Metabolic Issues With Atypical Antipsychotics in Primary Care: Dispelling the Myths

Gary S. Kabinoff, M.D., P.A.;
Patrick A. Toalson, R.Ph.; Kristine Masur Healey, Pharm.D.;
Hillary C. McGuire, M.Ed.; and Donald P. Hay, M.D.

Background: Recently, much attention has been focused on the increased rate of metabolic syndrome components among psychiatric patients, including glucose intolerance, hyperglycemia, diabetes mellitus, hyperlipidemia, hypertension, and weight gain. Various reports have identified cases of newly diagnosed diabetes during treatment with atypical antipsychotic agents. However, the question remains whether there is a relationship between atypical antipsychotic use and the metabolic syndrome or whether there is a higher risk in this population irrespective of medication use.

Method: Many articles on antipsychotics and metabolic issues are reviews of case reports or small, cross-sectional laboratory studies highlighting the suspected potential for differing rates of new-onset diabetes cases. We conducted a retrospective review of the literature from 1998 through 2002, using the MEDLINE database, and recent studies presented at major psychiatric medical conferences to create a broader perspective on the metabolic issues.

Results: We identified over 70 abstracts and published manuscripts, including case reports; cross-sectional lab studies; retrospective analyses of head-to-head, controlled clinical studies; retrospective database studies; pharmacoepidemiology studies; and prospective head-to-head studies presented in the past 4 years. Studies assessed differences in fasting plasma glucose, oral glucose tolerance tests (OGTT), modified OGTT, frequently sampled intravenous glucose tolerance tests, homeostasis model assessment–insulin resistance, odds or hazard ratios, prevalence, and incidence, as well as other elements of the metabolic syndrome.

Conclusion: Data from this large body of scientific evidence indicate that the psychiatric patient population may be at a higher risk for the development of obesity, glucose homeostasis dysregulation, and hyperlipidemia compared with the general population. The available data do not demonstrate a consistent or clinically significant difference in the risk of new-onset diabetes during treatment with the various atypical antipsychotic agents.

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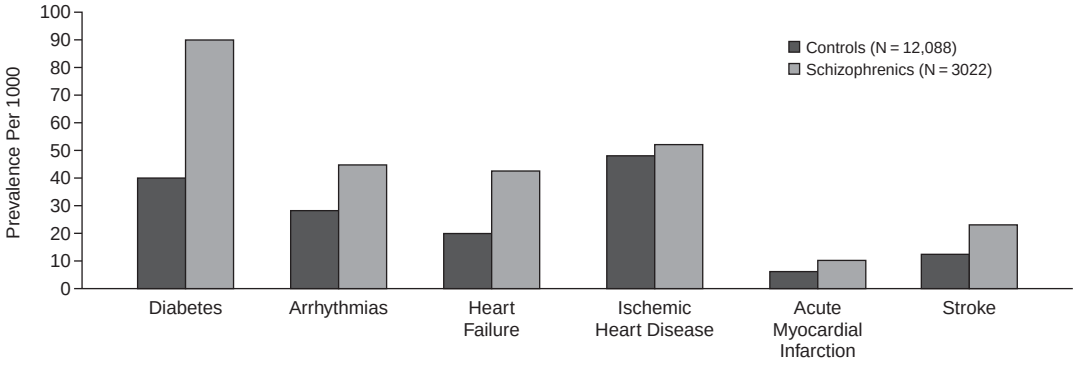
Corresponding author and reprints: Gary S. Kabinoff, M.D., 550 Heritage Drive, Suite 105, Jupiter, FL 33458 (e-mail: garykabinoff@cs.com).

Primary care physicians have been treating symptoms of psychiatric illness for decades, starting with the use of conventional antipsychotic agents and tricyclic antidepressants in the 1960s, benzodiazepines in the 1970s, selective serotonin reuptake inhibitors in the 1980s, cholinesterase inhibitors in the 1990s, and, most recently, atypical antipsychotic medications. Currently, there are 5 atypical antipsychotics marketed in the United States: clozapine, risperidone, olanzapine, quetiapine, and ziprasidone. Atypical antipsychotic medications have become more common in primary care practice. Atypical antipsychotics have superior clinical efficacy and a better safety profile regarding extrapyramidal symptoms and prolactin levels compared with conventional antipsychotics.

Despite this overall superior safety profile, however, the metabolic syndrome has recently been attributed to atypical antipsychotic use. This syndrome is defined by the presence of 3 of the following components: abdominal obesity, low high-density lipoprotein (HDL) particle concentration, hypertriglyceridemia, hypertension, and high fasting blood glucose.[1] As primary care physicians become more familiar with the use of atypical antipsychotic agents, we have a more informed and fundamental knowledge of the data surrounding these issues. This review will address potential myths and misinformation regarding atypical antipsychotics and the metabolic syndrome in an effort to help the primary care physician choose the optimal medication for each patient.

Figure 1. Prevalence of Cardiovascular Comorbidities in Schizophrenic Patients Versus Age- and Gender-Matched Controls, 1994–1995[a]



[a]Adapted from Curkendall et al.[13]

ATYPICAL ANTIPSYCHOTICS, HYPERGLYCEMIA, AND DIABETES

Hyperglycemia represents a spectrum of disorders from glucose intolerance to type 2 diabetes mellitus to insulin-dependent diabetes. Current standards of care include guidelines in which, when measured on at least 2 separate occasions, fasting glucose levels between 110 and 126 are classified as glucose intolerance and fasting glucose levels ≥ 126 mg/dL and random glucose levels ≥ 200 mg/dL are diagnostic for diabetes.[2,3]

The World Health Organization (WHO) states that the prevalence of all types of diabetes will more than double by the year 2025.[4] Over the past decade, the prevalence of diabetes has increased approximately 30%.[4] Almost 800,000 new cases occur annually, and about 30% of the U.S. diabetic population remains undiagnosed.[4]

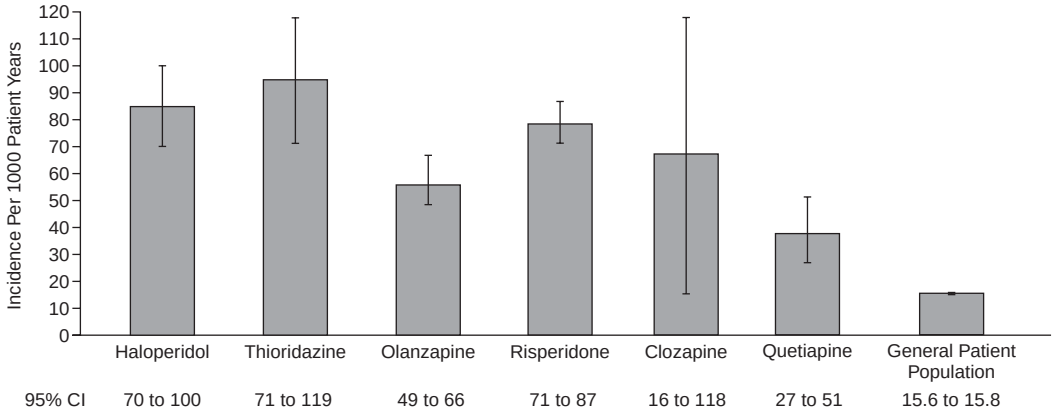
Type 1 diabetes mellitus is insulin-dependent. Type 2, which encompasses 90% of diagnoses for Americans with diabetes, is non–insulin-dependent, and its pathogenesis is multifactorial. There is a vast array of metabolic transformation along with genetic predisposition and environmental factors, all of which may play a role in its development. Occurring alone or in combination, decreased insulin production and an increase in insulin resistance are essential pathophysiologic components of this disorder and are implicated in the metabolic syndrome as well.

Myth #1: *There Are Consistent and Clinically Significant Differences in the Incidence of Diabetes in Patients Treated With Some Atypical Antipsychotics Compared With Others*

When reviewing the data surrounding atypical antipsychotics and diabetes, it has been reported that up to 30% of individuals with schizophrenia have a family history of type 2 diabetes, compared with 4.6% of healthy adult control subjects having a family history of type 2 diabetes.[5,6] Other reports have indicated that there is a 2- to 4-fold increase in diabetes in the schizophrenic and bipolar patient populations compared with the general population.[7–9] More recent studies continue to confirm these higher prevalence findings.[10–12] In a recent analysis of the Saskatchewan Health database,[13] the prevalence of diabetes and cardiovascular comorbidities was significantly higher in patients with schizophrenia versus age- and gender-matched controls (Figure 1). Since data regarding hyperglycemia and diabetes temporally associated with antipsychotic usage come from studies in schizophrenic and bipolar populations, data should be interpreted taking into account a higher population prevalence.

When examining large-scale pharmacoepidemiology studies, rates of newly diagnosed diabetes occurring during antipsychotic treatment can be compared to a control population. The largest epidemiology cohort study to date, reported by Cavazzoni and colleagues,[14] looked at newly diagnosed diabetes during treatment with new antipsychotic monotherapy, utilizing the Advance PCS prescription database. This study showed a significantly higher incidence of newly diagnosed diabetes in patients treated with antipsychotic medications (N = 58,751) compared with a general reference population group (N = 5,816,473) (Figure 2). A Cox proportional hazards ratio analysis showed a higher rate of diabetes during treatment with each antipsychotic measured versus the control group (Table 1). However, comparisons between 2 atypical antipsychotics—olanzapine and risperidone—indicate comparable rates of hyperglycemia without either agent showing a significantly higher incidence of diabetes. The PCS database does not include information on psychiatric diagnosis, ethnicity, or obesity, all factors that need to be evaluated regarding their association with the risk of diabetes development. Another limitation of this study is that atypical antipsychotic medications have not existed long enough to allow for sufficient cumulative

Figure 2. Annualized Incidence of Diabetes Mellitus in Specific Antipsychotic Treatment Cohorts[a]



[a]Adapted from Cavazzoni et al.[14]

clinical data to fully validate the epidemiologic analyses. Therefore, conclusions about the risk of diabetes in patients treated with the newer antipsychotics must be made with caution.

Sernyak and colleagues[15] reported a multicenter Veterans Administration study (N = 38,632) in which the prevalence of diabetes in atypical antipsychotic–treated patients with schizophrenia was compared with that of patients treated with older antipsychotic agents over a 4-month time period. Odds ratios were calculated based upon a variety of adjustments. Unlike the Advance PCS study,[14] these analyses calculated odds ratios compared to conventional antipsychotic medications only and not to a control group. Reported odds ratios were as follows: risperidone 1.05, olanzapine 1.11, clozapine 1.25, and quetiapine 1.31. These odds ratios were reported as being statistically significantly different from the conventional antipsychotic cohort for quetiapine, clozapine, and olanzapine cohorts, but not for the risperidone group. Odds ratios are common to cross-sectional studies and are based on prevalence. They represent an estimation of risk based upon 2 assumptions: the control group is a representative sample of the general population in terms of risk factors and the outcome being measured is a relatively uncommon event. In terms of clinical significance, an odds ratio that approximates 1 means there is no difference in risk, an odds ratio between 2 and 5 indicates a mild risk association, an odds ratio between 5 and 10 indicates a moderate association, and an odds ratio greater than 10 indicates a strong association.[16]

Due to the cross-sectional design of the study by Sernyak et al.,[15] patients may have been diagnosed with diabetes mellitus prior to receiving the antipsychotic medication they were taking during this 4-month time period. This study also did not take into account the amount of time a patient was treated with a particular medication. This is another crucial variable, as some patients might have recently switched from another antipsychotic, while others might have used the same antipsychotic for a long time period. Although the authors claim that the results strongly suggest a causal relationship, the findings merely point to a temporal association between the prescription of atypical antipsychotics and a diagnosis of diabetes mellitus. They do not demonstrate that atypical antipsychotics cause an increase in the odds of being diagnosed with diabetes mellitus. It is highly likely that patients with schizophrenia who are treated with atypical antipsychotics are different from those who are treated with conventional antipsychotics on a host of characteristics, including risk factors for diabetes mellitus, none of which were addressed in this study. Still, the study demonstrated that relatively small differences existed in absolute magnitude with respect to the odds of having a diagnosis of diabetes among the antipsychotic cohorts studied.

Caro and colleagues[17] retrospectively examined another large health claims database for treatment-emergent

Table 1. Hazard Ratios of Diabetes Mellitus in Antipsychotic Cohorts Relative to the General Advance PCS Patient Population[a]

Cohort	Hazard Ratio	95% CI	p Value
Conventional antipsychotics			
All agents combined	3.5	3.1 to 3.9	≤ .0001
Haloperidol	3.1	2.6 to 3.7	≤ .0001
Thioridazine	4.2	3.2 to 5.5	≤ .0001
Atypical antipsychotics			
All agents combined	3.1	2.9 to 3.4	≤ .0001
Olanzapine	3.0	2.6 to 3.5	≤ .0001
Risperidone	3.4	3.1 to 3.8	≤ .0001
Quetiapine	1.7[b]	1.2 to 2.4	.002
Clozapine	3.3	1.4 to 8.0	.007

[a]Adapted from Cavazzoni et al.[14] Hazard ratio and 95% CI values rounded to the first decimal place (Cox proportional hazards regression controlling for age and gender).
[b]Hazard ratio in the top quetiapine dose quartile was 3.1 (95% CI = 1.9 to 5.1; p ≤ .0001).

diabetes during exposure to either risperidone or olanzapine. Results from this study (N = 33,945) showed a numerically greater incidence of diabetes in the olanzapine cohort (1.7%) compared with the risperidone cohort (1.5%), with a reported odds ratio of 1.08. This study was limited by the fact that it included patients taking multiple antipsychotic medications and did not include a general population reference group. Additional epidemiology studies with smaller cohort sizes have also demonstrated comparable rates of new-onset diabetes among the patients treated with typical and atypical antipsychotic agents.[18,19] Due to the relatively short period of time since ziprasidone entered the market, no epidemiologic data have been published regarding the incidence of new-onset diabetes during treatment with ziprasidone; thus, this incidence rate remains unclear.[20]

Several small-scale cross-sectional studies[21–23] have looked at differences in glucose tolerance and insulin sensitivity, primarily in patients treated with risperidone, clozapine, and olanzapine. These studies have employed a variety of testing measures and mathematical calculations including oral glucose tolerance testing (OGTT), modified OGTT, frequently sampled intravenous glucose tolerance testing, and homeostasis model assessment–insulin resistance as methods to evaluate insulin resistance differences or similarities between drugs. These reports suggest relative abnormality in glucose utilization among clozapine-treated patients but have shown inconsistent results regarding patients treated with olanzapine and risperidone. They require extremely cautious interpretation since each study is seriously limited by its small size, uncontrolled confounding variables, and cross-sectional design, providing data only from a single timepoint. A more recent cross-sectional study by Newcomer and colleagues[24] utilized a euglycemic clamp methodology to compare levels of insulin sensitivity across patients receiving olanzapine, risperidone, or typical antipsychotics to both slim controls and control subjects with average body mass index. Although cross-sectional in design, this study used the "gold standard" clamp methodology for testing a patient's level of insulin resistance. The authors reported a robust finding of lowered levels of insulin-stimulated glucose disposal across all subject groups in comparison to slim controls. Their findings indicated that this decrease in insulin sensitivity was significantly associated with an increase in adiposity as measured by a patient's body mass index irrespective of the patient's antipsychotic treatment group. This study, although small in size, uses a more scientifically sound methodology and suggests comparable effects of these medications on insulin sensitivity changes.

A question remains among clinicians concerning the reports of diabetic ketoacidosis (DKA) occurring in patients taking atypical antipsychotics. In order for DKA to occur, there is an absolute (type 1 diabetes) or relative (type 2 diabetes) insulin deficiency of sufficient magnitude to allow ketogenesis to occur. In order to test the potential effects of antipsychotics on pancreatic insulin release, a recent randomized, placebo-controlled study[25] was conducted using a hyperglycemic clamp methodology, the gold standard for quantitating insulin secretion. In this procedure, a study subject's blood glucose level is maintained or "clamped" at a level of 200 mg/dL by a continuous intravenous glucose infusion over the 4-hour time period of the study. Blood glucose levels are measured every 5 minutes throughout the procedure and small adjustments made to the glucose infusion rate in order to maintain the "clamped" glucose level of 200 mg/dL. The body's normal response to this elevated glucose is to release insulin from the pancreas, and it is this increase in insulin levels and corresponding c-peptide levels that are measured at regular time intervals throughout the procedure. The study, reported by Sowell and colleagues, aimed to evaluate potential changes in beta cell function associated with decreased insulin secretion in patients treated with olanzapine or risperidone. Healthy volunteers were randomly assigned to treatment with olanzapine, 10 mg/day (N = 17); risperidone, 4 mg/day (N = 13); or placebo (N = 18) for 15 to 17 days. Insulin secretion was quantitatively assessed at baseline and endpoint using the hyperglycemic clamp. Neither olanzapine nor risperidone was associated with a decrease in insulin secretory response to a prolonged hyperglycemic challenge. This study did not find that olanzapine or risperidone directly impaired pancreatic beta cell function and thus does not support a hypothesis linking the agents to DKA via putative impairment of insulin secretion.

Summary

To date, based upon our understanding of the pathophysiology of diabetes and the pharmacology of these agents, there are insufficient data from large studies to demonstrate a consistent or clinically significant difference in the risk of insulin resistance during treatment with the various atypical antipsychotics. With the hyperglycemic clamp, no decrease in insulin production was evident. It appears, based on these data, that although hyperglycemia should always be a potential concern in these high-risk psychiatric populations, screening for diabetes that is now recommended for all adult Americans[3] may yield a more rapid recognition of those at risk for hyperglycemia and diabetes and still allow for appropriate use of these medications.

ATYPICAL ANTIPSYCHOTICS AND WEIGHT GAIN

Myth #2: *Certain Antipsychotics Always Cause Weight Gain*

Obesity and weight gain present a clinical dilemma for many clinicians who treat large numbers of patients.

However, the prevalence of being overweight or obese in individuals with schizophrenia and bipolar disorder is generally thought to be greater than in individuals without these disorders.[26,27] Additionally, many of the adverse medical consequences of obesity tend to be underdiagnosed and undertreated in mentally ill populations.[28] Patients treated with antipsychotic medications have shown varying degrees of weight gain.[29,30] The regulation of body weight is a complex interplay of genetic and environmental factors that affects satiety and appetite control, as well as the balance between energy intake versus energy expenditure.[31] Antipsychotic medications, particularly the newer atypicals, possess broad pharmacologic profiles. Many of the neurotransmitter systems and receptor subtypes within which these agents are active may also be involved to varying degrees in the regulation of food intake and energy homeostasis either centrally or peripherally in a complex cascade affecting weight regulation.[31]

Most of the existing data describing various hypothesized mechanisms of weight gain during antipsychotic treatment have focused on receptor antagonism actions, particularly the serotonin 5-HT_{2C} and histamine H_1 receptors, which may impact increased appetite. Serotonin is a well-known satiety factor, and serotonin antagonism has been shown to stimulate increased appetite.[32,33] Serotonin 5-HT_{2C} receptors are antagonized by various agents that have been temporally associated with weight gain, including tricyclic antidepressants and atypical antipsychotics; conversely, minimal treatment-emergent weight gain has been reported in patients treated with drugs with minimal impact on serotonin 5-HT_{2C} receptor effects, such as haloperidol. However, a recent analysis by Wirshing and colleagues[29] failed to correlate weight gain during treatment with clozapine, olanzapine, risperidone, and sertindole with serotonin 5-HT_{2C} affinity. Additionally, evidence against the serotonin 5-HT_{2C} receptor playing a major role is the observation that ziprasidone exhibits a high in vivo affinity for the serotonin 5-HT_{2C} receptor but is thought to have a favorable profile regarding weight gain.

Histamine H_1 receptor antagonism may also play a role in increased appetite and weight gain.[34–37] In a retrospective analysis of clinical records for 92 patients, Wirshing and colleagues[29] observed an exponential relationship between histamine H_1 receptor affinity and maximal weight gain in patients treated with clozapine, olanzapine, risperidone, sertindole, and haloperidol. Histamine H_1 receptor saturation occurs at very low doses for those antipsychotics with a high affinity for this receptor, which supports the observation that weight gain is generally not dose-dependent in patients treated with these agents. Other neurotransmitters such as γ-aminobutyric acid have been suggested to also play a role in weight regulation, along with leptin, prolactin, and various neuropeptides.

The plethora of peptides, hormones, neurotransmitter systems, and receptors having a possible role in the regulation of body weight makes predicting the potential for weight gain during treatment with a particular drug difficult in any one patient. In a retrospective analysis of 2 acute clinical trials, one comparing olanzapine and haloperidol (N = 1369) and the other comparing olanzapine and risperidone (N = 268), Basson and colleagues[38] identified a variety of factors that appear to influence weight change. The most robust predictors of weight gain were a low baseline body mass index (BMI), better clinical outcome, nonwhite race, and younger age. Czobor and colleagues[39] found with olanzapine and clozapine therapy that therapeutic response was closely related to an absolute and relative gain in weight and BMI. No association between weight gain and therapeutic response was found for risperidone or haloperidol. The rate of weight gain during treatment with atypical antipsychotic agents appears to be most rapid during the first 12 weeks of treatment and suggests the importance of early dietary and behavioral intervention with the patient exhibiting a significantly increased appetite and weight gain.[40–42]

Summary

Clinically significant weight gain may occur during treatment with atypical antipsychotics, but variations have been observed, and some literature reports have concluded that the variation is treatment-related. Many patients with mental illness are obese or overweight before the addition of an antipsychotic medication, which puts them at a possible increased risk for certain medical conditions regardless of antipsychotic choice.

Myth #3: *All Weight Gain Leads to Diabetes*

Excess body weight has been shown in numerous studies to increase the risk of morbidity for a variety of health conditions, including hypertension, dyslipidemia, type 2 diabetes mellitus, and coronary heart disease. Although antipsychotic-associated weight gain is presumably a self-limiting phenomenon in that it appears to plateau over time,[38,40,43] an important question is whether such weight gain may predispose or exacerbate certain medical conditions such as diabetes and heart disease. Numerous recently published reports have postulated association between antipsychotic treatment and glucose intolerance, hyperglycemia, diabetes, and cardiovascular disease.[44–53] However, in close to half of the cases there was no increase in weight gain reported, although these patients were overweight or obese prior to antipsychotic therapy initiation.[46]

Type 2 diabetes is a progressive disease linked to the development of insulin resistance over many years prior to the time a diagnosis of diabetes is recorded. Some of the patients observed in the aforementioned case reports may have been in a prediabetic state for years prior to their hyperglycemic presentation.

Typically, measurements of BMI have been used to define those persons who are considered to be overweight

or obese. Waist circumference and waist-to-hip ratio are also useful measurements in defining obesity because they are indicators of abdominal fat, which has been associated with a higher risk for development of dyslipidemia, hypertension, and glucose intolerance, together characterized as the "metabolic syndrome," the focus of increasing attention. An increased waist circumference can indicate an increased risk of disease even in a person of normal weight.[54] The excess adipose tissue often seen in psychiatric patient populations is often centrally distributed across the abdominal area leading to an increase in waist circumference.[55] This may explain the lack of recent weight gain being observed in a significant portion of the hyperglycemia case reports. Moreover, the available data have been confined to relatively short observation periods and relatively small sample sizes. Further study is needed to evaluate long-term changes in weight or weight-related health parameters, such as cardiovascular disease, in patients treated with antipsychotic medication.

Summary

Obesity is a common finding in psychiatric patients prior to treatment with antipsychotic medications. Moreover, this obesity often presents in a central adiposity distribution pattern, which carries a high degree of risk for the development of insulin resistance and glucose intolerance irrespective of any antipsychotic prescription. Per established American Diabetes Association and National Cholesterol Education Program guidelines, patients identified as having multiple preexisting risk factors should be routinely monitored for changes in blood glucose and lipids irrespective of changes in weight.

ATYPICAL ANTIPSYCHOTICS, HYPERLIPIDEMIA, AND HYPERTENSION

Myth #4: *Some Atypical Antipsychotics Have Been Shown to Have a Direct Medication Effect on Cardiovascular Function, Specifically on Lipids and Blood Pressure*

Research has been conducted to evaluate the risk for cardiovascular disease in patients with psychiatric illness. It is suggested that patients with psychiatric illness have an increased risk of cardiovascular disease, regardless of the treatment they receive. This increased risk has been attributed to multiple causes ranging from platelet aggregation differences to lifestyle differences, such as diet.[56,57]

Alterations in serum cholesterol have been well established as a risk factor for coronary heart disease (CHD).[58] Although more difficult to establish, elevated triglycerides also appear to be an independent risk factor for atherosclerosis and CHD.[59–62] Elevated triglycerides are associated with obesity and diabetes. Other factors linked with elevated triglycerides include physical activity, excess alcohol intake, high-carbohydrate diets, comorbid conditions, and some medications.[63]

As weight gain may occur in some patients using atypical antipsychotics,[30,40] an important question is whether this weight gain may predispose or exacerbate certain medical conditions such as heart disease by altering lipid levels or blood pressure. Recent reports in the literature have suggested a temporal association between the use of atypical antipsychotics and elevated triglycerides, as well as hypertension.[64–78] However, there are limited, prospective data available regarding the effects of antipsychotics on serum lipid levels and blood pressure. One such study, recently presented by Lindenmayer and colleagues, indicated a significant within-group effect for clozapine and olanzapine on increasing cholesterol levels over 14 weeks, while the increases seen with risperidone and haloperidol trended toward but failed to reach significance.[57,79]

Summary

The potential effects of any antipsychotic therapy on serum lipids or blood pressure should be evaluated in context of overall cardiovascular risk, including risk factors such as family history, cigarette smoking, physical activity, and atherogenic diet.

ATYPICAL ANTIPSYCHOTICS AND THE METABOLIC SYNDROME

Myth #5: *Some Atypical Antipsychotics Are Associated With Causing the Metabolic Syndrome*

The metabolic syndrome consists of the constellation of abdominal obesity with waist circumference of > 102 cm in men and > 88 cm in women; hypertriglyceridemia (i.e., triglycerides ≥ 150 mg/dL); HDL < 40 mg/dL in men and < 50 mg/dL in women; hypertension (i.e., blood pressure ≥ 130/85 mm Hg); and fasting blood glucose ≥ 110 mg/dL. By definition in the *Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)*,[1] presence of 3 of the 5 components comprises the metabolic syndrome, which can lead to vascular inflammation and premature arteriosclerosis. Using this Adult Treatment Panel III definition, Ford and colleagues[80] have estimated the prevalence of the metabolic syndrome between 22% and 24% in U.S. adults. Some patients treated with atypical antipsychotics may experience components of the metabolic syndrome. Appropriate screening, pursuant to the established guidelines of the American Diabetes Association and the National Cholesterol Education Program, and timely intervention, as clinically indicated, may help to avoid or lessen components of the metabolic syndrome in many patients. Some studies have found that behavioral interventions are effective for some patients in limiting

weight gain during antipsychotic treatment.[29,81–83] We must always keep in mind that the disease processes we are treating will themselves carry a degree of morbidity and mortality, and we should temper accordingly our decision making regarding therapeutic agents. The most practical example combining many of these issues is treatment of diabetes itself. The sulfonylureas are a mainstay of pharmacologic intervention of hyperglycemia. Unwanted effects of the sulfonylureas include weight gain without any beneficial effect on hypertension or lipids. A balance between risk/benefit ratios should always be considered based on side effect profiles, versus the degree of morbidity and mortality.

Summary

Overall, there is a rather high prevalence of the metabolic syndrome in the general population, and it is likely to occur at an increased rate among patients with mental illness due to their high degree of preexisting risk factors. The evidence implicating atypical antipsychotics as having a direct effect on causing different components of the metabolic syndrome appears more circumstantial than factual at this point. Moreover, there are no direct data to support an overall increase in cardiovascular morbidity or mortality connecting atypical antipsychotics with this component of the syndrome.

CONCLUSIONS

Current evidence suggests that physical disorders such as obesity, glucose homeostasis dysregulation, and hyperlipidemia appear to be significant comorbidities in patients with schizophrenia; whether these disorders are an integral part of the psychiatric disease process or sequelae of antipsychotic treatment remains somewhat unclear. The choice of antipsychotic medication for each patient is based on a multitude of factors including the symptoms the patient exhibits, the working diagnosis, potential benefits for the patient, potential side effects, potential for adequate adherence to the treatment recommendations, cost of the medication versus cost of total treatment with or without a particular medication, and comorbid conditions.

One of the most practical ways of choosing the medication becomes the 2-fold assessment of the risk/benefit ratio: "What is the risk versus benefit of this particular patient *taking* this particular medication?" versus "What is the risk versus benefit of this particular patient *not taking* this particular medication?"

Reviewing all the data, the benefits of treatment with an atypical antipsychotic medication would appear to be far more numerous and potentially meaningful for many patients than the risks of possible issues surrounding hyperglycemia and weight gain.

It is important for clinicians to focus patient management on controlling the devastating consequences of mental illness as well as the patient's medical concerns. Due to the seriousness of uncontrolled mental illness, it may be better for the patient whose improvement is benefiting from a particular antipsychotic agent to remain on that agent versus switching to another agent with possible reduced efficacy when comorbid medical conditions arise. Clinicians should consider initiating a standard monitoring regimen for those patients who exhibit known risk factors as identified by the American Diabetes Association and the National Cholesterol Education Program for the development of diabetes and cardiovascular disease. Patients who gain significant weight in the first few weeks of antipsychotic therapy should have initiation of meaningful dietary, behavioral, and/or pharmacologic interventions to minimize further weight gain.

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

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