Abnormalities of Glucose Metabolism Associated With Atypical Antipsychotic Drugs

John W. Newcomer, M.D.

The introduction of atypical antipsychotic drugs has provided a clear benefit for many schizophrenia patients, with less risk for the extrapyramidal side effects associated with conventional antipsychotics. However, some antipsychotics are associated with an increased risk of adverse metabolic outcomes, including weight gain, dyslipidemia, and hyperglycemia. Increases in adiposity and disturbances in glucose and lipid metabolism represent a serious health risk in a patient that may be predisposed to these metabolic conditions. The increased risk for diabetes with certain antipsychotics may be associated with the risk of treatment-induced weight gain. However, other mechanisms, including effects on central neurotransmitters and direct effects on glucose metabolism, may contribute to the development of disordered glucose metabolism. The purpose of this article is to review the association between antipsychotic medications and obesity, insulin resistance, and diabetes, including the mechanisms through which these changes might be effected.

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Atypical antipsychotic drugs have provided a clear benefit for many patients with disorders such as schizophrenia, in part due to their reduced propensity to cause extrapyramidal side effects often associated with older, conventional antipsychotics. However, some atypical antipsychotics can induce substantial weight gain in vulnerable individuals, and these agents have increasingly been associated with an increased risk for dyslipidemia and type 2 diabetes. The American Psychiatric Association, in conjunction with the American Diabetes Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity, recently sponsored a Consensus Position Conference concerning atypical antipsychotic agents and obesity and diabetes mellitus. The resulting Consensus Position Statement noted that treatment with both clozapine and olanzapine was associated with the greatest potential weight gain and consistent evidence for an increased risk of diabetes mellitus and dyslipidemia.[1] However, it was emphasized that physicians should consider multiple factors when evaluating the risks and benefits of prescribing specific antipsychotic agents and that the potential benefits of drugs with metabolic liabilities might, under certain circumstances, outweigh the potential risks (e.g., clozapine therapy in treatment-resistant schizophrenia).[1]

The development of obesity, dyslipidemia, the metabolic syndrome, or type 2 diabetes within an individual patient can depend on the contributions of drug effects (e.g., weight gain), as well as the contributions of individual host factors (e.g., family history, disease, or lifestyle), with host factors often difficult to modify in psychiatric populations. The effect of increasing adiposity on metabolic risk (e.g., insulin resistance) within populations is well known, and obesity remains a key target of primary and secondary prevention efforts by public health agencies. Emerging data may address some unanswered questions, but additional studies are clearly needed in key areas such as whether and how antipsychotic medications might alter insulin sensitivity or secretion independent of the effects of increasing adiposity in vulnerable individuals. In the meantime, current knowledge provides valuable insights that can be used by clinicians to guide treatment and monitoring decisions and provide patients with the highest standard of care.

Diabetes is a group of metabolic disorders characterized by hyperglycemia, caused by defects in insulin secretion, insulin action, or both. Diabetes is a chronic disease that represents a major burden on the health care system and a source of substantial disability to those afflicted with the disease. The American Diabetes Association estimates

From the Department of Psychiatry, Washington University School of Medicine, St. Louis, Mo.

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Corresponding author and reprints: John W. Newcomer, M.D., Department of Psychiatry, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110 (e-mail: newcomerj@psychiatry.wustl.edu).

that diabetes was associated with $132 billion in direct and indirect costs in the United States during 2002.[2] Individuals with diabetes mellitus have an increased risk for microvascular disease, including retinopathy, nephropathy, and neuropathy, as well as increased risk for macrovascular complications that include coronary heart disease and cerebrovascular disease (i.e., cardiovascular disease or the risk of myocardial infarction and stroke). Macrovascular or atherosclerotic complications produce most of the mortality associated with diabetes, currently the fifth leading cause of death in the United States.[3–6] Type 2 diabetes represents about 90% of all diagnosed cases and is often observed in association with obesity, older age, physical inactivity, and certain ethnicities. Individuals with prediabetic conditions such as impaired glucose tolerance can prevent or delay the onset of type 2 diabetes through interventions that include lifestyle management (e.g., regular exercise and monitored diet).[7]

Type 2 diabetes has been reported to occur at increased rates in psychiatric populations and sometimes in the absence of typical risk factors. The association of atypical antipsychotic treatment with the unmasking or precipitation of type 2 diabetes in some patients has led to a substantial increase in the attention given to the weight gain induced by some treatments, as well as interest in possible direct effects of drugs on insulin sensitivity and secretion.

OBESITY, DIABETES, AND ANTIPSYCHOTICS

Antipsychotic medications can cause weight gain, which is a concern given the propensity for obesity and related conditions in the United States as a whole,[8] the increased prevalence of obesity and diabetes in the schizophrenic population,[9,10] and the overall health consequences of overweight and obesity. Illustrating the increased metabolic risk faced by the psychiatric population even prior to the introduction of atypical antipsychotics, Allison and colleagues[9] analyzed data from the National Health and Nutrition Examination Survey III and reported that schizophrenia patients, particularly women, are more likely to be overweight or obese as compared with the general population. This conclusion is supported by smaller surveys; for example, a study of 226 patients being treated with depot formulations of conventional antipsychotics indicated that the prevalence of clinically relevant obesity was 4 times that of the general population.[11]

Investigators have estimated that obesity accounts for 60% to 90% of type 2 diabetes.[12] A recent study found that the prevalence of diabetes in 2001 was almost 8% in the general population of the United States, a 61% increase from 1990, and risk was significantly associated with overweight and obesity.[8] The most obese patients (body mass index [BMI] ≥ 40 kg/m^2) were 7 to 8 times more likely to have diabetes, and even patients who were simply overweight (BMI 25 to 29.9 kg/m^2) had approximately a 59% greater chance of having diabetes as compared with individuals with normal BMI. In addition, the risk of hypertension, hyperlipidemia, asthma, and arthritis was significantly increased in individuals who were overweight or obese.[8]

An earlier report on the association between obesity or weight gain and diabetes used a cohort of 114,281 female subjects from the Nurses' Health Study.[13] After 14 years of follow-up, patients with a BMI of at least 35 kg/m^2 had a 93-fold greater risk for developing diabetes mellitus. Subjects whose follow-up BMI was ≥ 25 kg/m^2 exhibited an 8-fold greater risk of developing diabetes. Subjects who started out with the highest BMIs at age 18 years and those who gained the most weight exhibited the greatest risks of subsequently developing diabetes. These relative risk ratios were supported by additional data from a different cohort[14] in which the relative risk of developing diabetes in patients who had one or both parents with diabetes and who had a BMI ≥ 40 kg/m^2 was approximately 90. As reviewed by Willett et al.,[15] the risk of developing diabetes is associated with BMI in both men and women, and increased risk occurs even in patients who are considered normal weight or slightly overweight.

The consequences of obesity are well studied and a source of major concern for public health agencies. A large study of subjects from 5 different cohort studies found that almost 300,000 deaths in the United States in 1991 could be attributed to obesity-related mortality and that more than 80% of those deaths occurred in subjects whose BMI was ≥ 30 kg/m^2.[16] Another study found that all-cause mortality associated with BMI occurred in a roughly "U"-shaped pattern and that the highest incidence of mortality was associated with the highest degrees of obesity.[17] Again, even moderate overweight was associated with increased mortality, with all-cause risk for mortality in male nonsmokers with a BMI ≥ 26.5 kg/m^2 significantly increased over those of normal weight. Obesity and weight gain are major risk factors for insulin resistance and diabetes,[18] leading to substantial concerns about the weight gain induced by some psychotropic treatment regimens, particularly certain antipsychotic medications.

A companion article[91] reviews the relationship between antipsychotic drugs and weight gain, so this will be only briefly reviewed here. Antipsychotic medications can cause weight gain in humans, with causality established by large placebo-controlled randomized clinical trials, the gold standard of evidence-based medicine. In addition, comparison of effect sizes relative to placebo, absolute weight gain observed in various trials, and head-to-head comparisons all indicate that the relative incidence and magnitude of weight gain are not equal among the different specific antipsychotic medications. A meta-analysis of both conventional (e.g., thioridazine, chlorpromazine) and newer antipsychotics (e.g., clozapine, olanzapine) revealed that most antipsychotics are associated with

some degree of weight gain after 10 weeks of treatment.[19] The estimated mean weight changes at 10 weeks for selected study drugs ranged from a maximal gain of 9 lb (4 kg) or more with olanzapine and clozapine to either no weight increase on ziprasidone or a small loss of 0.86 lb (0.39 kg) on molindone. A large retrospective study of 636 schizophrenic outpatients receiving a single antipsychotic (risperidone, olanzapine, quetiapine, or haloperidol) for at least 4 weeks found that the proportion of patients with clinically relevant weight gain (≥ 7%) was higher with olanzapine (45.7%) than with risperidone (30.6%) or haloperidol (22.4%). Olanzapine and risperidone were associated with greater risk for weight gain than haloperidol.[20]

Aripiprazole, a recently introduced atypical antipsychotic, also appears to exhibit limited risk of weight gain. A pooled analysis of 932 patients diagnosed with schizophrenia or schizoaffective disorder, most of whom were treated with aripiprazole for 4 to 6 weeks, found only minimal weight gain (1.5 lb [0.7 kg]),[21] with minimal changes in mean fasting plasma glucose no different than those observed on placebo.

Interestingly, the association of some antipsychotic treatments with insulin resistance or the onset of type 2 diabetes can occur in the absence of weight gain, suggesting that drug-related factors beyond adiposity or weight change may also contribute to risk. Newcomer et al.[22] measured effects of conventional and atypical antipsychotics on glucose regulation in chronically treated nondiabetic patients with schizophrenia compared with untreated healthy controls, with all patient and control groups matched for adiposity and age. Using a modified oral glucose tolerance test, patients receiving olanzapine and clozapine demonstrated significantly higher fasting and postload plasma glucose values compared with patients receiving conventional antipsychotics and untreated healthy controls. The risperidone-treated group did not differ from the conventional antipsychotic group but had higher postload glucose levels than the controls. Both olanzapine- and clozapine-treated patients had higher calculated insulin resistance in comparison with those treated with conventional agents, while risperidone- and typical antipsychotic-treated patients did not differ from the controls. Henderson and colleagues[23] conducted a 5-year naturalistic study of 82 outpatients with schizophrenia who were treated with clozapine. Thirty (36.6%) of the 82 patients were diagnosed with diabetes during follow-up, and while many experienced significant weight gain, others became diabetic in the absence of significant weight gain. Retrospective analyses of clozapine-, olanzapine-, and risperidone-associated cases of new-onset diabetes in the U.S. Food and Drug Administration (FDA) MedWatch database have suggested that while the majority of new-onset type 2 cases were associated with substantial weight gain or obesity, approximately 25% were not.[24–26]

INSULIN RESISTANCE, DIABETES MELLITUS, AND SCHIZOPHRENIA

A range of evidence suggests that treatment with certain antipsychotic medications, in comparison with no treatment or treatment with alternative antipsychotics, is associated with increased risk of insulin resistance, hyperglycemia, and type 2 diabetes mellitus.[27,28] Interpretation of this literature has been complicated by reports that patients with major mental disorders like schizophrenia have an increased prevalence of abnormalities in glucose regulation (e.g., insulin resistance) prior to the introduction of antipsychotic medications.[29,30] Waitzkin found that approximately 12% of 359 untreated schizophrenia patients under age 50 years, and 15% of 213 untreated schizophrenia patients over age 50 years, had diabetes, compared with a U.S. population prevalence of about 6% in 2000.[31–33] These early studies did not control for age, weight, adiposity, ethnicity, or diet, with most experts hypothesizing that differences between patients and controls on key factors such as diet and activity level can contribute to at least some of the abnormalities observed.

A recent cross-sectional study[34] in 26 hospitalized first-episode antipsychotic-naive schizophrenia patients found that 15% of these patients had impaired fasting glucose. Compared with control subjects matched for lifestyle and anthropometric measures, the schizophrenia patients exhibited higher mean fasting glucose concentrations (95.8 mg/dL vs. 88.2 mg/dL), insulin levels (9.8 μU/mL vs. 7.7 μU/mL), and cortisol levels (499.4 nmol/L vs. 303.2 nmol/L).[34] The elevated plasma cortisol levels observed in this sample probably contributed to some of the increase in insulin resistance and plasma glucose. However, hypercortisolemia is not typically observed in treated patients with schizophrenia,[22] so that this study may have overestimated the degree of insulin resistance and hyperglycemia that might be expected to persist past the acute psychotic and/or agitated condition that led to hospitalization. In any case, this study complements earlier reports in support of the view that patients with schizophrenia and perhaps other major mental disorders may have increased risk for insulin resistance and type 2 diabetes, independent of exposure to antipsychotic medications. Increased vulnerability to insulin resistance and type 2 diabetes prior to drug exposure could alternatively be viewed as (1) a reason to doubt subsequent drugs' effects on these endpoints or (2) a reason to increase clinical attention to drug effects on adiposity or other factors that could further enhance risk.

Evidence spanning case reports and case series, prospective observational studies, retrospective database analyses, and controlled experimental studies, including randomized clinical trials, has identified an association between certain antipsychotic medications and adverse metabolic events that include hyperglycemia, dyslipidemia, insulin resistance, exacerbation of existing type 1 and type

2 diabetes mellitus, new-onset type 2 diabetes mellitus, and diabetic ketoacidosis.[1,28] Adverse effects on glucose and lipid metabolism (e.g., diabetes and dyslipidemia) have more frequently and consistently been associated with treatment using clozapine and olanzapine. Relatively fewer reports have described similar events in association with quetiapine or risperidone treatment. Current evidence detailing limited short-term and long-term weight gain is consistent with little or no evidence for adverse effects on metabolic outcomes for ziprasidone and the most recently launched drug, aripiprazole.[27,28,35]

There are 3 levels of evidence that detail the association between certain antipsychotic medications and adverse metabolic events: (1) case reports, case series, and uncontrolled observational studies, typically useful for hypothesis generation; (2) retrospective database analyses, some using population-based data sets, often useful for hypothesis testing (discussed below; methodological issues can limit interpretability); and (3) controlled experimental studies, including randomized clinical trials, generally recognized as hypothesis testing.

Analyses of case reports submitted to the FDA MedWatch database concerning clozapine, olanzapine, and risperidone have suggested that most new-onset type 2 diabetes cases occur within the first 6 months of treatment initiation, are typically associated with substantial weight gain or obesity (i.e., 75%), and affect individuals without a family history of diabetes in as many as half of cases. Some cases have a close temporal relationship between treatment initiation and discontinuation and the development and/or resolution of the adverse event.[24,25] Koller and colleagues,[24–26] utilizing the FDA MedWatch surveillance database and published reports, reported on hyperglycemia associated with treatment with clozapine,[24] olanzapine,[25] and risperidone.[26] Two hundred forty-two cases of new-onset type 2 diabetes were reported in patients taking clozapine, 80 cases of metabolic acidosis or ketosis and 25 deaths during hyperglycemic episodes. Koller and Doraiswamy[25] identified 237 cases of diabetes or hyperglycemia associated with olanzapine treatment; 188 cases were new-onset diabetes. Eighty patients had metabolic acidosis or ketosis, and 15 patients died. Improved glycemic control was established in some patients subsequent to drug withdrawal or dose reduction. One hundred thirty-one reports of risperidone-associated hyperglycemia or diabetes were identified, 78 with newly diagnosed diabetes and 26 with acidosis or ketosis, along with 4 deaths.

Koller and colleagues reported on the incidence of pancreatitis associated with clozapine, olanzapine, risperidone, or haloperidol treatment,[36] noting that most cases of pancreatitis associated with these antipsychotics occurred within the first 6 months of therapy. Reports of pancreatitis occurred at higher rates in patients treated with clozapine (40%) and olanzapine (33%), in contrast to risperidone (16%) and haloperidol (12%). Wirshing and colleagues[37] conducted a chart review of 215 patients taking antipsychotics, including clozapine, olanzapine, risperidone, quetiapine, haloperidol, and fluphenazine, to assess the effect these medications have on metabolic parameters such as serum glucose or lipid concentrations. The authors found that clozapine, olanzapine, and haloperidol were associated with statistically significant increases in fasting glucose concentrations, while clozapine and olanzapine were associated with significant increases in serum triglyceride concentrations. Each antipsychotic assessed was associated with an increase in fasting serum glucose concentration, ranging from 21% with olanzapine to 3% with risperidone.

Several studies have noted an association between the use of selected atypical antipsychotics and increased insulin secretion, consistent with increased insulin resistance. Melkersson et al.[38] reported elevated insulin levels in 46% of patients receiving clozapine therapy, compared with 21% of patients receiving typical antipsychotics. A study[46,47,49,50] of olanzapine found that 71% of a limited number of patients (N = 14) exhibited elevated serum insulin levels. Additionally, the median serum concentration of insulin was significantly higher than the reference normal value. An in vitro study on pancreatic β-cells found that clozapine, but not several other antipsychotics, increased basal insulin release.[39] Similarly, increases in mean insulin and glucose levels were observed in 6 schizophrenia patients treated with clozapine.[40]

There are currently more than 20 reported retrospective analyses that aim to test the strength of the association between treatment with specific medications and the presence of diabetes mellitus using large administrative or health plan databases, with analyses funded primarily by pharmaceutical companies and a limited number published in indexed journals to date. The common underlying approach has been to measure the association within an existing database between use of specific antipsychotic medications and the presence of 1 or more surrogate indicators of diabetes mellitus (e.g., prescription of hypoglycemic agent or relevant ICD-9 codes). The clear majority of these studies indicate that drugs that induce more weight gain (e.g., olanzapine) are associated with increased risk of diabetes mellitus in comparison with no treatment, conventional treatment, or a drug producing less weight gain (e.g., risperidone). No study indicates that a drug with high weight gain potential (e.g., olanzapine) has a lower risk of diabetes mellitus in comparison with any alternative treatment condition. A minority of studies have detected no difference between groups or a nonspecific increase in the association for all treated groups versus untreated controls.

Limitations on the interpretation and generalizability of these retrospective database analyses include variable methodology, use of insurance or health plan versus population-based data sets in many but not all cases, un-

controlled cohort effects without access to relevant clinical parameters that might allow statistical controls (e.g., baseline and treatment-related weights, diet, family history, prior treatment history, and laboratory values), variable numbers of subjects exposed to comparison drugs for different periods of time leading to unequal sample sizes, limited comparability or exclusion of certain drugs, and, importantly, a limited history of prior antipsychotic and other drug exposures that makes it difficult to control for critical prior treatment effects (e.g., a 20-kg weight gain on prior treatment can impact current risk of type 2 diabetes mellitus). The most important problem with retrospective database analyses involves the use of insensitive, unreliable, surrogate diagnostic indicators for diabetes mellitus (e.g., prescription of hypoglycemic drug, ICD-9 codes). Based on American Diabetes Association[92] estimates that approximately 30% of individuals in the general population with type 2 diabetes mellitus are undiagnosed, many individuals with psychiatric disorders will have no associated hypoglycemic prescription or diabetes-related ICD-9 code to be detected in this type of analysis. Given that antipsychotic-related differences in diabetes mellitus prevalence are probably less than 33%, measurement error may complicate detection of potential relevant target signals. The significant problem with signal-to-noise ratio in studies of this type suggests that variable results, including potential failure to detect the target signal, can be expected.

Providing an example of the best of the retrospective database analyses, Koro et al.[41] used a case-control design and a large population-based sample (19,637 schizophrenia patients) from a United Kingdom database produced by a national health service that tends to encourage primary and secondary prevention (i.e., higher rates of detection of existing disease). This study found that patients treated with olanzapine had a significantly increased risk of developing diabetes compared with patients not treated with antipsychotics (odds ratio = 5.8) and compared with those taking conventional antipsychotics (odds ratio = 4.2). Patients taking risperidone had a nonsignificant increased risk of developing diabetes in relation to patients not treated with antipsychotics (odds ratio = 2.2) and those taking conventional antipsychotics (odds ratio = 1.6).[41]

Providing an example of a large study from the Veterans Administration, Sernyak et al.[42] studied a total of 38,632 patients who received either conventional neuroleptics or atypical antipsychotics (in this study, clozapine, olanzapine, risperidone, or quetiapine) over 4 months. These investigators found that patients who received atypical antipsychotics were 9% more likely to have diabetes than those who received typical antipsychotics when the effects of age were controlled and that the prevalence of diabetes was significantly increased for patients who received clozapine, olanzapine, and quetiapine, but not risperidone.[42] While a significant proportion of patients across all ages treated with either typical or atypical antipsychotics also presented with diabetes (about 19%), significant differences in the prevalence of diabetes were detected in younger age groups.

Gianfrancesco and colleagues[43] assessed the association of atypical antipsychotics and diabetes treatment in more than 16,000 patients from a large health plan database. Odds ratios based on 8 months of screening for preexisting type 2 diabetes and assuming 12 months of antipsychotic treatment were as follows: risperidone = 0.660 (95% CI = 0.311 to 1.408), olanzapine = 1.426 (95% CI = 1.046 to 1.955), quetiapine = 0.976 (95% CI = 0.422 to 2.271), and conventional antipsychotics = 1.049 (95% CI = 0.688 to 1.613), suggesting that patients treated with olanzapine for 12 months had a 42.6% greater likelihood of being treated for type 2 diabetes than untreated controls.

Buse and coworkers[44] used data from the AdvancePCS prescription claims database to examine the risk of developing diabetes in patients receiving typical or atypical antipsychotic monotherapy. Overall, 19,782 patients were treated with typical antipsychotics and 38,969 with atypical antipsychotics. Cox proportional hazard regression analysis, adjusting for age, gender, and treatment duration, showed significant increases in the risk of diabetes with all typical antipsychotics combined (hazard ratio [HR] = 3.5; 95% CI = 3.1 to 3.9; $p \leq .0001$) and all atypicals combined (HR = 3.1; 95% CI = 2.9 to 3.4; $p \leq .0001$) compared with the general population. Analysis of individual agents showed a significant increase in the risk of diabetes with haloperidol, thioridazine, risperidone, clozapine, olanzapine, and quetiapine compared with the general patient population.

An analysis of claims from the Iowa Medicaid program compared the incidence rates for diabetes in 552 patients receiving clozapine and 2461 patients receiving conventional antipsychotics (e.g., haloperidol, chlorpromazine hydrochloride) and found no significant differences in overall incidence rates for diabetes in patients receiving clozapine or conventional antipsychotics.[45] Overall, 4.0% of the 531 schizophrenia patients receiving clozapine developed diabetes (mean follow-up, 25.5 months), compared with 3.4% of the 2296 patients receiving typical antipsychotics (mean follow-up, 24.5 months). A higher relative risk for diabetes was, however, demonstrated among clozapine patients aged 20-34 years.

Shermock and colleagues[46] conducted a retrospective analysis of a Veterans Administration database to assess differences in the risk of developing diabetes during treatment with olanzapine, risperidone, haloperidol, or fluphenazine. Nearly 6000 patients were analyzed, with an overall diabetes rate of 6.3%. Olanzapine was associated with a 36% higher risk of developing diabetes compared with risperidone, while no significant differences were found between fluphenazine and risperidone or haloperidol and risperidone.

An additional U.S. case-control study[47] of more than 10,000 patients treated with antipsychotics found that while both olanzapine and risperidone were associated with increased risk of gaining at least 10 lb (4.5 kg) during the first year of treatment, only olanzapine was associated with an increased risk of developing diabetes. A population of 33,946 patients treated with olanzapine or risperidone was assessed from a Canadian database for their risk of developing new-onset diabetes; the analysis found that olanzapine was associated with a 20% increased risk of diabetes relative to risperidone, particularly within the first 3 months of treatment.[48] A retrospective study of more than 46,000 patients treated with antipsychotics found that psychiatric patients treated with thioridazine or risperidone had a higher risk of developing diabetes than did a general patient population from the same database.[49]

A case-control study using data from the California Medicaid system compared the risk of developing new-onset type 2 diabetes in schizophrenia patients treated with atypical (clozapine, olanzapine, risperidone, quetiapine) or conventional antipsychotics.[50] Patients were required to be at least 18 years old and have received continuous monotherapy during the 12 weeks prior to diabetes diagnosis. The diabetes cases were matched for age and gender with more than 8000 nondiabetic schizophrenia patients. The risk of diabetes was significantly higher with clozapine or quetiapine therapy than with typical antipsychotic treatment. Treatment with risperidone was not associated with a significantly increased risk of developing diabetes. Additional risk factors included treatment with other drugs, such as β-blockers, thiazide diuretics, or corticosteroids.

In contrast, a case-control study analyzed psychiatric patients at least 20 years of age diagnosed with new-onset diabetes (N = 7227) and compared them with a matched control group without diabetes (N = 6780), and found that clozapine treatment was not associated with an increased risk of diabetes.[51] In contrast, analysis of other antipsychotics showed an increased risk of diabetes with the typical agents chlorpromazine and perphenazine, but no increase in risk with haloperidol or risperidone.

In a retrospective study of more than 5800 patients, Fuller and colleagues[52] assessed the risk of diabetes for patients taking olanzapine or risperidone in comparison with patients treated with haloperidol or fluphenazine. The overall incidence of diabetes in the study population was 6.3%, with olanzapine treatment associated with a 37% higher risk of development of diabetes compared with risperidone or other atypical antipsychotic agents. There did not appear to be an increased risk of developing diabetes while taking risperidone relative to treatment with haloperidol or fluphenazine.[52]

A retrospective study of 76 psychiatric patients under age 60 years treated for at least 1 year with risperidone or olanzapine found that olanzapine-treated patients exhibited statistically greater increases at 1 year in triglyceride, total cholesterol, and fasting glucose concentrations than patients treated with risperidone.[53] Patients treated with olanzapine gained more mean weight (+20.4 lb [9.2 kg]) than did patients treated with risperidone (+11.9 lb [5.4 kg]), but this was not significantly different between groups. A limited number of patients also took lithium or valproate, which appeared to contribute to weight gain, particularly in the group treated with olanzapine.

In the absence of population-based epidemiologic studies using validated plasma indicators of diabetes mellitus, insulin resistance, impaired glucose control, and other measures of metabolic syndrome, physicians might make cautious use of these retrospective database analyses, for hypothesis-generation rather than hypothesis-testing, based on a thorough understanding of their limitations. Underdiagnosis, which might vary across treatment groups even in large studies, remains a concern. For example, cases of new-onset diabetes associated with some antipsychotics may not be recognized. One study of schizophrenia patients treated with clozapine in Veterans Administration medical centers found that 23% of patients who had not been previously diagnosed with type 2 diabetes had elevated plasma glucose levels, and 6% were diabetic.[54]

The third level of evidence for an association between antipsychotics and metabolic outcomes concerns controlled experimental studies, such as the Newcomer et al. study noted in an earlier section,[22] and randomized clinical trials. While several of the latter are currently in progress, a small number have been completed and are available for review.

One randomized, double-blind trial of 157 schizophrenia patients was conducted, consisting of an 8-week fixed-dose period and a 6-week variable-dose period of clozapine, olanzapine, risperidone, or haloperidol.[55] Patients were assessed for fasting plasma glucose and cholesterol concentrations at the end of both the 8-week and 6-week periods to determine the effect of these antipsychotics. There were significant increases in glucose levels at the end of the 6-week variable-dose period for patients treated with olanzapine and at the end of the 8-week fixed-dose period for patients given clozapine or haloperidol. Cholesterol levels were increased at the end of the 6-week variable-dose period for patients given olanzapine and at the end of the 8-week fixed-dose period for the patients given clozapine or olanzapine. This study was complicated by baseline and related endpoint weights in some groups that are not characteristic of those usually seen in clinical practice or other trials, underscoring the need to control for previous treatments and baseline status in future trials.

An initial review of ziprasidone clinical trial data reported no cases of treatment-emergent diabetes mellitus among the 3834 patients who had received ziprasidone.[56] Analysis of laboratory data from short-term studies shows that the incidence of abnormal elevations in random glucose measurements was the same in the ziprasidone and

placebo groups (8%). In one study, abnormal random glucose elevations occurred in 9% and 11% of patients receiving ziprasidone 80 mg/day and 160 mg/day, respectively, compared with 6% receiving placebo.[57] A study of 37 patients who were switched from other antipsychotics to ziprasidone found that following 6 weeks of ziprasidone treatment, mean nonfasting serum glucose concentrations fell from 105 mg/dL to 101 mg/dL but did not reach statistically significant difference from baseline.[58] In a study of 40 patients with mental retardation who gained excessive weight on other antipsychotic agents or were nonresponsive to treatment, ziprasidone was associated with significant weight loss and no significant change in mean fasting serum glucose concentrations after 6 months of treatment.[59]

Aripiprazole has not been associated with significant changes in glucose metabolism or new-onset diabetes. A pooled analysis of safety data from short-term (4–6 week) controlled trials of aripiprazole in schizophrenia patients found that changes in fasting serum glucose concentrations were similar between patients treated with aripiprazole and placebo.[21] The percentage of patients with fasting glucose values above the upper limit of normal was similar between the aripiprazole group (1.4%) and the placebo group (1.3%). A 26-week controlled study of aripiprazole for relapse prevention in 310 patients with schizophrenia found no clinically significant change from baseline in fasting glucose concentration.[60] At 26 weeks, aripiprazole was associated with a +0.13-mg/dL change from baseline compared with a +2.1-mg/dL change for placebo. Additionally, a 3-week controlled study of aripiprazole for acute bipolar mania found no differences in the incidence of elevated fasting serum glucose concentration between patients treated with aripiprazole and placebo.[61]

MECHANISMS OF ACTION

In the absence of data suggesting that psychiatric patients are any less susceptible to the adverse effects of adiposity than other humans, drug-induced weight gain continues to be an important focus of research interest concerning sources of metabolic risk. However, evidence that weight gain does not fully explain the association of many antipsychotics with new-onset diabetes raises questions about other mechanisms that can contribute to risk in treated patients. Considerable speculation has been directed at the possibility that similar chemical structures may confer similar patterns of adverse events, but there are currently no data to support a structure-function relationship for any metabolic outcome variable of interest. Most speculation has focused on the dibenzodiazepine-derived molecules clozapine and olanzapine that share structural similarities with quetiapine. More productive hypotheses have focused on receptor binding profiles of individual antipsychotics and the role that specific receptors play in glucose metabolism, weight gain, and appetite, including receptors for histamine, norepinephrine, and serotonin. Emerging data concerning the interaction of antipsychotic drugs and glucose transporters have also been a focus of some attention.

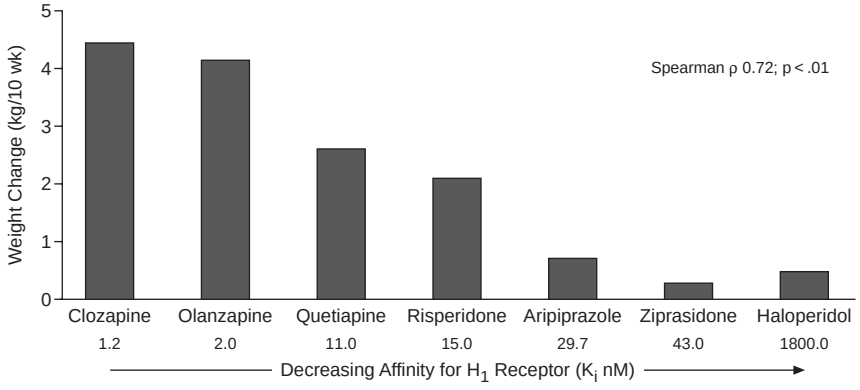
Histamine, Serotonin, and Norepinephrine

Many antipsychotics bind to and block histamine receptors, especially the H_1 receptor subtype. This activity probably contributes more to the weight gain associated with selected antipsychotics than to a direct effect on glucose metabolism. Activation of histamine receptors in the hypothalamus is associated with reduced food intake.[62] Furthermore, leptin, which is associated with anorectic behavior in animal models, may act through H_1 histamine receptors in the hypothalamus.[63] Wirshing and colleagues[64] performed a retrospective analysis of 92 male schizophrenia patients to assess the relative weight gain risk associated with clozapine, risperidone, olanzapine, sertindole, and haloperidol and found that antipsychotic-associated weight gain correlated with H_1 receptor affinity. Kroeze et al.[65] conducted a comprehensive analysis of the weight gain potential of antipsychotic agents in relation to their binding to the full range of biogenic amine receptors, reporting that binding affinity for the H_1 histamine receptor is highly predictive of the weight gain potential of individual agents (Figure 1). This result is consistent with the lower risk of weight gain associated with antipsychotics such as aripiprazole and ziprasidone that exhibit low affinity for the H_1 receptor subtype.[66,67]

Many antipsychotic drugs bind to serotonin receptor subtypes, some of which have been implicated in glucose metabolism and food intake. The 5-HT_{2C} receptor subtype appears to mediate serotonin-related effects on appetite in the hypothalamus.[68] Drugs that block the 5-HT_{2C} receptor increase food intake, and animals in which the 5-HT_{2C} receptor gene has been knocked out exhibit increased food intake and develop insulin resistance and impaired glucose tolerance.[69] Other studies suggest that serotonin affects insulin secretion from the pancreas through serotonin receptors in the pancreas and central nervous system.[70] These results have not to date been closely correlated with clinical effects of antipsychotics that might be predicted on the basis of their 5-HT_{2C} receptor affinity.[71,72]

Adrenergic receptors, which are subgrouped into 3 families (α_1, α_2, β), play a role in both appetite and glucose metabolism, and many antipsychotics exhibit marked affinity as antagonists at α-adrenergic receptors. Microinjection of α_1-adrenergic agonists in the paraventricular nucleus of rats suppresses feeding behavior; injection of α_2 agonists stimulates feeding.[73] Adrenergic receptor subtypes have also been associated with effects on glucose transport in various tissues. Activation of α-adrenergic receptors on adipose or cardiac tissue is associated with enhanced translocation of glucose transport proteins and in-

Figure 1. Histamine H_1 Receptor Affinity Predicts Weight Gain[a]



[a]Data from Allison and Casey,[10] Kroeze et al.,[65] and Marder et al.[21]

creased glucose uptake in animal models.[74,75] Kroeze et al.[65] found that α-adrenergic receptor affinity was a predictor of antipsychotic-induced weight gain; however, this effect was modest in relation to the predictive value of affinity at the histamine H_1 receptor. Activation of β_3-adrenergic receptors in brown adipocytes is also associated with increased glucose transport.[76] However, while the activity of antipsychotics at adrenergic receptors may contribute to some effects on weight and glucose control, it seems unlikely that this mechanism fully defines the ability of antipsychotics to precipitate these effects. Olanzapine, for example, has a lower affinity for α_1-adrenergic receptors than many other antipsychotics but is nonetheless associated with significant weight gain in contrast to drugs such as aripiprazole and ziprasidone.

Glucose Transporters

One of the primary mechanisms through which various tissues accumulate glucose is by facilitated transport through a family of proteins in the plasma membrane called glucose transporters. These proteins are responsible for facilitated glucose uptake in peripheral tissues, such as liver, muscle, and fat; at the blood-brain barrier of the central nervous system; and by both neuronal and glial cells.[77] The activity of these transport proteins is regulated closely by insulin. Activation of insulin receptors on cell membranes stimulates the recruitment or translocation of glucose transporters from the cytoplasm to the cell membrane and increased cellular uptake of glucose.[78]

The ability of antipsychotics to block glucose transport may be associated with the development of type 2 diabetes in schizophrenia patients. An assessment[79] of several antipsychotic drugs was made in a pheochromocytoma cell line (PC12) that mimics a neuronal phenotype when treated with nerve growth factor. Conventional antipsychotics such as chlorpromazine, fluphenazine, and pimozide were more cytotoxic than atypical antipsychotics including clozapine, quetiapine, and risperidone.[79] Conventional antipsychotics also potently inhibited glucose transport in the same cell line. An in vivo study extended these observations to acute hyperglycemia in an animal model, in which the ability of antipsychotics, including clozapine, quetiapine, and chlorpromazine, to induce acute hyperglycemia appeared to correlate with their potency as inhibitors of glucose uptake.[80]

The emerging data on inhibition of glucose transport by some antipsychotics are interesting in regard to work that associates tardive dyskinesia with dysregulated glucose metabolism. Several early reports cited a correlation between the incidence of tardive dyskinesia in schizophrenia patients and hyperglycemia,[81–85] which was at least partly attributed to effects of glucose on the binding of dopamine to its constituent receptors in the striatum, which contribute to movement control.[86] Animal studies noted that chronic administration of fluphenazine induced tardive dyskinesia in some animals and that those animals exhibited reduced glucose uptake in specific brain regions compared with treated animals who did not develop dyskinesia or control animals who received no drug.[87] Others have noted that insulin ameliorates some of the effects of tardive dyskinesia in schizophrenia patients.[88] Discrepant results across open studies investigating the relationship between dyskinesia and glucose tolerance have limited the interpretation of these results in relation to individual medications.[89,90]

CONCLUSIONS

A variety of data concerning the use of atypical antipsychotics indicate that some drugs in this class are associated with a significant risk of weight gain and disordered glucose and lipid metabolism. It is not clear that weight gain is a prerequisite for the development of insulin resistance, impaired glucose tolerance, dyslipidemia,

or diabetes. Additional research needs to be done to examine the pharmacologic factors that contribute to these adverse events in vulnerable individuals. While some agents have been associated with greater risk (i.e., clozapine and olanzapine), some newer atypical antipsychotics (i.e., ziprasidone and aripiprazole) appear to be associated with a reduced risk of weight gain and metabolic complications.

How then do clinicians incorporate this understanding of drug-related risk into the treatment of psychosis and care of the overall patient? One step is to closely monitor patients taking atypical antipsychotics for weight increase and related metabolic changes, particularly within the first several months of treatment. The American Diabetes Association recommends that fasting plasma glucose, lipid levels, and blood pressure be assessed within 3 months after initiation of antipsychotic drug therapy.[1] Subsequent assessments of plasma glucose should be scheduled at least annually, and more often for patients with other risk factors for diabetes. If patients exhibit clinical signs and symptoms of hyperglycemia (e.g., polyuria or polydipsia), clinicians should quickly assess plasma glucose concentrations and begin the process of treating and correcting any abnormalities. This would include medical or endocrine consultation with any needed acute modification of the treatment regimen (e.g., hypoglycemia agents), the active education of patients and families about advisable lifestyle changes, and consideration of the risks and benefits of switching antipsychotic medication if necessary to one that carries less relative risk of precipitating weight gain or diabetes. Clinicians should also recognize that some medication combinations may further exacerbate weight gain (e.g., an atypical antipsychotic and a mood stabilizer like valproate). For patients who exhibit increased risk of diabetes prior to treatment (e.g., overweight or obese individuals), education should be initiated immediately, and selection of a medication regimen should take the patient's comorbid condition into account. With careful monitoring and individualized treatment, patients can enjoy maximum benefit from atypical antipsychotics and physicians can continue to deliver the highest level of care.

Drug names: aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, Fazaclo, and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), molindone (Moban), olanzapine (Zyprexa), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), thiazide (Moduretic, Mylan, and others), thioridazine (Intensol), ziprasidone (Geodon).

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