ABSTRACT

Reports of diabetes, diabetic ketoacidosis, hyperglycemia, and dyslipidemias in patients treated with atypical antipsychotics have increased in recent years. This increase has led to growing concern about a possible link between these metabolic effects and atypical antipsychotic therapy. This review article provides an overview of the evidence for an association between glucose and lipid dysregulation and the 6 atypical antipsychotics currently available in the United States: clozapine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole.


OVERWEIGHT AND OBESITY

Overweight and obesity are increasing problems in the United States and throughout the Western world and have significant health implications. Trends in obesity prevalence over the past 40 years showed little change from 1960 to 1980, followed by a marked increase to the present day (men: 1980, 13%; 1991, 21%; 1999-2000, 28%; women: 1980, 17%; 1991, 26%; 1999-2000, 34%). The increasing prevalence of overweight has also been observed in children and adolescents. In children (6–11 years), the proportion overweight (body mass index [BMI] >95th percentile) increased from 4% in 1965 to 13% in 1999, whereas for adolescents (12–19 years), the percentage rose from 5% in 1970 to 14% in 1999.

Overweight and obesity are associated with increased rates of mortality and morbidity. Mortality rates increase for men and women throughout the range of moderate and severe overweight. Among obese individuals, the risk of death from all causes is 50% to 100% greater than for those of normal weight (BMI 20–25 kg/m²); most of the increased risk is because of cardiovascular causes. Estimates put the number of deaths attributable to obesity in the United States at 300,000 per year.

DIABETES MELLITUS: A GROWING HEALTH PROBLEM

Diabetes is a growing health problem, in the United States and worldwide. According to latest American Diabetes Association (ADA) estimates (based on 2002 census data), there are 13 million individuals with diagnosed diabetes in the United States—4.5% of the population. Other estimates put the prevalence of diagnosed diabetes in the United States at more than 7%. The ADA estimates 5.2 million individuals have undiagnosed diabetes. In addition,
large numbers of individuals in the United States have “prediabetes,” with blood glucose levels that are above normal, but not meeting the diagnostic criteria for diabetes. According to the ADA, an estimated 41 million people in the United States have “prediabetes,” in addition to the overall estimate of 18.2 million with diabetes."6

Diabetes is associated with increased mortality compared with the general population. Analysis of National Health and Nutrition Examination Survey (NHANES) 1 data showed that overall age-adjusted mortality in individuals with diabetes was approximately twice that in the nondiabetic population.4 Diabetes is also associated with increased morbidity. Individuals with the disease are at increased risk of morbidity because of retinopathy, nephropathy, neuropathy, peripheral vascular disease, and cardiovascular disease (CVD).

Diabetes mellitus is divided into 2 main types: type 1 and type 2.9 In addition, diabetes that develops during pregnancy—gestational diabetes—is recognized as a separate category of diabetes. There are also several other less common forms of diabetes, characterized by specific genetic abnormalities (eg, defects of beta-cell function or insulin action) or etiologic agents (eg, drugs or chemicals or infections).

THE METABOLIC SYNDROME

The metabolic syndrome has been broadly described by the National Cholesterol Education Program (NCEP) Expert Panel10 as a constellation of risk factors for coronary heart disease (CHD). The current NCEP clinical guidelines for its identification are shown in Table 1.10,11 Obesity and overweight, physical inactivity, and genetic factors can all contribute to the metabolic syndrome. The metabolic syndrome is closely associated with insulin resistance, although the mechanistic interactions between the factors are complex and not yet fully understood.

Approximately 47 million Americans are affected by the metabolic syndrome. Approximately 60% of BMI-calculated obese (≥30 kg/m^2) US men and 50% of obese US women are affected, underscoring the public health impact of this condition.2 The metabolic syndrome increases the risk for CHD at any given level of low-density lipoprotein (LDL) cholesterol, making it a target for therapeutic intervention. In a recent study, subjects with metabolic syndrome had a 3-fold increased risk of CHD and stroke.12 NCEP guidelines recommend that the metabolic syndrome should be addressed in addition to the reduction of LDL cholesterol levels. Weight reduction and increased activity are effective at reducing insulin resistance, whereas additional medication should be used to treat high blood pressure and the prothrombotic state.

MODIFIABLE RISK FACTORS FOR CARDIOVASCULAR DISEASE

The known effects of atypical antipsychotic medications on weight gain, together with their potential impact on glucose and lipid metabolism, have important health implications for patients with schizophrenia and other major mental health conditions treated with these medications. As discussed, weight gain and obesity, hyperglycemia, and dyslipidemia are modifiable risk factors for CVD. Weight gain and obesity have an adverse effect on glucose and lipid metabolism and are linked to an increased risk of hypertension.

<table>
<thead>
<tr>
<th>Table 1. The Metabolic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Five major features of the metabolic syndrome</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>– Excess total body fat</td>
</tr>
<tr>
<td>– Central fat distribution/upper body obesity</td>
</tr>
<tr>
<td>– Increase visceral fat</td>
</tr>
<tr>
<td>Insulin resistance/hyperinsulinemia</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>– Hypertriglyceridemia</td>
</tr>
<tr>
<td>– Decreased HDL cholesterol</td>
</tr>
<tr>
<td>– Increased LDL cholesterol</td>
</tr>
<tr>
<td>Impaired glucose tolerance/type 2 diabetes</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Clinical identification of the metabolic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factor</td>
</tr>
<tr>
<td>Abdominal obesity</td>
</tr>
<tr>
<td>- Men</td>
</tr>
<tr>
<td>- Women</td>
</tr>
<tr>
<td>Triglycerides</td>
</tr>
<tr>
<td>HDL cholesterol</td>
</tr>
<tr>
<td>- Men</td>
</tr>
<tr>
<td>- Women</td>
</tr>
<tr>
<td>Blood pressure</td>
</tr>
<tr>
<td>Fasting glucose</td>
</tr>
</tbody>
</table>

HDL = high-density lipoprotein; LDL = low-density lipoprotein. Data from NCEP Expert Panel10; Reaven11.
suggesting potential adverse treatment effects on 4 key modifiable risk factors for CVD.

Patients with schizophrenia and bipolar disorder are more likely to have an unhealthy lifestyle than the general population. 13 Lack of exercise and poor diet (ie, high in fat and low in fiber) tend to be more prevalent in those patients with these disorders, increasing their risk for weight gain, diabetes, and CVD. An estimated 75% of the schizophrenia population are smokers, 40% to 80% have a BMI 20% or higher than normal, and the symptoms of the disease lead to an inactive lifestyle, all increasing CVD risk. 14,15 Bipolar patients also have been found to have an increased propensity to be obese. It is the ideal goal of therapy when managing these disorders to use medications that do not further increase the risk of CVD.

**MENTAL ILLNESS AND EXCESS MORTALITY**

Several studies in the literature have demonstrated that mental illnesses, including schizophrenia, bipolar disorder, and depression, are associated with excess medical mortality. In schizophrenia, a meta-analysis of 18 studies16 showed a significant increase in mortality in all except 1 study involving the smallest patient cohort. Natural and unnatural deaths increased significantly in schizophrenia. Natural deaths accounted for 59% of excess mortality, whereas unnatural deaths made up 41% of excess mortality. Suicide was the single largest cause of excess mortality, accounting for approximately 28% of the excess deaths and 12% of all deaths in the meta-analysis.

Overall, CVD was the most common cause of mortality among patients with schizophrenia in the meta-analysis, accounting for 34% of deaths among male patients and 31% in female patients. 16 Mortality from CVD and respiratory disease, but not neoplastic disease, was significantly elevated in schizophrenia compared with the general population.

Increased mortality rates have also been observed in patients with affective disorders. Twelve studies involving large populations (>5000 individuals) or long observation periods (>5 years), summarized by Angst et al, all showed elevated mortality for affective disorder patients compared with the general population. 17 A long-term follow-up over 34 to 38 years of more than 400 patients with affective disorders (unipolar depression or bipolar disorder) showed elevated mortality compared with the general population. 17 Although suicide showed the greatest increase compared with the general population, patients with affective disorders also showed increased mortality for CVD/CHD (standard mortality rate = 1.61). The high mortality from vascular disease among patients with schizophrenia, bipolar disorder, and depression underlines the importance of attending to major risk factors.

**INCREASED RATES OF METABOLIC DISTURBANCE IN PATIENTS WITH PSYCHIATRIC DISORDERS**

Reports of abnormal glucose regulation among individuals with schizophrenia predate the introduction of antipsychotic therapy. 18 These early reports suggest that patients with psychotic disorders may have an elevated baseline risk for disturbances in glucose regulation, independent of any adverse medication effects. However, these findings should be viewed with caution as the definitions of diabetes and schizophrenia differ from current ones, and the studies are limited by their lack of assessment of or controls for age, weight, adiposity, activity, diet, or ethnicity. Nevertheless, these studies suggest that there may be an increased risk of type 2 diabetes in patients with schizophrenia. Evidence from several other studies19 suggests that this is not limited to schizophrenia, but could also affect patients with other psychiatric disorders, such as bipolar disorder and depression. Decreased insulin sensitivity has been reported for patients with depression compared with non-depressed individuals20,21 (for review, see Haupt and Newcomer18), suggesting abnormalities in glucose regulation associated with depression. However, as with the studies in schizophrenia patients, these reports have typically failed to characterize patient characteristics, such as adiposity, diet, and activity. Further large-scale studies in schizophrenia and other psychiatric disorders, controlling for factors such as BMI and medication, are therefore needed to further address the question of glucoregulatory disturbances in these patients.

**IMPACT OF WEIGHT GAIN**

Increases in body weight are typically associated with increases in adiposity, with abdominal adiposity in particular a known risk factor for cardiovascular morbidity and mortality. In addition, abdominal adiposity is associated with insulin resistance, so that adiposity can secondarily contribute to hyperglycemia and dyslipidemia, each independent risk factors for CVD.
Therefore, the effects of antipsychotic medications on body weight have significant implications for patient health. Weight gain is a well-established side effect of antipsychotic therapy, reported in up to 50% of patients receiving chronic treatment for schizophrenia. The causal effect of antipsychotic treatment to induce weight gain has been established in randomized, double-blind, placebo-controlled clinical studies. However, marked differences in weight-gain liability are seen among the different antipsychotic agents (Figure), which have led to the hypothesis that increased rates of diabetes, hyperglycemia, and dyslipidemia seen with some atypical antipsychotics could be primarily caused by their effect on body weight. This hypothesis has been supported by 3 levels of evidence. Studies can be considered hypothesis generating or hypothesis testing, depending on their methodology. Case reports, chart reviews, and open, observational studies all provide uncontrolled, largely anecdotal evidence, thus generally useful for hypothesis generation only. In contrast, controlled experimental studies, including prospective, randomized, controlled clinical trials, are designed to address specific questions, and can be useful for hypothesis testing.

Based on reports of these types, there is largely consistent evidence that the atypical agents associated with more weight gain (ie, clozapine and olanzapine) are associated with an increased risk of diabetes, hyperglycemia, and dyslipidemia. However, a considerable minority of reports of new-onset diabetes in the absence of obesity or substantial weight gain, along with a limited amount of experimental evidence for changes in glucose regulation and insulin resistance independent of adiposity, suggest that some atypical antipsychotics may also have adverse effects on insulin sensitivity that are independent of adiposity.

POSSIBLE MECHANISMS OF ANTIPSYCHOTIC-INDUCED WEIGHT GAIN AND METABOLIC EFFECTS

BODY WEIGHT

The mechanisms by which antipsychotic medications produce their effects on body weight and body composition are poorly understood, with many different receptor types (including 5-HT2A, 5-HT2C, H1 histamine, and alpha1 and alpha2 adrenergic receptors) hypothesized to be a relevant target of antipsychotic activity. Of these receptors, H1 histamine receptors are currently the focus of much interest, and the mechanisms by which H1 histamine receptor antagonism regulates weight gain is beginning to be understood.

A recent study suggests a strong association between the level of histamine H1 receptor affinity and antipsychotic-induced weight gain. The receptor-binding affinities of 17 typical and atypical antipsychotics (including the 6 atypicals included in this review) were examined for correlations with their short-term effects on body weight, as determined in a previous meta-analysis of the literature. H1-receptor–binding affinity showed a statistically significant relationship with weight gain, and 15 of 17 drugs were correctly classified into 2 groups—those that induce weight gain and those that do not—based on their H1-binding affinities using discriminant function analysis. Affinity for the 5-HT2C receptor did not correlate sig-

Figure. Mean Change in Body Weight with Antipsychotic Therapy

significantly with weight gain in this study, even though this was part of the significant predictive model in the discriminant function analysis. In addition, previous genetic studies have suggested a role for the 5-HT2C receptor in weight regulation in rodents and an earlier study suggested a link between weight gain and polymorphisms in the 5-HT2C receptor gene, hypothesizing that such genetic variation could predispose individuals to more or less weight gain via as yet unknown mechanisms.

Kroeze et al do not discount the role of other receptor types in the development of antipsychotic-induced weight gain. Sulpride can induce significant long-term weight gain in some patients with schizophrenia, even though it is a selective D2/D3 receptor antagonist with virtually no affinity for H1 receptors. Similarly, weight gain has been reported with depot formulations of the typical antipsychotics haloperidol and fluphenazine, although these agents also show relatively low H1-receptor affinity.

**GLUCOSE DYSREGULATION**

Mechanisms underlying the changes in glucose regulation associated with antipsychotic therapy are little understood. However, a number of studies suggest that the effect of antipsychotic treatment on insulin resistance, rather than insulin secretion, may be more important for most patients. For most individuals, changes in insulin resistance will occur secondary to increases in adiposity. However, a significant minority of patients may experience glucose dysregulation independent of weight or adiposity differences, suggesting the possibility of a direct effect of certain antipsychotic medications on insulin sensitivity or secretion.

One possible mechanism for antipsychotic drug effects that could occur independent of changes in adiposity would involve drug effects on glucose transporter function. Dwyer et al have shown that certain antipsychotic agents, including clozapine and its analogues, olanzapine, and chlorpromazine, can inhibit glucose uptake through interactions with glucose transporter proteins in in vitro studies using cloned cell lines, whereas other agents, such as haloperidol, had a marginal effect on glucose transport. These drugs can also induce hyperglycemia in mice in line with their effects on glucose transport. Risperidone can also interact with these intracellular proteins, but the limited lipophilic nature of this agent results in reduced tissue to plasma concentration ratios, suggesting that intracellular protein interactions and intracellular drug concentrations may be critical to the prediction of drug effects in this area. These findings suggest the hypothesis that differing effects on glucose transport can be hypothesized to underlie the clinical observation of different adiposity-independent antipsychotic drug effects on insulin sensitivity, although additional laboratory and clinical studies are needed.

Serotonin receptor activity may also have a role in glucose regulation. 5-HT1A and 5-HT2 receptors have been implicated, although the exact roles of these receptors appear complex, and the rank order of in vitro affinities of antipsychotic agents for serotonin receptors do not fit well with the rank order of their effects on glucose regulation.

Changes in norepinephrine and epinephrine turnover and plasma concentrations during clozapine treatment may also be relevant to understanding drug effects on glucose metabolism that could occur independent of changes in adiposity. Increases in circulating norepinephrine and epinephrine could be predicted to reduce beta-cell function and increase glucose release from hepatocytes. It remains to be seen what role, if any, such changes in adrenergic function play in the development of abnormalities in glucose or lipid metabolism during antipsychotic treatment.

**ATYPICAL ANTIPSYCHOTICS**

Although metabolic issues were seen in the earlier typical antipsychotics, they were not well studied. The focus of this review is to highlight the potential impact of some but not all of the atypical antipsychotics on metabolic parameters, reports of changes in glucose regulation, lipid levels, and body weight.

**CLOZAPINE**

Clozapine was the first atypical antipsychotic marketed in the United States, producing improvements in positive and negative symptoms of schizophrenia, but without the significant risk of various movement disorders usually seen with typical antipsychotic agents. In addition, clozapine remains unique as an agent with established, and US Food and Drug Administration (FDA)-labeled, efficacy for individuals with treatment-resistant schizophrenia and for the prevention of suicide. It was introduced in the United States in 1990, although it had been used in Europe since the 1980s. Clozapine treatment is associated with
a small risk of agranulocytosis, which means that it is now used almost exclusively in treatment-resistant individuals. Consequently, it accounts for a relatively small proportion of atypical antipsychotic prescriptions.

Considered together, the various case reports, 34-36 the majority of database analyses, 46-51 and controlled experimental studies, including randomized clinical trials, 18,28,52 consistently suggest that clozapine treatment increases the risk of significant weight gain, insulin resistance, hyperglycemia, and diabetes mellitus. The risk of acute complications, such as diabetic ketoacidosis, may also be increased; however, these infrequent events are more difficult to study and quantify outside of case series.

The association between clozapine treatment and weight gain is well documented, 23,53 and weight gain and obesity are established risk factors for diabetes. This raises the possibility that the increased risk of diabetes with clozapine therapy could be partly related to treatment effects on body weight. Although the contributions of weight gain are very likely to play a role in observed population effects and individual risk for many patients, a number of observations argue that weight gain is not a factor in a substantial minority of cases. In some reported cases of diabetes or diabetic ketoacidosis, patients showed no increase in body weight. In the 5-year clozapine study from Henderson et al, data analysis of that sample did not detect a significant association between weight, change in weight, BMI, or change in BMI and the risk of diabetes, although body weight increased significantly during the study. 54 The rapid occurrence of diabetes following treatment initiation in some patients also does not support a primary role for weight gain in all cases.

Results of clinical trials and chart reviews suggest that clozapine therapy is associated with increases in triglyceride levels. Significant increases in mean plasma triglyceride from baseline were observed with clozapine therapy in one controlled clinical trial. 55 4 retrospective chart reviews, 38,56-58 and in a 12-month open-label study in patients with schizophrenia or schizoaffective disorder. 35 The effects of clozapine treatment on total cholesterol levels are less clear and more difficult to interpret. Although 2 studies report significant increases in total cholesterol levels from baseline with clozapine treatment, 45,52 other studies report no significant changes from baseline. 56-59

**Olanzapine**

Olanzapine was the third atypical antipsychotic approved for use in the United States and has been widely used since its introduction in 1996. A large body of literature exists examining the association between olanzapine therapy and diabetes mellitus, hyperglycemia, and abnormal glucose and lipid regulation. This includes case reports, FDA MedWatch Drug Surveillance information, retrospective database analyses, and controlled experimental studies including randomized clinical trials.

Considered together, the case reports, 44,60 the majority of the retrospective database analyses, 46,48,49,61-66 and the controlled experimental studies, including randomized clinical trials, 18,28,29,52,67-72 consistently suggest that olanzapine treatment increases the risk of significant weight gain, insulin resistance, hyperglycemia, and/or diabetes mellitus. The risk of acute complications, such as diabetic ketoacidosis, may also be increased; however, these infrequent events are more difficult to study and quantify outside of case series.

Virtually all of the large retrospective database analyses showed a significant increase in the risk of developing diabetes with olanzapine therapy. The risk of diabetes increased significantly with olanzapine therapy compared with no antipsychotic treatment 44,61-65 and compared with treatment with typical antipsychotics. 46,49,65,73 Three database analyses also showed a significantly greater risk of developing diabetes with olanzapine therapy compared with risperidone. Weight gain and obesity, and increased adiposity in general, are well-established risk factors for diabetes. This strongly suggests that the well-documented occurrence of significant weight gain with olanzapine therapy 23,53 could be a key factor in the increased risk of diabetes seen with this agent. However, several observations suggest that at least in some cases, weight gain may not play a primary role. A significant minority of reported cases of new-onset diabetes were not accompanied by substantial weight gain or obesity. The rapid onset of diabetes following olanzapine initiation and prompt resolution with treatment withdrawal in some cases also do not suggest that the effects of olanzapine on glucose regulation in these individuals occur simply through actions on weight and adiposity.

Findings from chart reviews, database analysis, and clinical trials, supported by case reports, suggest consistent evidence that olanzapine treatment has a potentially adverse effect on plasma lipids, particularly plasma triglyceride. Significant increases in triglycerides from pretreatment levels were observed with olanzapine therapy in randomized clinical trials and
observational studies\(^{55,68,74,75}\) and in 2 retrospective chart reviews.\(^{56,76}\) Significantly more patients developed high triglyceride levels with olanzapine therapy than with ziprasidone treatment during a 28-week comparison study.\(^{70}\) Increases in body weight are well documented with olanzapine therapy\(^{23,53}\) and may affect the changes in triglyceride levels seen with olanzapine therapy.

Findings from the analyses of total cholesterol levels were less clear, and total cholesterol in general is more difficult to interpret in comparison to specific lipid fractions (eg, LDL or high-density lipoprotein [HDL]). Changes in LDL and HDL cholesterol have been little studied. One published report shows significant improvements in LDL cholesterol levels from baseline with olanzapine therapy.\(^{56}\) However, these improvements were accompanied by significant adverse changes in HDL cholesterol levels. In contrast, Simpson et al reported significant increases in LDL cholesterol from baseline.\(^{69}\)

**Risperidone**

Although risperidone has been prescribed extensively since its introduction in the United States in 1993, fewer published reports are available concerning the risk of diabetes with risperidone as compared with clozapine or olanzapine treatment. However, a considerable body of literature examines the potential associations between risperidone therapy and the risk of weight gain, insulin resistance, hyperglycemia, diabetes, and lipid dysregulation.

Together, the individual case reports, data-base analyses,\(^{46,48,61-65,73,83}\) and studies of glucose levels, insulin resistance, and diabetes\(^{24,52,72}\) suggest that risperidone treatment is not associated with a consistent or substantial increase in the risk of developing diabetes. However, a possible increase in risk would be predicted to occur in association with any treatment that produces increases in weight and adiposity, with risperidone typically producing limited weight gain.

The relative scarcity of published case reports of diabetes or ketoacidosis with risperidone therapy suggests the lack of a clear link between risperidone treatment and development of diabetes. Risperidone has been used extensively since its introduction in 1993 and currently accounts for approximately 37% of atypical antipsychotic prescriptions in the United States. Therefore, the small number of case reports, compared with olanzapine or clozapine therapy, is not simply a consequence of its limited usage.

Most database analyses showed no statistically significant increase in diabetes risk with risperidone therapy compared to typical antipsychotic treatments or with no antipsychotic therapy. When the risk of diabetes was assessed according to patient age,\(^{16}\) risperidone therapy—in common with clozapine, olanzapine, and quetiapine (the other atypical antipsychotics analyzed in the study)—was associated with a significant increase in diabetes risk in patients younger than 40 years. The authors suggest that this finding, taken together with the lack of a significant effect of atypical therapy on diabetes risk in older patients (>60 years), implies that atypical antipsychotics could be thought to hasten the onset of diabetes.

Findings from studies of glucose levels in patients receiving risperidone therapy are largely consistent with the results of the database analyses and case study reports. Minimal increases in fasting glucose levels were observed with risperidone therapy compared to pretreatment values in 2 chart reviews\(^{56,76}\) and 1 controlled study.\(^{52}\) This minimal increase is in contrast to the significant changes observed with olanzapine and clozapine therapy.

Chart reviews, case reports, database analyses, and clinical trials all suggest that risperidone treatment has a limited, if any, adverse impact on plasma lipid levels.\(^{52,55,66,76,84-87}\) In general, evidence does not suggest an adverse effect of risperidone treatment on plasma cholesterol levels, with less consistent but still largely negative results regarding plasma triglyceride levels. Increases in triglyceride levels were reported in 3 studies, suggesting that risperidone may be linked to adverse changes in triglyceride levels, although these changes were statistically significant in only 1 study.\(^{76}\) Risperidone therapy is associated with modest weight gain during short- and long-term treatment.

Risperidone therapy is not associated with a consistent or substantial increase in the risk of developing diabetes or dyslipidemia. However, a possible increase in risk would be predicted to occur in association with any treatment that produces increases in weight and adiposity.

**Quetiapine**

Quetiapine was introduced in 1998 and is currently a highly prescribed atypical antipsychotic in the United States, along with risperidone and olanzapine. However, its relatively recent introduction does mean that studies and analyses investigating the potential metabolic effects of quetiapine are still limited. Reports examining the possible association between
quetiapine treatment and the development of diabetes are currently limited to 4 analyses of healthcare databases and a few case reports. In addition, changes in glucose levels have been examined in 2 chart reviews and a naturalistic study involving a small number of quetiapine-treated patients, whereas the effects on lipid levels are reported from 3 chart reviews and a 6-week randomized study.

The limited amount of data evaluating the metabolic effects of quetiapine therapy and the contradictory nature of some results preclude definitive assessment of the metabolic risks associated with its use. Findings suggest that quetiapine therapy is not associated with a consistent or substantial increase in the risk of developing diabetes or dyslipidemia. However, a possible increase in metabolic risk would be predicted to occur in association with any treatment that produces increases in weight and adiposity, with quetiapine typically producing modest weight gain. Although the modest weight gain risk clearly appears similar to risperidone, the limited availability of metabolic data precludes the same level of confidence that this modest weight-gain risk profile (or other drug effects) will similarly yield a low risk of diabetes or dyslipidemia.

Reports of changes in lipid levels with quetiapine therapy are also limited and somewhat contradictory.

**ZIPRASIDONE**

Ziprasidone was approved for use in the United States in 2001 and currently accounts for a small proportion of atypical antipsychotic prescriptions. Consequently, limited published data are available examining the possible association between ziprasidone therapy and the development of diabetes, hyperglycemia, and/or dyslipidemia. Treatment with this atypical antipsychotic is associated with minimal impact on body weight. Package insert data indicate weight gain of 7% or greater in 10% of ziprasidone-treated patients compared with 4% of placebo controls over 4 or 6 weeks of treatment. These data are consistent with findings from the 28-week comparison study versus olanzapine, in which 9.6% of ziprasidone-treated patients experienced a 7% or greater increase in weight from baseline—significantly less than the 37.2% reported for the olanzapine group. In switch studies, in which patients previously on olanzapine or risperidone were placed on ziprasidone, patients lost weight and had improvements in their lipid profiles as a result.

Based on short- and long-term data currently available, ziprasidone treatment has a minimal effect on weight and adiposity, and also appears to have minimal impact on the risk of developing diabetes, hyperglycemia, or lipid dysregulation. Initial indications from available data suggest that ziprasidone does not have an adverse effect on glucose or lipid levels, and may lead to beneficial changes in some lipid parameters, such as triglycerides, when patients switch to ziprasidone and discontinue agents associated with adverse effects.

**ARIPIPRAZOLE**

Aripiprazole is the most recent antipsychotic agent to become available on the market. In the absence of case reports describing metabolic risk or adverse events, or any studies of aripiprazole using retrospective database analyses, the reports of drug effects on weight and possible effects on plasma glucose and lipid levels are all provided by randomized clinical trials. Aripiprazole treatment is associated with minimal changes in body weight. Pooled data from 5 short-term (4- or 6-week) trials in 932 patients treated with aripiprazole showed that aripiprazole was associated with a mean increase in weight of 0.71 kg, similar to that reported with haloperidol (0.56 kg). The proportion of patients experiencing clinically significant weight gain (≥7% increase) in these studies was low (8%), in comparison to placebo (3%).

Minimal changes in weight have also been reported with longer-term treatment. Data from a 52-week, double-blind comparison study (n = 1294) of aripiprazole versus haloperidol showed that mean change in weight from baseline to study endpoint (LOCF) was not significantly different between the aripiprazole (1.05 kg) and the haloperidol (0.39 kg) treatment groups. In a 26-week placebo-controlled study in chronic, stable patients with schizophrenia (n = 310), aripiprazole was associated with a 1.26-kg decrease in body weight.

Based on short- and long-term data currently available, aripiprazole treatment has a minimal effect on weight and adiposity, and on blood glucose levels. Aripiprazole treatment is associated with neutral effects on serum lipid levels, comparable to placebo. In 1 analysis, aripiprazole was also associated with significantly reduced risk for development of the metabolic syndrome, in comparison to olanzapine, in patients with acute and chronic schizophrenia.
**GENERAL DISCUSSION**

Weight gain is a well-established side effect of typical and atypical antipsychotic therapy. However, this drug-induced adverse event occurs to a markedly different degree among the atypical agents, with clozapine and olanzapine therapy associated with a common risk of significant weight gain, risperidone and quetiapine with mild to moderate weight gain, and ziprasidone and aripiprazole with minimal effects on weight. There is a reasonable hypothesis that much of the effect on glucose regulation observed with the different atypicals can be explained simply as a function of their effect on weight and adiposity.

Atypical antipsychotic medications may also have a direct (i.e., adiposity-independent) effect on glucose regulation in some individuals. This is supported by results from controlled studies investigating changes in glucose and insulin measures while controlling for confounding factors, such as weight, BMI, and age. Much speculation has focused on the dibenzodiazepine-derived compounds clozapine, olanzapine, and quetiapine, which are all structurally related and distinct from the other atypicals. The possible mechanism by which clozapine and olanzapine (and possibly quetiapine) may affect glucose regulation independent of adiposity is unclear, and there are no structure-function data to support what are currently ad hominem arguments against the subclass. The reports of rapid-onset, and often rapidly reversible, diabetic ketoacidosis or severe hyperglycemia in certain individuals suggest a possible direct effect on beta-cell function in those vulnerable persons.

As with the differing pattern of drug effects on glucose regulation, the differing effects of different atypical agents on blood lipid levels suggest that these changes do not reflect a broad class effect of atypical antipsychotic treatment. Significant increases in triglyceride levels were reported with clozapine and olanzapine therapy, and olanzapine treatment was also associated with a significantly increased risk of hyperlipidemia. Although some increases in triglycerides have been observed with risperidone therapy, other studies have found no effect or only modest, non-significant changes. No adverse changes in mean blood lipid levels have been observed with ziprasidone or aripiprazole therapy—indeed, favorable changes in lipid profiles have been reported in several study cohorts for both treatments—whereas the limited data available for quetiapine have been contradictory. The impact of weight gain on lipid profiles is less clear and requires further study. Some studies with olanzapine, clozapine, and risperidone report a significant association between weight gain and increased triglyceride levels, whereas other studies do not. In general, high correlations between weight and lipids, or glucose, should not be routinely expected in small studies, given the range of intervening host factors (e.g., the delay between decreased insulin sensitivity and beta-cell failure). This is in contrast to the well-established relationship between weight or adiposity and metabolic risk in population samples.

The differing effects of the atypical antipsychotics on body weight, glucose regulation, and lipid profiles discussed in this overview are in line with the published findings from a recent consensus development conference on antipsychotic drugs, obesity, and diabetes. This conference brought together experts from the areas of psychiatry, diabetes, and obesity to consider the relationship between atypical antipsychotics and the development of obesity, diabetes, and dyslipidemia. The published Consensus Statement, based on consideration of all the available evidence, concludes that there are differences between the various atypical antipsychotics in their effects on body weight and risk for diabetes and dyslipidemia (Table 2).

<table>
<thead>
<tr>
<th>Weight gain</th>
<th>Risk for diabetes</th>
<th>Worsening lipid profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>D</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>D</td>
</tr>
<tr>
<td>Ziprasidone*</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Aripiprazole*</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Newer drugs with limited long-term data.
+ = increased effect; - = no effect; ADA = American Diabetes Association; APA = American Psychiatric Association; D = discrepant results.

GUIDANCE FOR PATIENT MONITORING

Individuals with mental illnesses, including schizophrenia, bipolar disorder, and depression, have increased mortality rates when compared with the general population and are at increased risk of a number of illnesses, including CVD, hypertension, and diabetes. The lifestyles of individuals with serious mental illness are likely to be an important contributor to poor overall health because risk factors, such as obesity, poor diet, lack of exercise, high rates of smoking, and alcohol use, are more prevalent in these individuals than in the population as a whole. Furthermore, the antipsychotic agents used to treat these individuals may in some cases contribute to adverse health outcomes by increasing risk factors, such as weight, blood glucose and lipids, and the metabolic syndrome.

Growing concerns about the impact of antipsychotic treatment on these risk factors, and the implications for the overall health of a vulnerable patient population, have led to increased interest in careful screening and monitoring of patients to improve their long-term health. This issue was discussed at the recent ADA/APA (American Psychiatric Association) consensus development conference, and their published statement provides recommendations for the monitoring of patients. Recommended baseline screening measures include weight and height (for BMI calculation), waist circumference, blood pressure, fasting glucose and lipid profile, and personal and family history of obesity, diabetes, dyslipidemia, hypertension, or CVD (Table 3). Atypical agents with a low propensity for weight gain and glucose intolerance, such as ziprasidone and aripiprazole, should be considered for patients with diabetes or who are at increased risk of the disease. Follow-up weight monitoring is recommended 4, 8, and 12 weeks after initiating or switching antipsychotic therapy, then quarterly at routine visits. Glucose and lipid level assessments are recommended 3 months after treatment initiation, then every year for glucose and lipids, unless baseline risk or treatment-emergent events indicate the need for increased attention to some or all of these parameters. (The ADA recommendation for every 5-year follow-up on lipids is now thought by many academics to underestimate the risk of dyslipidemia in this population, with annual screening offering a more prudent minimum target.) The current review suggests that elevated baseline risk and treatment-emergent adverse metabolic events can be expected in many treated patients, suggesting that many patients will have clinical indications for closer and more detailed monitoring. For those patients that show weight gain (≥5% increase) or worsening glycemia or dyslipidemia, a switch to another atypical agent not associated with significant weight gain or diabetes risk should be considered along with other interventions.

Similar recommendations for weight, glucose, and lipid monitoring come from the Mount Sinai conference, which brought together psychiatrists and other medical experts to develop guidelines for the routine monitoring of adult schizophrenia patients receiving antipsychotic therapy. However, these guidelines do recommend that patients with schizophrenia should be considered at high risk for CHD. Therefore, based on the NCEP guidelines, their lipid profile may need to be monitored more frequently (ie, every 2 years for normal LDL cholesterol levels, and every 6 months for elevated baseline risk and treatment–emergent adverse metabolic events can be expected in many treated patients, suggesting that many patients will have clinical indications for closer and more detailed monitoring. For those patients that show weight gain (≥5% increase) or worsening glycemia or dyslipidemia, a switch to another atypical agent not associated with significant weight gain or diabetes risk should be considered along with other interventions.

Similar recommendations for weight, glucose, and lipid monitoring come from the Mount Sinai conference, which brought together psychiatrists and other medical experts to develop guidelines for the routine monitoring of adult schizophrenia patients receiving antipsychotic therapy. However, these guidelines do recommend that patients with schizophrenia should be considered at high risk for CHD. Therefore, based on the NCEP guidelines, their lipid profile may need to be monitored more frequently (ie, every 2 years for normal LDL cholesterol levels, and every 6 months for elevated baseline risk and treatment–emergent adverse metabolic events can be expected in many treated patients, suggesting that many patients will have clinical indications for closer and more detailed monitoring. For those patients that show weight gain (≥5% increase) or worsening glycemia or dyslipidemia, a switch to another atypical agent not associated with significant weight gain or diabetes risk should be considered along with other interventions.

Table 3. Protocol for Monitoring Patients on Atypical Antipsychotics Recommended by the 2004 ADA/APA Consensus Statement

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>Quarterly</th>
<th>Yearly</th>
<th>Every 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal/family history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

More frequent monitoring may be warranted based on clinical status.
ADA = American Diabetes Association; APA = American Psychiatric Association; BMI = body mass index.
LDL cholesterol >130 mg/dL) than is recommended by the ADA/APA consensus statement.

The introduction of regular routine monitoring should allow for the early detection of changes in these important risk factors, and thereby improve the overall long-term health of patients with schizophrenia and other mental illnesses.

**Conclusions**

Evidence from the published literature indicates that atypical antipsychotic agents differ in their effects on weight and adiposity, and on blood glucose and lipid levels. An extensive body of evidence, including data from prospective clinical trials, shows marked differences in the weight-gain liabilities of atypical antipsychotics. Clozapine and olanzapine are associated with substantial risk of clinically significant weight gain, risperidone and quetiapine with generally mild to moderate weight gain, and ziprasidone and aripiprazole with minimal impact on weight. Studies using a variety of methodologies indicate, with few exceptions, that clozapine and olanzapine treatments are associated with an increased risk of developing diabetes mellitus and elevations in plasma triglyceride levels. Risperidone therapy is not associated with a consistent or substantial increase in the risk of developing diabetes or dyslipidemia. However, a possible increase in risk would be predicted to occur in association with any treatment that produces increases in weight and adiposity. Quetiapine therapy is not associated with a consistent or substantial increase in the risk of developing diabetes or dyslipidemia. However, limited data suggest a possible modest increase in the risk of hypertriglyceridemia with quetiapine treatment, and a possible increase in risk would be predicted to occur in association with any treatment that produces increases in weight and adiposity. Available data suggest that ziprasidone and aripiprazole treatments are not associated with an increase in the risk of developing diabetes or dyslipidemia, or any adverse effect on plasma glucose or lipid levels in treated patients. Further research is needed to improve our understanding of the interactions between disease states, antipsychotic medications, and glucose and lipid metabolism in patients with psychiatric disorders for improving psychiatric and medical health outcomes.

**References**

19. Regenold WT, Thapar RK, Marana C, et al. Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with bipolar I affective and schizoaffective disorders independent of psychotropic drug use [published cor-


