Atypical Antipsychotics and Glucose Dysregulation: A Series of 4 Cases

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There have been reports in the psychiatric literature of the association of glucose dysregulation and diabetes mellitus with the use of atypical and typical (conventional) antipsychotics. We present a series of 4 additional cases in which psychotic disorders (DSM-IV) were treated with atypical antipsychotics, and patients subsequently developed glucose dysregulation or diabetes mellitus. The implications of these findings are discussed.

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Reports of glucose dysregulation and diabetes mellitus associated with antipsychotics date back to the 1950s.[1–4] The earliest report indicating that antipsychotics might directly interfere with glucose metabolism was based on animal data from Norman and Hiestand[5] and Ryall.[6] They reported that diabetic mice treated with chlorpromazine had elevated blood glucose levels and higher mortality when compared with diabetic mice not treated with chlorpromazine. Based on these findings, there was speculation that chlorpromazine may counter insulin effects by blocking the uptake of glucose into cells.[6] There are reports of altered glucose metabolism and diabetes with all the atypical antipsychotics,[7] namely clozapine,[8–14] risperidone,[15] olanzapine,[16–20] and quetiapine.[21] In addition, diabetic ketoacidosis has also been reported with these agents.[14,22] No data are currently available on ziprasidone, which was approved by the U.S. Food and Drug Administration in February 2001 for treatment of schizophrenia. In many instances, the changes in blood glucose were not related to significant weight gain, and the alterations in blood glucose were noted in the first 12 weeks of treatment.

A study by Casey also indicated that a high proportion of patients receiving long-term therapy with olanzapine, 136 (50%) of 272 patients, or clozapine, 29 (69%) of 42 patients, gained more than 7% of their baseline weight.[23] Weight increased for 9% of olanzapine-treated patients and 15% of clozapine-treated patients. Elevated fasting glucose levels were also reported in 7 (18%) of the 39 patients taking olanzapine and 6 (38%) of the 16 patients taking clozapine.[23] Goldstein et al.[17] reported that olanzapine induced diabetes in 7 patients (6 patients on 10 mg/day, 1 patient on 20 mg/day; mean time after starting treatment = 26 weeks). Similarly, Wirshing et al.[7] reported 6 cases of new-onset diabetes mellitus in patients receiving olanzapine or clozapine with little or no weight gain.

Abnormalities in glucose metabolism and diabetes can also occur independently of increased adiposity. In a study by Newcomer,[24] schizophrenia patients being treated with olanzapine (N = 3), clozapine (N = 8), or risperidone (N = 5) and 31 healthy control subjects, matched for age and body weight, were given a 50-g oral dextrose challenge. At 75 minutes after the glucose load, the olanzapine and clozapine groups had significantly higher glucose levels and plasma insulin than did the risperidone patients or healthy subjects.[24] A report from Sweden indicated findings of elevated levels of insulin, leptin, and blood lipids in patients diagnosed with schizophrenia spectrum disorders.[25]

In this case series, we report 4 additional cases of diabetes mellitus with risperidone, clozapine, and olanzapine from a group of patients followed in a continuing day treatment program.

CASE 1

Mr. A, a 57-year-old white man who was separated from his wife, was admitted to the continuing day treatment program in August 1999 with a DSM-IV diagnosis of chronic undifferentiated schizophrenia and alcohol dependence. His family history was significant for a sister with depression who had attempted suicide in the past and a son who was also diagnosed with schizophrenia. His

drug and alcohol history revealed that he started using alcohol in his early 20s, and it became a problem at age 30. He had been in alcohol rehabilitation 6 times. The patient denied using drugs, and a urine drug screen was negative. His medical problems included peptic ulcer disease, scoliosis, hyperlipidemia, and spasmodic torticollis. There was a family history of diabetes in his mother.

Mr. A had an extensive past psychiatric history dating to age 19 when he first developed auditory hallucinations and was hospitalized at the local psychiatric hospital for 8 months. He had numerous psychiatric hospitalizations since that time. Prior to admission to the continuing day treatment program, he had been hospitalized 3 times in 1999. During the first admission, he was treated with therapeutic dosages of fluphenazine, lithium carbonate, and citalopram for an exacerbation of psychotic symptoms and low mood. His fasting blood glucose level at that time was 101 mg/dL. The patient developed severe antipsychotic-induced parkinsonism and was treated with benztropine, and fluphenazine was discontinued. The patient was maintained off antipsychotic drugs due to problems with antipsychotic-induced parkinsonism.

Psychiatrically, Mr. A did well until January 2000 when he had an exacerbation of psychotic symptoms in the form of delusions and auditory hallucinations. At that time, olanzapine therapy was started in a dosage of 2.5 mg at bedtime and increased to 5 mg at bedtime. He also developed depressive symptoms and was started on paroxetine, 20 mg daily.

In September 1999, prior to being placed on olanzapine, he was diagnosed with hyperlipidemia: cholesterol, 224 mg/dL; triglyceride level, 251 mg/dL; high-density lipoprotein (HDL), 28 mg/dL; low-density lipoprotein (LDL), 146 mg/dL; very-low-density lipoprotein (VLDL), 50 mg/dL. In March 2000, his psychotic symptoms were well controlled on olanzapine, 5 mg at bedtime, and no extrapyramidal side effects were present. During this time, the patient had been steadily gaining weight. His fasting blood sugar (FBS) in July 2000 was 150 mg/dL, and his fasting lipid profile was cholesterol, 184 mg/dL; triglyceride level, 277 mg/dL; HDL, 38 mg/dL; LDL, 91 mg/dL; and VLDL, 55 mg/dL. He was diagnosed with non–insulin-dependent diabetes mellitus and was placed on an 1800-calorie American Diabetes Association (ADA) diet. His FBS was 153 mg/dL in September 2000, which was also the highest recorded FBS while his glycosylated hemoglobin was 6.2%. His weight had increased from 159 to 194 lb (71.6 to 87.3 kg). At the end of October 2000, because of weight gain, he was gradually switched to quetiapine fumarate, 100 mg b.i.d., without any significant problems and is presently maintained on 400 mg/day of quetiapine in divided dosage.

His mental status examination revealed an overweight white man who was oriented in all spheres with normal speech. Symptoms of psychosis were well controlled, although he had sad mood and restricted affect. His thought process was goal oriented, and his memory was intact. There was no sleep or appetite disturbance. He appeared to be distressed about the financial problems of his son. There was no suicidal or homicidal ideation. The patient's judgment and insight were fair.

In summary, this patient had a family history of diabetes mellitus and developed diabetes and weight gain after being started on olanzapine treatment.

CASE 2

Mr. B, a 48-year-old black man who was separated from his wife, was admitted to the continuing day treatment program in October 1999 with a DSM-IV diagnosis of schizoaffective disorder depressive type, alcohol dependence, and nicotine dependence.

His family history revealed 3 sisters and his mother having non–insulin dependent diabetes mellitus. The family psychiatric history was significant for his father having alcoholism. His medical history included chronic pancreatitis, anemia, hepatitis, closed head injury in 1997 without loss of consciousness, and chronic obstructive pulmonary disease. He had a past surgical history of cholecystectomy, splenectomy, and removal of pancreatic cysts. The patient started using alcohol at age 16, and his alcohol use became a problem at age 23 according to his report. He had been to multiple alcohol and drug rehabilitation programs. There was a past history of drug abuse, which included cannabis and cocaine without any recent use. There was no history of intravenous drug usage. His past psychiatric history revealed a long history of depression and psychosis, with his first hospitalization at age 43 due to psychotic symptoms. In 1999, he was hospitalized due to an increase in depressive and psychotic symptoms and received 9 electroconvulsive therapy treatments without improvement according to his report. His last psychiatric hospitalization occurred in November 2000 due to suicidal ideation while he was in an inpatient alcohol rehabilitation program.

His medications at admission to the continuing day treatment program included lithium, 900 mg daily; venlafaxine XR, 150 mg q.a.m., 75 mg at bedtime; diphenhydramine, 50 mg at bedtime; clozapine, 300 mg daily (started in June 1999 in divided dosage); budesonide inhaler, 200 μg, 3 puffs q.a.m.; pancrelipase, 9000 daily; montelukast, 10 mg at bedtime; and lansoprazole, 30 mg b.i.d.

At admission to this program, Mr. B was experiencing a combination of depressive and psychotic symptoms. His clozapine was titrated up to 600 mg daily in divided dosage, and after an adequate trial of venlafaxine, he was switched to citalopram, started at 20 mg daily and increased to 40 mg daily. He was encouraged to participate in a dual-diagnosed group (because of his alcohol depen-

dence), a clozapine group, and a thought disorder group; he was also referred to case management services.

Mr. B has not had a period when his mood was neutral and he was free of psychotic symptoms. His physical health has gradually deteriorated. He has had ongoing alcohol usage and complaints of chronic pain in the right upper quadrant of his abdomen, which had progressively increased. He also has had progressive weight loss, attributed to his poor dietary habits, and he had a complete dental extraction in June 2000. He had no prior complaints of polyuria or polydipsia. His weight dropped from 180 lb (81.0 kg) at admission to the continuing day treatment program to 164 lb (73.8 kg) as of October 2000. He was referred to his medical doctor, who diagnosed diabetes. His glycosylated hemoglobin in June 2000 was 6.1% and his FBS, 214 mg/dL. As of October 2000, his fasting lipid profile revealed the following: triglyceride level, 244 mg/dL; cholesterol, 216 mg/dL; LDL, 82.1 mg/dL; HDL, 84.9 mg/dL; and VLDL, 49 mg/dL, and the glycosylated hemoglobin had increased to 12.4 mg/dL. In February 1999, his FBS was 135 mg/dL. He was referred to the diabetes clinic for management of diabetes with insulin. He continued to use alcohol and was unable to perform glucometer readings. Testing at the diabetic clinic revealed the following blood sugar level results for November 1–3, 2000: –246 mg/dL, –109 mg/dL, and –179 mg/dL, respectively. Mr. B was referred for inpatient alcohol rehabilitation because of ongoing problems with alcohol.

In summary, this patient developed diabetes 12 months after starting clozapine in the presence of weight loss.

CASE 3

Ms. C, a 36-year-old single white woman, was admitted to the continuing day treatment program in January 1999 with a diagnosis of DSM-IV depression not otherwise specified with borderline intellectual functioning. Her medical history revealed significant obesity and chronic obstructive pulmonary disease. Her admitting weight in January 1999 was 249 lb (112.1 kg). She was diagnosed with hyperlipidemia in March 2000 due to significant abnormalities in her fasting lipid profile (HDL, 50 mg/dL; cholesterol, 190 mg/dL; triglyceride level, 183 mg/dL; LDL, 103 mg/dL; and VLDL, 37 mg/dL). At that time, her blood glucose level was 80 mg/dL. Her family psychiatric history was significant for a maternal aunt with postpartum depression and a strong family history of alcoholism. The family medical history was significant for diabetes in the father.

She had an extensive past psychiatric history beginning at age 20. She had multiple psychiatric admissions, with the last hospitalization occurring in October 2000 due to suicidal thoughts lasting 8 days. During a previous hospitalization on the psychiatric unit in August 2000, she was started on risperidone, 1 mg at bedtime, due to auditory hallucinations telling her to take her life. She was discharged on paroxetine, 20 mg daily; risperidone, 1 mg at bedtime; and trazodone, 50 mg at bedtime. The risperidone was increased to 2 mg at bedtime in September 2000, and subsequently to 4 mg at bedtime in October 2000 during her hospitalization, as the auditory hallucinations persisted, and she continued to report depressive symptoms. Her hospitalizations appeared to be precipitated by social stressors resulting in symptoms of depression and suicidal ideation. In October 2000, her fasting blood glucose was found to be elevated at 166 mg/dL and 182 mg/dL on 2 occasions. She was seen by the medical service and was started on an 1800-calorie ADA diet and an exercise program for weight reduction. The patient was referred to the diabetic clinic. It should be noted that despite a family history of diabetes in the father, none of the other siblings had diabetes. A lipid profile done in October revealed no improvement (HDL, 51mg/dL; LDL, 89 mg/dL; VLDL, 60 mg/dL; cholesterol, 200 mg/dL; and triglyceride level, 298 mg/dL). Her weight was 259 lb (116.6 kg), an increase of 10 lb (4.5 kg) over 22 months.

Currently Ms. C is doing well on her present medication regimen. The auditory hallucinations and depressive symptoms are well controlled. Her psychosocial stressors are being addressed. At the last visit, her mental status examination revealed her to be a young obese woman who was short, with clear speech normal in rate and good eye contact. Her mood had improved, and her affect was less anxious. Her thought process was organized without any overt psychotic features. She had no suicidal ideation or plan. Her judgment and insight were fair, and her memory was intact.

In summary, this patient had glucose dysregulation and gained 10 lb (4.5 kg) over 22 months. She was diagnosed as having hyperlipidemia prior to being started on risperidone in March 1999. Blood glucose elevation was noted 8 weeks after starting risperidone.

CASE 4

Mr. D, a 41-year-old never-married white man at the continuing day treatment program, had a DSM-IV diagnosis of chronic schizophrenia and alcohol and drug dependence. His past psychiatric history was significant for psychiatric problems starting in his mid-20s, characterized by auditory hallucinations and delusions of persecution with impaired functioning. His history indicated multiple previous psychiatric hospitalizations and suicide attempts by medication overdose and wrist slashing.

He started using drugs and alcohol in his early teenaged years. He attended inpatient alcohol and drug treatment programs several times. His medical history revealed coronary artery disease, hypertension, hypercholesterolemia (since 1992), gastritis, and chronic recurring balanitis. In August 1996, he was noted to have elevated

liver function. In November 1996, a fasting lipid profile revealed his triglyceride level was 746 mg/dL; cholesterol, 274 mg/dL; and his HDL was low at 32 mg/dL. Due to persistent elevation of liver function, he was not placed on systemic cholesterol-lowering agents. Cholestyramine was continued along with a low cholesterol diet. In March 1997, his liver functions continued to be elevated, but his triglyceride level declined to 131 mg/dL; HDL, 40 mg/dL; and total cholesterol, 274 mg/dL. He continued on a regimen of exercise and a 1500-calorie ADA and low cholesterol diet. In December 1999, the oral hypoglycemics were discontinued, and he continued to follow the 1500-calorie ADA diet. He continued to use alcohol episodically. His fasting blood glucose was 106 mg/dL in October 2000. A fasting lipid profile revealed his triglyceride level at 295 mg/dL; cholesterol, 261 mg/dL; HDL, 45 mg/dL; and VLDL, 59 mg/dL, and his liver function had normalized.

Family history revealed that his mother had coronary artery disease and diabetes. Mr. D had a long history of exposure to antipsychotic medications such as chlorpromazine, thioridazine, and thiothixene prior to being placed on risperidone. He was started on risperidone in January 1995 with the highest dose of 12 mg daily prescribed in 1996. He was diagnosed with non–insulin dependent diabetes mellitus in March 1996 and was placed on a 1500-calorie ADA diet; metformin hydrochloride, 1000 mg twice daily; and glimepiride, 2 mg daily. His FBS at that time was 271 mg/dL.

At the present time, he is being maintained on risperidone, 7.5 mg at bedtime; propranolol, 10 mg twice daily; zolpidem, 10 mg at bedtime; fluoxetine, 40 mg daily; and vitamin C, 500 mg daily. He remains on the 1500-calorie ADA diet and exercise. His psychotic symptoms as well as depression are stabilized on his current medication regimen. He attends a group for patients who are mentally ill with comorbid drug and alcohol problems.

At the last visit to the continuing day treatment program, his mental status examination revealed him to be an obese man, alert and oriented in all spheres, with good eye contact. He was mildly anxious with an appropriate affect. He denied suicidal or homicidal thoughts. There were no overt delusions or hallucinations, and thought disorder was improved. There were no significant depressive symptoms. Judgment and insight were much improved.

In summary, Mr. D was diagnosed as having diabetes within 15 months after being on risperidone therapy. He also had lipid abnormalities, which predated his being started on risperidone.

DISCUSSION

These 4 patients suffered from psychotic disorders. All were diagnosed with diabetes after being started on an atypical antipsychotic at variable intervals of time. In the case of patient 3, the tightest link was observed between starting risperidone in August 2000 and being diagnosed as having glucose dysregulation in October 2000. For patient 1 who was taking olanzapine, there was a 6-month lag time, whereas in the case of patient 2 who was taking clozapine, there was a 15-month lag time. In the case of patient 4 who was taking risperidone, there was about a 15-month lag time between being started on risperidone in January 1995 and the diagnosis of diabetes in March 1996. Patient 4 had received up to a maximum of 12 mg/day of risperidone. It should be noted that all 4 patients had a family history of diabetes mellitus in first-degree relatives, and 3 of the patients were also significantly overweight. While the literature suggests that diabetes mellitus has occurred in patients taking atypical antipsychotics without significant weight gain, the family history issues have not been well addressed.[26] In these patients, the cause of diabetes mellitus may be multifactorial with the atypicals (as a class), along with other therapies, contributing to the problem in those patients who are already predisposed.

There is speculation that antipsychotic-induced alterations in glucose regulation might exacerbate preexisting glucoregulatory disturbances associated with schizophrenia.[24] Others suggest that the association of antipsychotics with diabetes is a function of drug affinity for the 5-hydroxytryptamine (5-HT) receptors, which are also involved in glucose homeostasis.[7] Though there is no conclusive evidence of the mechanism of antipsychotic-induced glucose dysregulation, possible mechanisms may be speculated upon based on the animal literature. Prazosin, a potent α_1 receptor antagonist, is associated with hyperglycemia in animals. Atypical antipsychotic agents such as clozapine and risperidone are potent inhibitors of the α_1-adrenergic receptors, and hence may have hyperglycemic effects.[27,28] Another possible mechanism for hyperglycemia may be related via 5-HT_2 receptor antagonism, which is associated not only with weight gain, but also with hyperglycemia.[29] The atypical antipsychotic agents cause antagonism at the 5-$HT_{2A/C}$ receptors.[28] Drugs such as methysergide and metergoline, which are 5-HT_2 receptor antagonists, are also associated with hyperglycemia.[30] Hence, this may be a likely mechanism for hyperglycemia associated with the atypical antipsychotics.

The schizophrenic population has a 2 to 4 times higher rate of diabetes mellitus compared with the general population.[31–33] In the case of bipolar patients, a 2 to 3 times higher rate of diabetes has been reported compared to the general population.[34] If we take into account poor eating habits, lack of exercise, and obesity, it is difficult to establish a strong correlation between the atypical agents and glucose dysregulation. Additionally, all of these case patients had hyperlipidemia. None of them displayed QTc abnormalities on the electrocardiogram. As there are past

reports from animal studies and reports of glucose dysregulation with chlorpromazine dating back to the 1950s, these findings cannot be ignored. There is a need for controlled studies to better assess the correlation of antipsychotic agents to hyperglycemia. In these trials, factors such as diet, family history, and weight should be adequately controlled for. Currently, there are no such published controlled studies with a large sample size investigating atypical antipsychotic-induced hyperglycemia and diabetes.

In the interim, psychiatrists, primary care physicians, and other mental health professionals should be well educated about glucose dysregulation associated with the atypical antipsychotics. With patients who are being treated with antipsychotics, primary care physicians and psychiatrists should monitor for glucose abnormalities and diabetes. Polydipsia and polyuria (symptoms of diabetes) are also associated with schizophrenia, hence fasting blood glucose would be an important screening test. Primary care physicians should be aware of such issues, as schizophrenic patients as a group are less likely to spontaneously complain about the common symptoms of diabetes. The current literature does not preclude using one or the other atypical antipsychotic medication.[35] The antipsychotic treatment should be individualized on a patient-to-patient basis, keeping the interest of the patient in the forefront.

Drug names: benztropine (Cogentin and others), budesonide (Rhinocort), chlorpromazine (Thorazine and others), cholestyramine (Prevalite), citalopram (Celexa), clozapine (Clozaril and others), diphenhydramine (Benadryl and others), fluoxetine (Prozac), glimepiride (Amaryl), lansoprazole (Prevacid), metformin hydrochloride (Glucophage), montelukast (Singulair), olanzapine (Zyprexa), pancrelipase (Cotazym and others), paroxetine (Paxil), prazosin (Minipress and others), propranolol (Inderal and others), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), venlafaxine (Effexor), ziprasidone (Geodon), zolpidem (Ambien).

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