Diabetes Mellitus Associated with Atypical Antipsychotic Medications: New Case Report and Review of the Literature

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Background: **Since the introduction of atypical antipsychotic medications, beginning with clozapine in 1990, several case reports in the psychiatric literature have suggested that they might be associated with new onset of diabetes mellitus as well as with diabetic ketoacidosis.**

Methods: **We report the case of a 38-year-old patient with schizophrenia who suddenly developed diabetes mellitus and ketoacidosis 12 months after starting olanzapine. Similar cases in the literature were found through a MEDLINE-assisted search using the key words "schizophrenia," "diabetes mellitus," "ketoacidosis," and "adverse drug reaction."**

Results: **Including this case, 30 patients have been reported in the literature to have developed diabetes or have lost diabetic control after starting clozapine, olanzapine, or quetiapine. Twelve of these 30 developed diabetic ketoacidosis. Two limited quantitative studies have added evidence toward this association.**

Conclusion: **Although a causal relation has not been definitively proved, the number of cases reported in the literature suggests there might be an association between atypical antipsychotic medications and diabetes mellitus. Primary care physicians who care for patients with schizophrenia should be aware of this possible association. (J Am Board Fam Pract 2001;14:278–82.)**

During the past 6 years several case reports have surfaced in the literature that seem to associate diabetes mellitus with use of new atypical antipsychotic medications. Although these cases most likely represent type 2 diabetes mellitus, several of the patients initially had diabetic ketoacidosis, raising interesting questions about possible causal mechanisms besides the weight gain known to be associated with these atypical antipsychotic medications. We describe the case of a patient with schizophrenia who came to our office with new-onset diabetes and diabetic ketoacidosis, possibly associated with his use of olanzapine. We review other cases thus far reported in the literature concerning this association.

Methods

We report the case of a 38-year-old patient with schizophrenia who suddenly developed diabetes mellitus and ketoacidosis 12 months after starting olanzapine. Similar cases in the literature were found through a MEDLINE-assisted search using the key words "schizophrenia," "diabetes mellitus," "ketoacidosis," and "adverse drug reaction."

Case Report

A 38-year-old white man established care at our office in December 1997 for management of his nonpsychiatric medical problems. His schizophrenia and auditory hallucinations were being treated through the county mental health system. His medications at his initial visit included valproic acid, paroxetine, risperidone, and ibuprofen for headaches. His height and weight were 5 ft 10 in and 187 pounds. His body mass index was 27 kg/m^2. His medical history was notable for hepatitis A infection several years earlier, intravenous methamphetamine abuse, and multiple psychiatric admissions. He smoked one pack of cigarettes per day, rarely used alcohol, and denied any further use of illicit drugs. He was unsure of his family medical history but thought his father might have had juvenile-onset diabetes.

During the next year, he came to our office only twice, complaining of leg pain, tension headaches, and onychomycosis. At the same time, his nurse

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practitioner in the county mental health system was attempting to adjust his psychiatric medications to control his auditory hallucinations as well as side effects, primarily weight gain. By early 1999 his weight had increased by 30 pounds to 217 pounds, for a body mass index of 31 kg/m^2. A random blood glucose level measured as part of his drug monitoring was 170 mg/dL. He was referred to our office, where two separate fasting blood glucose measurements were 73 and 97 mg/dL. During a psychiatric hospitalization in April 1999, his medication was switched from risperidone to olanzapine. During the next 9 months he was seen only twice, for an upper respiratory tract infection and headache, but within that time he had an additional 30-pound weight gain.

In April 2000 he complained of polyuria and polydipsia. He was alert and feeling normal otherwise. His medications included 20 mg of olanzapine daily, as well as venlafaxine, valproic acid, atorvastatin, and propranolol. His capillary blood glucose level was higher than the range of the office glucometer, but his urine dipstick was negative for ketones. He was considered to have new-onset type 2 diabetes. As his condition appeared to be stable, he began outpatient treatment. Laboratory tests were ordered, and 500 mg of metformin twice daily was prescribed. At a follow-up visit 2 days later, he continued to appear stable. His polydipsia and polyuria were resolving, and his capillary blood glucose level was improving at 360 mg/dL. Three days later he returned to the office, complaining of nausea, vomiting, and dizziness with standing. His capillary blood glucose level was again above the range of the office glucometer, and now his urine was positive for ketones. He was transferred to the hospital for treatment.

His admission laboratory tests were as follows: sodium 123 mEq/L, potassium 4.7 mEq/L, chloride 84 mEq/L, bicarbonate 15 mEq/L, blood urea nitrogen 34 mg/dL, creatinine 2.2 mg/dL, glucose 765 mg/dL, calcium 9.2 mg/dL, ketone bodies 100 mg/dL, serum osmolality 342 mOsm/kg, urine osmolality 651 mOsm/kg, triglycerides 6589 mg/dL, white cell count 11.3 $\times$10/μL, hematocrit 42.5%, platelets 337$\times$10/μL, and hemoglobin A_{1C} 13.4%. His condition was diagnosed as diabetic ketoacidosis, and he was started on an insulin drip and intravenous fluid resuscitation. His nausea and vomiting resolved overnight, and his blood glucose dropped to just above 200 mg/dL. He required large doses of intravenous insulin (9 U/h) and then subcutaneous insulin (80 U of 70/30 human insulin in the morning and 35 U in the evening) initially to control his blood glucose level.

No source of infection was found, and he was not given antibiotics. The patient took part in diabetes and dietary education and was released from the hospital 4 days after admission. Two months after discharge, his insulin requirements were halved. Blood tests were negative for islet cell antibodies and glutamic acid decarboxylase antibodies, making it unlikely the patient had an autoimmune type 1 diabetes mellitus. After discussion with his mental health nurse practitioner, we decided to continue olanzapine because it so effectively controlled his hallucinations.

Discussion

The newer atypical antipsychotic medications include clozapine (Clozaril), risperidone (Risperdal), olanzapine (Zyprexa), and quetiapine (Seroquel). Introduced first with clozapine in 1990, they have been widely prescribed. Olanzapine has been administered to more than 1.2 million patients.[1] Atypical antipsychotic medications are more effective than the conventional antipsychotic medications (eg, chlorpromazine and haloperidol), especially for treating such symptoms of schizophrenia as social withdrawal, blunting of affect, impoverished speech, and apathy. Atypical antipsychotic medications are also better tolerated, causing fewer tardive dyskinesias and extrapyramidal side effects.[2,3]

Beginning in 1994, case reports began appearing in the psychiatric literature expressing possible associations between clozapine and diabetes mellitus.[4–11] Beginning in 1998, reports surfaced associating olanzapine with diabetes.[1,11–16] There has been one case reported concerning diabetes and quetiapine,[17] and there have been no reports associating diabetes with risperidone. Table 1 details the 29 cases previously reported in the literature, as well as this current case.[1,5–13]

Only two studies thus far have attempted to quantify the association between atypical antipsychotic medications and diabetes mellitus. Hagg et al[18] compared a cohort of 63 patients taking clozapine with 67 patients taking conventional depot neuroleptic medications. None of the patients were known to have diabetes before the study. All were

Table 1. Patients (30) in 16 Reports of Possible Association Between Atypical Antipsychotic Medication and Either New-Onset Diabetes Mellitus, Loss of Diabetes Control, or Diabetic Ketoacidosis.

Patient No. and Author	Year	Medication	Age	Diagnosis	Weight Change (Pounds)	Event
1. Kamran et al[4]	1994	Clozapine	41	Schizophrenia	NR	New-onset diabetes mellitus
2. Koval et al[5]	1994	Clozapine	34	Schizophrenia	NR	Diabetic ketoacidosis
3. Kostakoglu et al[6]	1996	Clozapine	42	Psychotic disorder	NR	Diabetic ketoacidosis
4. Peterson & Byrd[7]	1996	Clozapine	46	Schizophrenia	0	Diabetic ketoacidosis
5. Ai et al[8]	1997	Clozapine	30	Schizophrenia	NR	Diabetic ketoacidosis
6. Koren et al[9]	1997	Clozapine	37	Schizophrenia	NR	New-onset diabetes mellitus
7. Popli et al[10]	1997	Clozapine	32	Schizophrenia	+8	Diabetic ketoacidosis
8. Popli et al[10]	1997	Clozapine	44	Schizoaffective disorder	+3	New-onset diabetes mellitus
9. Popli et al[10]	1997	Clozapine	51	Schizophrenia	0	Loss of diabetic control
10. Popli et al[10]	1997	Clozapine	51	Schizophrenia	NR	Loss of diabetic control
11. Wirshing et al[11]	1997	Clozapine	47	Schizophrenia	+24	New-onset diabetes mellitus
12. Wirshing et al[11]	1997	Clozapine	32	Schizoaffective disorder	+56	Diabetic ketoacidosis
13. Wirshing et al[11]	1997	Clozapine	43	Schizophrenia	+7	New-onset diabetes mellitus
14. Wirshing et al[11]	1997	Clozapine	41	Not reported	0	New-onset diabetes mellitus
15. Wirshing et al[11]	1997	Olanzapine	38	Schizophrenia	+14	New-onset diabetes mellitus
16. Wirshing et al[11]	1997	Olanzapine	56	Schizophrenia	0	New-onset diabetes mellitus
17. Fertig et al[12]	1998	Olanzapine	32	Psychotic disorder	NR	New-onset diabetes mellitus
18. Gatta et al[13]	1998	Olanzapine	31	Schizophrenia	−9	Diabetic ketoacidosis
19. Goldstein et al[1]	1999	Olanzapine	42	Schizoaffective disorder	+71	Diabetic ketoacidosis
20. Goldstein et al[1]	1999	Olanzapine	40	Schizophrenia	+10	Diabetic ketoacidosis
21. Goldstein et al[1]	1999	Olanzapine	41	Bipolar disorder	NR	New-onset diabetes mellitus
22. Goldstein et al[1]	1999	Olanzapine	47	Schizoaffective disorder	+30	New-onset diabetes mellitus
23. Goldstein et al[1]	1999	Olanzapine	43	Bipolar disorder	+25	New-onset diabetes mellitus
24. Goldstein et al[1]	1999	Olanzapine	39	Schizoaffective disorder	−6	New-onset diabetes mellitus
25. Goldstein et al[1]	1999	Olanzapine	38	Schizophrenia	0	New-onset diabetes mellitus
26. Lindenmayer & Patel[14]	1999	Olanzapine	50	Schizophrenia	+21	Diabetic ketoacidosis
27. Ober et al[15]	1999	Olanzapine	45	Major depression	NR	Loss of diabetes control
28. Sobel et al[17]	1999	Quetiapine	42	Bipolar disorder	NR	Diabetic ketoacidosis
29. Bettinger et al[16]	2000	Olanzapine	54	Personality disorder	+28	Loss of diabetes control
30. Muench & Carey	2000	Olanzapine	38	Schizophrenia	+30	Diabetic ketoacidosis

NR – not reported.

screened with two random blood glucose measurements. Those with an abnormal screening result were tested more definitively with a 2-hour glucose tolerance test. In the clozapine group, 12% had diabetes and 10% had impaired glucose tolerance. In the conventional medication group, 6% had diabetes and 3% had impaired glucose tolerance. This difference between the two groups did not quite reach a statistical significance of $P = .05$ (the P value was .06) possibly because the control group was significantly older than the clozapine group.

Recently, Henderson et al[19] reported on a 5-year follow-up study of 82 outpatient clinic patients taking clozapine. The average age for this group was 36.4 years, and mean body mass index was 26.9. During the follow-up period, 36.6% of these patients had diabetes diagnosed. Although there was no comparison group, this level of diabetes incidence in a younger population seems greater than one would expect by chance.

Is there truly a higher than normal incidence of diabetes and diabetic ketoacidosis in these patients? Even though there are enough case reports in the literature to cause concern, the two quantitative studies are hampered by small size and lack of a control group. There have been no good large-scale epidemiologic trials or randomized controlled trials proving a causal relation. Previous studies in the past several decades seem to indicate that persons with schizophrenia have a higher rate of dia-

betes than the general population.[20] In the past, an association was described between diabetes and the older, conventional neuroleptic medications,[21–23] but other studies were unable to verify this association.[20,24–26]

Perhaps the most unusual aspect of these diabetes case reports is the frequency of diabetic ketoacidosis in patients with new-onset type 2 diabetes. The frequency of ketoacidosis episodes with type 2 diabetes has not been well quantified, although it is known to occur. One study reviewed all 226 admissions to a hospital for diabetic ketoacidosis during a 6-year period. Of these 226 episodes, 106 were in patients with known type 1 diabetes, 58 were in patients with known type 2 diabetes, and the remaining 62 episodes were in patients with new-onset diabetes of unknown type. In this last group, of those who were able to be observed for at least 1 year, 24.3% did not require insulin. Nineteen of the unknown-type group were checked for islet cell antibodies, and only two were found to be positive.[27] Clearly, patients who fit the description of having type 2 diabetes can have diabetic ketoacidosis, but good epidemiologic data are needed to answer the question of whether the frequency is as high as in the series of these reported cases (12 out of 30, if this current case is included).

If there is an association between the new antipsychotic drugs and diabetes, why might that be? Although these new medications are known to cause weight gain, an important risk factor for type 2 diabetes,[28–31] in at least seven of these reported cases, new-onset diabetes, worsening of diabetes, or diabetic ketoacidosis occurred in the absence of weight gain (Table 1). Furthermore, insulin resistance associated with weight gain does not explain the frequent occurrence of diabetic ketoacidosis in these cases. Several authors have speculated on possible mechanisms by which these medications might decrease insulin output, including a toxic effect on pancreatic islet cells, sympathetic nervous system dysregulation, or the physiologic effect of serotonin antagonism on the β cells.[1,11] In the absence of epidemiologic or experimental data, however, these ideas are simply speculation.

In conclusion, although the associations among schizophrenia, atypical antipsychotic medications, and diabetes mellitus (including diabetic ketoacidosis) have not been fully delineated or quantified, physicians who provide primary medical care for psychiatric patients should be vigilant concerning the possible diabetogenic effect of these medications, especially olanzapine and clozapine. Henderson et al[19] suggest that patients taking clozapine be screened for diabetes every 6 months. If atypical antipsychotic medications do contribute to obesity and diabetes, physicians should also be very concerned about possible coronary artery disease in these patients.

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