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A case report and literature review of olanzapine-associated hyperglycemia with previous history of gestational diabetes

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Abstract

Background: Olanzapine (Zyprexa) package labeling includes a warning for hyperglycemia, stating physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus or having borderline increased blood glucose levels. A case report of olanzapine-associated hyperglycemia in a patient with a history of gestational diabetes mellitus (GDM) is presented and literature review is discussed.

Case Report: A 33-year-old female with a past medical history of bipolar disorder, cocaine and amphetamine use disorder, hypertension, and GDM was initiated on olanzapine 5 mg PO daily which was subsequently titrated to 25 mg daily. On day 15 of admission, she developed signs and symptoms of hyperglycemia, with blood glucose readings >500 mg/dL. Insulin was initiated, olanzapine was discontinued, and her blood glucose began improving. She was later discharged on ziprasidone 20 mg PO twice daily.

Discussion: There have been several case reports published on olanzapine-induced hyperglycemia. This is the first case report to specifically recognize a history of GDM as a potential risk factor for developing olanzapine-associated hyperglycemia.

Conclusion: Adverse effect profiles and patient-specific risk factors should be considered when selecting appropriate antipsychotic treatment. Olanzapine may not be an ideal medication choice for a person with a history of GDM; however, if olanzapine is indicated, then close blood glucose monitoring is recommended.

Keywords: olanzapine, hyperglycemia, gestational diabetes

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Background

Olanzapine (Zyprexa) is a second-generation antipsychotic (SGA) FDA-approved for schizophrenia and bipolar 1 disorder as monotherapy or in combination with lithium or valproate.[1] The American Psychiatric Association 2020 Schizophrenia Guidelines state antipsychotic medications, particularly clozapine and olanzapine, are associated with an increased risk of hyperglycemia and diabetes mellitus.[2] Due to these risks, the FDA states physicians should consider the risks and benefits when prescribing SGAs to patients with an established diagnosis of diabetes mellitus or borderline increased blood glucose level (fasting 100-126 mg/dL, nonfasting 140-200 mg/dL).[1]

Studies have shown that receiving antipsychotics during pregnancy may increase the risk of gestational diabetes

TABLE 1: Olanzapine dose, blood glucose, and insulin administered

Day	Olanzapine Dose, mg	Capillary Blood Glucose, mg/dL	Units of Insulin Aspart (Novolog)	Units of Insulin Detemir (Levemir)
1	None	146		
2	None			
3	5	90		
4	5			
5	10			
6	10			
7	10			
8	15			
9	20			
10	20			
11	20			
12	20			
13	25			
14	25			
15[a]	5	>500		
		>500		
		416		
		364		
16[b] A1c = 8%	25	341[c]	46	30
		406		
		364		
		390		
17[d] Olanzapine discontinued	5	343[c]	49	45
		292		
		305		
		385		
18[e]		300[c]	74	80
		308		
		310		
		300		
		288		
19		309[c]	63	100
		266		
		191		
		225		
20		293[c]	91	110
		273		
		363		
		265		
21		251[c]	65	120
		216		
		127		
		164		

TABLE 1: Olanzapine dose, blood glucose, and insulin administered (continued)

Day	Olanzapine Dose, mg	Capillary Blood Glucose, mg/dL	Units of Insulin Aspart (Novolog)	Units of Insulin Detemir (Levemir)
22		211[c]	64	120
		280		
		206		
		217		
23		306[c]	43	124
		198		
		375		
		283		
		276		
24 Patient discharged		159[c]	18	70

[a]Day 15: Due to transfer, only morning dose of olanzapine 5 mg received; received 10 units of regular insulin (Humulin R).

[b]Days 16-24: All doses of insulin detemir were scheduled.

[c]Fasting blood glucose, all other blood glucoses were random.

[d]Day 17: Morning dose of olanzapine 5 mg daily administered prior to olanzapine discontinuation; includes insulin aspart 10 units 3 times daily scheduled plus sliding scale.

[e]Days 18-24: Includes insulin aspart 15 units 3 times daily scheduled plus sliding scale.

mellitus (GDM). A study by Park et al[3] supports this claim and found continuation of olanzapine or quetiapine during pregnancy had an increased risk of developing GDM. It is unknown if a history of GDM increases the risk of olanzapine-associated hyperglycemia. Therefore, all patients taking SGAs should be regularly monitored for uncontrolled hyperglycemia regardless of risk factors. Fasting blood glucose testing is recommended at the beginning of treatment and periodically thereafter.[2]

A case of olanzapine-associated hyperglycemia in a 33-year-old female with history of GDM is discussed. A literature review summarizing previous case reports is also presented.

Case Report

A 33-year-old female was admitted for suicidal ideations and acute psychosis. She had a past medical history of bipolar disorder, cocaine and amphetamine use disorder, hypertension, and GDM. She weighed 63.9 kg with a body mass index of 24 kg/m^2, blood pressure of 141/94 mm Hg, and heart rate of 108 beats/min at admission. She had 2 random blood glucose levels of 146 mg/dL and 90 mg/dL on day 1 and 3, respectively. Urine drug screen was positive for amphetamines, marijuana, and cocaine. Her only home medication was hydrochlorothiazide 25 mg PO daily.

Upon admission to inpatient psychiatry, she required an emergency treatment order of chlorpromazine 100 mg intramuscular and lorazepam 3 mg intramuscular because of acute psychosis, severe agitation, and an attempt to elope and attack staff. Because of minimal improvement in severity of psychotic symptoms, on day 3 she was initiated on olanzapine 5 mg PO at bedtime and subsequently titrated to olanzapine 5 mg every morning and 20 mg PO at bedtime. Iron studies were completed on day 3 and ferrous sulfate 325 mg PO 3 times daily was initiated. Amlodipine 5 mg PO daily was initiated on day 6 and titrated to 10 mg daily on day 12 because of elevated blood pressure. On day 15, she complained of frequent urination and unquenchable thirst for the last 2 days. Blood glucose was checked, and she had 2 critical readings >500 mg/dL. No other blood glucose readings were taken after olanzapine was initiated; therefore, the onset of hyperglycemia was unknown. She was transferred to the emergency department and admitted to the inpatient hospital for further management. Table 1 shows olanzapine total daily dose, blood glucose readings, and units of insulin administered throughout her admission.

On day 16, her hemoglobin A1c (HbA1c) was 8% and insulin aspart sliding scale and insulin detemir 15 units subcutaneously twice daily were initiated. Olanzapine was continued by the hospitalist and psychiatry was consulted. Additionally, hydrochlorothiazide 25 mg PO daily was resumed, and ferrous sulfate was reduced to 325 mg PO daily. On day 17, the psychiatric pharmacist recommended to the psychiatrist to discontinue olanzapine as this may have contributed to her sudden onset of hyperglycemia and to initiate an alternative antipsychotic. The psychiatrist discontinued olanzapine; however, no alternative antipsychotic was initiated during the medical admission.

TABLE 2: Olanzapine-induced hyperglycemia case reports[4-35]

Citation	Age, y, and Sex	BMI, kg/m^2	History of Diabetes Mellitus	Total Daily Dose, mg	Onset of Hyperglycemia	Blood Glucose Improved After Olanzapine Discontinued	New Antipsychotic
Agarwal et al[4] (2016)	45 M	...	...	...	3 mo	Yes	Risperidone
Avella et al[5] (2004)	37 F	43.5	No	15	3 y	...	...
	27 M	42.3	No	...	...	...	...
	34 M	23	No	...	4 mo	...	...
Bettinger et al[6] (2000)	54 M	25	Yes	10	12 d	Yes	Quetiapine
Bonanno et al[7] (2001)	31 M	30.7	No	10	6 wk	Yes	Perphenazine
	44 M	26	No	15	4 mo	...	No
Fertig et al[8] (1998)	32 M	34.3	No	20	6 wk	Yes	Chlorpromazine
Frise et al[9] (2016)	27 F	37	No	20	3 wk	No	None
Gatta et al[10] (1999)	31 M	40	No	10	3 mo	Yes	Unknown[a]
Goldstein et al[11] (1999)	42 F	24.5	No	10	6 mo	Yes	Quetiapine
	40 F	27.2	No	10	17 mo	Yes	Risperidone
	41 F	...	No	10	6 mo	Yes	Yes (NR)
	47 M	...	No	10	5 wk	Yes	Quetiapine
	43 M	...	No	10	6 mo	Yes	Quetiapine
	39 M	39	No	10	3.5 mo	Yes	Risperidone
	38 M	31.3	No	10	3 mo	No	NR
Howes et al[12] (2004)	41 F	29.3	No	20	3 mo	...	No
Iwaku et al[13] (2017)	32 M	16.8	No	5	3 mo	Yes	Quetiapine
Johnson et al[14] (2002)	49 M	34.2	No	20	11 mo	...	No
Lindenmayer et al[15] (1999)	50 M	...	No	30	>6 mo	Yes	Fluphenazine monotherapy continued
Kohen et al[16] (2008)	89 M	28	No	10	3 d	Yes	Aripiprazole
Kumar et al[17] (2011)	54 M	...	No	...	10 d	Yes	Trifluoperazine
	33 M	...	No	...	40 d	Yes	Aripiprazole
	48 M	...	No	...	2 wk	Yes	Pimozide
	37 M	...	No	...	11 d	Yes	Quetiapine
Kyriazis et al[18] (2006)	33 M	...	No	20	4 mo	Yes	Risperidone
Muench et al[19] (2001)	38 M	27	No	20	12 mo	...	No
Ober et al[20] (1999)	45 M	...	Yes	10	4 mo	Yes	NR
Ragucci et al[21] (2001)	46 F	39	No	15	14 mo	Yes	Risperidone
Ramankutty et al[22] (2002)	51 F	27	Yes	30	3 wk	Yes	Zuclopenthixol
Rigalleau et al[23] (2000)	55 M	28	No	20	4 mo	Yes	NR
	41 M	40	No	...	3 mo	Yes	NR
Roefaro et al[24] (2001)	51 M	...	No	20	6 mo	Yes	NR
Seaburg et al[25] (2001)	27 M	27	No	10	29 mo	...	No
Selva et al[26] (2001)	16 F	...	Yes	15	6 mo	Yes	Risperidone
Straker et al[27] (2002)	44 F	...	No	25	1 mo	Yes	Ziprasidone
Torrey et al[28] (2003)	45 M	32.7	No	30	1 mo	...	...
Tsuchiyama et al[29] (2004)	28 M	28.7	No	10	1 mo	Yes	NR
Van Meter et al[30] (2001)	Unknown M	...	No	20	3 y	Yes	Haloperidol
Varma et al[31] (2007)	35 F	28.4	No	10	6 wk	No	Risperidone
Waldman et al[32] (2002)	33 M	23	No	30	3 mo	Yes	Quetiapine

TABLE 2: Olanzapine-induced hyperglycemia case reports[4-35] (continued)

Citation	Age, y, and Sex	BMI, kg/m²	History of Diabetes Mellitus	Total Daily Dose, mg	Onset of Hyperglycemia	Blood Glucose Improved After Olanzapine Discontinued	New Antipsychotic
Wilson et al[33] (2003)	48 M	...	No	30	10 mo	...	No
	38 F	...	No	15	2 mo	...	No
Wirshing et al[34] (1998)	38 M	...	No	25	3 mo	...	No
	56 M	...	No	25	3 mo	...	No
Wong et al[35] (2007)	22 M	24.6	No	10	3 y	Yes	Haloperidol

F = female; M = male; NR = none reported.

[a]Case report does not specify which antipsychotic(s) were prescribed; olanzapine was added to his typical neuroleptics and olanzapine was discontinued after hyperglycemia. Case report states he was discharged on usual antipsychotic treatment without olanzapine.

There were no overt manic symptoms, psychosis, or suicidal or homicidal ideation documented in the psychiatry progress notes. Additional medication changes on day 17 included 1 dose of as needed hydroxyzine pamoate 25 mg, lisinopril 10 mg PO daily which was increased to 40 mg on day 19. Increasing amounts of insulin were required, despite discontinuing olanzapine and initiating a 45-gram consistent carbohydrate diet on day 18. Her blood glucose stabilized on insulin detemir 60 units subcutaneously twice daily and insulin aspart 15 units subcutaneously 3 times daily with meals in addition to sliding scale insulin aspart. On day 22, she was transferred back to inpatient psychiatry, and a 3 kg weight increase was noted from day 1.

Once she transferred back to inpatient psychiatry, she was largely at baseline and no longer experienced symptoms of acute psychosis, mania, or suicidal ideation. She agreed to begin ziprasidone 20 mg PO twice daily with meals for bipolar disorder maintenance therapy because of the lower metabolic risk compared to olanzapine. On day 24, her fasting blood glucose was 159 mg/dL, and she was discharged from inpatient psychiatry. Discharge diagnoses included bipolar disorder, amphetamine and cocaine use disorder, hypertension, microcytic anemia, and new onset diabetes mellitus. The discharge medication list included ziprasidone 20 mg PO twice daily with meals, insulin detemir 60 units subcutaneously twice daily, insulin aspart 15 units subcutaneously 3 times daily, lisinopril 40 mg PO daily, amlodipine 10 mg PO daily, hydrochlorothiazide 25 mg PO daily, and ferrous sulfate 325 mg PO daily. No follow up on blood glucose control could be obtained after discharge.

Literature Review

A review of the literature was completed using PubMed to identify previous case reports of olanzapine-induced hyperglycemia to establish whether a history of GDM was a known risk factor. Keywords searched included *olanzapine*, *hyperglycemia*, *diabetes mellitus*, and *gestational*. Similar article results and references of included cases were searched to identify additional case reports. No date restrictions were applied and only case reports available in English were included.

A total of 47 previous cases[4-35] of olanzapine-induced hyperglycemia were identified, and they are summarized in Table 2. Age ranged from 16 to 89 years (mean = 40.8 years, median = 40.5 years). Ethnicity was primarily White (n = 16) and African American (n = 14), however ethnicity was not reported in 13 cases and listed as "other" in 4 cases. Additionally, most cases were male (n = 35) and either overweight (n = 11) or obese (n = 12).[4-35] Only 4 cases[6,20,22,26] reported a history of diabetes mellitus, 2 of which were female with no known history of GDM.[22,26] One case[9] of GDM was identified, the diagnosis occurred during a fourth pregnancy while taking olanzapine.

Olanzapine daily dose ranged from 5 to 30 mg (mean = 16.5 mg). Onset of hyperglycemia after initiating olanzapine ranged from 3 days to 3 years (mean = 6.5 months, median = 3 months). Most cases required treatment for hyperglycemia with insulin, although a small proportion were managed on oral diabetes medications.[4-35] Olanzapine was continued in 9 cases, most commonly because of significant improvement in psychiatric symptoms or well-controlled blood glucose with oral diabetes medications or low dose insulin.[7,12,14,19,25,33,34] Olanzapine was discontinued in 34 cases and an alternative antipsychotic was initiated in 27 cases, the most common alternatives were risperidone (n = 7) and quetiapine (n = 7).[4-35] Once the antipsychotic was switched from olanzapine, some cases were able to reduce insulin dosing or discontinue diabetes treatment altogether.* Three case reports[16,30,32] included a rechallenge of olanzapine, and all reported a recurrence of hyperglycemia.

References 4, 6, 8, 10, 11, 15, 18, 20-25, 29, 33

Discussion

There are several proposed mechanisms of olanzapine-induced hyperglycemia, all of which are not fully understood. Antipsychotics may cause hyperglycemia by reduced insulin secretion and increased insulin resistance. It is well known SGAs may cause a rapid weight gain within 6 to 8 weeks of initiation, which may contribute to insulin resistance and subsequently hyperglycemia. Additional mechanisms are thought to be present because of cases where hyperglycemia develops rapidly with minimal to no change in weight.[36] In addition to weight gain causing insulin resistance, antipsychotics likely have a direct effect by inhibiting insulin signaling pathways.[37] Antipsychotics may also reduce insulin secretion involving effects on multiple receptors including dopamine, serotonin, muscarinic, and alpha-adrenergic receptors.[37] They may further reduce insulin secretion by direct damage to pancreatic beta-cells causing impairment or cell death.[36-38] In women who develop GDM, similar mechanisms may cause hyperglycemia including dysfunction of pancreatic beta-cells because of excessive insulin production as well as insulin resistance.[39] Pregnancy itself is an insulin resistant state, and additional risk factors for developing GDM include multiple pregnancies, increasing maternal age, obesity, and a family history of diabetes mellitus.[9]

In the case presented, the onset of hyperglycemia was faster compared to many previously identified cases of olanzapine-induced hyperglycemia; however, it is possible hyperglycemia was identified and treated earlier since she was hospitalized. She was not overweight nor obese, however, she had a prior history of GDM. GDM is an independent risk factor for developing type 2 diabetes mellitus later in life and is a common complication affecting approximately 15% of pregnancies worldwide.[39,40] GDM is diagnosed when hyperglycemia is present in a woman with no known history of diabetes mellitus, as measured by an oral glucose tolerance test performed at or after 24-weeks gestation.[41] Risk factors for development of GDM include obesity, age, and family history of diabetes.[39]

Additionally, a recent systematic review and meta-analysis[42] reported an increased risk of GDM in women using antipsychotics during pregnancy; however, more research is needed to stratify the risk of various antipsychotics. This literature review identified 1 case[9] of GDM development during a fourth pregnancy while taking olanzapine. Olanzapine was continued throughout the affected pregnancy, and GDM was treated with metformin. She delivered via emergency cesarean section due to severe euglycemic ketoacidosis precipitated by vomiting. Hyperglycemia persisted after delivery, and metformin was continued. During her previous pregnancies she was not taking antipsychotics, and the pregnancies were not complicated by GDM. Furthermore, GDM occurred in 1 case[43] involving the use of clozapine. Clozapine was continued during pregnancy, and blood glucose was controlled with insulin.

In this case, ziprasidone was initiated after olanzapine was discontinued because of lower metabolic risk. A case report by Spivak et al[44] suggests ziprasidone as a potential alternative for patients who develop olanzapine-associated hyperglycemia, however 3 case reports[45-47] of ziprasidone-associated hyperglycemia have been reported. Previous literature reviews have also identified case reports of hyperglycemia induced by aripiprazole, clozapine, quetiapine, and risperidone.[48] Given their collective metabolic risks, SGA selection in any patient should consider a variety of factors including patients' diagnoses, past medication trials, medication allergies, comorbidities, and past medical history, including GDM.

This case report further contributes to reports of olanzapine-induced hyperglycemia and identifies a history of GDM as an additional risk factor. A Naranjo score of 5 was calculated, indicating a probable adverse drug reaction. The score was calculated based upon previous conclusive reports (+1), the adverse event appeared after suspected drug was administered (+2), the adverse reaction improved when the drug was discontinued or a specific antagonist was administered (+1), and the adverse event was confirmed by objective evidence (+1). All other questions on the probability scale scored zero. A notable limitation of this case report is the possibility of undiagnosed type 2 diabetes mellitus, as evidenced by the patient's insulin needs at discharge and an inpatient HbA1c of 8%. It is possible olanzapine exacerbated underlying hyperglycemia. Therefore, this case emphasizes the importance of obtaining baseline laboratory monitoring for all patients beginning SGAs, especially those with a history of GDM.

Conclusion

There are several previous case reports of olanzapine-induced hyperglycemia, however this is the first case report to identify GDM as a potential risk factor. This case emphasizes the importance of obtaining baseline glucose monitoring for all patients beginning olanzapine treatment, especially those with a history of GDM. If hyperglycemia develops, olanzapine may need to be discontinued and/or treatment with oral diabetes medication or insulin may be necessary. Pharmacists are well positioned to identify a history of GDM as a potential risk factor for developing olanzapine-induced hyperglycemia and recommend appropriate adjustments to treatment.

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