REVIEW ARTICLE

Atypical Antipsychotics and Metabolic Syndrome in Patients with Schizophrenia: Risk Factors, Monitoring, and Healthcare Implications

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Background: Metabolic syndrome is a leading cause of morbidity and mortality in patients with schizophrenia, with a prevalence rate double that of nonpsychiatric populations. Given the amount of evidence suggesting a link between atypical antipsychotic medications and metabolic syndrome, several agencies have recommended regular clinical monitoring of weight, symptoms of hyperglycemia, and glucose in chronically medicated patients with schizophrenia.

Objectives: To summarize the current literature on atypical antipsychotic-induced metabolic syndrome in patients with schizophrenia, outline some of the molecular mechanisms behind this syndrome, identify demographic and disease-related risk factors, and describe cost-effective methods for surveillance.

Discussion: The differential prevalence of metabolic syndrome associated with various atypical antipsychotic medications has been evidenced across numerous studies, with higher effects seen for certain antipsychotic medications on weight gain, waist circumference, fasting triglyceride level, and glucose levels. Given the association of these symptoms, all atypical antipsychotic medications currently include a warning about the risk of hyperglycemia and diabetes, as well as suggestions for regular monitoring. Despite this, very little data are available to support adherence to these monitoring recommendations. Lack of awareness and resources, diffusion of responsibility, policy implementation, and organizational structure have all been implicated.

Conclusion: The treatment of schizophrenia involves a balance in terms of risks and benefits. Failing to treat because of risk for complications from metabolic syndrome may place the patient at a higher risk for more serious health outcomes. Supporting programs aimed at increasing monitoring of simple laboratory and clinical measures associated with metabolic syndrome may decrease important risk factors, improve patients' quality of life, and reduce healthcare costs.

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Am Health Drug Benefits. 2011;4(5):292-302
www.AHDBonline.com

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Despite treatment advances in prevention, cardiovascular disease (CVD) remains the leading cause of mortality globally. CVD is responsible for 30% of all deaths and represents one of the leading long-term health considerations in the population as a whole.[1] CVD is also the most common cause of natural mortality in schizophrenia, accounting for a total of 34% of deaths among male patients and 31% of deaths in female patients and is surpassed only by suicide.[2] In fact, it has been estimated that the prevalence of dyslipidemia, hypertension, obesity, and type 2 diabetes is approximately 1.5 to 2 times higher in individuals with schizophrenia and other serious mental illness compared with the general population.[3] Although the exact prevalence of metabolic syndrome in adults with schizophrenia varies greatly (between 20% and 60%), common estimates typically place this at twice that of the normal healthy population.[4]

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The Scope of the Problem

Given that schizophrenia occurs in approximately

1.1% of the population aged >18 years, or 2.2 million Americans, this has a significant impact on healthcare utilization and expenditures. Increased awareness of metabolic syndrome as a risk factor for CVD, as well as associated guidance for screening, monitoring, and treatment are urgently needed.

This article concentrates on issues germane to adult schizophrenia, but excessive morbidity and mortality linked to metabolic syndrome and CVD is not limited to this population. These concerns also affect adolescents with schizophrenia, as well as adults and adolescents with severe mental illness such as bipolar disease and other psychiatric diagnoses who may be prescribed atypical, or second-generation, antipsychotic medications.

Adverse events associated with the use of atypical antipsychotic medications are thought to be largely, but not singularly, contributory to cardiometabolic and endocrine side effects constituting metabolic syndrome; and children and adolescents receiving atypical antipsychotic medications are particularly vulnerable to these effects.[5]

It should be noted that in addition to psychotic disorders, atypical antipsychotic medications are often prescribed off-label for the treatment of a variety of pediatric and adult disorders that are associated with aggressive and disruptive behaviors, such as pervasive developmental disorder, disruptive behavior disorders, mental retardation, severe attention-deficit/hyperactivity disorder, tic disorders, obsessive-compulsive disorder, and Alzheimer's disease. In these indications, the risks of eventually developing metabolic syndrome have to be judged against the more immediate risks of the aggressive behavior in terms of harm to the patient and others.

As noted, the link between schizophrenia and CVD is typically viewed in terms of metabolic syndrome, which is merely a combination of medical risk factors and disorders. Clinical criteria for what constitutes metabolic syndrome are diverse, with the most widely adopted criteria created by the World Health Organization (WHO), the European Group for the Study of Insulin Resistance, and the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III. All these organizations agree that the core components of metabolic syndrome include obesity, insulin resistance, dyslipidemia, and hypertension. However, they differ in how they apply criteria to identify symptom clusters.

The WHO and NCEP ATP III define metabolic syndrome on the basis of easily measured clinical features and laboratory measures. According to the International Diabetes Federation definition, criteria for metabolic syndrome include central obesity plus any 2 of the following 4 factors: elevated triglyceride level, reduced high-density lipoprotein cholesterol, elevated blood pressure (BP), and elevated fasting plasma glucose (FPG) or previously diagnosed type 2 diabetes (**Table 1**).[6]

KEY POINTS

- Cardiovascular disease (CVD) is the most common cause of natural mortality in schizophrenia.
- Given that schizophrenia occurs in approximately 1.1% of the adult population, or 2.2 million Americans, this has a significant impact on healthcare utilization and expenditures.
- Side effects associated with atypical antipsychotics are thought to contribute significantly to cardiometabolic and endocrine adverse events constituting metabolic syndrome.
- Metabolic syndrome differences among various antipsychotic agents have substantial cost implications for society. Direct medical costs associated with macrovascular complications and hyperglycemia can become considerable.
- Ongoing patient monitoring of simple laboratory and clinical measures may help decrease important adverse events in multiple organ systems and ultimately improve patients' quality of life and reduce healthcare costs.
- Increased awareness of metabolic syndrome as a risk factor for CVD is urgently needed.

Mechanisms Underlying Metabolic Syndrome in Schizophrenia

The putative mechanisms linking atypical antipsychotic medications to metabolic syndrome are multifactorial, and likely include the interplay of dopamine, histamine, orexigenic (anabolic) neuropeptides, adrenergic and muscarinic receptors, and failed glucose homeostasis, as well as the interaction of these with modifiable and nonmodifiable risk factors.[7] On a clinically relevant level, weight gain has been a well-known side effect of atypical antipsychotic medications, although references to excessive weight gain exist for first-generation antipsychotic agents, such as chlorpromazine, as well.

Sedentary lifestyle and other risk factors, such as smoking and poor diet, may be contributory; however, atypical antipsychotic agents induce changes in weight that are primarily responsible for changes in glucose metabolism. There is also some evidence that impairments in glucose metabolism may be independent of adiposity, as glucose and lipid metabolism abnormalities may occur without weight gain.[8,9]

Furthermore, weight gain tends to be generally observable within the first few months of treatment,

and increases at that time may not be dose-dependent. Individuals with low body mass index (BMI) at baseline are particularly vulnerable to these effects. Weight gain, especially when manifested as intra-abdominal obesity (often operationalized as increased waist circumference), plays a significant role in the development of metabolic syndrome and remains a significant long-term health issue with implications for overall quality of life in patients with schizophrenia.

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Risk Factors

There are numerous risk factors that influence the prevalence of metabolic syndrome in schizophrenia, some of which are modifiable. Variables as diverse as genetic polymorphisms, the unique pharmacology of atypical antipsychotic agents, and lifestyle factors (eg, physical activity, support system, cigarette smoking, and alcohol and drug abuse) also appear to moderate atypical antipsychotic–induced metabolic syndrome.[9]

Racial and ethnic differences in the presentation of metabolic syndrome are well-described. For example, a positive metabolic syndrome screen for blacks and whites may be associated with increased risk for CVD, whereas a positive metabolic screen for Hispanics and Filipino Americans may be associated with increased risk for diabetes. Furthermore, increased waist circumference has been reported in persons with BMI values that fell well within the "normal" ranges for blacks, Asian Americans, and Hispanics, suggesting that these populations may be at intrinsically increased risk for metabolic syndrome.[10] The reasons for these disparities are varied but suggest potential genotypic differences in the applicability of risk factors that constitute metabolic syndrome. Recent pharmacogenetic research has identified genetic factors related to variability in antipsychotic

Table 1 Core Criteria for Diagnosing Metabolic Syndrome

International Diabetes Federation (2006)[1]	US National Cholesterol Education Program Adult Treatment Panel III (2001)[2]
Central obesity—defined as waist circumference[a] with ethnicity-specific values—plus any 2 of the following: • Raised triglycerides: ≥150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality • Reduced HDL-C: <40 mg/dL (1.03 mmol/L) in men, <50 mg/dL (1.29 mmol/L) in women, or specific treatment for this lipid abnormality • Systolic BP ≥130 or diastolic BP ≥85 mm Hg, or treatment of previously diagnosed hypertension • FPG ≥100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes; glucose tolerance test strongly recommended (but not necessary) for FPG >5.6 mmol/L or 100 mg/dL	At least 3 of the following: • Central obesity: waist circumference >102 cm or 40 in (men), >88 cm or 35 in (women) • Dyslipidemia: triglycerides ≥1.7 mmol/L (≥150 mg/dL) • Dyslipidemia: HDL-C <40 mg/dL (men), <50 mg/dL (women) • BP: ≥130/85 mm Hg • FPG: ≥110 mg/dL

[a]If BMI is >30 kg/m^2, central obesity can be assumed and waist circumference does not need to be measured.
BMI indicates body mass index; BP, blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol.
1. Adapted with permission from the International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. 2006. www.idf.org/webdata/docs/IDF_Meta_def_final.pdf.
2. *Source:* US Department of Health and Human Services. National Cholesterol Education Program: ATP III Guidelines At-A-Glance Quick Desk Reference. May 2001; publication no 01-2205. www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf.

drug response, including therapeutic response and adverse events.[11]

In an effort to clarify a potential genetic substrate, researchers examined a group of severely mentally ill patients receiving antipsychotic medications and selected genes that possibly could serve as candidates for future studies of the direct effects of some antipsychotic medications on hyperlipidemia, hypertriglyceridemia, or hypercholesterolemia.[12] They conducted a search for single-nucleotide polymorphisms (SNPs) associated with these direct effects that are not explained by obesity. It was hypothesized that olanzapine, quetiapine, and chlorpromazine may increase lipids directly, whereas other antipsychotic medications not associated with similar clinical presentations would serve as control medications. A total of 165 patients taking olanzapine, quetiapine, or chlorpromazine were compared with 192 control patients taking other antipsychotic medications. A cross-sectional sample of these 357 patients was genotyped using a DNA microarray with 384 SNPs. After initial nondirected candidate selection, a directed search identified 3 genes that may be contributory: acetyl-coenzyme A carboxylase alpha (*ACACA*) SNP in the hypertriglyceridemia model, and neuropeptide Y (*NPY*) and acetyl-coenzyme A carboxylase beta (*ACACB*) in the hypercholesterolemia model. This approach suggested that *ACACA*, *ACACB*, and *NPY* genes may be good candidates for studies of the direct effects of some antipsychotic agents on hyperlipidemia; as such, these genes may be promising candidates for future studies.

Obviously, the pharmacologic properties of atypical antipsychotic medications are also contributory, and a recent study suggested that variations in genes encoding for receptor proteins mediating the antipsychotic effect could also be candidates (such as *HTR2C* polymorphisms). Researchers investigated 4 *HTR2C* genetic variants in 112 patients with schizophrenia who were mainly using clozapine, olanzapine, and risperidone, and reported that 3 of the 4 *HTR2C* polymorphisms were associated with an increased risk of metabolic syndrome.[13]

Choice of Atypical Antipsychotics

Differential metabolic profiles associated with several common atypical antipsychotic medications were suggested by the retrospective literature,[14] and many prospective trials have confirmed the association. However, even untreated patients suffering from schizophrenia are at an increased risk for developing many medical conditions classically associated with metabolic syndrome, and the interaction of antipsychotic treatment and disease with environmental factors has been incompletely explored. Nevertheless, differential effects across compounds have been described regardless of potential confounding variables.

For example, as part of the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) of more than 600 patients with schizophrenia, Meyer and colleagues have shown that the prevalence of metabolic syndrome for olanzapine increased over 3 months from a baseline of 34.8% to 43.9%, but decreased for ziprasidone from 37.7% to 29.9%.[15] Others have confirmed this notion by reporting significant differences in the cumulative incidence of metabolic syndrome between treatments, with a nearly 20% incidence of metabolic syndrome in the olanzapine group compared with approximately 13% incidence in the placebo group, and an 8% incidence in the aripiprazole group, which represents a 69% relative risk reduction for aripiprazole compared with olanzapine.[16]

The CATIE researchers also reported that despite variable effect sizes across subgroups, at 3 months olanzapine and quetiapine were associated with the largest mean increase in waist circumference (0.7 in for both), followed by risperidone (0.4 in). This is in comparison to no changes evidenced for ziprasidone (0.0 in) and a decrease in waist circumference for perphenazine (−0.4 in). Olanzapine was also associated with significant changes in fasting triglycerides at 3 months (+21.5 mg/dL) compared with ziprasidone (−32.1 mg/dL).[15] Substantially greater weight gain with olanzapine (0.9 kg/month) than with quetiapine or risperidone (both 0.2 kg/month) was also reported. Perphenazine and ziprasidone were associated with losses of 0.1 kg/month.[17]

Similar to industry-sponsored studies that have a registration intent, CATIE most likely enrolled patients who had many years of previous drug exposure and, as such, their exposure might have underestimated the magnitude of drug effect on weight. Trials of drug-naive patients or patients with very little exposure have suggested much larger increases in weight with these drugs (**Table 2**, see print issue).

Why Do Atypical Antipsychotics Differ?

As previously suggested, some atypical antipsychotic medications seem to carry higher risks for metabolic syndrome than others. Researchers have attempted to determine which molecular binding sites are most closely linked with specific side effects, such as weight gain, glucose dysregulation, diabetes, and dyslipidemia, across a variety of antipsychotic agents. Despite a greater understanding of the biochemical effects of many of these medications in recent years, the pharmacologic mechanisms underlying their respective therapeutic properties and related side effects remain uncertain.

For example, in addition to dopamine D_2 receptor

antagonism, which is a characteristic feature of all atypical antipsychotic drugs, these agents also bind to a range of nondopaminergic targets, including serotonin, glutamate, histamine, alpha-adrenergic, and muscarinic receptors and their subtypes.[18] Parsing molecular mechanisms associated with an effective antipsychotic agent from those associated with dyslipidemia and other components of metabolic syndrome has been challenging and generally not very clinically informative.

Despite this, it is apparent that metabolic consequences of atypical antipsychotic medications vary greatly with respect to receptor pharmacology, with mutual touch points suggesting common pathophysiologic mechanisms. For example, it has long been observed that the 2 drugs that appear to have the largest effect on body weight (olanzapine and clozapine) also have high affinity for 5-HT2C and histamine H_1 receptors.[19] Furthermore, it has been speculated that drugs whose actions work primarily on peripheral M_3 muscarinic receptors and central 5-HT2C receptors seem to have an effect on diabetes that is independent of obesity. Other receptors that may be implicated in synergistic effects include D_2 receptor antagonistic enhancement of 5-HT2C–mediated effects on food intake, and disinhibition of prolactin control mechanisms, which influences glucose metabolism.

Downstream effects and mechanisms not shared by antipsychotic drugs are undoubtedly contributory, and many of the more reductionistic comparisons fail to take into account subtle distinctions in receptor-binding properties, such as partial agonism, inverse agonism, or synergistic effects across different processes in this association. In addition, the role of various metabolic syndrome biomarkers—such as leptin, ghrelin, and adiponectin—in providing a molecular bridge between antipsychotic medication use and heightened cardiovascular comorbidity needs to be more fully delineated.

Taking as many of the above factors into account as possible, Reynolds and Kirk assessed the relative affinities at relevant receptors for currently used antipsychotic drugs and provided substantive evidence that both olanzapine and clozapine are qualitatively more problematic than other drugs in both the severity of associated weight gain and the risk of glucose intolerance.[19] They also reported that, compared with patients receiving antipsychotic monotherapy, patients receiving antipsychotic polytherapy seem to have higher rates of metabolic syndrome and lipid markers of insulin resistance.[19]

This is an important finding, because the use of multiple antipsychotic medications is very common in schizophrenia (in as much as 30%-40% of patients). However, Reynolds and Kirk noted that antipsychotic polytherapy was not independently associated with the prevalence of metabolic syndrome according to logistic regression but was instead dependent on demographic, clinical, and anthropometric risk factors such as higher BMI, older age, a diagnosis of bipolar disorder or schizophrenia, and cotreatment with a first-generation antipsychotic medication.[19] Other researchers have confirmed that some association between polytherapy (polypharmacy) with antipsychotic agents and metabolic syndrome exists even after correcting for lifestyle differences.[20]

Patient Monitoring

In 2004, the US Food and Drug Administration (FDA) required manufacturers of atypical antipsychotics to include a label warning about the risks of hyperglycemia and diabetes, and suggested regular clinical monitoring of weight, symptoms of hyperglycemia, and glucose. Manufacturers of atypical antipsychotic medications were required to send letters to healthcare professionals informing them of these warnings and advising them of the need for glucose testing in patients receiving atypical antipsychotic medications who also had a diagnosis of diabetes, risk factors for diabetes, or symptoms of hyperglycemia.

In advance of this labeling, the American Diabetes Association (ADA), in conjunction with representatives of the American Psychiatric Association (APA), American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity, held a meeting in November 2003 to review the available data on metabolic effects of atypical antipsychotic medications and solicit input from industry experts in the fields of psychiatry, obesity, and diabetes, as well as from the FDA. This mix of therapeutic expertise reflects the multidisciplinary approach that is essential for both detection and treatment of metabolic syndrome in this patient population.

The consensus recommendations for metabolic monitoring of patients receiving atypical antipsychotic agents have been widely published. These include assessments at baseline, 4 weeks, 8 weeks, 12 weeks, quarterly, annually, and every 5 years for factors such as personal/family history, weight (BMI), waist circumference, BP, FPG, and fasting lipid profile.[21] Specifically, this guidance recommends testing of FPG levels (at baseline, 12 weeks, then annually) and a fasting lipid profile (at baseline, 12 weeks, then every 5 years if normal; **Table 3**, see print issue). These recommendations embody a basic principle about the healthcare of patients with chronic mental illness: that this group often receives inadequate healthcare monitoring outside of the psychiatric clinical setting.[22]

Despite some discordant definitions, all guidelines support a common course of action for the evaluation of

patients when initiating and maintaining therapy with antipsychotic drugs that includes recognition of both nonmodifiable and modifiable risk factors. Nonmodifiable risk factors include increasing age, sex (with increased rates of obesity, diabetes, and metabolic syndrome in treated female patients); personal and family history of obesity, diabetes, heart disease; and ethnicity (with increased rates of diabetes, metabolic syndrome, and coronary heart disease in patients of non-European descent). Modifiable risk factors include obesity, visceral obesity, smoking, physical inactivity, and dietary habits. The impact of smoking, ubiquitous in patients with schizophrenia, is particularly notable on major outcomes, such as cancer, pulmonary disease, and CVD.[23]

Despite these explicit requirements, little data are available to suggest uniform clinician adherence to monitoring recommendations with wide variability noted among medical specialties, institutions, and regions. In some clinical settings, for example, less than one third of patients treated with atypical antipsychotic medications undergo any blood glucose or lipid testing. In addition, promulgation of guidance does not necessarily result in a change in surveillance.

Morrato and colleagues examined a 3-state population of Medicaid recipients and found that diabetes and dyslipidemia screening among patients receiving atypical antipsychotic medications was low and did not increase after the FDA warnings or recommendations from the ADA and APA.[24] They compared surveillance activity before and after the FDA warning in a group of 109,451 patients receiving atypical antipsychotic agents and a control group of 203,527 patients who began taking albuterol but who did not receive antipsychotic medication. Baseline glucose and lipid testing rates for atypical antipsychotic–treated patients were low at 27% and 10%, respectively. After the FDA warning, glucose testing and lipid testing rates only increased by a marginal 1.7%.[24] Strikingly, testing rates and trends among atypical antipsychotic–treated patients were no different from those in the albuterol control group. Testing rates were moderated by several variables, including location, ethnicity, sex, and type of antipsychotic medication, emphasizing a consensus that efforts used to enhance surveillance must be tailored to the environment where the care is actually delivered.

Reasons for lack of adherence to monitoring that have been described are related to factors such as availability of clinic resources, lack of awareness of the enhanced liability of metabolic syndrome, inconsistent dissemination of guidance in psychiatry, and possibly the nature and complexity of the guidance itself. For example, Cohn and colleagues have suggested that top-down guidance, such as that currently in use, may be better served by a combined approach that uses both top-down and bottom-up strategies, utilizing representatives of both community and nongovernmental organizations in addition to academic healthcare professionals.[25]

The nature of the recommended process for surveillance itself represents a complexity that cannot be approached in a real-world monitoring setting where available equipment, patient cooperation, and time constraints limit application of the full montage of recommended tests. A default simple measure of waist circumference as a reflection of central obesity may be informative in the absence of the full spectrum of laboratory measures, although it too has been inconsistently applied.[26]

Not all research on adherence to guidance has been disconcerting. For example, Barnett and colleagues reported that patients taking atypical antipsychotic medications were more likely than those patients taking first-generation drugs to undergo glucose testing (odds ratio [OR], 1.38) and lipid testing (OR, 1.43).[27] Patients taking atypical antipsychotic agents were also more likely to receive both glucose and lipid testing in the 6 months after initiation of antipsychotic treatment, particularly if they were tested during the 6 months before initiation of antipsychotic medication. Individual second-generation antipsychotics—aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone—were also reportedly associated with higher rates of testing.

In addition, in the year after the FDA warnings, 60% to 80% of psychiatrists reported monitoring glucose and lipid levels at regular intervals.[28] A national survey of community mental health centers also indicated that two thirds of community mental health centers reported having protocols or procedures to screen for common medical problems, such as diabetes and dyslipidemia.[29] Obviously, this finding belies the objective data from Morrato and colleagues on the US Medicaid databases previously cited.[24]

Whatever the actual rates, it is clear that increased monitoring does not appear to occur universally in the population with schizophrenia receiving atypical antipsychotics and may be strongly influenced by setting (eg, urban mental healthcare centers and tertiary care hospitals vs private clinics) and geographic regions where these data have been derived (eg, United States, United Kingdom, Japan, India). Therefore, more research is needed to better understand these factors before improvements can be made in diabetes and dyslipidemia screening for this at-risk population.

Responsibility for Surveillance

One reason for inconsistent monitoring is that opin-

ion is divided on whose responsibility it is to undertake monitoring. Some suggest that psychiatrists who prescribe the medication and see the patients more frequently are the most appropriate to assume monitoring responsibilities, because patients with schizophrenia are less likely to have access to a general practitioner who might be able to integrate all healthcare interventions. Other researchers have taken the view that there needs to be a much more coordinated approach between primary and secondary care. There is also some general agreement that patients should be encouraged to self-monitor, especially for the signs and symptoms of emergent diabetes or diabetic ketoacidosis, particularly during the first few months of antipsychotic treatment (when risk is the highest).

However, self-monitoring may not be achievable in a large segment of the population with schizophrenia, because the illness itself is characterized by diminished cognitive function, poor insight, denial of illness, and impaired ability to recognize and verbalize physical complaints. All of these factors lead to an increased responsibility for intervention on the part of healthcare professionals and caregivers. Cohn and colleagues have argued that monitoring, but not necessarily medical treatment of metabolic syndrome, falls within the scope of psychiatric practice and should include screening for metabolic disturbance as well as tracking the effects of antipsychotic treatment, given that the primary (and perhaps only) point of contact with the healthcare system is through the psychiatric treatment team.[25]

Hasnain and Vieweg also opined that effective communication between the primary care physician and the psychiatrist is particularly important for the mentally ill, because of the patients' impaired capacity to care for themselves.[9] The authors agreed that monitoring for metabolic side effects is primarily the responsibility of the physician prescribing antipsychotic medication. In most cases, that would be the psychiatrist, with a primary care physician (if involved) providing additional vigilance. Should the psychiatrist not have the expertise to manage any detected abnormalities, the primary care physician would most likely take over both monitoring and management. In practice, local resources and service arrangements may help determine who is most appropriately placed to monitor patients with clear communication between clinicians being paramount.

What Should Be Monitored?

The decision as to who has primary responsibility for monitoring is dependent on parameters being monitored, and numerous studies have suggested ≥1 test as being the most beneficial. Given guidance and the importance of directly monitoring glucose, several researchers have attempted to reduce both time and costs associated with glucose monitoring specifically. For example, a much shorter duration of fasting for glucose intolerance and metabolic syndrome has been suggested by McLellan and colleagues, who reported that the positive predicted value of elevated capillary glucose at 4 hours for predicting elevated levels obtained on repeat testing after an 8-hour fast was 57%.[30] In addition, a novel dynamic insulin sensitivity and secretion test (DISST) used for measuring insulin sensitivity has been developed and can be performed in approximately 30 minutes. The DISST is a low-cost, low-intensity alternative to the glucose clamp, with the added benefits of measuring beta-cell function and the ability to differentiate individual variations in pathophysiology.[31]

In addition to these direct laboratory-based assessments, Stahl recommended an integrated clinical approach including a directive to (1) weigh patients and track BMI at each visit; (2) determine the presence of risk factors at baseline and at intervals after treatment initiation; (3) obtain a baseline fasting glucose level and lipid profile for psychiatric patients who have a BMI ≥27 kg/m^2, then track glucose and lipid levels at regular intervals, especially if further weight gain occurs; and (4) monitor glucose levels frequently, including shortly after beginning a new antipsychotic agent and when treating a patient with diabetes.[32] However, studies have found that even simple measurements of waist circumference are rarely conducted and that overall monitoring for metabolic adverse events of antipsychotic medication (eg, hypertension and hyperglycemia) is poor.[26,33,34]

In a more rigorous application of monitoring, Straker and colleagues examined a consecutive group of 100 psychiatric inpatients treated with at least 1 atypical antipsychotic medication.[35] They measured BP and waist circumference at the level of the umbilicus, as well as FPG and lipid levels. They reported that 29% of patients fulfilled criteria for metabolic syndrome and the presence of metabolic syndrome was associated with older age, higher BMI, and higher values for each individual criterion of metabolic syndrome, but not with the specific diagnoses or antipsychotic treatment regimens.

Among the 5 criteria used to predict metabolic syndrome, abdominal obesity had the highest sensitivity, correctly identifying 92.0% patients. Elevated FPG served as the most specific criterion, with normal values appropriately categorizing 95.2% of patients without metabolic syndrome. When abdominal obesity and/or FPG were combined, 100% of patients with metabolic syndrome were correctly identified, whereas combining abdominal obesity and/or elevated BP resulted in the correct identification of 96.2% of patients.

Others researchers, such as Lin and colleagues, have

taken these simple combinations of risk factors to the next level by using artificial neural network (ANN) and multiple logistic regression techniques to identify metabolic syndrome.[36] This approach may be applicable in healthcare settings characterized by access to a common data set and predictive modeling capabilities. In a group of 383 patients with schizophrenia and schizoaffective disorder, these researchers suggested that waist circumference and diastolic BP were the most predictive variables, with 93% of metabolic syndrome cases and 87% of nonmetabolic syndrome successfully identified by the ANN model, and approximately 86% of metabolic syndrome and 84% of nonmetabolic syndrome successfully predicted by a logistic regression model.

This finding implies that most patients with metabolic syndrome treated with an atypical antipsychotic could be successfully identified by model prediction using only a few easily and immediately available clinical variables (eg, waist circumference, diastolic BP, BMI, and female sex), contingent on choice of predictive modeling adopted. Currently, physicians rely mostly on a univariate examination of laboratory data when diagnosing metabolic syndrome. However, with data supporting both high sensitivity and negative predictive values, multivariate algorithmic models show promise for assisting physicians in the clinical screening of metabolic syndrome.

Healthcare Implications

Schizophrenia is a chronic and costly illness that requires life-long treatment with antipsychotic medications that have a wide range of associated side effects. Given the diversity of stakeholders involved in the provision of healthcare, the impact of metabolic syndrome associated with atypical antipsychotics can vary appreciably. Costs related to schizophrenia medication treatment and supportive care have often been viewed as being outside the auspices of managed care, given the preponderance of patients who receive treatment with sole advocacy and aegis by state and government agencies, such as Medicaid. However, regardless of the payer involvement, metabolic syndrome differences among various antipsychotic agents (and their effect on efficacy, safety, tolerability, and adherence) have substantial cost implications for society.

Several studies have assessed the role of various antipsychotic medications in healthcare costs, and surprisingly, much of the available data do not support drastic cost differences between schizophrenic patients with and without metabolic syndrome at least over short time frames, with very little impact of monitoring cost overall. For example, Vera-Llonch and colleagues used a Markov model to examine outcomes and costs of care in patients with chronic schizophrenia or schizoaffective disorders receiving risperidone or olanzapine over a 1-year period.[37] They examined incidence of relapse and selected side effects, including extrapyramidal symptoms, prolactin-related disorders, and diabetes, and change in body weight. The expected incidence of diabetes mellitus, although low, was slightly higher for olanzapine. Furthermore, approximately 25% and 4% of patients treated with olanzapine and risperidone, respectively, were projected to experience an increase in body weight ≥7%. The expected mean total costs of care per month of therapy were $2163 for risperidone and $2316 for olanzapine.

Overall, the costs associated with antipsychotic therapy, diagnosis and treatment of side effects, and discontinuation and switching of antipsychotic therapy were higher among patients treated with olanzapine. Compared with risperidone, treatment with olanzapine was associated with greater increases in body weight, higher rates of therapy discontinuation, and resulting higher costs of medical care services.

There is little justification from a purely economic point of view for more broad-based surveillance after brief durations of therapy. However, it is difficult to determine if relatively small differences in costs between medication groups, which are commonly noted within the first year of treatment initiation eg, would be amplified and sustained over longer periods of time (5-10 years). There is some notion that adverse events associated with metabolic risk increase as patients mature. Although indirect costs associated with loss of workplace productivity may not be as substantive in a population that is typically unemployed or employed only in a supported environment, direct medical costs associated with macrovascular complications and hyperglycemic episodes can be considerable over the course of many years. Also, large cost drivers, such as stroke and heart disease, may not develop until much further into the metabolic process. Given the relatively low cost of monitoring with very little if any safety implications resulting from the monitoring procedures, it seems prudent to adopt policies that would enhance surveillance in the schizophrenia patient population to prevent morbidity and mortality.

In terms of impacting cost, point of care (POC) testing, or diagnostic testing/therapeutic monitoring carried out at or near the site of the patient, may be beneficial. Adoption of this procedure has been demonstrated to reduce labor costs and manual procedure steps in other settings and eliminates the time lag associated with laboratory testing, leading to quicker therapeutic action and improved outcomes. This approach is not new to medicine, with more than

90,000 medical offices performing POC testing in the United States, including tests to determine blood glucose, pregnancy, strep throat, substances of abuse, and prothrombin time.[38]

As the volume of POC testing increases, costs relative to manual procedures decline. In the setting of a systematic treatment care team, POC testing has been shown to be effective in assessing for metabolic syndrome by merely checking for the combination of elevated abdominal obesity and FPG levels, thus providing a practical method for identifying metabolic risk in patients taking atypical antipsychotic medications.[39]

The treatment of schizophrenia involves a delicate balance in terms of risks and benefits, because failing to treat as a result of risk for or complications from metabolic syndrome may place the patient at a higher risk for more serious problems, or even suicide.

In addition, the availability of POC testing methods for blood glucose levels creates new opportunities for behavioral healthcare providers, because instant glucose meters and strips are Clinical Laboratory Improvement Amendments–waived by the FDA, and thus can be used in office environments. The need for a shift in reimbursement policy to encourage POC testing in the behavioral health arena would represent a unique challenge for payers that have historically favored laboratory-driven versus practitioner-driven tests. It also is possible that this increase in accessibility and shift in policy regarding reimbursement could decrease the reluctance of some practitioners to both prescribe and monitor the effects of antipsychotic medications in both schizophrenia and other patient indications, but this remains to be tested.

Conclusions

The treatment of schizophrenia involves a delicate balance in terms of risks and benefits, because failing to treat as a result of risk for or complications from metabolic syndrome may place the patient at a higher risk for more serious problems, or even suicide. Although atypical antipsychotic medications differ in the prevalence of metabolic syndrome, the molecular mechanisms subtending their effects are not well understood, and the prospects of "designing out" the propensity for metabolic syndrome with innovative antipsychotic medications remain uncertain for the immediate future.

Surveillance systems are particularly noteworthy, because increased monitoring of simple clinical and laboratory measures of metabolic syndrome may help decrease important adverse events in multiple organ systems and ultimately improve patients' quality of life. Activities to enhance surveillance include the recognition that each patient touches a system of care in which coordinated services are required from multiple healthcare providers in an interdependent manner. POC systems and predictive modeling now in development have the potential to expand access to monitoring and increase compliance with monitoring guidance. ■

Author Disclosure Statement

Dr Riordan, Dr Antonini, and Dr Murphy are salaried employees of Worldwide Clinical Trials, an international, full-service, contract research organization that specializes in clinical research activities in support of the pharmaceutical industry. Relationships exist with multiple (>100) pharmaceutical companies as part of their primary business activity.

References

1. World Health Organization. Preventing chronic diseases: a vital investment. 2005. www.who.int/chp/chronic_disease_report/full_report.pdf. Accessed August 15, 2011.
2. Brown S. Excess mortality of schizophrenia. A meta-analysis. *Br J Psychiatry*. 1997; 171:502-508.
3. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs*. 2005;19(suppl 1):1-93.
4. Saddichha S, Manjunatha N, Ameen S, Akhtar S. Metabolic syndrome in first episode schizophrenia—a randomized double-blind controlled, short-term prospective study. *Schizophr Res*. 2008;101:266-272.
5. De Hert M, Dobbelaere M, Sheridan EM, et al. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: a systematic review of randomized, placebo controlled trials and guidelines for clinical practice. *Eur Psychiatry*. 2011;26:144-158.
6. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. International Diabetes Federation (IDF), 2006. www.idf.org/webdata/docs/IDF_Meta_def_final.pdf. Accessed August 15, 2011.
7. Coccurello R, Moles A. Potential mechanisms of atypical antipsychotic-induced metabolic derangement: clues for understanding obesity and novel drug design. *Pharmacol Ther*. 2010;127:210-251.
8. Haupt DW. Differential metabolic effects of antipsychotic treatments. *Eur Neuropsychopharmacol*. 2006;16(suppl 3):S149-S155.
9. Hasnain MR, Vieweg WV. Acute effects of newer antipsychotic drugs on glucose metabolism. *Am J Med*. 2008;121:e17; author reply e19.
10. Prussian KH, Barksdale-Brown D, Dieckmann J. Racial and ethnic differences in the presentation of metabolic syndrome. *J Nurse Pract*. 2007;3:229-239.
11. Correll CU, Frederickson AM, Kane JM, Manu P. Does antipsychotic polypharmacy increase the risk for metabolic syndrome? *Schizophr Res*. 2007;89:91-100.
12. de Leon J, Susce MT, Johnson M, et al. A clinical study of the association of antipsychotics with hyperlipidemia. *Schizophr Res*. 2007;92:95-102.
13. Mulder H, Cohen D, Scheffer H, et al. HTR2C gene polymorphisms and the metabolic syndrome in patients with schizophrenia: a replication study. *J Clin Psychopharmacol*. 2009;29:16-20.
14. Meyer JM. A retrospective comparison of weight, lipid, and glucose changes between risperidone- and olanzapine-treated inpatients: metabolic outcomes after 1 year. *J Clin Psychiatry*. 2002;63:425-433.
15. Meyer JM, Davis VG, Goff DC, et al. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: prospective data from phase 1. *Schizophr Res*. 2008;101:273-286.
16. L'Italien GJ. Pharmacoeconomic impact of antipsychotic induced metabolic events. *Prev Med Manag Care*. 2003;3(suppl 2):S38-S42.
17. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353:1209-1223. Erratum in *N Engl J Med*. 2010;363:1092-1093.
18. Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. *Mol Psychiatry*. 2008;13:27-35.
19. Reynolds GP, Kirk SL. Metabolic side effects of antipsychotic drug treatment—pharmacological mechanisms. *Pharmacol Ther*. 2010;125:169-179.

20. Misawa F, Shimizu K, Fujii Y, et al. Is antipsychotic polypharmacy associated with metabolic syndrome even after adjustment for lifestyle effects: a cross-sectional study. *BMC Psychiatry*. 2011;11:118.
21. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27:596-601.
22. Jin H, Meyer JM, Jeste DV. Atypical antipsychotics and glucose dysregulation: a systematic review. *Schizophr Res*. 2004;71:195-212.
23. Prochaska JJ. Smoking and mental illness—breaking the link. *N Engl J Med*. 2011; 365:196-198.
24. Morrato EH, Libby AM, Orton HD, et al. Frequency of provider contact after FDA advisory on risk of pediatric suicidality with SSRIs. *Am J Psychiatry*. 2008;165:42-50.
25. Cohn TA, Remington G, Zipursky RB, et al. Insulin resistance and adiponectin levels in drug-free patients with schizophrenia: a preliminary report. *Can J Psychiatry*. 2006;51:382-386.
26. Waterreus AJ, Laugharne JD. Screening for the metabolic syndrome in patients receiving antipsychotic treatment: a proposed algorithm. *Med J Aust*. 2009;190:185-189.
27. Barnett M, VonMuenster S, Wehring H, et al. Assessment of monitoring for glucose and lipid dysregulation in adult Medi-Cal patients newly started on antipsychotics. *Ann Clin Psychiatry*. 2010;22:9-18.
28. Suppes T, McElroy SL, Hirschfeld R. Awareness of metabolic concerns and perceived impact of pharmacotherapy in patients with bipolar disorder: a survey of 500 US psychiatrists. *Psychopharmacol Bull*. 2007;40:22-37.
29. Druss BG, Marcus SC, Campbell J, et al. Medical services for clients in community mental health centers: results from a national survey. *Psychiatr Serv*. 2008;59:917-920.
30. McLellan RK, Comi RJ, Mackenzie TA, et al. The usefulness and cost of a shorter duration of fasting in workplace screening for glucose intolerance and metabolic syndrome. *Diabetes Res Clin Pract*. 2009;84:e6-e8.
31. Goodman A. Diabetes screening of high-risk people is cost-effective. *Am Health Drug Benefits*. 2010;3 suppl:S1-S12.
32. Stahl S. The metabolic syndrome: psychopharmacologists should weigh the evidence for weighing the patient. *J Clin Psychiatry*. 2002;63:1094-1095.
33. Newcomer JW, Nasrallah HA, Loebel AD. The atypical antipsychotic therapy and metabolic issues national survey: practice patterns and knowledge of psychiatrists. *J Clin Psychopharmacol*. 2004;24(5 suppl 1):S1-S6.
34. Mackin P, Bishop DR, Watkinson HM. A prospective study of monitoring practices for metabolic disease in antipsychotic-treated community psychiatric patients. *BMC Psychiatry*. 2007;7:28.
35. Straker D, Correll CU, Kramer-Ginsberg E, et al. Cost-effective screening for the metabolic syndrome in patients treated with second-generation antipsychotic medications. *Am J Psychiatry*. 2005;162:1217-1221.
36. Lin CC, Bai YM, Chen JY, et al. Easy and low-cost identification of metabolic syndrome in patients treated with second-generation antipsychotics: artificial neural network and logistic regression models. *J Clin Psychiatry*. 2010;71:225-234.
37. Vera-Llonch M, Delea TE, Richardson E, et al. Outcomes and costs of risperidone versus olanzapine in patients with chronic schizophrenia or schizoaffective disorders: a Markov model. *Value Health*. 2004;7:569-584.
38. Glazer WM. Point-of-care tests in behavioral health. *Behav Healthc*. 2006;26:37-39.
39. Schneiderhan ME, Batscha CL, Rosen C. Assessment of a point-of-care metabolic risk screening program in outpatients receiving antipsychotic agents. *Pharmacotherapy*. 2009;29:975-987.

STAKEHOLDER PERSPECTIVE

The Complexities of Treating Mental Illness

MEDICAL/PHARMACY DIRECTORS: Here is what we know—atypical antipsychotic medications are the standard of care for pharmacologic treatment of schizophrenia. We also know that these medications can significantly increase the risk for cardiovascular disease because of the metabolic syndrome association. What we seem to have forgotten, or have opted to ignore, is that metabolic syndrome can be screened and effectively prevented or treated when diagnosed.

The article by Riordan and colleagues in this issue of *American Health & Drug Benefits* provides an excellent review of the literature regarding atypical antipsychotics and the mechanism of their link to metabolic syndrome. Other review articles regarding this issue have focused on treatment options for metabolic syndrome,[1] but the present article by Riordan and colleagues provides important information on techniques to screen for metabolic syndrome, such as point of care testing focusing on abdominal obesity and fasting blood glucose, as well as the coordination of care between primary care and specialty care providers.

The authors also provide some insight into the complexities of providing appropriate care to patients with serious mental illness. Whether you have directly provided care to patients with serious mental illness or not, it is apparent how difficult this can be. To a certain extent, this difficulty is a microcosm of some of the general challenges we have in providing appropriate care to any patient in this country.

One of the common challenges is the coordination of care between a primary care provider and a specialty care provider. Once a patient has been seen by a psychiatrist, or an oncologist for that matter, and is prescribed therapy for a new diagnosis that can increase the risk for diabetes, is it the responsibility of the specialist or of the primary care physician to screen and treat for diabetes? The ideal situation would involve an open dialogue between both providers to ensure that

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STAKEHOLDER PERSPECTIVE (*Continued*)

the patient is receiving appropriate care, but this does not happen as often as it should.

Another challenge is ensuring adherence to prescribed pharmacologic therapy. This is a challenge encountered in the general population for several reasons (eg, intolerance to therapy, inability to afford medications, illiteracy) and is very common in the treatment of patients with schizophrenia. Ideally, patients with schizophrenia will have medications available that effectively control their illness with minimal side effects. The use of depot formulations should also be considered.

The authors also provide some insight into the costs associated with metabolic syndrome caused by atypical antipsychotics, and these costs are very significant. Indeed, although the focus of the article is on schizophrenia, atypical antipsychotics are often being used for the treatment of depression, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, and other conditions. In addition, with changes in healthcare coverage taking place on a national level as a result of the healthcare reform, more patient-specific illnesses will have access to treatment with atypical antipsychotics. This will all add to a difficult situation we are facing today in the use of atypical antipsychotics and the incidence of metabolic syndrome.

ALL STAKEHOLDERS: As healthcare professionals, it is important for all of us to read the current article by Riordan and colleagues in *American Health & Drug Benefits*—to get a better understanding of the challenges in screening and treating metabolic syndrome associated with atypical antipsychotics, and to implement appropriate solutions to these challenges. In the absence of appropriate solutions, we will be transitioning from complexities to chaos.

1. Pramyothin P, Khaodhiar L. Metabolic syndrome with the atypical antipsychotics. *Curr Opin Endocrinol Diabetes Obes*. 2010;17:460-466.

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