Hyperglycemia Associated With the Use of Atypical Antipsychotics

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The available literature suggests that patients with schizophrenia are at risk for diabetes mellitus and taking antipsychotic medication further increases the chance of developing non–insulin-dependent hyperglycemia. Case reports, chart reviews, and some results from clinical drug trials implicate a relationship between glucose levels and treatment with clozapine or olanzapine in patients with schizophrenia, although a few cases of hyperglycemia have also been reported in patients taking risperidone and quetiapine. These studies indicate that hyperglycemia is not dose dependent, is reversible on cessation of treatment with clozapine or olanzapine, and reappears on reintroduction of these therapies. The postulated underlying mechanisms involved in this process in patients with schizophrenia include (1) a decreased sensitivity to insulin that is independent of atypical medication, (2) an increased insulin resistance related to atypical medications, (3) the effects of atypical medications on serotonin receptors, and (4) overuse of insulin due to weight gain. These mechanisms are discussed in detail, and recommendations for the administration of atypical antipsychotics are offered. Overweight, ethnicity, family or personal history of diabetes mellitus or hypertension, and weight gain during the course of treatment have all been identified as risk factors in the development of hyperglycemia in patients with schizophrenia. However, it is difficult to statistically assess the true incidence of diabetes within each type of antipsychotic medication group with the exclusive dependence on available case studies and without proper epidemiologic research.

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Traditionally, diabetes mellitus is classified into 3 groups: type 1, type 2, and gestational diabetes mellitus. Type 1, or insulin-dependent diabetes mellitus, usually has its onset in childhood or the early teenage years and therefore used to be called "juvenile-onset diabetes." Individuals with type 1 diabetes mellitus are insulin-dependent at all times. Total loss of pancreatic β-islet function occurs, and its mechanism is probably of autoimmune and strong genetic origin. The onset of type 2, or non–insulin-dependent diabetes mellitus, is usually between 30 and 45 years of age. The underlying mechanism relates to insulin resistance, and, in most cases, these patients can be maintained on treatment with oral antiglycemic drugs. Gestational diabetes occurs during some pregnancies in women without a previous history of type 1 or type 2 diabetes and disappears after pregnancy. The type of diabetes pertinent to hyperglycemia in patients with schizophrenia is type 2.

According to the American Diabetes Association,[1] symptoms of diabetes are polyuria, polydipsia, unexplained weight loss, and hyperphagia. Polyuria is due to the osmotic changes produced by high levels of glucose in the bloodstream that drain the water out of the tissue compartment. Casual plasma glucose levels of ≥ 200 mg/dL, a fasting plasma glucose level of > 126 mg/mL, and a 2-hour-postglucose level of ≥ 200 mg/dL during an oral glucose tolerance test with 75 g of glucose are strong indicators of diabetes. If these criteria are met on a subsequent day by any of the 3 methods listed, the diagnosis of diabetes is established.

Type 1 diabetes mellitus can develop rapidly and sometimes with acute symptoms, whereas type 2 tends to develop more gradually. A very common risk factor for type 2 diabetes mellitus is obesity (> 20 lb [> 9 kg] over regular weight). Acute ketoacidosis can sometimes be life-threatening and can be due to unrecognized diabetes mellitus with resulting high glucose and ketone levels. However, patients who develop acute ketoacidosis are generally

diagnosed and treated. The long-term complications of diabetes mellitus are extremely important in terms of morbidity and mortality of patients diagnosed with diabetes mellitus. The main complications include long-term microvascular effects, such as retinopathies that lead to blindness, nephropathies that culminate in kidney failure, and peripheral neuropathies, which can be extremely physically painful. Pain in the legs is one example that can be attributed to peripheral neuropathies. Additionally, other long-term outcomes are macrovascular complications due to high levels of cholesterol and triglycerides, peripheral vascular complications, and autonomic neuropathies.

The pathophysiologic processes underlying diabetes mellitus are complex and involve disturbances in insulin, carbohydrate, and fat metabolism. Important features are the loss of function of the pancreatic β-islets that control insulin secretion and insulin resistance at the tissue and hepatic level. The main function of insulin is to help transport glucose from the bloodstream into tissue, predominately into the tissue of the liver, forming glycogen, and into muscle tissue. If hepatic glucose production does not function properly or if insulin function is not sufficient, hyperglycemia will result. In patients with type 2 diabetes mellitus, a number of factors may contribute to the illness. For example, there may be susceptibility genes for diabetes mellitus that code for a human leukocyte antigen that in turn stimulates cellular autoimmune mechanisms directed at insulin-producing β-islet cells. Autoantibodies that recognize insulin and glutamic acid decarboxylase, viral infections, chemicals, and drugs have all been identified as leading to type 1 diabetes mellitus. Type 2 diabetes mellitus is due to insulin resistance that may be related to deficient functioning of the insulin receptor. The underlying receptor deficiency may be due to the membrane glycoprotein PC-1, which turns off insulin receptors.

PREVALENCE OF DIABETES MELLITUS

In the General Population

According to the 1995 National Health Interview Survey,[2] the prevalence of diabetes mellitus in the general population of individuals between 18 and 44 years old is 1.2%; in those between 45 and 64 years old, it is 6.3%. In a larger study of the U.S. population older than 20 years, Harris et al.[3] reported a 7.8% prevalence. This prevalence increases with age and is higher in women, blacks, Hispanics, and Native Americans. As a group, Native Americans appear to have the highest prevalence of diabetes mellitus in the nation.[4,5]

In Schizophrenia Patients Before
the Introduction of Antipsychotic Medications

The available literature on glucose studies in patients with schizophrenia before the introduction of antipsychotics indicates an enhanced risk for type 2 diabetes

mellitus in this population, even before considering the effects of conventional or atypical antipsychotics. Differences in insulin metabolism between patients with and without schizophrenia have been documented since 1926.[6] Thonnard-Neumann[7] reported a 4.2% prevalence of type 2 diabetes mellitus in patients with schizophrenia. In a study that compared outcomes of insulin loadings in 29 patients with schizophrenia and 25 normal controls, Braceland et al.[8] showed that, in subjects without schizophrenia, a normal curve arrived at its nadir at the 30-minute mark and showed a loss of > 50% of the fasting value. This indicated that glucose decreased in response to insulin. However, in the patients with schizophrenia, the nadir of the curve occurred 5 minutes later and showed only a 35% reduction in the glucose load.

Braceland et al. also administered Exton's 2-dose 1-hour glucose tolerance test to patients with schizophrenia who were not taking any antipsychotic treatment.[8] After glucose was administered, 65 of 102 patients with schizophrenia showed a flat or descending curve, indicating an overactivity of the vagoinsular system. Forty-nine of these 65 patients with schizophrenia showed an abnormal increase in the second half hour, whereas, in normal subjects, glucose levels showed a decrease during the second half hour. Thus, patients with schizophrenia demonstrated an atypical reaction to the glucose tolerance test: the glucose level after the glucose tolerance test increased more slowly, subsequently declined more gradually, and was higher overall than in normal subjects.

In Schizophrenia Patients After the
Introduction of Atypical Antipsychotics

After the introduction of phenothiazines in 1956, the prevalence rates of type 2 diabetes mellitus in patients with schizophrenia indicate a striking development. Thonnard-Neumann, who reported 4.2% in 1956,[7] found an increase to 17.2% in 1968.[9] In most studies, prevalence rates ranged from 11%[10] to 18%,[9] although a particularly low value of 2.27% was reported in Australia.[11] It appears that the prevalence of diabetes mellitus was already well known to clinicians during that time. In fact, these cases were referred to as "phenothiazine diabetes" in the literature. However, in the face of the overwhelming improvement shown in patients with schizophrenia with the introduction of antipsychotics, the occurrence of diabetes mellitus was considered to be a manageable side effect at that time.

In a recent and extensive study of U.S. national schizophrenia samples, Dixon et al.[12] examined the incidence of type 2 diabetes mellitus in 3 sample groups with schizophrenia: patients on Medicare (N = 14,182), patients on Medicaid (N = 6066), and patients from a field study (N = 719; Table 1). The investigators established a lifetime prevalence of type 2 diabetes mellitus of 14.9% and a current prevalence of 10%. The mean age of all individuals with schizophrenia was 43 years. In terms of gender

Table 1. Gender and Race Correlates of Diabetes: Field Study, Medicaid, and Medicare Samples From U.S. National Schizophrenia Samples[a]

Sample	Gender			Race			
	Men (%)	Women (%)	p	Whites (%)	Blacks (%)	Other Races (%)	p
Field study (N = 719)	10.8	21.9	< .001	11.5	18.5	17.7	< .05
Medicaid (N = 6066)	4.3	15.0	< .001	9.4	11.6	13.2	< .01
Medicare (N = 14,182)	8.8	16.7	< .001	11.7	15.5	11.4	< .001

[a]Adapted from Dixon et al.[12]

and ethnicity in the subgroups, there was a significantly higher prevalence of female patients, black patients, and "others" (ethnicity unspecified), indicating a higher risk for these individuals. Most of these patients were treated with typical antipsychotics.

International studies have revealed similar results. Tabata et al.[13] found that the prevalence of type 2 diabetes mellitus in patients with schizophrenia in Japan was 8.8%, compared with 5% in age- and sex-matched sedentary office workers. In an Italian sample, Mukherjee et al.[14] reported a 12.9% incidence of type 2 diabetes mellitus in the 50- to 59-year-old age group of patients with schizophrenia and 18.9% in the 60- to 69-year-old age group. The onset of psychosis usually preceded the onset of diabetes mellitus. In the general Italian population, the incidence was 3% and 5.5%, respectively.

ATYPICAL ANTIPSYCHOTICS AND HYPERGLYCEMIA

In reviewing case reports of hyperglycemia and diabetes mellitus during treatment with atypical antipsychotics since 1994, clozapine stands out as the agent most frequently associated with hyperglycemia (17 reports),[15–31] followed by olanzapine (10 reports).[17,29,32–39] Case reports of glucose dysregulation associated with quetiapine (4 reports)[29,33,40,41] or risperidone (2 reports)[23,42] appear less frequently in the literature. In 1 report, risperidone was administered to a patient with preexisting insulin-dependent diabetes mellitus (IDDM).[43] IDDM was controlled except during periods of acute exacerbation of psychosis when the patient failed to maintain his diet. However, it is difficult to statistically assess the true incidence of diabetes within each type of antipsychotic medication group given the exclusive dependence on available case studies and the lack of proper epidemiologic research.

In the absence of such data, it is difficult to assess the relative risk of developing new-onset diabetes mellitus while on antipsychotic therapy. Data from 2 large database studies[44,45] provide somewhat opposite results. The first is a study using the Advance PCS prescription claim database, which contains more than 300 million prescription claims per year for more than 50 million members.[44] The

incidence of diabetes was determined using prescription claims for antidiabetic agents in the general population cohort and in those who also received a prescription for a single antipsychotic medication. When patients receiving conventional and atypical antipsychotics were compared, there was no significant difference in the risk of developing diabetes, which ranged from 3.0 to 3.4 for most drugs (relative risk = 0.966, confidence interval [CI] = 0.8 to 1.1, p = .6). At the same time, the relative risk of 1.7 for quetiapine was the lowest for all of the tested antipsychotics. The hazard ratio for quetiapine climbed to levels comparable with those of the other antipsychotics when used in the top quartile of the dosing range. These data support the hypothesis that hyperglycemia may be related more closely to the underlying pathophysiology of schizophrenia than to the drugs administered for treatment.

In a contrasting study using claims data from 7933 patients with psychosis within health plans encompassing 2.5 million lives, Gianfrancesco et al.[45] reported on the frequency of newly reported diabetes mellitus in untreated patients and in patients treated with risperidone, olanzapine, clozapine, and high- and low-potency conventional antipsychotics. At 12 months of treatment, the odds of having diabetes mellitus for risperidone-treated patients were not significantly different from those of untreated patients (OR = 0.88, 95% CI = 0.37 to 2.07). The odds of developing diabetes mellitus with olanzapine, clozapine, and high-potency conventional antipsychotics were significantly higher than with risperidone (p < .05).

In most instances, hyperglycemia is not dose dependent, is reversible on cessation of treatment with olanzapine or clozapine, and reappears on the reintroduction of clozapine or olanzapine. The time to occurrence ranges from 10 days to 18 months, with an average of 3 months. An interesting observation by Mir and Taylor[46] is that there is a clear difference in the time to emergence of hyperglycemia or ketoacidosis for patients treated with clozapine compared with olanzapine. These adverse conditions may take twice as long to occur in patients treated with olanzapine than in those treated with clozapine. However, the authors acknowledge that patients taking clozapine are generally monitored more closely, and therefore hyperglycemia may simply be detected earlier in these patients. We have observed from prevailing literature that, among the traditional neuroleptics, chlorpromazine[47,48] and thioridazine are the most frequently associated with diabetes mellitus.

It seems that schizophrenia in itself is a risk factor for type 2 diabetes mellitus. This risk is enhanced if the patient is prescribed clozapine or olanzapine, and it is enhanced somewhat less with risperidone, quetiapine, and some low-potency conventional neuroleptics. One common

Table 2. Olanzapine-Treated Patients With Elevated Glucose Levels in 2 Studies of Inpatients With Refractory Schizophrenia (N = 55)[a]

Criterion for Elevated Glucose	Patients With Persistent Hyperglycemia		Patients With ≥ 1 Elevated Glucose Level		Patients With ≥ 1 Elevated Glucose Level Who Returned to Normal Glucose Levels on Continued Treatment With Olanzapine	
	N	%	N	%	N/N	%
Glucose > 140 mg/dL	3	5.5	6	10.9	3/6	50.0
Glucose > 126 mg/dL	4	7.2	9	16.4	4/9	44.4

[a]Data from Lindenmayer et al.[49] and Smith et al.[50]

Figure 1. Levels of Glucose at Baseline and During Treatment With Olanzapine (A) and Change in Glucose Values During Treatment With Olanzapine (B) (N = 55)[a]
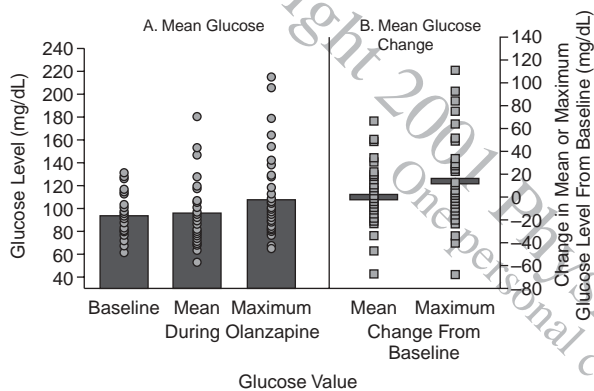
[a]Data from Smith et al.[50]

factor among clozapine, olanzapine, and low-potency conventional neuroleptics is a tricyclic molecular structure. A possible hypothesis, then, is that the glucose metabolism of patients with schizophrenia is especially sensitive to drugs with this particular molecular structure.

Data from our own studies differ from the case reports on the tendency of olanzapine and clozapine to be associated with increased occurrence of hyperglycemia or type 2 diabetes mellitus and are more consistent with the results from analyses reviewed above of large databases of patients on treatment with antipsychotic drugs. For example, in 2 studies[49,50] with a total of 55 treatment-refractory patients with schizophrenia participating in evaluations of the efficacy of olanzapine on clinical symptoms and cognition, we measured glucose levels at baseline, before starting olanzapine, and at several timepoints during 5 months of treatment (Table 2, Figure 1). Although these blood samples were drawn early in the morning, we cannot be sure that these were all fasting glucose levels. During treatment with olanzapine, only 3 (5.5%) of 55 patients had persistently elevated glucose levels by World Health Organization standards (> 140 mg/dL), and 4 (7.2%) of 55 had persistently elevated glucose by American Diabetes Association stan-

dards (> 126 mg/dL). These rates are not higher than the incidence rates of hyperglycemia or diabetes reported in a large survey of the U.S. population (6%–8%).[3] The 3 patients who developed a persistent increase in glucose levels (> 140 mg/dL) had a personal or family history of diabetes. The patients treated with olanzapine showed a significant increase in weight (7.2 lb [3.2 kg]); however, further analysis revealed no relationship between weight or weight increase and glucose levels or increase in glucose levels. Racial trends were observed: African American and Hispanic patients tended to have an increase in maximum glucose levels during treatment with olanzapine, whereas white patients tended to show a small decrease in glucose levels.

Preliminary data from another chart-review study[50] we performed of 82 patients at the same institution, which surveyed routine nonfasting glucose and lipid levels in patients treated with olanzapine or clozapine, also showed low rates of hyperglycemia using the > 126 mg/dL or > 140 mg/dL cutoff points for random glucose levels. Hyperglycemia occurred at rates of 3.7% to 4.5% and 0% to 3.1% in patients treated with olanzapine and clozapine, respectively. However, there was a relatively high proportion of patients with increased triglyceride levels (> 250 mg/dL) among the clozapine- and olanzapine-treated patients.

Risperidone also influences glucose regulation. For example, in a controlled study that we are currently performing, the most striking case of hyperglycemia and diabetes occurred in a patient who had been previously treated for approximately 2 years with risperidone (A. Khandat, M.D.; M. Wahab, M.D.; J.-P.L., et al., manuscript submitted).

In contrast to patients described in case reports by others, the patients in our studies who were treated with olanzapine or clozapine showed relatively low rates of hyperglycemia or diabetes. The reasons for the variance of our findings with those reported by other investigators is not clear. Our hospital has a large number of patients who have been hospitalized continuously for long periods and serves a relatively high percentage of African American and Hispanic patients. Because these patients are at increased risk for developing diabetes, our results should have been biased toward finding higher rates of hyperglycemia rather than the relatively low rates we reported. One explanation for our findings may lie in the possibility of selective screening. Consequently, we do not have a simple explanation for our somewhat different results.

Further information on the relative risk for hyperglycemia associated with treatment with atypical antipsychotics comes from a study from Newcomer et al. comparing 48 patients with schizophrenia with 31 healthy controls who were matched for body mass index (BMI) and age.[51] Seventeen subjects were treated with typical neuroleptic medication; 9, with clozapine; 12, with olanzapine;

and 10, with risperidone. Patients who had diabetes mellitus or possible diabetes mellitus were excluded from the study. All patients had normal glucose levels at the start of the study. Although not significant statistically, a slight difference in mean glucose pretesting levels existed, with the healthy controls having the lowest mean and the olanzapine-treated group having the highest mean. When challenged with a modified glucose tolerance test (i.e., 75-minute-postglucose challenge), the olanzapine-treated group displayed significant elevations in postload glucose levels at all timepoints, in comparison to those of untreated controls and haloperidol-treated subjects. The finding was similar for patients treated with clozapine, with an additional striking finding that mean glucose levels continued to rise at the 75-minute measurement. There were no significant differences between patients receiving typical antipsychotics and controls at any timepoints. With regard to patients treated with risperidone, mean glucose levels were significantly different at 45 and 75 minutes postload glucose, but only compared with the control group.

When plasma insulin levels during the same modified glucose tolerance test were examined, the mean for patients receiving clozapine and olanzapine was significantly higher than that of those receiving haloperidol and controls 75 minutes after administration of insulin. This suggests that patients receiving clozapine or olanzapine may generate higher levels of insulin. One possible explanation for this is that their insulin is less effective because of changes in the sensitivity of insulin receptors or in the effect of insulin on mechanisms involved in glucose transport.

UNDERLYING MECHANISMS

Decreased Tissue Sensitivity to Insulin

Several hypotheses have been postulated for the impaired glucose regulation in patients with schizophrenia, independent of the introduction of atypical medication. Even before the neuroleptic age, patients with schizophrenia showed a delay in the return of blood sugar to a normal level after administration of an intravenous dextrose solution.[52] In an early attempt to explain these findings, Meduna et al.[52] theorized that this disturbance of carbohydrate metabolism might be due to a low insulin level in the blood, slow mobilization of insulin, or the overactivity of some product of the endocrine system that inhibits the production of normal insulin. Patients with schizophrenia acquire an augmented tolerance to insulin, which increases with the duration of the psychosis and especially in the later stages.[53]

Increased Insulin Resistance

Insulin resistance is a characteristic feature of patients with impaired glucose tolerance, particularly those with type 2 diabetes mellitus. Newcomer et al.[51] proposed insulin resistance and decreased insulin secretion due to decreased pancreatic β-cell function in the development of type 2 diabetes mellitus. Similarly, clozapine and olanzapine were viewed as associated with hyperglycemia through a mechanism of insulin resistance. Homeostasis model assessment (HOMA) was used to assess insulin resistance and β-cell function using fasting glucose and insulin concentrations. HOMA measures of insulin resistance and β-cell function have been validated for characterizing diabetes and impaired glucose tolerance in population-based studies. Newcomer et al.[51] found increases in HOMA insulin resistance values in patients treated with olanzapine and clozapine compared with patients receiving typical antipsychotic medication. These increases suggest that clozapine and olanzapine might be associated with increased insulin resistance (independent of differences in adiposity).

Similar results were found in a study that compared insulin resistance in olanzapine-treated patients with schizophrenia with ziprasidone-treated patients with schizophrenia.[54] Body weight, fasting serum insulin concentrations, HOMA insulin resistance, cholesterol, and triglycerides were significantly elevated in the olanzapine group compared with baseline, suggesting a worsening of insulin resistance with olanzapine, even after accounting for weight changes. A role for insulin antibodies during treatment with clozapine or olanzapine has also been suggested[55]; however, there is at present no evidence that insulin antibodies lead to increased insulin resistance.

Insulin resistance can develop due to abnormalities at any step in the signaling pathway, including alterations in insulin receptor kinetics and signaling mechanisms. It is possible that atypical antipsychotics induce insulin resistance directly at the insulin receptor site by altering binding characteristics. Alternatively, atypical antipsychotics may decrease the number or half-life of insulin-sensitive glucose transporters, or they may interfere with transporter trafficking from the microsome to the plasma membrane.[56] The latter hypothesis has been suggested by studies demonstrating that chronic exposure to high concentrations of glucose and insulin reduces the subsequent ability of insulin to maximally stimulate glucose transport translocation.[57]

Hyperlipidemia and Hyperglycemia

Another mediating factor for hyperglycemia is weight gain. Both increased insulin secretion and hyperleptinemia may be the mechanism underlying weight gain in patients treated with atypical antipsychotics, especially olanzapine.[38] In a study of 14 olanzapine-treated patients, Melkersson et al.[38] found that 21% of the patients had elevated fasting blood glucose levels, indicating hyperglycemia, and most patients also had hyperinsulinemia and hyperlipidemia. Triglyceride concentrations were correlated with blood glucose and insulin levels. Since hyperlipidemia and hypertriglyceridemia may be associated with insulin resistance, the authors proposed that enhanced insulin secretion may be secondary to insulin resistance.

Hyperinsulinemia was demonstrated by low insulin-dependent insulin-like growth factor binding protein-1, suggesting that there was no insulin resistance at the hepatic level. However, it is not clear whether treatment with olanzapine caused hyperinsulinemia by inducing direct peripheral insulin resistance at the cellular level or by an indirect effect on lipid metabolism with secondary insulin resistance and hyperinsulinemia. Insulin is known to stimulate leptin production in adipocytes,[58] and insulin resistance with hyperinsulinemia has been associated with increased leptin levels.[59] Hence, elevated leptin levels in olanzapine-treated patients may be due to increased insulin levels and insulin resistance. Leptin is known to affect pancreatic β-cell function, where both inhibitory and stimulatory effects on insulin secretion have been reported.[60]

Effects of Atypical Antipsychotics on Serotonin Receptors

Wirshing et al.[30] postulate that the effects of olanzapine and clozapine on serotonin may partly explain the development of insulin resistance. Olanzapine and clozapine both have markedly increased binding affinity to 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_{2C}$ receptors compared with haloperidol and other conventional neuroleptics. Both olanzapine and clozapine have much greater affinities for 5-HT$_{2A/C}$ than for 5-HT$_{1A}$ receptors. It has been demonstrated in rats[61] that 5-HT$_{2C}$ antagonism plays a role with the weight gain liability of atypical antipsychotics, and 5-HT$_{2A}$ antagonism and 5-HT$_{2C}$ antagonism are processes involved in the mechanism of action of the newer atypical antipsychotics. Furthermore, clozapine, risperidone, and olanzapine block 5-HT–induced hyperglycemia in rodents.

The 5-HT$_1$ and 5-HT$_{2A}$ serotonin receptors may have opposite effects on glucose homeostasis. For example, the agonism of 5-HT$_{1A}$ receptors decreases blood glucose levels, while the antagonism decreases insulin levels and thereby produces hyperglycemia. Decreased serum insulin levels are secondary to 5-HT$_{1A}$–induced decreases in pancreatic β-cell responsiveness to blood sugar levels. In predisposed subjects, this effect might be sufficient to cause diabetes mellitus.

Although atypical antipsychotics have some activity at 5-HT$_{1A}$ sites, they are more potent at 5-HT$_{2A/C}$ sites and thus may alter glucose homeostasis. Two specific 5-HT$_{2A/C}$ receptor agonists, ($\pm$)-2,5-dimethoxy-4-iodoamphetamine and α-methyl-5-HT, have been shown to induce hyperglycemia.[62] Ketanserin, a specific antagonist of 5-HT$_{2A/C}$, was shown to have blocked the intraperitoneal 5-HT–mediated induction of hyperglycemia. At the same time, administration of ritanserin, an antagonist of 5-HT$_{2A/B/C}$ receptors, caused no alteration in blood glucose levels.[62] Thus, 5-HT$_{2A/C}$ receptors appeared to have effects opposite from those of 5-HT$_{1A}$ receptors in the glucose homeostatic network. It is therefore difficult to predict the outcome of the simultaneous blockade of 5-HT$_{1A}$ and 5-HT$_{2A/C}$ receptors

that occurs with atypical antipsychotics. Consequently, any serotonergic link between atypical antipsychotics and hyperglycemia remains speculative.

Overutilization of Insulin Due to Weight Gain

Drugs that antagonize serotonergic transmission, like atypical antipsychotics, have been found to increase food intake and thus produce weight gain. The degree of weight gain is correlated with each drug's affinity for H$_1$ receptors. Clozapine and olanzapine have been shown to induce significant weight gain in patients with schizophrenia, more than that induced by risperidone.[30] H$_1$ antagonism is well known to cause weight gain and is the suspected mechanism by which conventional medications cause weight gain. Risperidone has less H$_1$ antagonism compared with olanzapine and clozapine and may therefore cause less weight gain and be less of a risk factor for the eventual development of hyperglycemia. Thus, one potential mechanism of diabetes mellitus induction is weight gain, caused by an increase in adipose tissue that in turn leads to insulin insensitivity, glucose intolerance, and, if sufficiently severe, diabetes mellitus. It has been calculated that there is a 4.5% increase in risk for type 2 diabetes mellitus with every kilogram increase in weight.[30]

Our group examined weight gain in 151 treatment-refractory patients with schizophrenia who were randomly assigned to clozapine, olanzapine, risperidone, or haloperidol and treated for 14 weeks at conventional dose ranges (P. Czobor, Ph.D.; J. Volavka, M.D., Ph.D.; B. B. Sheitman, M.D., et al., manuscript submitted). All subjects had been treated for years with antipsychotics and had a history of suboptimal antipsychotic response. The highest net weight gain was seen in patients treated with olanzapine (mean $\pm$ SD = 5.4 $\pm$ 4.6 kg [12.0 $\pm$ 10.2 lb]), followed by that in patients treated with clozapine (mean = 4.2 $\pm$ 4.7 kg [9.3 $\pm$ 10.4 lb]). Both of these increases from baseline weight were statistically significant. Patients taking risperidone showed a modest increase in weight (mean = 2.3 $\pm$ 2.8 kg [5.1 $\pm$ 6.2 lb]), and those treated with haloperidol had basically no weight gain (mean = 0.2 $\pm$ 0.2 kg [0.4 $\pm$ 0.4 lb]). Patients who had the greatest weight gain demonstrated the best antipsychotic response. Consequently, weight gain remains a liability in patients who have been treated with various antipsychotics and continues to occur throughout the medication period. Allison et al.[63] argue that if a weight loss of as little as 5% in obese individuals can result in clinically meaningful reductions in morbidity and risk of early mortality, then weight increases of just 5% in these individuals could result in corresponding increases in morbidity and risk of early mortality.

Besides the postulated serotonergic effects of olanzapine and clozapine, some investigators suggest that the sedative effects of these atypical antipsychotics could lead to less activity and less caloric utilization.[64] Anticholinergic activ-

ity contributes to weight gain because of increased thirst that leads to increased intake of caloric drinks. Because weight gain eventually plateaus, the mechanism involved may be the resetting of controls that tend to maintain weight. However, the current literature does not support this hypothesis.

ASSESSING RISK FACTORS

Overall, it appears that various factors have to be combined to increase the risk of type 2 diabetes mellitus in patients with schizophrenia who are taking antipsychotic medication. A helpful model to interpret the various findings is an additive risk model. Risk factors that increase the probability of developing diabetes mellitus are being diagnosed with schizophrenia, being overweight prior to onset of treatment (BMI > 30 kg/m^2), and experiencing a weight increase of more than 10% during treatment. A previous history of glucose dysregulation and hypertension (> 140/90 mm Hg) further increase the risks of developing type 2 diabetes mellitus. Demographic risk factors include ethnicity (African Americans and Hispanics have higher probabilities) and a family history of diabetes mellitus. From an analysis of individual case studies, however, Mir and Taylor[46] emphasized that at least two thirds of patients had no personal history of hyperglycemia and that at least half of the subjects had no family history of hyperglycemia. Although history was not always reported, the authors stressed that an absence of a personal or family history did not prevent patients with schizophrenia who were treated with atypical antipsychotics from developing hyperglycemia.

Among the atypical antipsychotics, review of published case studies and a few small case series suggests that treatment with clozapine or olanzapine may further increase the risk for the development of diabetes mellitus. More research on the effects of quetiapine is required to establish if it poses a risk for diabetes mellitus in patients with schizophrenia. The risk of developing diabetes mellitus with treatment with risperidone appears to be somewhat less than that with clozapine and olanzapine. Based on early study results, ziprasidone, which has recently been released, may have a low liability in this regard.[54] However, firm conclusions about the relative risk for development of hyperglycemia in the context of antipsychotic treatment can only come from large epidemiologic studies with patients on treatment with various antipsychotics and adequate control populations.

CONCLUSION AND
RECOMMENDATIONS

Even before the introduction of antipsychotic medication, abnormalities in glucose regulation were reported in patients with schizophrenia. Phenothiazine diabetes was well known to clinicians and was reported in 1956.[7] Hyperglycemia during treatment with atypical antipsychotics has been well documented, with clozapine and olanzapine being implicated over risperidone. Presently, data with quetiapine and ziprasidone are somewhat limited and need further attention. However, the true incidence of hyperglycemia induced by different atypical medications is not known and will be definitively resolved only with data from proper epidemiologic studies. The mechanisms underlying glucose dysregulation during treatment with antipsychotics are not fully known, but probably involve the development of insulin resistance.

Our recommendation is to perform a risk-benefit analysis based on an additive risk model and to include the patient in the discussion of his/her treatment plans. If the patient has a high-risk profile, clinicians should consider changing or tailoring the antipsychotic treatment to the risk factors that relate to the particular patient.

Baseline and 6-month monitoring of fasting plasma glucose levels, fasting cholesterol levels, and triglyceride levels is recommended during treatment with all antipsychotics. In addition, in patients from high-risk groups, we recommend measurements every 3 months of the glycosylated hemoglobin levels, because this allows regular monitoring of glucose level elevations over time.

Baseline weight and regular follow-up weight measurements are also recommended to monitor the risk for development of hyperglycemia. If weight gain occurs, a weight reduction program should be immediately implemented.

If hyperglycemia develops during treatment with atypical medications, the patient's fasting plasma glucose level should be measured. If the results are questionable, a glucose tolerance test should be performed, and the risk-benefit factors for treatment with the antipsychotic should be reassessed. Alternatives to be considered are continuing with the same antipsychotic medication together with an antiglycemic drug regimen or switching to a different antipsychotic. Clinicians should consider using quetiapine or ziprasidone in a patient who develops hyperglycemia while treated with clozapine, olanzapine, or risperidone and who requires a change of medication.

Further studies are needed to elucidate the underlying mechanisms contributing to hyperglycemia in patients with schizophrenia who are treated with atypical antipsychotics. Given the implications for increased morbidity and mortality due to diabetes, clinicians need to be aware of the risk factors for hyperglycemia and their management.

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