Clinical Experience With Insulin Resistance, Diabetic Ketoacidosis, and Type 2 Diabetes Mellitus in Patients Treated With Atypical Antipsychotic Agents

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Numerous reports have associated atypical antipsychotic agents with hyperglycemia, diabetes mellitus, and diabetic ketoacidosis. Although the mechanisms are poorly understood, clinical experience suggests that these adverse effects are major areas of concern and require attention by the psychiatric team and primary care clinicians. This article discusses my clinical experience with glucose metabolism impairment related to treatment with antipsychotic medications.

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BLOOD GLUCOSE DISORDERS

DKA and Type 2 Diabetes Mellitus

Recently, case reports have linked clozapine and olanzapine to diabetic ketoacidosis (DKA), diabetes mellitus (DM), and hyperglycemia.[1–14] The reports of DKA with clozapine and olanzapine and possible increased incidence of type 2 diabetes mellitus may represent 2 separate populations with varying risks. Several cases of DKA associated with clozapine and olanzapine have been reported, with the majority of these cases resulting in partial or complete remission when the drug was discontinued.[1–3,5,6,8–10,12–18] Additionally, several cases of DKA resolved after clozapine or olanzapine was discontinued, only to have hyperglycemia return upon reinstitution of the drug. That DKA patients taken off the drug achieved remission strongly suggests that insulin secretion is affected in these patients.[1,2,5,6,8,9,12,17]

A group from the U.S. Food and Drug Administration (FDA) Research program identified 11 reports of exacerbation of existing diabetes and 131 cases of clozapine-associated new-onset diabetes from the FDA's Medwatch surveillance program.[19] The Medwatch surveillance program only captures a small percentage of likely cases. There were 37 cases of probable diabetic ketoacidosis and 8 deaths. The majority of DKA episodes occurred in the first 6 months of treatment with clozapine. One patient actually developed diabetes immediately following an accidental 500-mg dose of clozapine. This highlights the serious potential risk associated with DM and DKA and should alert clinicians to be proactive in monitoring and preventing medical morbidity associated with psychotropic medications.

A recent case report[20] described a 42-year-old, white, human immunodeficiency virus (HIV)-positive man with a history of chronic depression with psychotic features admitted to the hospital for DKA while taking risperidone, fluoxetine, and trazodone. It is unclear whether the patient received other medications that could impair glucose metabolism. Patients receiving the HIV-1 protease inhibitors often develop impaired glucose tolerance or diabetes, most likely due to an induction of insulin resistance.[21] Risperidone was discontinued, the DKA resolved, and the patient was discharged with quetiapine and subcutaneous insulin. A recent case report[22] described a 42-year-old man with a history of bipolar disorder admitted to the hospital for new-onset diabetes, requiring insulin, 1 month after beginning treatment with quetiapine. Quetiapine was discontinued, and the insulin requirement steadily declined until it was discontinued 5 months after hospitalization. Additionally, Wilson et al.[23] described 14 patients who developed diabetes and DKA (N = 5) while receiving treatment with clozapine, olanzapine, or quetiapine.

We reported a 5-year naturalistic study[15] to examine, in 101 clozapine patients with schizophrenia, the incidence of treatment-emergent DM in relation to other factors including weight gain, lipid abnormalities, age, clozapine dose, and treatment with valproate. Clozapine dose, use of valproate, and laboratory results were recorded at 6-month intervals. Nineteen patients were eliminated from the

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study secondary to a history of diabetes preclozapine, or the baseline preclozapine glucose values were not available. Diabetic patients treated with clozapine required nearly a 2-fold increase in insulin requirement or a switch to insulin from an oral hypoglycemic agent.

The mean ± SD age at the time of clozapine initiation of the 82 patients studied was 36.4 ± 7.8 years and 22 (27%) were women. During the 60-month study, 43 (52%) of the 82 patients experienced at least 1 elevated fasting blood glucose (FBG ≥ 140 mg/dL [7.7 mmol/L]) using the "old" American Diabetes Association criteria[24] and 55 (67%) of 82 patients experienced at least 1 elevated fasting blood glucose with the "new" American Diabetes Association criteria (FBG ≥ 126 mg/dL [6.9 mmol/L]).[25] Thirty (37%) of 82 patients were actually diagnosed with diabetes during the 5-year follow-up. Weight gain, valproate, and clozapine total daily dose were not significant risk factors for developing diabetes mellitus. Some patients gained weight and developed DM, while others did not gain weight but also developed diabetes. Also, several patients developed a cluster of medical disorders similar to metabolic syndrome X, which include central obesity, hyperinsulinemia, hypertension, increase in very-low-density lipoprotein (VLDL)-triglyceride and LDL-cholesterol, decrease in high-density lipoprotein cholesterol, atherosclerosis, procoagulant state, and hyperglycemia.

New patients exhibited abnormal fasting glucose values every 6 months, leading to a diagnosis of DM. It appears that the risk for developing diabetes continues as long as patients receive treatment with clozapine.

Insulin Resistance

There are a number of potential mechanisms for the association of atypical antipsychotic medications with hyperglycemia. Typically, insulin resistance is an early feature, which is initially compensated in part by increased production of insulin by pancreatic β cells (i.e., hyperinsulinemia).[26] Eventually, as β cells become exhausted, the combined effects of insulin resistance and decreased insulin production reduce insulin-mediated glucose uptake and utilization by muscle cells and prevent insulin-mediated inhibition of hepatic glucose production.

Antagonism at serotonin $(5\text{-HT})_{1A}$ receptors by atypical antipsychotic agents may decrease pancreatic β cell responsiveness to blood sugar levels, resulting in impairment of glucose metabolism.[10] However, Melkersson et al.[27] found that olanzapine-treated patients exhibited higher fasting insulin levels. Eleven (79%) of 14 patients were normoglycemic, and 3 showed increased blood glucose values. Most patients (10/14; 71%) had elevated insulin levels (i.e., above the normal limit). Eight (57%) of 14 patients had hyperleptinemia, 62% (8/13) had hypertriglyceridemia, and 85% (11/13) had hypercholesterolemia. (In 1 patient, serum lipid assessments were not performed.) Olanzapine treatment was associated with weight gain and elevated levels of insulin, leptin, and blood lipids as well as insulin resistance, with 3 patients diagnosed as having diabetes mellitus. The elevated insulin values would argue against the role of serotonin antagonism, which theoretically could reduce β cell insulin production.

We presented preliminary results of a cross-sectional study comparing clozapine-, olanzapine-, and risperidone-treated non-obese body mass index ([BMI] < 30 mg/kg^2) schizophrenia subjects who had a frequent-sampled intravenous glucose tolerance test using Bergman's Minimal Model Analysis.[28] There were no differences between the 3 groups for age, sex, race, family history of diabetes mellitus, BMI, percentage of body fat, and fasting glucose, fasting insulin, cortisol, and leptin levels. Preliminary results suggest that there is a significant difference between the 3 groups for the insulin sensitivity index with clozapine and olanzapine exhibiting significant insulin resistance. The acute insulin response to glucose (AIR), a measure examining the initial response of β cells to a glucose load, was not impaired. In fact, subjects treated with clozapine and olanzapine had a nonsignificant, but greater, AIR compared with risperidone-treated subjects, whose values were considered within normal limits. Additionally, differences between risperidone and olanzapine and risperidone and clozapine were shown for glucose effectiveness, suggesting potential impairment of glucose utilization. Glucose effectiveness represents the ability of glucose, independent of insulin, to increase glucose uptake and suppress endogenous glucose production. This function is independent of glucose transporters. It is possible that administration of clozapine and olanzapine results in insulin resistance and impairs glucose effectiveness, thereby placing patients at risk for DM. Combined with other risk factors, patients may develop DM in weeks to years after initiating treatment with atypical antipsychotic agents.

Risk Assessment and Risk Factors for Diabetes Mellitus

Before placing a patient on an atypical antipsychotic agent, it is important to perform a risk factor assessment for DM and other metabolic disorders. A risk assessment should include baseline serum values, weight, BMI, age, race, family history, level of physical activity, and diet. There are a number of factors that may place someone at risk for developing diabetes. Elevated plasma glucose and insulin is a risk factor for DM.[29] High fasting insulin can be considered a reflection of insulin resistance. High BMI is a well-known risk factor for DM and is associated with insulin resistance. Family history is a significant predictor of diabetes and reflects the importance of genetic predisposition in abnormal glucose-insulin metabolism.[30]

Obesity is also a significant risk factor for diabetes mellitus. Psychotropic medications, in general, may produce significant weight gain, and the antipsychotic agents are no exception.[31] In our 5-year naturalistic study,[15] we found

that some patients treated with clozapine continued to gain weight for up to 46 months. The risk for diabetes has been reported to be approximately 2-fold in mildly obese, 5-fold in moderately obese, and 10-fold in severely obese persons.[32] The duration of obesity is a more important determinant of the risk for developing diabetes. Based on my clinical experience, patients that develop DM years after initiating treatment with an atypical antipsychotic agent had gained a considerable amount of weight that was sustained. If a patient gains a weight and maintains this weight, his or her risk for developing DM appears to be increased.

Age is another significant risk factor for diabetes. Mukherjee et al.[33] found in schizophrenic patients the risk of DM increased with age (over the age of 50 years), and we found that, in clozapine patients, the development of DM correlated with age.[15]

Race also appears to be a risk factor for diabetes. A number of populations appear to have reduced glucose metabolism and an increased risk of diabetes. This may also be the result of other factors, such as lifestyle, activity, body frame type, and diet. Many of the reports showed clozapine-associated DKA to occur in African Americans. In particular, Native Americans, Asian Indians, Australian Aborigines, Mexican Americans, Hispanics, Polynesians, and Micronesians appear to be at highest risk for type 2 diabetes mellitus, while African Americans appear to be at moderate risk.[34]

Finally, physical activity also plays a major role in glucose metabolism. Exercise expends calories and promotes leanness while lowering blood glucose and improving insulin sensitivity.[34] The sedative and fatiguing effects of antipsychotic agents may contribute to reduced activity and exercise in schizophrenic patients and thereby negatively impact glucose metabolism.

Medical consequences of diabetes: morbidity and mortality. The long-term complications from diabetes are significant and well documented in the medical literature. While the atypical antipsychotic agents appear to improve quality of life and lengthen life expectancy for schizophrenia sufferers, the potential long-term effects of diabetes may alter the life-expectancy gains.

Ophthalmic complications include diabetic retinopathy and diseases of the anterior chamber that affect vision. Diabetic neuropathy may present with sensory symptoms or deficits, motor abnormalities, or autonomic dysfunction. Diabetic nephropathy may cause proteinuria, hypertension, and a decline in glomerular filtration rate leading to renal failure. Vascular diseases are accelerated in diabetic patients. Severe peripheral vascular disease produces ischemia and predisposes to infections. Macrovascular disease leads to stroke and myocardial infarction. Diabetic enteropathy affects gastrointestinal motility. Diabetic foot is a manifestation of chronic neuropathy and vascular insufficiency.

Finally, no studies have examined the diabetic complications in the schizophrenia population. The atypical antipsychotic agents, with potential higher risk of DM, are fairly new, and DM complications often occur after years of hyperglycemia. In time, it is likely that schizophrenia patients with atypical antipsychotic agent–associated DM will experience the serious complications of hyperglycemia. Comorbidity is of great concern, as many patients will also experience obesity, hypertension, and elevated serum lipids, all risk factors for cardiovascular disease.

DOSE CHANGES OR SWITCHING AGENTS

Patients who experience an episode of DKA while receiving treatment with an atypical antipsychotic agent should be considered for alternative treatment therapies immediately. A number of reports in the literature of atypical antipsychotic agent–associated DKA suggest that when the agent is discontinued, the diabetes may resolve completely, which is also highlighted by the fact that when the agent is restarted, patients may again suffer hyperglycemia and risk another episode of DKA.

Unfortunately, for the true treatment-resistant schizophrenic patient, there are few options when DKA occurs in the context of clozapine use. The trade-off related to switching to another antipsychotic agent is the risk of worsening psychopathology, risk of hospitalization, and overall poorer outcomes. We attempted to openly switch clozapine-treated patients to olanzapine.[35] Eight (42%) of 19 patients were considered responders. Seven patients decompensated seriously enough to require hospitalization. All 7 of these patients were restabilized on clozapine treatment in the hospital, and olanzapine was discontinued. In an additional 4 patients, clinical status worsened and clozapine doses were titrated upward while olanzapine was slowly discontinued. Responders had been treated for a significantly shorter period of time with clozapine prior to the switch compared with nonresponders and were receiving a lower dose of clozapine. Some patients, particularly low-dose clozapine responders and conventional agent treatment–intolerant clozapine patients, may be candidates for a switch to an alternative agent; however, the risks are quite high for others.

We presented a case of recurrent DKA in a young Hispanic male that appeared to be dose related.[15] After the first episode of DKA, the clozapine dose was lowered from 400 mg/day to 200 mg/day, and a conventional neuroleptic was added. One month later, the clozapine dose was increased to 300 mg/day because of psychiatric decompensation. Within 4 weeks of the increase, he experienced another episode of DKA. Subsequently, the patient remained stable on 200 mg/day of clozapine, haloperidol decanoate 100 mg i.m. q. 4 weeks, and insulin. In this case, the DKA may have been dose related, and at higher doses his risk increased dramatically.

Some of our clozapine patients that developed DM have successfully resolved the DM by lifestyle changes and interventions that reduce other contributing factors to the development of DM. These include efforts for a more appropriate diet, weight loss, control of hypertension, reduction in serum lipid values, and increasing physical activity. However, when these significant lifestyle changes were abandoned, some patients experienced a reemergence of DM. If lifestyle changes are effective, they must be frequently and persistently reinforced to produce a lasting change and consistent improvement of hyperglycemia.

When unable to switch agents, an effort to find the lowest effective clozapine dose, while assuring an adequate clinical response, should be attempted. The addition of another antipsychotic agent as an adjuvant may be useful in this situation. Reinstein and colleagues[36] reported that a combination of quetiapine and clozapine resulted in reduced weight and an improvement in glucose metabolism in the 20% of patients who developed diabetes on clozapine alone. The report suggests that quetiapine may reverse the complications of weight gain and diabetes secondary to clozapine. However, upon initiation of quetiapine, clozapine doses were reduced by 25%, which may have had a greater impact than quetiapine itself. We have routinely added risperidone, as well as conventional agents, to clozapine partial responders, which may improve psychotic symptoms while also allowing for a reduction in clozapine dose.[37] However, in my experience, these interventions have done little to effectively reverse diabetes mellitus in clozapine patients.

When DM or DKA occurs in the context of other atypical antipsychotic agents (not clozapine), efforts should be made to switch to other agents. Some patients, because of the clinical response, request to continue on their present agent. However, patients who experience a DKA episode, because of the risk of mortality, should be immediately switched to another agent and lifestyle issues addressed.

TREATMENT OF DIABETES IN THE SCHIZOPHRENIA POPULATION

The majority of patients with atypical antipsychotic agent–associated DM can be effectively treated with oral hypoglycemic agent. However, a percentage of patients will require subcutaneous insulin treatment. These patients are more likely to have experienced metabolic syndrome X, which includes abdominal or central obesity, hyperglycemia, hypertension, and elevated serum lipids. In my experience, these patients gained an incredible amount of weight (up to 100 lb [45 kg] or more) after treatment with the antipsychotic agent. Occasionally, weight reduction and nutrition programs may reduce or eliminate the insulin requirement, and patients can be switched to oral hypoglycemic agents. Additionally, risperidone has been reported in the literature to be used without complications in schizophrenic patients with comorbid diabetes mellitus.[10,38,39]

When initiating an atypical antipsychotic agent in a patient with a history of diabetes, monitoring fasting as well as random glucose is vital to assure patient safety. It is possible, with the addition of an agent that impacts on glucose metabolism, that hyperglycemia will be more difficult to control. In addition, an increase in weight and serum lipids may make it difficult to maintain glucose values at desired levels. The risk of DKA may also increase significantly in this population.

CONCLUSION

The psychiatric clinic must take an active role in assisting the primary care clinicians in monitoring serum glucose values, educating patients, and encouraging appropriate diabetic diet and exercise. Communication between primary care clinicians and the psychiatric treatment teams is vital for patient compliance and safety. Some schizophrenic patients have a great deal of difficulty with regular monitoring of their serum glucose with glucometers. The psychiatric team should play a role in monitoring and educating schizophrenia patients who develop diabetes mellitus. In our clinic, we have a glucometer available to monitor patients and provide education on the appropriate use of these devices. The psychiatric team must also play an aggressive role in ensuring medical care for the medically ill psychiatric patients. A number of cases of atypical antipsychotic agent–associated DKA occurred in the context of other medical conditions such as infections and pancreatitis. An elevated white blood cell count in a clozapine-treated patient should be aggressively pursued to reduce the risk of DKA.

Although the majority of reports of atypical antipsychotic agents have been in schizophrenic patients, we have observed similar patterns in bipolar patients treated with these agents. Additionally, at an affiliate clinic, which treats Indochinese immigrants, several patients diagnosed with posttraumatic stress disorder developed DM after receiving treatment with olanzapine for mild psychotic symptoms. This treatment is complicated by the high rates of DM in this population in general, but highlights a population that may be at greater risk for atypical antipsychotic agent–associated DM.

Psychiatrists must monitor for hyperglycemia with fasting serum glucose value in this population, and relying on clinical symptoms of diabetes is risky. Patients are not likely to report classic symptoms of DM, and either psychiatrists are unlikely to ask about them or symptoms are interpreted as medication side effects. Finally, the symptoms of DM may be masked by common side effects of psychotropic medications.

In my experience, schizophrenia patients are capable of complying with fasting glucose measurements provided

that extensive outreach to families, halfway house staff, and outreach workers is conducted. Monitoring serum glycohemoglobin may be a useful alternative along with the mean glucose, which is commonly measured with the glycohemoglobin. Glycohemoglobin is commonly used to monitor a DM patient's control of hyperglycemia. However, decision parameters must be developed for psychiatrists to intervene before glycohemoglobin reaches diabetic levels (which may be weeks after a patient has already converted to DM). Monitoring every 6 months seems reasonable in this population and represents a significant increase in monitoring compared with the recommended regimen for the general population. In our study,[15] we were able to identify 29 of 30 patients with DM by fasting serum glucose at 6-month intervals.[15] While 6-month monitoring was adequate, it required an extensive program that included reaching out to supportive staff and families, education, and communication with primary health care providers.

Drug names: clozapine (Clozaril and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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