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Clozaphobia: Is avoidance of clozapine in diabetes warranted?

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ABSTRACT

Despite its superior efficacy, clozapine is an underutilized agent, primarily owing to the "Clozaphobia"-fear of clozapine's adverse effects. Emergent cautions on metabolic side-effects have contributed to avoidance of clozapine prescription. Here, we describe our clinical experience with nine patients having schizophrenia/schizoaffective disorders with comorbid diabetes mellitus and treated with clozapine. Interestingly, all patients could be maintained on optimal glycemic control even after clozapine. In conclusion, a critique on the potential risks versus benefits of clozapine amidst our observations from this case series adds further supporting evidence to the emerging literature on the clinical utility of clozapine in treating schizophrenia patients with diabetes mellitus.

1. Introduction

Clozapine is the most efficacious drug in schizophrenia, especially in treatment-resistant patients (Siskind et al., 2016). Most treatment guidelines recommend initiation of clozapine at the earliest phase of treatment resistance. It has a clinical superiority in patients with higher suicidal risk, aggression and propensity for extrapyramidal side effects. However, surveys suggest that clozapine is one of the most under-utilized psychotropic agents (Sharma and Grover, 2013). Apprehension about the adverse effects of clozapine is the major deterrent (Tungaraza and Farooq, 2015). The risk of metabolic syndrome which includes obesity, hyperlipidemia and diabetes mellitus (DM), with their subsequent complications counts among the top most reasons for the reluctance (Tungaraza and Farooq, 2015).

Nonetheless, with regards to DM, some preliminary literature suggests that clozapine is less likely to induce diabetes at any rate higher than general population (Schulte et al., 2016). This is important, since DM is a frequent medical comorbidity with schizophrenia (Cooper et al., 2016); hence, understanding the potential impact of clozapine on DM has immense clinical significance.

In this report, we describe our clinical experience in schizophrenia spectrum disorder patients ($N = 9$) with comorbid DM who were treated with clozapine over the last 1 year in our clinic. Interestingly, all these nine patients could be maintained on optimal glycemic control even after treatment with clozapine.

2. Case series

Case 1: Mrs. K, a 33-year-old female homemaker presented with 11 years of schizophrenia. She had failed adequate trials (> 1000 mg chlorpromazine equivalent dose for > 4–6 weeks) of risperidone, amisulpride, aripiprazole, along with failure of combination treatments of aripiprazole and iloperidone; aripiprazole and olanzapine; depot flupenthixol and iloperidone. She developed DM while on combination treatment with risperidone, amisulpride and aripiprazole 2 years ago (fasting blood glucose (FBG) 287 mg/dl, HbA1c 9.1%, body mass index (BMI) 31). In view of resistance to multiple antipsychotics, clozapine was started 10 months before. Currently patient is maintaining well without psychotic symptoms and with improvement in metabolic parameters (FBG 111 mg/dl, HbA1c 6.6%, BMI 27.15).

Case 2: Ms. SS had diagnoses of schizoaffective disorder, bipolar type with hypothyroidism, obesity and polycystic ovarian disease. Psychotic symptoms failed to remit with adequate trials of oral risperidone, ziprasidone, iloperidone and trifluoperazine, in combination with valproate. Though good response was noted on treatment with olanzapine 20 mg, she developed significant weight gain (from 79 to 96 kg with BMI 34.7) and diabetes (FBS 297 mg/dl, PPBS 135 mg/dl, HbA1c 6.6), within 10 months. Hence, switching to quetiapine 800 mg was attempted but with partial success, associated with repeated relapses on attempts to taper off olanzapine. Metformin and voglibose did not help in ameliorating the metabolic disturbances even with good adherence. In view of significant relapses and with a plan for long-term management olanzapine was cross tapered with clozapine (200 mg/

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day). During 2nd and 4th month follow-up, symptoms of psychosis and diabetes were well under control with HbA1c 5.7% and a reduction of 9 kg in her body weight (87 kg).

Case 3: Mrs. AL, a 40-year-old physician suffering from schizophrenia for 15 years had failed adequate trials of oral and depot risperidone, haloperidol, flupenthixol, depot fluphenazine, aripiprazole and asenapine. She developed DM after 5 years of starting clozapine, and hence stopped medicines. She presented 2 years later with psychotic symptoms, severely deranged lipid profile (triglycerides 235 mg/dl, total cholesterol 262 mg/dl) and uncontrolled diabetes (FBG 404 mg/dl, HbA1c 8.4%). Clozapine was restarted and later augmented with aripiprazole 10 mg and fluoxetine 20 mg with simultaneous treatment for DM. Following this she attained near total improvement in symptoms and stable metabolic profile (HbA1c 5.5) was seen at the latest i.e. 10th year follow-up of initiating clozapine.

Case 4: Mr P, a 36-year-old male presented with 15 years of schizophrenia. He was on clozapine 300 mg/day for 3 years after non-response to olanzapine 10 mg/day, amisulpride 400 mg/day and fluphenazine 15 mg/day, each for durations more than 3 months. On detailed evaluation he had BMI of 22.87, elevated fasting and post-prandial blood glucose and HbA1C of 7 suggesting new onset DM. Because of persisting positive symptoms and suicidality clozapine was continued with further increase in dose to 375 mg/day along with metformin 1 g/day for DM. In subsequent follow-up because of persisting hallucinations and delusions (though significantly less than earlier) and onset of depressive symptoms with suicidal ideations, electroconvulsive therapy was offered and clozapine was continued with risperidone augmentation. In the most recent visit his blood glucose was normal with HbA1c of 5.5%, BMI of 24 and significant improvement in behavioural problems, but for some residual hallucinatory experiences.

Case 5: Ms. VL with illness duration of 7 years was diagnosed with schizoaffective disorder, bipolar type, and presented with predominant 2nd person auditory hallucinations. She initially responded to olanzapine 20 mg and lithium 1050 mg/day but because of obesity (BMI 28.5 kg/m^2) was switched to risperidone 8 mg alongside lithium, with poor response. During a repeat trial of olanzapine 20 mg with fluoxetine 20 mg she was noted to have diabetes mellitus (FBG 160 mg/dl, Hb1Ac 6.2 with weight 73 kg, BMI 28.5) hence prescribed metformin 1000 mg/day and glimepiride 1 mg/day. Clozapine was initiated at 100 mg/day in view of resistant psychosis along with fluoxetine. On next follow-up at 3rd month (HbA1c 6.0%), 4 kg reduction in weight was noted. Clozapine was further reduced to 75 mg after 6 months in view of excess sedation and hypersalivation with good improvement in psychiatric condition and functioning, which was maintained till the latest visit at 10th month of clozapine.

Case 6: Mrs. A is a 63-year-old lady having paranoid schizophrenia characterized by 3rd person auditory hallucinations. After failed trial of amisulpride and haloperidol, clozapine was initiated and increased to 150 mg/day. At 2-year follow-up, DM remains under control (FBS 122 mg/dl), with mild clinical symptoms.

Case 7: Mrs. V, a 52-year-old lady diagnosed with schizophrenia, polycystic ovarian disease, hypertension, and obesity, presented with 6 years of 2nd and 3rd person auditory hallucinations, delusion of persecution, reference and bizarre delusions. Failed trials of risperidone, quetiapine and aripiprazole led to initiation of clozapine (150 mg/day). At commencement of clozapine she had a BMI of 30, RBS 396 mg/dl, weight 69 kg. On follow-up 6 months later, she had a RBS of 159 mg/dl, although her weight had increased to 72 kg.

Case 8: Mrs. R had suffered from psychosis for 12 years when she presented to us at 27 years of age. She had failed trials of quetiapine, depot haloperidol, olanzapine, risperidone, chlorpromazine and 22 sessions of electroconvulsive therapy (on 3 different occasions for acute exacerbations of psychotic symptoms). Clozapine was started 8 years back with a significant clinical improvement. 5 years later she delivered a healthy female baby. DM was identified 2 years back with high triglyceride levels (202 mg/dl), without other metabolic derangements. She is maintaining well on metformin and clozapine for last 2 years with latest HbA1c 6.3%.

Case 9: Mr. M, a 42-year-old male with schizophrenia for 26 years, had failed adequate treatment trials of haloperidol, chlorpromazine, olanzapine, depot flupenthixol and risperidone. He was started on clozapine 10 years back with which he had improvement in delusions and aggressive behaviour. He continues to have auditory hallucinations despite multiple augmentations of clozapine by antipsychotics, mood stabilizers and brain stimulation techniques. He developed diabetes mellitus and hypertension 5 years back, though the BMI was 22.4. Currently he is maintaining a reasonable metabolic profile (BMI 22.4, HbA1c 6.2%) although his hallucinations persist.

3. Discussion

We have described nine patients suffering from schizophrenia spectrum disorder (seven schizophrenia and two patients with schizoaffective disorder) who had comorbid type 2 diabetes mellitus and were receiving clozapine. Delay in initiation of clozapine (> 3 AP trial) was noted in six of the seven patients. On reviewing the medical records, it was inferred that at least in five of the six patients delay in clozapine initiation might have been due to apprehension about metabolic side effects including diabetes risk among others. In an earlier report, the delay in initiation of clozapine is estimated to be more than 60% of the treatment resistant schizophrenia in teaching hospitals in India (Sharma and Grover, 2013). This may be much higher in non-academic clinical settings (Nielsen et al., 2010). A survey (Tungaraza and Farooq, 2015) has reported that the most common (up to 80%) reason cited by physicians for delaying clozapine was the fear of metabolic adverse effects (Table 1).

Significant weight loss (> 5% of body weight) was noted in three of the patients after switching to clozapine from other antipsychotics (one patient on olanzapine, other on combination of olanzapine and quetiapine and the third on aripiprazole, amisulpride and risperidone combination). One of the patients also received fluoxetine augmentation as it is known to augment efficacy by increasing the clozapine:-norclozapine ratio but keeping the side effects minimal (Legare et al., 2013). But, as this patient was receiving fluoxetine even before the initiation of clozapine it is unlikely to be the major contributor for weight loss in this patient. None of the others had a significant weight gain after starting clozapine. Loss of weight with clozapine has been documented earlier in literature in some of the patients but the exact mechanism is unknown (Tungaraza, 2016). This subgroup of patients has been hypothesized to have some genetic underpinning as they can be clozapine responders who engage in diet and exercise as well as in non-responders.

Even though metabolic adverse effects were dreaded and clozapine was delayed, most of the patients in this case series received olanzapine trial before clozapine. Clozapine has been traditionally attributed with the highest risk of metabolic problems (Lehman et al., 2004) based on expert consensus; but the unequivocal evidence base for its greatest propensity for metabolic side effects in comparison with all other antipsychotics (both older and newer) is yet to be established. Clozapine which is often given in treatment-resistant cases would have patients of longer duration of illness and higher age group (Mitchell et al., 2013). They would usually have a higher cumulative risk with prior exposure to other antipsychotics, which would give a biased evidence against clozapine in cross sectional studies. Literature based on naturalistic studies as well as controlled trials are challenging this stance (Schulte et al., 2016). A recent guideline notes olanzapine to be the antipsychotic with the highest risk for metabolic syndrome, and clozapine to be not significantly greater than other medium risk agents (quetiapine, risperidone and paliperidone); nonetheless, clozapine was placed in the highest risk category due to high variance of reported metabolic changes (Cooper et al., 2016).

Nevertheless, the risk of metabolic problem is present with cloza-