse effects, including agranulocytosis, increased risk of seizures and gastrointestinal side effects, as well as the severest metabolic adverse effects amongst commonly used antipsychotics. Clozapine's side-effect profile, one of the main reasons for ceasing clozapine treatment in our patient, is the most common cause of treatment discontinuation, accounting for nearly half of therapy dropouts [23]. Clozapine treatment requires close blood monitoring, refusal of which contributes to poor compliance with medication [4].

Unlike clozapine, cariprazine acts as a partial agonist at dopamine D2/D3 receptors, with high affinity for D3 receptors, particularly at low to intermediate doses of 1－3 mg/day [7]. Partial agonism at D3 receptors in high dopaminergic areas of a brain can dampen dopamine neuronal firing, in theory reducing the clinical effects of psychosis in a dose-dependent relationship [6]. Cariprazine's preference for dopamine D3 receptors may contribute to a reduced propensity for inducing extra-pyramidal side effects [24], in addition to improvements in mood, cognition, executive function and negative symptoms [12]. Moreover, cariprazine acts as a partial agonist at serotonin 5-HT1A receptors, the effect of which may increase dopamine release in the mesocortical pathway, accounting for additional antidepressant effects and improvement of negative symptoms [7], while mild antagonism at the serotonin 5-HT2A, 5-HT2C, and 5-HT7 receptors can in theory also account for anti-depressant effects [6,7].

In contrast to clozapine, cariprazine treatment has little or no effect on metabolic parameters [7] and has been associated with a reduction in low density lipoprotein cholesterol [5]. Moreover, it seems to be better tolerated, requires only standard antipsychotics blood monitoring and, like in this case, may be an option for patients who cannot tolerate regular blood sampling. Finally, one of cariprazine's active metabolites, didesmethyl-cariprazine, has a half-life of 2－3 weeks (compared to 2－3 days for clozapine), thus potentially allowing for longer intervals between doses [7], which could be of benefit to individuals with a history of poor adherence to treatment.

This report describes a young patient presenting with debilitating psychotic symptoms who failed to respond to treatment using therapeutic dosages of different atypical antipsychotics he received in hospital, including clozapine, each for an appropriate period of time, and who markedly improved following two weeks of treatment using therapeutic doses of cariprazine. He also tolerated cariprazine treatment well, which facilitated his discharge from hospital and the gradual resumption of his activities in the community, as well as his long-term adherence to treatment, thereby preventing relapse of his symptoms during follow-up.

In the absence of evidence-based treatments for TRS patients who do not respond to clozapine, the possibility that cariprazine may represent a therapeutic option for this highly vulnerable patient group warrants further scrutiny. Further research is required to investigate whether cariprazine's putative mode of action may offer an alternative and more acceptable pharmacological approach to clozapine in the management of TRS.

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■ Conflicts of Interest

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

■ Author Contributions

Conceptualisation: Luiz Dratcu. Data Acquisition: Adam Montgomery, Marianna Rogowska. Writing—original draft: Adam Montgomery, Marianna Rogowska. Writing—review and edit: Luiz Dratcu, Adam Montgomery, Marianna Rogowska.

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