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Case Report

Implications of Clozapine Complications in Geriatric Patients with Type II Diabetes Mellitus

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Abstract

Second-generation antipsychotics, have known metabolic side effects; specifically, clozapine is implicated in worsening or causing hyperglycemia, hypercholesterolemia and weight gain. Recently, there has been an increased interest in the safe use of clozapine in patients with diabetes. In March 2018, a 65-year-old female with a diagnosis of schizophrenia was admitted for inpatient hospitalization to a psychiatric hospital in Buffalo, NY for further stabilization after receiving two months of treatment at a comprehensive psychiatric emergency program (CPEP). Her medical diagnoses included type 2 diabetes mellitus (T2DM), vitamin D deficiency, hyperlipidemia, glaucoma, and constipation. Upon admission, the patient was continued on clozapine, and fluphenazine for treatment of schizophrenia. Her medical medications upon admission included acetaminophen, cholecalciferol, multivitamin, and timolol maleate eye drops. Low blood glucose results at the beginning of her hospitalization led to discontinuation of fingerstick blood glucose readings as the patient was

prescribed a controlled diet, and her most recent hemoglobin A1c (HgbA1c) level was 6.8% on March 23, 2018. Clozapine was initiated and titrated over the next four months of inpatient treatment. The patient became psychiatrically stable and was prepared for discharge. During her final medical and psychiatric evaluation laboratory findings included a HgbA1c of 14.4% - a total increase of 7.6% over the course of 31 weeks**.** Clozapine is implicated in causing health-related complications that include agranulocytosis, seizures, constipation, and hypersalivation, as well as, metabolic side effects such as weight gain and hyperglycemia. Clozapine can also exacerbate pre-existing diabetes or lead to a new diagnosis of T2DM. If not controlled, these metabolic effects can lead to serious long-term consequences. Clozapine was prescribed prior to hospital admission and further titrated during the patient's hospitalization at a long-term psychiatric facility. The patient had a diagnosis of T2DM but did not receive pharmacotherapy due to well controlled blood glucose and a HgbA1c level within goal. Pending discharge, a final psychiatric and medical examination determined that the patient's HgbA1c had more than doubled. The significant increase in HgbA1c in a geriatric patient with diet-controlled T2DM confirms that psychiatric medication changes can cause dysregulation of T2DM. Further research is needed to explore any potential increased likelihood, or magnitude of effect, of these drug induced metabolic consequences in older adults.

Keywords
Type II Diabetes Mellitus; T2DM; clozapine; second-generation antipsychotics; hyperglycemia; hemoglobin A1c; geriatric

1. Introduction

Hemoglobin A1c (HgbA1c) is an effective and reliable measure of glycemic control over the previous two to three months [1, 2]. A lower HgbA1c is predictive of a decreased risk of complications of diabetes mellitus, and the American Diabetes Association (ADA) has established a HgbA1c goal of <7% in nonpregnant adults [3]. A less stringent goal of <8% may be appropriate in patients with an increased risk of hypoglycemia, shorter life expectancy, or additional complications and conditions. A stricter HgbA1c goal of <6.5% may be appropriate in patients who are not at an increased risk of hypoglycemia, have an extended life expectancy, and are without serious cardiovascular disease.

Antipsychotics are used to treat a variety of mental health illnesses [4]. Second generation antipsychotics (SGA) are beneficial for use in patients due to their reduced risk of causing movement disorders but carry their own unique side effect profile risk of worsening metabolic effects that can lead to loss of glucose control and diabetes [5]. In 2004, the ADA recommended that patients prescribed an antipsychotic should be monitored for diabetes on an annual basis [6]. However, only 55% of patients receive the screening according to guideline recommendations [7]. Antipsychotic-induced diabetes is proposed to occur by one of three mechanisms: inhibiting the insulin signalling pathway, antipsychotic-induced obesity resulting in inflammation and insulin resistance, or damage to beta cells [8, 9]. Not all antipsychotics are reported to cause metabolic

syndrome and weight gain to the same degree. Clozapine and olanzapine are two antipsychotics that are most often implicated in causing these effects [10, 11].

Clozapine is a second-generation antipsychotic associated with blood glucose level increases and it is the antipsychotic that is most often associated with diabetes and hyperglycemia [12]. It has strong dopamine-4 (D_4) and serotonin receptor activity and it differs from other antipsychotics in that it has weak dopamine-2 (D_2) receptor activity [13]. Clozapine is considered the most effective antipsychotic in treatment-resistant schizophrenia, however the hallmark risk of agranulocytosis discourages more frequent use and the additional undesirable side effects including, but not limited to, hypersalivation, enuresis, myocarditis, urinary incontinence, constipation, seizures, and metabolic effects present ongoing challenges with use [13-15]. Metabolic side effects include weight gain and hyperlipidemia, and exacerbation of pre-existing diabetes or leading to newly diagnosed type two diabetes mellitus (T2DM) or diabetic ketoacidosis [10, 13, 14].

Studies have shown a two-fold increased risk of diabetes mellitus and greater impairment of glucose tolerance in patients prescribed clozapine [13, 16]. Hyperglycemia can occur due to a decrease in insulin sensitivity in patients who have weight gain secondary to clozapine treatment [17, 18]. Some reports have noted that hyperglycemia and exacerbation of diabetes mellitus can also occur in patients without weight gain, and glucose intolerance can occur in 10% of patients [10, 13, 19, 20]. Several cases of diabetes mellitus have resolved after the discontinuation of clozapine [21, 22].

This case report discusses the adverse effects experienced by an older adult inpatient diagnosed with T2DM upon initiation and titration of clozapine during acute and long-term treatment for psychiatric destabilization. There are minimal reports of HgbA1c changes in patients with a diagnosis of T2DM treated with clozapine, and none exploring the potentially exaggerated effects in older adults. However, there are reports on diabetic ketoacidosis, including fatal cases after initiation of clozapine [23].

2. Case Description

In January 2018, a 65-year-old African American female was admitted to a comprehensive psychiatric emergency program (CPEP) in Buffalo, NY after presenting to the emergency department. A family member reported increasing odd behavior after the patient self-discontinued all medication three months prior and decreased consumption of food. Upon admission to CPEP, the patient weighed 84 pounds (Table 1) with a body mass index (BMI) of 12.2, making her underweight. She stated, “I am all teeth”, “I’ve eaten everything inside”.

The patient had previously been diagnosed with bipolar disorder in her forties, but her diagnosis was updated to schizophrenia upon this current admission. She had been hospitalized for mental health complications on at least seven occasions and had a history of one suicide attempt in 2015 by drowning after purposefully ingesting an acetaminophen overdose following the death of a family member. Her psychiatric medication pharmacotherapy in CPEP consisted of clozapine and fluphenazine.

Table 1 Weight trends before and during clozapine treatment.

Date	Weight (lb.)
1/4/2018	84
3/26/2018	112.5
4/4/2018	116
4/30/2018	123.5
6/2/2018	129
7/2018*	127
8/1/2018	125

*date unspecified

The patient's medical diagnoses include T2DM, vitamin D deficiency, hyperlipidemia, glaucoma, and constipation. On January 1, 2018, her HgbA1c was recorded as 6.2% (Table 2), and on January 12, 2018, her blood glucose was recorded as 93 mg/dL. T2DM was not pharmacologically treated due to control with diet as indicated by recorded blood glucose levels (Table 3). Her other medical diagnoses were managed as follows: cholecalciferol 2,000 IU for vitamin D deficiency, timolol maleate 0.5% eye drops for glaucoma, and polyethylene glycol 17 g for constipation. Additionally, the patient was prescribed a daily multivitamin, and acetaminophen 650 mg as needed. The patient was prescribed atorvastatin 40 mg daily at CPEP but it was discontinued due to the patient's elevated liver function tests (LFTs) with an aspartate transaminase (AST) and alanine transaminase (ALT) of 101 and 40 units/L respectively, on March 14, 2018. Her blood glucose was monitored between March 13th and 16th of 2018 and considered controlled (Figure 1) as she prepared for transfer to our facility.

Table 2 Hemoglobin A1c before and during clozapine treatment.

Date	HgbA1c
1/6/2018	6.2%
3/26/2018	6.8%
8/2/2018	14.4%
1/2/2019	7.5%

Table 3 Blood glucose levels at CPEP prior to admission to the inpatient psychiatric hospital.

Date	Blood Glucose (mg/dL)
1/12/2018	93
3/13/2018	101
3/14/2018	92
3/15/2018	107
3/16/2018	93
3/22/2018	122

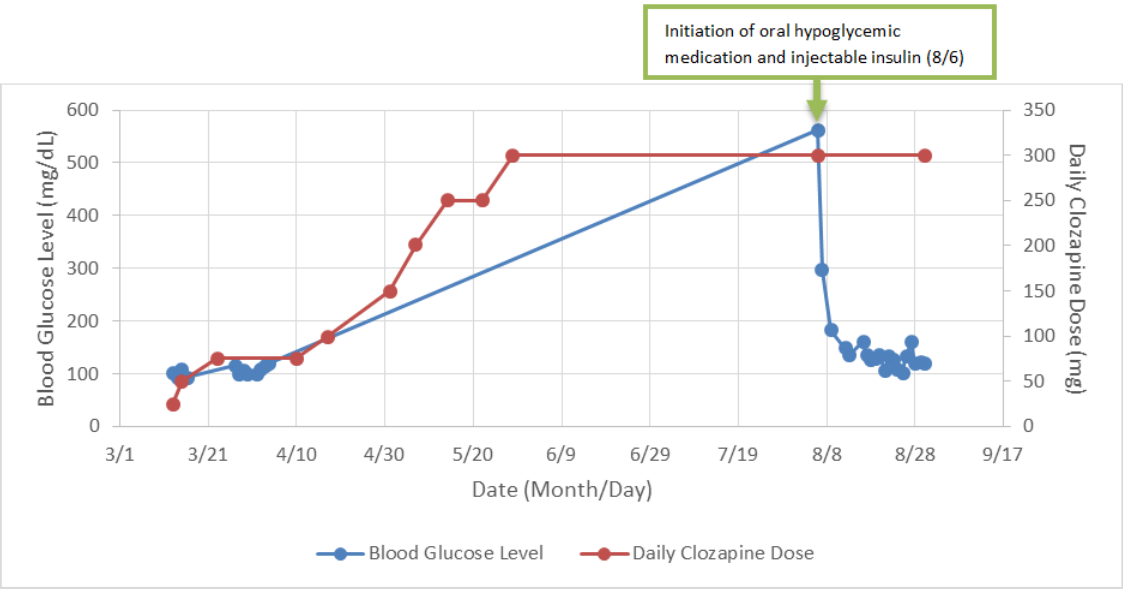

Figure 1 Blood glucose changes during clozapine titration.

On March 23, 2018 the patient was transferred to an inpatient psychiatric hospital in Buffalo for further stabilization. Due to her age, she was transferred to the geriatric and medically compromised unit. Pharmacotherapy from her CPEP hospitalization was continued upon admission. Due to her diagnosis of T2DM, the patient had her blood glucose tested every morning. Normalized blood glucose results (Table 4) led to discontinuation of daily blood glucose readings as the patient was controlled with diet, and her most recent HgbA1c level was 6.8% (Table 2) on March 23, 2018. She was placed on a regular calorie diet of 2200 kcal without concentrated sweets.

Table 4 Fasting blood glucose levels during admission to the inpatient psychiatric hospital.

Date	Blood Glucose (mg/dL)
3/27/2018	116
3/28/2018	98
3/29/2018	104
3/30/2018	97
4/1/2018	97
4/2/2018	109
4/3/2018	114
4/4/2018	120

Clozapine was continued upon admission at a dose of 25 mg every morning and 50 mg at bedtime. She also continued fluphenazine 5 mg twice daily and fluphenazine decanoate 37.5 mg injection, a long-acting injectable (LAI) antipsychotic, every two weeks. Her clozapine dose continued to be titrated (Table 5) over the next two months. The patient was maintained on weekly clozapine blood monitoring according to the clozapine Risk Evaluation Mitigation Strategy

(REMS) program. As the facility prepared for a goal discharge date of August 16, 2018, final psychiatric and medical examinations were completed. On August 2, 2018, over four months of clozapine therapy, the patient's HgbA1c, cholesterol, and triglycerides were elevated when compared to baseline, at 14.4%, 276 mg/dL, and 155 mg/dL, respectively (see Tables 1-4). Additionally, the patient's weight increased (Table 1) during hospitalization to a maximum of 125 pounds on August 1, 2018.

Table 5 Clozapine titration schedule.

Date	Clozapine Dose	Total Daily Dose
3/13/2018	12.5 mg twice daily	25 mg
3/15/2018	25 mg twice daily	50 mg
3/23/2018	25 mg daily and 50 mg at bedtime	75 mg
4/10/2018	25 mg daily and 50 mg at bedtime	75 mg
4/17/2018	50 mg twice daily	100 mg
5/1/2018	50 mg every morning and 100 mg at bedtime	150 mg
5/7/2018	50 mg every morning and 150 mg at bedtime	200 mg
5/14/2018	50 mg every morning and 200 mg at bedtime	250 mg
5/22/2018	250 mg at bedtime	250 mg
5/29/2018	300 mg at bedtime	300 mg

Due to her elevated HgbA1c, the patient's blood glucose was evaluated and recorded as 562 mg/dL on August 8, 2018. The patient was previously prescribed metformin 1000 mg for her T2DM, but because she was unable to swallow the large tablets, the medication was discontinued prior to her admission to CPEP. Her elevated HgbA1c and blood glucose changes lead to initiation of sliding scale insulin lispro (Table 6), 11 units of insulin glargine daily, and metformin 1000 mg in two 500 mg tablet doses daily to alleviate her swallowing issue on August 6, 2018. Atorvastatin 40mg daily was also reinitiated due to elevated cholesterol. Insulin glargine was increased to 16 units daily on August 9, 2018. As the patient was maintained on oral and injectable diabetic pharmacotherapy, her blood glucose was monitored and reflected a decreasing trend (Figure 1). On August 21, 2018, four times daily blood glucose monitoring was reduced to twice daily due to blood glucose levels within normal limits.

Table 6 Sliding scale intervention of insulin lispro.

Blood glucose level (mg/dL)	Intervention
Less than 70	Call medical provider
71-199	No intervention
200-249	2 units of insulin lispro
250-299	4 units of insulin lispro
300-349	6 units of insulin lispro
350-399	8 units of insulin lispro
400-449	10 units of insulin lispro and call medical provider
Equal to or greater than 450	Call medical provider

3. Discussion

Adiposity and hyperglycemia secondary to clozapine treatment can occur regardless of a previous diagnosis of T2DM. However, the use of clozapine can exacerbate blood glucose levels in someone with a history of T2DM. Uncontrolled diabetes can lead to complications including neuropathy, retinopathy, diabetic ketoacidosis, cardiovascular disease, stroke, or death. Upon admission and initiation of clozapine, the patient's blood glucose levels and HgbA1c of 6.8% indicated her T2DM was well controlled with diet alone, as she was not on pharmacotherapy management. The patient did not complain of increased thirst, fatigue, urination, or other symptoms that would indicate increasing blood glucose levels, however, over a four-month period, her HgbA1c more than doubled to 14.4% despite well controlled blood glucose levels during initiation and titration of clozapine and weight gain. The patient was prescribed both oral antidiabetic and injectable insulin pharmacotherapy in an attempt to control her rising blood glucose levels.

Prior to admission for psychiatric destabilization, the patient was nonadherent to pharmacotherapy, and was underweight at 84 pounds due to a lack of food consumption secondary to her psychiatric exacerbation. Interestingly, the patient was initiated on oral and LAI fluphenazine as well as clozapine. LAI antipsychotics are typically viewed as monotherapeutic agents, however, they are often continued after oral challenge overlap and data indicates they are often used in combination with oral antipsychotic therapy without a plan to taper or discontinue [24, 25]. In most cases, oral in combination with LAI antipsychotics are prescribed longer than recommended by the Food and Drug Administration (FDA) [25]. However, there is not much proven rationale behind the use of oral and LAI antipsychotic polypharmacy.

The patient's weight increased by 28 pounds during her two-month acute inpatient hospitalization. However, her blood glucose levels were considered controlled, even during this weight gain. The patient continued to gain weight and was on a diet that restricted concentrated glucose intake. Due to the exacerbation of T2DM, the patient was not discharged despite psychiatric stabilization.The patient was prescribed metformin and insulins lispro and glargine to control her blood glucose levels.

Current literature supports the use of clozapine in the treatment of refractory schizophrenia [26]. Clozapine is superior in efficacy for patients with schizophrenia and mental illness and has an FDA indication of decreasing suicidality in schizophrenia [27, 28]. It is considered underutilized in the United States due to potential side effects [27, 28]. Literature suggests that clozapine can lead to changes in body weight and blood glucose levels [29]. However, diabetes is not a contraindication to clozapine use. The patient discussed in this case report experienced extreme changes in blood glucose levels leading to a doubling in HgbA1c levels. The patient's discharge was delayed due to her uncontrolled diabetes.

It is most likely that clozapine exacerbated the patient's type two diabetes mellitus due to weight gain and decreased insulin sensitivity leading to hyperglycemia. During initial weight gain, the patient's blood glucose levels were maintained at a level that did not require pharmacotherapy and led to a discontinuation of blood glucose draws. As clozapine treatment duration increased, blood glucose levels also increased, until a maximum HgbA1c of 14.4% was discovered. It should be noted that as clozapine duration increased, so did the patient's dose of clozapine. Current research associates dose and serum concentration with clozapine induced

weight gain and metabolic side effects, however, these effects can also occur at doses considered "very low" [30-32].

In retrospect, the patient was appropriately treated on the geriatric psychiatric unit given her age. She was also initiated on clozapine, which is an agent used in refractory schizophrenia and benefits those experiencing suicidality. However, the patient was initiated on both oral and depot fluphenazine, which could have led to an increase in side effects, especially those potentially harmful in elderly patients. The depot fluphenazine could have led to additional skin irritation, and the patient may have had low muscle mass as indicated by her age and weight upon initiation. Her history of T2DM in addition to her age should have made her a candidate for closer metabolic monitoring. Although her blood glucose levels were within normal limits upon initiation and titration of clozapine, clozapine's history of know metabolic side effects to include changes in weight, blood glucose, and triglycerides should have indicated a need for continuous blood glucose monitoring. Monitoring could have allowed the patient to receive treatment for her T2DM in a timelier manner, increasing patient safety and care.

4. Conclusions

Despite the evidence that suggests that clozapine can result in serious medical complications that include metabolic changes, This medication is often a patient's only possible path to psychiatric stability. The patient discussed in this case report experienced adverse effects that included significant and rapid changes in blood glucose and HgbA1c levels as the result of clozapine initiation and titration along with diet and lifestyle changes. Although the patient's age is a notable factor in this case and may have contributed to the rapid and excessive magnitude of increase, it is important to note that her clozapine regimen successfully resulted in psychiatric stability. Providers should be made aware of the elevated risk of worsening T2DM and regularly monitor blood glucose and HgbA1c levels in patients with both controlled and uncontrolled T2DM. Had the patient's blood glucose levels been monitored throughout her clozapine treatment, the patient could have been medically stabilized and may have been controlled on oral pharmacotherapy alone, or in combination with long-acting injectable insulin and her discharge would not have been delayed, reducing the cost associated with prolonged hospitalization. Geriatric patients with T2DM may need a greater focus on management and monitoring of blood glucose and HgbA1c levels during the initiation, titration, and continued use of clozapine. Further research is needed to explore any potential increased likelihood, or magnitude of effect, of these drug induced metabolic consequences in older adults.

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Author Contributions

Charisse Chehovich, PharmD collected the data and wrote the manuscript.

Tammie Lee Demler, BS, PharmD, MBA, BCGP, BCPP serves as Principle Investigator of the IRB of record at the institution as well as assisting in writing the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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