Case Report
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Add-on Cariprazine in Patients with Long-term Clozapine Treatment and Treatment Resistant Schizophrenia: Two Cases of Psychotic Deterioration and Pisa Syndrome

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An increasing number of studies deal with medical options for treatment resistant schizophrenia. If no remission can be achieved with clozapine, a combination of antipsychotics can be considered. The combination of clozapine and cariprazine is rarely studied. Cariprazine is a partial agonist on dopamine D_2 and D_3 receptors and a pharmaceutically rational add-on to clozapine. Stimulating D_3 receptors has been linked to improved cognition and mood, with negligible extrapyramidal side effects. We present two patients with long-term treatment resistant schizophrenia receiving cariprazine and clozapine. Whereas psychotic symptoms worsened, the patients developed extrapyramidal side effects with a Pisa syndrome. The syndrome remitted after discontinuation of cariprazine. Possible explanations by pharmacodynamic interactions and drug specific receptor profiles are discussed.

KEY WORDS: Cariprazine; Clozapine; Treatment resistance; Schizophrenia; Pisa syndrome.

INTRODUCTION

Schizophrenia is a severe mental disorder affecting around 1% of the population worldwide [1]. It is characterized by positive, negative and cognitive symptoms leading to significant functional impairment [1]. One third of patients with schizophrenia are affected by treatment resistance characterized by a reduced responsiveness to at least two antipsychotics with permanent psychotic symptoms and cognitive dysfunctions [2,3]. The gold standard is clozapine with a $5HT_{2A}$ and D_2 receptor antagonism [4]. It is the only medication with an indication for treatment resistant schizophrenia (TRS) according to the US Food and Drug Administration [3]. 30–60% of TRS respond to clozapine [1]. In case of non response, a combination of different agents may be considered [3]. As one option, cariprazine is partially agonizing dopamine D_2 and D_3 receptors [5]. While cariprazine acts like an antagonist at higher dopamine levels, it increases the dopamine receptor activity at lower dopamine levels [6,7]. It also is an antagonist at $5HT_{2A\&B}$ receptors and a partial agonist at $5HT_{1A}$ receptors [5].

So far, there are no randomized controlled studies testing the combination of cariprazine and clozapine, but regarding the complementing receptor profiles, a potential combination of both agents seems promising, especially for cases of patients with TRS treated with clozapine [8]. In a case report of Berardis *et al.* [5], a clozapine combination with cariprazine showed a remarkable effect in TRS in two cases. No adverse effects were reported at a combination of 300/400 mg/die clozapine and 3 mg/die cariprazine [5]. In contrast to this, we report on two cases of TRS receiving this combination, who subsequently experienced psychotic deterioration and Pisa syndrome. The Pisa syndrome is an adverse effect of antipsychotic therapy, referring to a tonic flexion of the trunk, laterally or backwards, and slight rotation of the body. Risk factors include female sex, higher age, organic brain alterations or combined pharmacotherapy [9,10].

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in its present form.

CASE

Case 1

A 41-year-old retired, unmarried, non-smoking woman with the first psychotic episode after giving birth to her daughter in 2006 was diagnosed with TRS 6 years later. Since 2014 she received clozapine. She partially remitted receiving clozapine but had recurrent psychotic episodes during treatment. Variation of doses (100 to 375 mg/die) in combination with amisulpride, flupentixol, aripiprazole or sertraline, did not alleviate her symptoms or lead to full remission.

At her recent admission she received a monotherapy with 350 mg/die clozapine (serum level 533 μg/L, reference: 350−600 μg/L; norclozapine 253 μg/L, reference: 100−300 μg/L) still suffering from hyperarousal as well as dysphoria, flattened affect, audible and delusional thoughts fearing to sexually harass her 14-year-old daughter. In her psychiatric history, the patient benefitted from high clozapine through levels (700−850 μg/L). An obsessive-compulsive disorder was excluded. Cranial magnetic resonance imaging (cMRI) was unsuspicious; the electroencephalogram exposed minor abnormalities consistent with clozapine intake.

The weekly clozapine through levels were stable. Due to non-response or side effects with aripiprazole, flupentixol, sertraline and amisulpride, a combination with cariprazine was offered. The initial dose of 1.5 mg/die was titrated after two weeks until 3 mg/die. Since dysphoria and delusional thoughts worsened after 2 weeks, the dosage was further titrated up to 6 mg/die. After 10 days on 6 mg/die, she developed a distinct lateral dystonia of the trunk, fulfilling the criteria of the Pisa syndrome, persisting while standing and sitting. She increasingly suffered from hypomimia, inhibition, restricted thinking and acoustic hallucinations producing delusions of guilt. Cariprazine was discontinued on day 39 according to the patients' preference (Naranjo scale 6) [11]. The last documented clozapine level, which was taken 5 days before Pisa syndrome, was 553 μg/L (norclozapine 271 μg/L). Lorazepame and biperiden reduced the Pisa syndrome and it disappeared three days after discontinuation of cariprazine. Electrocardiogram (ECG) was normal. Finally, an increased monotherapy of clozapine (400 mg/die) and psychotherapy with psychoeducation and skills training yielded a stabilized state at discharge.

Case 2

A 63 year old retired, married, non smoking man with his first episode of schizophrenia in young adulthood and early diagnosed TRS received clozapine since 2013 in varying doses of 100 to 650 mg/die. Previously, clozapine had been combined with haloperidol, aripiprazole, sertraline, valproate, amisulpride and mirtazapine, but a complete remission of symptoms was never achieved. He suffered from catatonia, delusions and pressured and restricted thinking with logorrhea. Electroconvulsive therapy had been administered in earlier years.

At the recent admission he was on mirtazapine (30 mg/die), clozapine (850 mg/die; serum level 399.9 μg/L; norclozapine 161.7 μg/L), valproate (2,000 mg/die; serum level 67.5 mg/L, reference: 50−100 mg/L), amisulpride (200 mg/die), pipamperone (140 mg/die) and pirenzepine (100 mg/die). Psychopathology included logorrhea with pressured thinking, rumination culminating in obsessive thoughts about potential acts of violence and sex, loss of concentration, suicidal ideation and restlessness. cMRI was normal upon admission.

Cariprazine was added while amisulpride was reduced and discontinued. The initial dose of 1.5 mg/die cariprazine was titrated after 4 days to 3 mg/die. After 7 days on 3 mg/die he suffered from a distinct laterally dystonia of the trunk, persisting in standing and sitting and fulfilling the criteria of the Pisa syndrome. His pressured thinking, logorrhea and restlessness became worse. Cariprazine (level: 3.9 μg/L; reference: 10−20 μg/L) was reduced to 1.5 mg/die on day 12 and discontinued on day 18 (Naranjo scale 7) [11]. A further intravenous administration of 5 mg biperiden yielded to a regression of Pisa syndrome. ECG was normal. One day later, the clozapine through levels were elevated compared to admission but within the therapeutic range (527.5 μg/L; norclozapine 211 μg/L).

A combination of clozapine and pipamperone with aripiprazole, increased doses of valproate (2,300 mg/die) and mirtazapine (45 mg/die), as well as 6 electroconvulsive therapies resulted in a stabilized state at discharge.

DISCUSSION

Cariprazine add-on to clozapine is rarely studied. This combination yielded a rapid efficacy in the treatment of two subjects with inadequate response to clozapine [5]. Especially the D_3 receptors, stimulated by cariprazine, are linked to cognition, mood and negligible extrapyramidal side effects due to the high concentration in the ventral striatum [5,12]. Our cases demonstrate a combination of clozapine and cariprazine followed by an increase of side effects, which are known to occur when combining antipsychotics [3].

Looking at these two cases, there are several issues to discuss:

First, cariprazine is metabolized by CYP3A4 and CYP2D6. It is a weak competitive inhibitor of these enzymes, which are—next to CYP1A2—involved in clozapine metabolism [13-15]. To illustrate the power of CYP3A4 in clozapine metabolism, Tóth *et al.* [7] showed a 2-fold higher normalized clozapine concentration and a halved dose-requirement in low CYP3A4 expressers. In case 1 the through levels of clozapine were stable 5 days before Pisa syndrome. No increase in clozapine or decrease in norclozapine level was determined. In case 2 the through level of clozapine before starting cariprazine was 414.2 µg/L. One day after the occurrence of Pisa syndrome, the through levels were in range, but elevated without dosage changes (527.5 µg/L). In this case, the blood level of cariprazine was low (while no measurements are available for case 1). The expression or activity of metabolizing enzymes may be a useful predictor for the individual drug concentration, dose requirements and combination with other antipsychotics [7]. In our cases, we did not find elevated through levels of clozapine. However, the increase of clozapine level in combination with cariprazine one day after Pisa syndrome in case 2 (414.2 µg/L to 527.5 µg/L) seems noteworthy. This could indicate a relevant pharmacodynamic interaction for case 2 and could partially explain the contrast to the reported remarkable, positive effects in two cases of cariprazine add-on with clozapine, reported by Berardis *et al.* [5].

Second, the Pisa syndrome is observed more frequently under long term medication with antipsychotics [9]. This causes an increased probability in older patients with a longer history of schizophrenia and may explain the contrasting positive effects of cariprazine clozapine combination in two younger schizophrenia patients (29 and 35 years old) [5]. Several cases regarding clozapine induced Pisa syndrome have been reported, although clozapine could reverse Pisa syndrome in some patients [16]. Pisa syndrome can be connected to a dopaminergic-cholinergic imbalance with an excess of cholinergic activity or a decrease of dopaminergic activity [16]. A $5HT_{2A}$ receptor antagonism potentiates D_2 receptor antagonist-mediated efficacy [4]. Positron emission tomography imaging studies demonstrate an association of clinical antipsychotic response with at least 65% occupancy of striatal D_2 dopamine receptors, while over 80% occupancy is associated with extrapyramidal side effects [4]. After repeated oral dosing of cariprazine D_2/D_3 receptor occupancy reaches $>$ 90% at 3 mg/die [15]. A dose of 400–600 mg/die clozapine yields an occupancy of $<$ 60% [4]. The high concentration of the D_3 receptors in the ventral striatum—stimulated by cariprazine—are discussed to reduce adverse effects including extrapyramidal side effects by Berardis *et al.* [5]. Both, the combination of $5HT_{2A}$ receptors antagonized by both medications (cariprazine at a lower impact), as well as an increased occupancy on D_2 receptors, may play a role in the adverse effects of our contrasting cases [4]. Regarding the deterioration of psychotic symptoms using cariprazine in our patients after long-term clozapine treatment, the partial agonism of cariprazine on D_2 and D_3 receptors seems particularly relevant.

Third, side effects of cariprazine are related to dosage [6]. In our cases, the use of different dosages resulted in comparable side effects (case 1: 6 mg/die cariprazine and 450 mg/die clozapine, case 2: 3 mg/die cariprazine and 850 mg/die clozapine). A combination of high dosage of clozapine and mean dosage of cariprazine as well as mean dosage of clozapine and high dosage of cariprazine and fast/slow titration (4 and 14 days versus 1 and 3 weeks at Berardis *et al.* [5]) resulted in Pisa syndrome. Nevertheless, through levels are important for the clinical improvement during clozapine treatment. Both patients have been treated with clozapine over years, which might have had an impact on the onset of this syndrome.

Regarding the presented cases it is important to stress, that we had to end the prescription of cariprazine quickly due to the subjective severity of the described side effects and in accordance with the preferences of both patients. Therefore, beneficial effects with a reduced dose (especially

case 1) cannot be ruled out. Although during reduction of 6 days after Pisa syndrome in case 2 no beneficial effects evolved, the short period of overall cariprazine titration (12 days) must be considered in this case. This period is most likely too short to finally evaluate all potentially beneficial effects of cariprazine.

To our knowledge, these are the first two reported cases of deteriorating psychosis and Pisa syndrome when combining cariprazine and clozapine.

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■ **Conflicts of Interest**

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

■ **Author Contributions**

Conceptualization: Sven Speerforck and Judith Weise. Data acquisition and review of patient records: Judith Weise. Supervision: Sven Speerforck and Georg Schomerus. Writing—original draft: Judith Weise. Writing—review & editing: Sven Speerforck and Georg Schomerus.

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