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Reversal of 'treatment resistance' status of schizophrenia with clozapine: A case report

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INTRODUCTION

Schizophrenia is a major mental disorder with a chronic course, significant dysfunction and poor quality of life. Treatment-resistant schizophrenia (TRS) occurs in about a third of those with the illness (Correll et al., 2021), and it is defined as an insufficient response to two or more adequate trials of antipsychotics, preferably from different classes (Correll et al., 2021). Clozapine is the only approved medication for TRS. However, it is a treatment challenge owing to its intolerable side effects, which are often life-threatening, and the need for regular clinical monitoring (Mishra et al., 2015).

Dopamine supersensitivity (DS) is often implicated in the development of TRS (Potkin et al., 2020). The efficacy of clozapine in TRS may be explained by its unique action profile (transient dopamine D_2-receptor occupancy, potent serotonin 5-HTA antagonism, and modulation of D_1, D_4, and gluteminergic receptors (Potkin et al., 2020). Another consequence of DS is the development of tardive disorders like tardive dyskinesia (TD), wherein clozapine has also shown therapeutic benefits, with some reports demonstrating a complete reversal of the condition (Tamminga et al., 1994).

Therefore, a theoretical possibility exists of a similar reversal of 'treatment resistance' in some schizophrenia patients following a period of clozapine therapy. However, such a scenario has never been reported in the literature. Hereby, we discussed a patient with TRS previously maintained on clozapine, requiring cessation of the drug following severe side effects, but subsequently well-maintained on another non-clozapine antipsychotic.

CASE PRESENTATION

A 34-year-old female from a middle socio-economic status with nil-contributory birth, developmental and family history was diagnosed with paranoid schizophrenia in 2014. Over the next five years, she showed an inadequate response to sequential trials of different antipsychotics [Positive and Negative Symptoms Scale of Schizophrenia (Kay et al., 1987), PANSS: 96-112], including haloperidol (up to 15 mg/day), olanzapine (up to 20 mg/day), and depot flupenthixol (20 mg every third week). Finally, in 2019, she was diagnosed with TRS and was started on clozapine with a gradual hike to 450 mg/day. With clozapine, her symptoms significantly improved (PANSS: 59), particularly in terms of reduced delusional conviction and preoccupation, lesser frequency, duration and intensity of auditory hallucinations, better affect reactivity, social interaction, attention and overall functionality. She initially experienced sedation, which lessened over two months, and occasional constipation, treated with laxatives as needed.

While on clozapine, regular monitoring of clinical parameters revealed no abnormality until a year later (in 2020), her fasting glucose levels were 162 mg/dl. She was diagnosed with type 2 diabetes mellitus (T2DM) by a general physician and was advised oral hypoglycemics and a modified lifestyle. Controlling her diabetes alongside clozapine therapy posed a challenge, requiring repeated adjustments in her treatment regimen. Before the index presentation, she was on metformin 1500 mg/day, glimepiride 3 mg/day, and clozapine (reduced to) 350 mg/day. She was a non-smoker.

In May 2022, she was admitted on an emergency basis with complaints of nausea, vomiting, stomach pain and confusion. There was no history of fever, diarrhoea, head trauma, falls or seizures. Her relevant laboratory reports revealed serum glucose 480 mg/dL, arterial pH 7.24, bicarbonate 14 mEq/L, anion gap 18 mmol/L, and strongly positive serum and urinary ketones suggestive of diabetic ketoacidosis (DKA). She was managed with intravenous fluids, insulin and potassium infusion till the resolution of acidosis and clinical improvement. Clozapine, the probable offending drug (Naronjo score: 6) (Naranjo et al., 1981), was stopped, and she was discharged on insulin (at a sliding scale regimen) and Aripiprazole 15 mg/day. She however maintained her psychiatry follow-ups

regularly, and in the above-mentioned treatment regimen for the next nine months, she showed no deterioration in her physical or mental condition (PANSS: 64) and good glycemic control.

DISCUSSION

Over a third of patients on clozapine develop T2DM within five years of initiating therapy (Henderson et al., 2000). DKA is a known complication in these patients, even when the clozapine doses are low (Vuk et al., 2017). Also, the duration of treatment showed no association with the occurrence of such hyperglycemic events (Henderson et al., 2000). In our case, the patient developed T2DM one year after commencing clozapine and presented with DKA in another two years (while she was maintained at 350 mg/d clozapine). Though clozapine levels could not be measured, the dosing was within the recommended range.

The patient was discharged on aripiprazole, which was preferred due to its favourable metabolic profile (Pakpoor & Agius, 2014). Interestingly, though she had previously responded poorly to some potent first and second-generation antipsychotics, her psychotic symptoms were well controlled following discharge with aripiprazole monotherapy. It is possible that the patient was a case of pseudo-resistance, with chances that the previous antipsychotic trials, although in adequate doses, were not for an adequate duration (which ranges from 2-3 weeks to 6-8 weeks according to different guidelines) (Howes et al., 2017). However, apparently, good family support and illness awareness, regular clinical visits (with documentation) and a detailed history corroborated by multiple family members make it less likely. Also, multiple antipsychotic trials reflect the common practice of prescribing clozapine after thoroughly exhausting most other options. Another explanation could be that the illness followed its natural course of spontaneous remission independent of the treatments offered. Also, the acute ketotic/hyperglycemic event may have a therapeutic role, but any scientific evidence supporting such a claim is lacking. The patient also did not have any seizures during the ketotic/hyperglycemic episode, thus ruling out a possible electroconvulsive effect.

Alternatively, it may be hypothesised that the clozapine therapy subsequently somehow resulted in a favourable therapeutic response to another antipsychotic (aripiprazole). Such a reversal of 'treatment resistance' with clozapine is theoretically not implausible and is also supported by current evidence. Continuous antipsychotic use, particularly one with higher potency, causes upregulation of postsynaptic D_2-receptors leading to a breakthrough of psychosis (DS psychosis), which is considered the

Table 1: Evidence of reversal of dopamine supersensitivity with clozapine

Study	Type	Findings
Animal studies		
Park et al. 2010	Cocaine-sensitised mice treated with clozapine	Subchronic clozapine treatment reduced locomotory activity caused by cocaine sensitisation. Clozapine reversed some of the sensitisation-induced biochemical changes (increased phosphorylation of GSK-3beta and CREB).
Cha & Kang 2014	Cocaine-sensitised male ICR mice were treated with clozapine, haloperidol, and fluoxetine	Clozapine reversed the sensitised state (as measured by the reduction in locomotory activity). Fluoxetine partially reversed, and haloperidol did not reverse the condition.
Human studies		
Gerbino et al.1980 (as in Lieberman et al. 1991)	Open trial with clozapine on 24 patients with TD	Three patients maintained 100% remission of TD symptoms even when clozapine was withdrawn after one year
Tamminga et al. 1994	Trial with clozapine/haloperidol on 32 patients with TD	Long-term clozapine caused 100% remission of TD, along with DS, in some patients
Nakata et al. 2017	Case series on 15 patients with DS psychosis	13 of 15 patients had no further DS psychotic episodes over 2.5 years following clozapine therapy

DS: dopamine supersensitivity, TD: Tardive dyskinesia, GSK: glycogen synthase kinase, CREB: cAMP-response element binding protein

underlying neurobiology in a subset of TRS patients (Potkin et al., 2020). There is evidence that clozapine can reverse DS (*Table 1*): a) lab mice repeatedly treated with psychostimulants (causing dopaminergic sensitisation) have demonstrated reversal with clozapine administration (Cha & Kang, 2014; Park et al., 2010), b) spontaneous reversal of TD (also caused by DS) have been reported in some patients receiving clozapine (Lieberman et al., 1991; Tamminga et al., 1994), with a recent systematic review showing a negative correlation between duration of clozapine use and severity of TD (Pardis et al., 2019), and c) anecdotal reports of 100% remission in DS psychosis following clozapine therapy (Nakata et al., 2017). Clozapine binds loosely to D_2-receptors and, therefore, gets easily replaced by endogenous dopamine resulting in a gradual reversal of DS. This is further facilitated by its actions at alternate molecular targets (D_1, D_3 and D_4 antagonism, and serotonin $5HT_{2A}$ and $5HT_{1A}$ antagonism). Clozapine may therefore help reverse antipsychotic-induced DS psychosis, presenting as TRS. This furthers the need to identify the subset of TRS patients who could possibly reverse with clozapine therapy. Potential clinical pointers are TRS with a past initial response to antipsychotics and currently responding to clozapine (as in our described case), and TRS with TD responding to clozapine (Potkin et al., 2020). Aripiprazole, a partial D_2-agonist, has low propensity for DS, justifying its role in the described case (Pakpoor & Agius, 2014).

CONCLUSIONS

This is the first case study describing the possibility of 'treatment resistance' reversal with clozapine. There is a clinical need to identify the subset of TRS patients who can be benefited by switching back to regular antipsychotics following intermediate clozapine therapy. The full potential of clozapine in schizophrenia treatment needs further evaluation in future research.

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