The Metabolic Effects of Antipsychotic Medications

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Objectives: To review current evidence for the hypothesis that treatment with antipsychotic medications may be associated with increased risks for weight gain, insulin resistance, hyperglycemia, dyslipidemia, and type 2 diabetes mellitus (T2DM) and to examine the relation of adiposity to medical risk.

Methods: We identified relevant publications through a search of MEDLINE from the years 1975 to 2006, using the following primary search parameters: "diabetes or hyperglycemia or glucose or insulin or lipids" and "antipsychotic." Meeting abstracts and earlier nonindexed articles were also reviewed. We summarized key studies in this emerging literature, including case reports, observational studies, retrospective database analyses, and controlled experimental studies.

Results: Treatment with different antipsychotic medications is associated with variable effects on body weight, ranging from modest increases (for example, less than 2 kg) experienced with amisulpride, ziprasidone, and aripiprazole to larger increases during treatment with agents such as olanzapine and clozapine (for example, 4 to 10 kg). Substantial evidence indicates that increases in adiposity are associated with decreases in insulin sensitivity in individuals both with and without psychiatric disease. The effects of increasing adiposity, as well as other effects, may contribute to increases in plasma glucose and lipids observed during treatment with certain antipsychotics.

Conclusion: Treatment with certain antipsychotic medications is associated with metabolic adverse events that can increase the risk for metabolic syndrome and related conditions such as prediabetes, T2DM, and cardiovascular disease.

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Clinical Implications

- Patients with severe mental illnesses are at increased metabolic risk.
- Psychiatric medications can increase metabolic risk through obesity-related mechanisms.
- Treatment decisions have implications for metabolic risk and outcomes.

Limitations

- Currently, knowledge of the cost-effectiveness of different interventions to lower metabolic risk is limited.
- Questions remain concerning how to implement clinical strategies that would improve quality and disparities of care in mental illness.
- Future studies are needed to identify the mechanisms that allow medications to cause adiposity and changes in insulin sensitivity.

Key Words: *antipsychotic medications, adverse effects, metabolic syndrome, type 2 diabetes mellitus, dyslipidemia, hyperglycemia, cardiovascular disease*

Second-generation, or atypical, antipsychotic drugs can offer important benefits for individuals with disorders such as schizophrenia, including a reduced risk for the extrapyramidal side effects associated with conventional antipsychotics. However, certain atypical antipsychotics have been reported to produce substantial weight gain and an increased risk for dyslipidemia and T2DM (1). In general, patients with mental illness have elevated rates of mortality and medical comorbidity related to increased rates of conditions such as T2DM and CVD (2). While it is possible that genetic factors play a role in the increased risk seen in mental illness, it is likely that lifestyle issues (for example, reduced activity and poor nutrition) also play a key role. As a result, primary and secondary prevention targeting risk factors for these diseases may be particularly important in psychiatric populations.

A key risk factor for CVD is excess adiposity, which can be indirectly estimated according to BMI. Increasing BMI is associated with increasing risk of medical illness and mortality (3,4). However, not all body fat is associated with the same degree of risk. For example, increased abdominal adiposity, particularly visceral abdominal fat, is strongly associated with decreased insulin sensitivity (5). Decreased insulin sensitivity, sometimes referred to as insulin resistance, is associated with widespread physiologic changes. Insulin resistance is associated with impaired glucose control, an atherogenic dyslipidemia that involves increases in plasma triglyceride and more highly oxidized LDL particles, increased blood pressure, increased risk of blood clotting, and increases in markers of inflammation, all of which are associated with an increased risk for CVD (6). According to the US National Cholesterol Education Program ATP III guidelines (7), a patient with any 3 of the following is considered to have the metabolic syndrome, an important risk factor for T2DM (8) and CVD (9): obesity (defined as waist circumference greater than 102 cm for men or 88 cm for women), low levels of HDL cholesterol (< 40 mg/dL for men or < 50 mg/dL for women), high triglyceride levels (≥ 150 mg/dL), elevated blood pressure (≥ 130 mm Hg systolic or 85 mm Hg diastolic), or increased fasting blood glucose levels (≥ 110 mg/dL).

The long-term risks of having hyperglycemia and T2DM include microvascular disease (that is, retinopathy, nephropathy, and neuropathies) and macrovascular disease (the latter encompassing atherosclerosis-related CVD, that is, coronary heart disease, cerebrovascular disease, and peripheral vascular disease). In addition, T2DM is associated with a risk of short-term complications, including DKA and nonketotic hyperosmolar states that, although relatively uncommon, can be severe (6,10–14). The mortality risk of DKA is about 2% in optimal clinical settings and rises as high as 20% in elderly patients, with mortality risk generally increasing with age, intercurrent illness, and delay in initiating insulin therapy (15,16).

An American Diabetes Association consensus development report (17), cosponsored by the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity, noted that, among second-generation antipsychotics, clozapine and olanzapine treatment are associated with the greatest potential weight gain, with consistent evidence for an increased risk of T2DM and dyslipidemia. The report emphasized that physicians should consider multiple factors, including the presence of medical and psychiatric conditions, 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 (for example, use of clozapine therapy in patients with treatment-resistant schizophrenia).

This article reviews current evidence that treatment with antipsychotic medications can be associated with increased risk for weight gain, insulin resistance, hyperglycemia, dyslipidemia, and T2DM; it also examines the general relation of adiposity to medical risk. We summarize key studies in this emerging literature, including case reports, observational studies, retrospective database analyses, and controlled experimental studies.

Abbreviations used in this article

ATP III	Adult Treatment Panel III
BMI	body mass index
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CI	confidence interval
CVD	cardiovascular disease
DKA	diabetic ketoacidosis
FDA	Food and Drug Administration
HDL	high-density lipoprotein
HR	hazard ratio
LDL	low-density lipoprotein
OR	odds ratio
RCT	randomized clinical trial
RR	relative risk
SD	standard deviation
SE	standard error
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus

Obesity, Diabetes, and Antipsychotics

Certain antipsychotic medications can cause clinically significant weight gain—a growing concern given the known health consequences of obesity. Because obesity and weight gain are major risk factors for insulin resistance and T2DM (18), there are concerns about the weight gain induced by some psychotropic treatment regimens, with the greatest concern focused on certain antipsychotic medications.

While it has been suggested that weight gain is a risk factor only in the general population and is not related to the risk of T2DM during antipsychotic treatment of schizophrenia (19), this hypothesis seems to depend on the existence of unknown protective factors in schizophrenia patients that possibly block the otherwise well-established adverse effects of adiposity in various animal species and human populations. Given the evidence for a higher rather than lower prevalence of diabetes in psychiatric populations in almost all data sets examined to date (20–29), it seems unlikely that such protective factors are operating in individuals with psychiatric illness. Therefore, it seems prudent to assume that antipsychotic-induced weight gain, like any increase in total fat mass, may be associated with the same range of adverse physiological effects as have been established in other populations.

A review of absolute weight gain in various placebo-controlled trials and head-to-head comparisons found that the relative incidence and magnitude of weight gain was not equal among antipsychotic medications (1). Short-term treatment with various agents has been reported to produce increases in body weight ranging from < 1 kg to > 4 kg (30,31). However, studies of the long-term effects of antipsychotic drugs on weight are more relevant to clinical practice. When multiple doses assessed in the clinical trial programs are pooled, aripiprazole (32–35) and ziprasidone (30,36,37) are associated with a mean weight gain of about 1 kg over 1 year; amisulpride with a gain of about 1.5 kg over 1 year (31); quetiapine and risperidone with a gain of 2 to 3 kg over 1 year (38,39); and olanzapine with a gain of > 6 kg over 1 year (40–45). A mean weight gain of > 10 kg was observed in patients who received olanzapine at daily doses between 12.5 and 17.5 mg, the highest dosages tested in large-scale pivotal trials (40). The results of prospective randomized comparisons of individual agents have been consistent with the results of these estimates for individual agents from the pivotal trials. For example, after subjects were treated for 6 months with amisulpride (n = 189) and olanzapine (n = 188), olanzapine was associated with a significantly greater mean increase in body weight (3.9 kg, compared with 1.6 kg; $P <$ 0.01) (46).

The CATIE study is a major prospective trial sponsored by the US National Institute of Mental Health. It was designed to assess the efficacy of the second-generation antipsychotic agents olanzapine, quetiapine, risperidone, and ziprasidone, with perphenazine included as a first-generation agent. The trial included 1493 patients with schizophrenia at 57 sites in the United States. The primary outcome measure was time to all-cause discontinuation. This measure aimed to integrate patients' and clinicians' judgments of efficacy, safety, and tolerability into a global measure of effectiveness (47). Secondary outcome measures include assessment of the reasons for discontinuation (for example, lack of efficacy compared with intolerability owing to side effects, the latter including weight gain and metabolic disturbances).

Phase I results were published in September 2005. Although the CATIE design has limited ability to interpret metabolic outcomes, the results are in many ways consistent with evidence concerning metabolic side effects. Patients in the olanzapine group gained more weight than patients in any other group, (mean weight gain was 0.9 kg monthly), and 30% of patients in the olanzapine group gained 7% or more of their baseline body weight (compared with 7% to 16% in the other groups, $P < 0.001$).

Recent studies testing the effects of switching from one specific medication to another suggest the short-term utility of switching from medications with higher weight-gain risk to a medication with lower weight-gain risk. Two studies indicate statistically significant reductions in body weight and BMI over periods of 6 to 8 weeks after a switch from risperidone or olanzapine to either aripiprazole (48) or ziprasidone (49). The study involving a switch to ziprasidone also detected a significant reduction in nonfasting total plasma cholesterol and triglycerides. A 58-week study examined the effects on weight and fasting lipids of switching from olanzapine, risperidone, or first-generation antipsychotics to ziprasidone (50). Clinically significant, sustained improvements in weight, BMI, and plasma lipids were observed among patients switched from risperidone or olanzapine. At 58 weeks, mean weight reductions from baseline were 9.8 kg ($P < 0.001$) and 6.9 kg ($P < 0.005$) for the groups previously treated with olanzapine and risperidone, respectively. The results from the CATIE Phase 1 also demonstrate that randomized long-term treatment with ziprasidone can induce statistically significant weight loss (0.73 kg, SE 0.5), with similar weight loss possible with aripiprazole (1.37 kg loss after 26 weeks of treatment in one study) (51). The observation of weight loss is important because the registration trials noted above indicate that both of these medications can induce minimal weight gain and there is no indication that any currently available antipsychotic is intrinsically a weight-loss drug.

Insulin Resistance, Diabetes, and Antipsychotic Treatment

A range of evidence suggests that treatment with certain antipsychotic medications is associated with an increased risk for insulin resistance, hyperglycemia, and T2DM, compared with no treatment or treatment with alternative antipsychotics (2). Interpretation of the literature has been complicated by reports that patients with major mental disorders such as schizophrenia have an increased prevalence of abnormalities in glucose regulation (for example, insulin resistance) before the initiation of antipsychotic therapy (52). However, early studies did not control for age, body weight, adiposity, ethnicity, or diet, and most experts hypothesize that differences between patients and control subjects in key factors such as diet and activity level contribute to at least some of the observed abnormalities.

A recent cross-sectional study in 26 hospitalized, first-episode, antipsychotic-naive patients with schizophrenia found that 15% of these patients had impaired fasting glucose (29). The schizophrenia patients had significantly higher values when compared with control subjects matched for lifestyle and with anthropometric measures for the following parameters: mean fasting plasma glucose (95.8 and 88.2 mg/dL, respectively; Student's 2-tailed t test, $t_{25} = 2.17$, $P < 0.03$), insulin (9.8 and 7.7 U/mL, respectively; $t_{25} = 2.05$, $P < 0.05$), and cortisol levels (499.4 and 303.2 nmol/L, respectively; $t_{25} = 5.11$, $P < 0.01$). The elevated plasma cortisol levels observed in this sample probably contributed to some of the increase in insulin resistance and plasma glucose concentrations. However, hypercortisolemia is not typically observed in patients with schizophrenia during chronic antipsychotic treatment (53), so this study possibly overestimated the degree of insulin resistance and hyperglycemia that can be expected to persist past the acute psychotic episode and (or) agitated condition that led to hospitalization. This group also reported increased intraabdominal fat in drug-naive patients, in contrast to other larger samples showing no differences in drug-naive patients (54–56). However, this patient sample had an uncharacteristically long period of untreated illness and a higher mean age than most reported samples of first-episode patients (57). Other investigators have not found increased abdominal fat in drug-naive patients, and it remains unclear whether this is or is not a generalized finding in drug-naive samples. In any case, these studies complement earlier reports (see Haupt and Newcomer for review; 27,58) that patients with schizophrenia and other major mental disorders may have an increased risk for insulin resistance and T2DM, independent of their exposure to antipsychotic medications.

Level 1 Evidence: Case Reports and Other Uncontrolled Observational Studies

Evidence from case reports and prospective observational studies (typically useful for hypothesis generation); retrospective database analyses (often useful for hypothesis testing, although methodological concerns can limit interpretability, as we discuss later); and controlled experimental studies, including RCTs (generally recognized as hypothesis testing), have identified an association between certain antipsychotic medications and adverse metabolic events that include hyperglycemia, dyslipidemia, insulin resistance, exacerbation of existing T1DM or T2DM, new-onset T2DM, and DKA (2).

Case reports of adverse effects on glucose and lipid metabolism (for example, T2DM and dyslipidemia) have more frequently and consistently been associated with clozapine and olanzapine treatment than with quetiapine or risperidone treatment (17). Reports detailing limited short- and long-term weight gain with ziprasidone, amisulpride, and aripiprazole are consistent with little or no evidence of adverse effects on metabolic outcomes (2,17,58,59).

Retrospective analyses of cases of new-onset T2DM associated with clozapine (15), olanzapine (60), and risperidone (61), drawn from the US FDA MedWatch database, suggest that, whereas most new-onset T2DM cases were associated with substantial weight gain or obesity, about 25% were not. These analyses also suggest that most new-onset cases of T2DM occurred within the first 6 months after initiation of treatment. These cases were typically (that is, about 75% of the time) associated with substantial weight gain or obesity, and as many as one-half of them involved individuals with no family history of diabetes. Some of the cases exhibited a close temporal relation between initiation and discontinuation of treatment and development and resolution of the hyperglycemia-related adverse event.

Many of the case reports describe patients who have experienced serious hyperglycemic complications, including DKA-related deaths. A case series for clozapine that included data from the FDA MedWatch Drug Surveillance System (January 1990 to February 2001) identified a total of 384 cases of hyperglycemia (15). Metabolic acidosis or ketosis accompanied hyperglycemia in 80 cases, most of which (n = 73) were new-onset diabetes. There were 25 deaths during hyperglycemic episodes; acidosis or ketosis was reported in 16 of these.

A case series for olanzapine that included data from the FDA MedWatch Drug Surveillance System (January 1994 to mid-May 2001), published reports (MEDLINE to mid-May 2001), and meeting abstracts over a similar period identified a total of 237 cases of diabetes or hyperglycemia in association with olanzapine therapy (60). Metabolic acidosis or ketosis

was reported in 80 of the 237 cases (33.8%). In addition, the proportion of fatalities among the cases of DKA was high (11.3%) relative to the optimal outcomes generally reported in nonpsychiatric samples (for example, 3% to 5%), with acidosis or ketosis reported in 9 of the 15 deaths observed in the olanzapine cases. In an addendum to the paper, the authors report on an additional 52 cases of hyperglycemia identified by extending their FDA MedWatch search to February 2002 (60). Again, the incidence of diabetic ketoacidosis was relatively high, with 20 reports of ketosis or acidosis associated with hyperglycemia (38.5%). There were also 5 reports of pancreatitis among the cases. In all, 10 deaths occurred among these 52 patients.

A case series for risperidone that included data from the FDA MedWatch Drug Surveillance System (1993 to February 2002), published reports (MEDLINE to February 2002), and selected abstracts from national psychiatric meetings was previously used to identify a total of 131 cases of diabetes or hyperglycemia (61). Metabolic acidosis or ketosis was reported for 26 patients treated with risperidone, most of whom ($n = 22$) experienced new-onset diabetes. There were 4 deaths among patients receiving risperidone monotherapy—3 of these patients had acidosis or ketosis.

A case series for quetiapine that included data from the FDA MedWatch Drug Surveillance System (January 1997 to the end of July 2002) and published reports (MEDLINE from January 1997 to the end of July 2002) identified 46 cases of quetiapine-associated diabetes or hyperglycemia (62). There were 21 reports of diabetic acidosis or ketosis. Of the 11 patients who died, 7 had acidosis or ketosis. In an addendum to the paper, the authors report on a further 23 cases that they identified by extending their search to the end of November 2003. There were 8 reported cases of acidosis or ketosis associated with hyperglycemia and 2 reports of pancreatitis. In all, there were 3 deaths among the 23 patients.

Currently, only one case report of DKA associated with aripiprazole has been published, and no reports have associated amisulpride or ziprasidone with DKA (63). Of note, the case involving aripiprazole occurred in a 34-year-old African-American woman with a 10-year history of T2DM but without previously reported episodes of DKA. Four days prior to admission, aripiprazole 30 mg daily was added to her ongoing regimen of olanzapine 20 mg daily. One combined case of rhabdomyolysis, hyperglycemia, and pancreatitis has been associated with ziprasidone treatment (59).

In general, case reports can be difficult to interpret owing to the lack of control data, such as the number of treated patients who did not experience the event, and potential reporting bias. The most common reporting bias is underreporting; for example, only 1% to 10% of adverse events are reported to MedWatch, the FDA postmarketing surveillance program, with most reports occurring in the first 2 years of market experience. With respect to the number of patients who had to be exposed to a given drug to observe the reported adverse events, the higher number of adverse events reported for clozapine and olanzapine, compared with risperidone, for example, cannot be explained by a larger number of patient-years of drug exposure with either of the former agents.

Level 2 Evidence: Observational Database Analyses

Several reported observational analyses have used large administrative or health plan databases to test the strength of the association between treatment with specific antipsychotic medications and the presence of T2DM (64–80). Their common approach has been to identify the association within a database between the use of specific antipsychotic medications and the presence of one or more surrogate indicators of T2DM (for example, prescription of an oral hypoglycemic medication or relevant ICD-9 codes). About two-thirds of these studies report findings suggesting that drugs associated with greater weight gain were also associated with an increased risk for T2DM, compared with either no treatment, conventional treatment, or a drug associated with less weight gain. The other one-third of studies reported to date have either detected no difference between groups or a nonspecific increase in the association for all treated groups, compared with untreated control subjects.

These studies share several methodological limitations related to the use of medical claims databases, including the lack of verification of psychiatric diagnosis and treatment adherence, high rates of polypharmacy, and limited, if any, knowledge of previous treatment conditions. Most important, these studies lack direct measures of metabolism, relying instead on surrogate markers for the presence of diabetes. Such surrogate markers require the successful diagnosis of T2DM in the study sample, but underdiagnosis of diabetes is common, with up to one-third of cases in North America undiagnosed (81). Given that these database studies may involve samples that underestimate the prevalence of diabetes and that the hypothesized difference in prevalence rates across treatment conditions may be less than the prevalence of undiagnosed diabetes, it is possible that the methodological noise may exceed any signal in some cases. This could explain some of the variability in these studies.

In an effort to clarify the findings in this area and to address some of the interstudy variability in results, Newcomer and others recently conducted a metaanalytic review of the relevant literature to quantify the relation between various antipsychotic treatments and risk for diabetes (82). The published datasets allow quantitative examination of the relation between use of

atypical antipsychotics and the development of new-onset diabetes across multiple studies, application of a common referent group to these effect estimates (for example, conventional antipsychotics), and comparison of effects by agent.

A search of MEDLINE and Current Contents (from January 1990 to September 2004) was performed for all relevant publications identifying studies using atypical antipsychotics to treat schizophrenia and related disorders and calculating summary ORs, RR, or HRs. Fourteen primary studies were analyzed (65–69,71,73–79,80). All the included studies were retrospective analyses of existing databases; 11 retrospective cohort studies represented most patients (n = 232 871). As well, there were 5 case–control studies (n = 40 084) of large health care plans (such as Medicaid, Blue Cross/Blue Shield, and Veterans Affairs). Six studies (n = 122 270) included only schizophrenia diagnoses, and 10 studies included patients with various psychotic illnesses (n = 150 685). Data were available for clozapine, olanzapine, quetiapine, and risperidone. Metaanalyses of the association of diabetes incidence among patients treated with atypical antipsychotics were performed with conventional antipsychotics or no antipsychotic treatment used as the comparator groups. All ORs, RRs, and HRs included in the metaanalyses were adjusted by study authors for various covariates, most commonly, treatment duration, age, and sex.

This analysis indicated that clozapine was consistently associated with increased risk for diabetes (compared with conventional antypsychotics, OR 1.37; 95%CI, 1.25 to 1.52, and compared with no antipsychotics, OR 7.44; 95%CI, 1.59 to 34.75). Olanzapine was also associated with increased risk for diabetes (compared with conventional antipsychotics, OR 1.26; 95%CI, 1.10 to 1.46, and compared with no antipsychotic, OR 2.31; 95%CI, 0.98 to 5.46). Neither risperidone (compared with conventional antipsychotics, OR 1.07; 95%CI, 1.00 to 1.13, and compared with no antipsychotic. OR 1.20; 95%CI, 0.51 to 2.85) nor quetiapine (compared with conventional antipsychotics, OR 1.22; 95%CI, 0.92 to 1.61, and compared with no antipsychotic, OR 1.00; 95%CI, 0.83 to 1.20) was associated with an increased diabetes risk. The results of this quantitative analysis of the association between atypical antipsychotic use and incident diabetes in large real-world databases suggests that the risk of diabetes varies among atypical antipsychotics, ranging from increases in risk relative to multiple comparators to no increase in risk relative to any tested comparator.

Level 3 Evidence: Controlled Experimental Studies, Including RCTs

The final level of evidence for an association between some antipsychotic medications and adverse metabolic outcomes is derived from controlled experimental studies and RCTs. A growing body of evidence supports the key observation that treatments producing the greatest increases in body weight and adiposity are also associated with a consistent pattern of clinically significant adverse effects on insulin resistance and changes in blood glucose and lipid levels. However, simple correlations between change in weight and change in plasma glucose values are frequently weaker than correlations between weight change and change in insulin resistance, since it is common for compensatory hyperinsulinemia to buffer plasma glucose when insulin resistance increases with increasing adiposity. Therefore, it is important to realize that unchanged plasma glucose levels in any given study do not preclude clinically significant increases in insulin resistance.

Psychiatrists must be mindful of the established risks posed by increasing adiposity. The well-established relation between adiposity and insulin resistance and the host of changes in physiology associated with insulin resistance, including the potential for a progressive loss of glucose tolerance, remains an important clinical consideration (6). From the standpoint of predictive value, an overweight or obese individual (BMI > 25) has a 50% probability of having insulin resistance; this increases to 70% probability in the setting of a fasting plasma triglyceride greater than 130 mg/dL and culminates in a 78% probability of insulin resistance if this individual also meets ATP III criteria for the metabolic syndrome (83).

Randomized Clinical Trials. An increasing number of RCTs have included measures of weight or adiposity, fasting or postload plasma glucose, and plasma lipids, as well as various indicators of insulin resistance. Several studies are underway that estimate insulin resistance with more sensitive techniques, such as a frequently sampled oral glucose tolerance test, or with direct and sensitive measures, such as minimal model–derived insulin sensitivity values from frequently sampled intravenous glucose tolerance tests or measurements based on gold standard hyperinsulinemic euglycemic clamp techniques. This discussion is organized in terms of increasing duration of drug exposure, increasing sample size, and (or) increasing sensitivity of measures.

Howes and colleagues reported a prospective assessment of clozapine's effects on insulin resistance, as measured by an oral glucose tolerance test, in 20 schizophrenia patients switched to clozapine from various other medications (84). There was no control group. After a mean of 2.5 months of treatment, SD 0.95, mean fasting glucose level increased by 0.55 mmol/L ($t_{19} = -2.9$, $P = 0.01$), and mean 2-hour glucose level increased by 1.4 mmol/L ($t_{19} = -3.5$, $P = 0.002$). There was no significant change in insulin level ($t_{14} = 0.128$, $P = 0.9$) or insulin resistance level measured by the homeostasis model assessment ($t_{14} = -0.9$, $P = 0.37$). Mean BMI increased by 0.82 kg/m^2, although this was not statistically significant ($t_{17} = -1.325$, $P = 0.2$).

A nonblinded crossover study of 15 schizophrenia patients examined the effects of olanzapine or risperidone on weight and fasting lipid profile after 3 months of treatment (85). BMI decreased from mean 25.7 kg/m^2, SD 3.1, to mean 24.2 kg/m^2, SD 3.1, in the group switched to risperidone and increased from mean 24.8 kg/m^2, SD 4.0, to mean 25.9 kg/m^2, SD 4.3, in the group switched to olanzapine ($P = 0.015$). Plasma triglycerides decreased from mean 211.8 mg/dL, SD 134.9, to mean 125.8 mg/dL, SD 90.8, in patients switched to risperidone and increased from mean 112.4 mg/dL, SD 76.3, to mean 196.7 mg/dL, SD 154.8, in patients switched to olanzapine ($P = 0.001$).

A randomized, double-blind trial in 157 schizophrenia patients consisted of an 8-week fixed-dose period and a 6-week variable-dose period of treatment with clozapine, olanzapine, risperidone, or haloperidol (86). There were significant increases from baseline in mean glucose levels at the end of the 6-week variable-dose period in patients who received olanzapine ($n = 22$, $P < 0.02$) and at the end of the 8-week fixed-dose period in patients who received clozapine ($n = 27$, $P < 0.01$) or haloperidol ($n = 25$, $P < 0.03$). The authors indicated that a trend-level difference was seen between treatments at the end of the 8-week fixed-dose period ($P = 0.06$) but not at the end of the 6-week variable-dose phase. Mean cholesterol levels were increased at the end of the 6-week variable-dose period in patients who received olanzapine ($P < 0.01$) and at the end of the 8-week fixed-dose period in patients who received clozapine or olanzapine ($P < 0.02$ and $P < 0.04$, respectively). However, in some groups, interpretation was complicated by baseline and endpoint body weights that were not consistent with those seen in clinical practice or clinical trials.

A randomized, double-blind, 6-week study comparing olanzapine and ziprasidone therapy in 269 inpatients with acute exacerbation of schizophrenia or schizoaffective disorder assessed glucose, insulin, and lipid parameters (87). Significant increases from baseline in median fasting plasma insulin levels ($P < 0.0001$) and homeostasis model assessment insulin resistance ($P < 0.0001$) were observed with olanzapine therapy. Median body weight increased by 7.2 lb (3.3 kg) from baseline with olanzapine treatment, compared with 1.2 lb (0.5 kg) with ziprasidone, and median body weight was significantly higher in the olanzapine group at endpoint ($P < 0.0001$). In this relatively young sample that demonstrated significant compensatory hyperinsulinemia, plasma glucose in the olanzapine-treated subjects did not increase significantly, despite increased insulin resistance. In a 6-month, blinded, follow-up study comparing olanzapine ($n = 71$) and ziprasidone ($n = 62$) therapy in patients with schizophrenia or schizoaffective disorder (88), statistically significant increases from baseline in median fasting glucose and insulin levels were seen with olanzapine therapy. No statistically significant changes were observed with ziprasidone after 6 months of treatment.

The comparative efficacy and safety of olanzapine and ziprasidone was again assessed in a 28-week prospective, randomized, double-blind study (89,90). In it, 277 schizophrenia patients were randomized to olanzapine 10 to 20 mg daily (mean 15.27 mg daily, SD 4.52), and 271 schizophrenia patients were randomized to ziprasidone 80 to 160 mg daily (mean 115.96 mg daily, SD 39.91) at a standardized initial dose of each; any further clinically determined dose changes were performed according to standardized increments. The proportion of patients with treatment-emergent hyperglycemia (≥ 126 mg/dL during treatment) did not differ significantly between the 2 groups (olanzapine, 11.5%; ziprasidone, 7.4%; $P = 0.159$). However, 35% of olanzapine-treated patients, compared with 5% of ziprasidone-treated patients, experienced weight gain, defined in this report as a 7% or greater increase over baseline weight ($P < 0.001$); mean weight gain was 3.06 kg, SD 6.87, in the olanzapine group and –1.12 kg, SD 4.70, in the ziprasidone group. Respectively, the olanzapine group and the ziprasidone group showed a change in fasting glucose of +5.04 mg/dL, SD 30.24, compared with –0.18 mg/dL, SD 21.42 ($P = 0.38$); a change in total cholesterol of +3.1 mg/dL, SD 36.74, compared with –12.76 mg/dL, SD 31.32 ($P = 0.002$); a change in triglyceride level of +34.54 mg/dL, SD 105.4, compared with –21.26 mg/dL, SD 96.54 ($P < 0.001$); a change in LDL of +0.77 mg/dL, SD 29.8, compared with –10.44 mg/dL, SD 25.91 ($P = 0.02$); and a change in HDL of –2.32 mg/dL, SD 10.05, compared with 0.77 mg/dL, SD 9.67.

A pooled analysis from 4-week to 6-week controlled trials of aripiprazole in schizophrenia patients found changes in fasting serum glucose concentrations that were similar for aripiprazole ($n = 860$) and placebo ($n = 392$) (91). A 26-week controlled study of aripiprazole for relapse prevention in 310 schizophrenia patients found no clinically or statistically significant change from baseline in fasting glucose concentration (+0.13 mg/dL) (92).

A 6-week, placebo-controlled study of aripiprazole treatment in schizophrenia patients examined changes in fasting blood glucose (32). Pooling data from 3 aripiprazole groups (10 mg daily, 15 mg daily, or 20 mg daily) showed minimal mean changes in blood glucose from baseline (–0.37 mg/dL, $n = 120$), similar to those observed with placebo (–5.03 mg/dL, $n = 34$). Comparable effects on fasting serum glucose with aripiprazole and placebo have also been seen in patients with bipolar I disorder (93).

Long-term schizophrenia trials have demonstrated similar effects. In a 26-week relapse prevention study involving

patients with chronic stable schizophrenia (34), no clinically significant change from baseline was observed in fasting glucose levels of aripiprazole-treated patients or placebo-treated patients (for aripiprazole, a +0.13 mg/dL change; for placebo, a +2.1 mg/dL change). A 26-week, multicentre, double-blind, randomized trial compared weight change and metabolic indices during treatment with olanzapine (n = 161) and aripiprazole (n = 156) (51). The olanzapine group, compared with the aripiprazole group, experienced statistically significant differences in mean changes in triglycerides (+79.4 mg/dL and –6.5 mg/dL, respectively; $P < 0.05$) and HDL levels (–3.39 mg/dL and +3.61 mg/dL, respectively; $P < 0.05$). In addition, 47% of olanzapine-treated patients with normal baseline lipids demonstrated total cholesterol values higher than 200 mg/dL at endpoint, compared with 17% of aripiprazole-treated patients. Similar between-group differences among patients with normal baseline lipids were seen for LDL levels higher than 130 mg/dL at endpoint (38% with olanzapine and 19% with aripiprazole) and triglyceride levels higher than 150 mg/dL at endpoint (50% with olanzapine and 18% with aripiprazole). Despite the significant weight gain and dyslipidemia, there was no statistically significant difference in mean change in fasting glucose in this 26-week trial.

Results from a prospective 16-week study showed elevated glucose levels both when fasting and following an oral glucose tolerance test in 7 of 13 patients receiving clozapine treatment but not in any of 12 patients receiving amisulpride (94). Significant increases in insulin resistance indices were only reported during clozapine therapy.

Oral glucose tolerance tests were used to assess changes in glucose levels from baseline to endpoint in a small (n = 30), randomized, 21-day study of olanzapine therapy given at 20 to 40 mg daily (95). Glucose tolerance worsened in one patient (from impaired glucose tolerance to T2DM) and improved in 2 patients (from impaired glucose tolerance to normal) during the study. No evidence of dose-related changes in glucose tolerance were observed.

At least 5 studies have reported statistically significant increases in plasma insulin levels during olanzapine treatment, compared with various control conditions ($P < 0.05$ for all) (96–100), suggesting increased insulin resistance, and 2 of these studies reported a significant increase in calculated insulin resistance from baseline during olanzapine therapy ($P < 0.05$) (98,99). Two studies reported elevated insulin levels in 31% to 71% of patients receiving olanzapine treatment ($P < 0.05$) (101,102). The findings of these studies are consistent with the evidence from general-population samples (103,104) suggesting that any condition that increases adiposity tends to be associated with increases in insulin resistance. This insulin resistance can lead to compensatory insulin secretion in individuals with pancreatic beta-cell reserve and to hyperglycemia in individuals with relative beta-cell failure.

A study of healthy subjects taking olanzapine for 2 weeks showed an increased insulin response and decreased insulin sensitivity with both olanzapine and risperidone treatments, compared with placebo (105). These changes in insulin response correlated with changes in BMI. After regression analyses, and adjusting for the effects of weight gain seen with active treatment, no statistically significant changes in insulin response or sensitivity were detected with olanzapine or risperidone therapy, suggesting that the adverse effects were largely related to changes in adiposity. A more recent study examining insulin sensitivity in healthy volunteers receiving olanzapine (n = 22), risperidone (n = 14), or placebo (n = 19) for 3 weeks, with restricted access to food, showed no statistically significant changes from baseline in the insulin sensitivity index with olanzapine or risperidone therapy (106). Using 2-step, hyperinsulinemic, euglycemic clamp methodology, Sowell and colleagues found no statistically significant difference in the mean change in insulin sensitivity index from baseline between the olanzapine, risperidone, and placebo groups during either clamp stage. However, fasting insulin and fasting glucose levels both increased statistically significantly from baseline to endpoint in the olanzapine group, whereas they showed small decreases in the risperidone group. Another study in patients with schizophrenia or related psychotic disorders showed no statistically significant changes in peripheral insulin resistance after at least 2 months of olanzapine treatment (107). Finally, Berry and Mahmoud reported significant improvements in insulin resistance and beta-cell function in schizophrenia patients following a change from olanzapine to risperidone treatment (108).

The limited findings available for quetiapine suggest that it is not associated with a consistent increase in the risk for T2DM or related dyslipidemia. However, since quetiapine typically produces modest (for example, about 2 to 3 kg long-term) weight gain, a possible increase in metabolic risk would be predicted in association with quetiapine or with any treatment that produces similar increases in body weight and adiposity. A 6-week randomized study of atypical antipsychotics in 56 schizophrenia patients (specifically, clozapine, olanzapine, quetiapine, and risperidone; each n = 14) found significant changes from baseline in triglyceride levels with quetiapine therapy (11.64 mg/dL, $P < 0.05$) (109). However, this mean increase was about 3 times less than that observed in clozapine recipients (36.28 mg/dL, $P < 0.01$) or olanzapine recipients (31.23 mg/dL, $P < 0.01$) (109). No significant increase from baseline in triglyceride levels was observed in risperidone-treated patients ($P = 0.76$).

Using data pooled from two 26-week, randomized, double-blind, controlled trials (34,35), L'Italien observed the effects

of aripiprazole, olanzapine, and placebo on the incidence of worsening metabolic syndrome in 624 subjects (110). The cumulative incidence of metabolic syndrome worsening varied across treatments, from a mean incidence of 19.2%, SE 4.0%, with olanzapine to a mean 12.8%, SE 4.5%, with placebo and a mean 7.6%, SE 2.3%, with aripiprazole. A significant difference between the 3 groups ($P = 0.003$) was observed, with a 69% RR reduction for aripiprazole, compared with olanzapine (110,111).

In the CATIE trial, olanzapine-treated patients showed the greatest increases in total cholesterol (mean increase 9.7 mg/dL, SD 2.1), triglycerides (mean increase 42.9 mg/dL, SD 8.4), and glycosylated hemoglobin (mean increase 9.7 mg/dL, SD 2.1), with statistically significant differences between treatment groups in each of these indices (47). Interpretation of the CATIE results should, however, be tempered by several factors. For example, many subjects randomized to olanzapine were already being treated with olanzapine, raising the possibility that any potential increases in adiposity or lipids were attenuated by a ceiling effect. In addition, an unknown number of nonfasting samples are included in the results, along with an unusual methodology of averaging values from different timepoints prior to analysis.

Effects Independent of Changes in Adiposity

In general, the relative risk for T2DM during antipsychotic treatment appears to match the rank order of weight-gain potential for the different agents. However, while drug-induced increases in adiposity may be the most common mechanism contributing to drug-induced changes in glucose metabolism, a significant minority of patients may experience glucose dysregulation independent of weight or adiposity differences (15,53,60,61,112,113). These observations suggest the hypothesis that antipsychotic medications may have a direct effect on insulin sensitivity or secretion. A recent study using euglycemic hyperinsulinemic clamps to study the effect of antipsychotics on insulin sensitivity in freely roaming Wistar rats found a highly significant dose-dependent reduction in insulin sensitivity within 2 hours of initial exposure to clozapine or olanzapine but not to ziprasidone or risperidone (114).

Two important cross-sectional studies also suggest that weight gain may not explain all the observed metabolic adverse effects. Newcomer and others compared the effects of conventional and atypical antipsychotics on glucose regulation in chronically treated nondiabetic patients with schizophrenia and in untreated healthy control subjects (53). Patient and control groups were carefully matched for adiposity and age. According to a modified oral glucose tolerance test, patients receiving olanzapine ($n = 12$) and clozapine ($n = 9$) had significantly higher fasting and postload plasma glucose values, compared with patients receiving conventional antipsychotics ($n = 17$) and untreated healthy control subjects ($n = 31$) ($P < 0.001$ for all comparisons). The risperidone group did not differ from the conventional antipsychotics group but did have higher postload glucose levels, compared with control subjects ($P < 0.01$). Patients who received olanzapine and clozapine had higher calculated insulin resistance, compared with those who received conventional agents ($P < 0.05$ and $P < 0.08$, respectively), whereas those who received risperidone or typical antipsychotics did not differ from control subjects. Similar findings were reported by Henderson and colleagues, who used frequently sampled intravenous glucose tolerance tests to study nondiabetic patients chronically treated with clozapine, olanzapine, or risperidone (115). Treatment groups were carefully matched for adiposity, age, sex, and ethnicity. Patients treated with clozapine and olanzapine showed significant insulin resistance, as measured by minimal model–derived insulin sensitivity, compared with subjects treated with risperidone. There was no significant difference between clozapine and olanzapine in insulin resistance. Both of these studies were limited by adiposity matching that relied on BMI values, which may fail to capture treatment-related differences in abdominal fat mass (that is, despite equal BMI, some treatment groups may have larger abdominal fat mass), leading to differences in insulin sensitivity that may actually be driven by differences in fat mass rather than by an adiposity-independent mechanism.

Conclusions

Data from various sources on the use of atypical antipsychotics indicate that some drugs in this class are associated with a significant risk for weight gain and disordered glucose and lipid metabolism. However, it is clear that weight gain is not an absolute prerequisite for the development of insulin resistance, impaired glucose tolerance, dyslipidemia, or T2DM. Additional research is needed to examine the pharmacologic factors that contribute to these adverse effects in vulnerable individuals. These adverse effects are likely related to the elevated rates of cardiovascular morbidity and mortality seen in schizophrenia patients. Future research in this area will be helpful, not only to clinicians but also to regulatory agencies as they consider potential adverse effects associated with the use of these agents.

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Résumé : Les effets métaboliques des antipsychotiques

Objectifs : Examiner les données probantes actuelles de l'hypothèse selon laquelle le traitement aux antipsychotiques peut être associé à des risques accrus de prise de poids, d'insulinorésistance, d'hyperglycémie, de dyslipidémie, et de diabète non insulinodépendant (DNID) de type 2, et examiner la relation de l'adiposité au risque médical.

Méthodes : Nous avons identifié les publications pertinentes grâce à une recherche dans MEDLINE, de 1975 à 2006, à l'aide des principaux paramètres de recherche suivants : « diabète ou hyperglycémie ou glucose ou insuline ou lipides » et « antipsychotique ». Des résumés d'assemblées et des articles antérieurs non indexés ont aussi été examinés. Nous avons résumé les études clés de cette nouvelle documentation, y compris les études de cas, les études observationnelles, les analyses de bases de données rétrospectives, et les études expérimentales contrôlées.

Résultats : Le traitement à différents antipsychotiques est associé avec des effets variables sur le poids corporel, allant d'augmentations modestes (par exemple, moins de 2 kg) entraînées par l'amisulpride, le ziprasidone et l'aripiprazole, à des augmentations importantes avec des agents comme l'olanzapine et la clozapine (par exemple, de 4 à 10 kg). De substantielles données probantes indiquent que les augmentations d'adiposité sont associées avec des diminutions de l'insulinosensibilité chez les personnes souffrant de maladie psychiatrique et chez celles qui n'en souffrent pas. Les effets de l'augmentation d'adiposité, et d'autres effets, peuvent contribuer aux augmentations de glucose et de lipides du plasma observées durant le traitement à certains antipsychotiques.

Conclusion : Le traitement à certains antipsychotiques est associé à des effets métaboliques indésirables qui peuvent accroître le risque de syndrome métabolique et des affections qui s'y rapportent comme le prédiabète, le DNID et la maladie cardiovasculaire.