# Metabolic Considerations in the Use of Antipsychotic Medications: A Review of Recent Evidence

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Compared with the general population, persons with schizophrenia have up to a 20% shorter lifespan, with cardiovascular disease as the leading cause of death. In addition, persons with schizophrenia have increased prevalence of the metabolic syndrome (obesity, insulin resistance, dyslipidemia, impaired glucose tolerance, and hypertension), increased prevalence of risk factors such as smoking, poverty, and poor nutrition, and reduced access to medical care. Results from the recent Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) provide further evidence of the metabolic risk associated with different atypical antipsychotics. Based on this study and a growing number of other randomized clinical trials, clozapine and olanzapine treatment can produce substantial mean changes in weight and an increased risk of associated metabolic disturbances. Risperidone and quetiapine treatment can produce intermediate changes in mean weight in comparison to treatment with other atypical antipsychotics, with discrepant results with respect to metabolic risk. Aripiprazole and ziprasidone treatment induced the lowest mean changes in weight gain and had no effect on risk for adverse metabolic changes, among currently available atypical agents. Considerable evidence indicates that mentally ill patients often do not receive adequate recognition of, monitoring of, or care for their medical illnesses. There is a critical need for psychiatrists and primary care professionals to increase awareness of and attention to the physical health problems of persons with mental illness, including appropriate management of metabolic adverse events associated with psychiatric medications.
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Atypical antipsychotic drugs offer important benefits for many patients with disorders such as schizophrenia. Finding the most appropriate antipsychotic treatment for individual patients depends on weighing the risks and benefits of any treatment. Recent studies indicate that certain metabolic abnormalities occur more commonly in psychiatric patients and are known to contribute to cardiovascular disease (CVD), a leading cause of death in this population. There is a need to rank the importance of treatment-related adverse events and to give increased attention to treatment-related metabolic abnormalities, as these are key modifiable risk factors that can contribute to morbidity and mortality in patients with major mental disorders.

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## THE EPIDEMIC

Compared with the general population, individuals with schizophrenia and affective disorders have an increased risk of death from medical causes and up to a 20% shorter lifespan.[1] Although patients with schizophrenia are 10 to 20 times more likely than the general population to commit suicide (related to the rarity of suicide in the general population), more than two thirds of patients with schizophrenia, compared with approximately one half in the general population, die of coronary heart disease (CHD).[2] A meta-analysis of 18 studies looking at causes of death in patients with major mental illness showed that CVD (the combination of cerebrovascular disease, coronary heart disease, and peripheral vascular disease) is the leading cause of death in patients with schizophrenia.[3]

A recent study[4] published through the Centers for Disease Control and Prevention (CDC) compared the mortality of public mental health clients in 8 states with the mortality of the states' general populations, for 1997 through

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**Table 1. Age at Time of Death and Years of Potential Life Lost (YPLL) for Public Mental Health Clients With Major Mental Illness Diagnoses (MMI clients)[a,b,c]**

| State and Year | Age at Death, y | Years of Potential Life Lost[b] |
|---|---|---|
| Missouri | | |
| 1997 | 59.6 | 25.1 |
| 1998 | 57.1 | 27.0 |
| 1999 | 56.9 | 27.6 |
| 2000 | 54.3 | 29.5 |
| Oklahoma | | |
| 1997 | 56.7 | 27.2 |
| 1998 | 56.6 | 27.3 |
| 1999 | 53.7 | 29.7 |
| Rhode Island | | |
| 2000 | 59.1 | 25.4 |
| Texas | | |
| 1997 | 54.3 | 28.9 |
| 1998 | 54.6 | 29.0 |
| 1999 | 53.8 | 29.4 |
| Utah | | |
| 1998 | 53.0 | 30.5 |
| 1999 | 57.8 | 26.7 |
| Virginia (inpatient only) | | |
| 1998 | 65.5 | 21.0 |
| 1999 | 67.5 | 19.0 |
| 2000 | 70.0 | 16.4 |

[a]Adapted from Colton and Manderscheid.[4] Data are from the 6 states that submitted to this study with clients' causes of death. All values are means.
[b]YPLL is a mortality measure that provides information about the risk of premature death by using the difference between client age at death and current life expectancy, or mean survival age for living cohorts of the same age and sex as each decedent during the year of death. The average YPLL for clients in each state during each year was estimated using current life expectancy tables for the U.S. population, which are developed and published annually by the Centers for Disease Control and Prevention.
[c]Diagnoses of MMI include Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) schizophrenia, major depressive disorders, bipolar disorders, delusional and psychotic disorders, and attention deficit/hyperactivity disorders.

**Table 2. The Metabolic Syndrome**

| |
|---|
| Five Major Features of the Metabolic Syndrome[a] |
| Obesity |
| Excess total body fat |
| Central fat distribution/upper body obesity |
| Increased visceral fat |
| Insulin resistance/hyperinsulinemia |
| Dyslipidemia |
| Hypertriglyceridemia |
| Decreased HDL cholesterol |
| Increased LDL cholesterol |
| Impaired glucose tolerance/type 2 diabetes |
| Hypertension |
| Clinical Identification: ≥ 3 Risk Factors ≥ Defining Levels Shown = The Metabolic Syndrome[b] |
| Abdominal obesity: waist circumference |
| Men > 40 in (>102 cm) |
| Women > 35 in (> 88 cm) |
| Triglycerides ≥ 150 mg/dL |
| HDL cholesterol |
| Men < 40 mg/dL |
| Women < 50 mg/dL |
| Blood pressure ≥ 135/80 mm Hg |
| Fasting glucose > 110 mg/dL |

[a]Adapted with permission from Newcomer.[6]
[b]Adapted with permission from the National Cholesterol Education Program.[5]
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

2000. In all the study states, mental health clients had a higher relative risk of death than the general populations of their states and died at much younger ages compared with their cohorts nationwide, with the largest risks attributed to patients with major mental illnesses. In all the states studied, heart disease was found to be the leading cause of death in mentally ill patients. Further, the study showed that mental health clients had lost decades of potential years of life, with averages (in those states where both outpatient and inpatient data were available) exceeding 25 years (Table 1).

## THE METABOLIC SYNDROME

In considering modifiable risk factors for the development of CVD, much attention has been focused on the metabolic syndrome, which has been defined by the National Cholesterol Education Program (NCEP) Expert Panel[5] as an interrelated constellation of CVD risk factors, linked by insulin resistance, including obesity, dyslipidemia, impaired glucose tolerance, and hypertension. On the basis of the NCEP guidelines, a patient with 3 or more of the risk factors shown in Table 2[5,6] is considered to have the metabolic syndrome.

The metabolic syndrome has been shown to be an important risk factor in the development of both type 2 diabetes mellitus (T2DM) and CVD. The presence of the metabolic syndrome increases the risk for the development of CVD at any given level of low-density lipoprotein (LDL) cholesterol, thus making it a prime target for therapeutic intervention.[6] In a study conducted in Sweden and Finland, individuals with the metabolic syndrome were 3 times more likely than those without the syndrome to develop CHD and stroke.[7]

The distribution of fat (adiposity) within the body is a key factor mediating the effect of increasing weight on health status. Abdominal fat distribution, particularly visceral adiposity, increases the risk of dyslipidemia, glucose intolerance, and CVD.[8] Central to the metabolic syndrome is the concept of insulin resistance, or reduced sensitivity to the normal tissue effects of insulin. The risk of insulin resistance increases with adiposity, particularly the amount of visceral adiposity. Overweight persons (body mass index [BMI] ≥ 25) have a 50% probability of being in the top tertile of insulin resistance, increasing to a 70% probability of being in the top tertile of insulin resistance when they also have plasma triglyceride (TG) levels > 130, or a 78% probability for being in the top tertile of insulin resistance when they meet criteria for the metabolic syndrome.[9] Insulin resistance may be, in part, related

to the amount of free fatty acids secreted by adipose tissue, which may reduce the sensitivity of skeletal muscle and the liver to the effects of insulin and also impact pancreatic beta-cell function, thereby reducing insulin secretion.[10]

Insulin resistance is associated with impaired glucose control, increased plasma TG, reduced high-density lipoprotein (HDL) cholesterol, increased blood pressure, increased risk of blood clotting, and increases in markers of inflammation, all of which are associated with an increased risk for CVD.[6] Thus, markers of insulin resistance, such as elevated fasting plasma TG level, can be key in monitoring and evaluating a patient's risk for developing both the metabolic syndrome and CVD.

## INCREASED RATES OF METABOLIC DISTURBANCE IN PATIENTS WITH SCHIZOPHRENIA

Limited research suggests that patients with schizophrenia may be predisposed to elevated rates of glucose intolerance and diabetes, independent of treatment.[11] However, it is unclear whether the reported increased rates of metabolic abnormalities in this population are a function of some genetic or biological component of the disease itself or the consequences of the disease on patients' lifestyle. Most of the studies that suggest abnormal glucose regulation in patients with schizophrenia predate the introduction of antipsychotic therapy and are limited by lack of controls for age, weight, adiposity, activity, diet, family history, and ethnicity.[6]

Indeed, compared with other populations, people with major mental illness have a higher prevalence of lifestyle risk factors, including smoking, overweight and obesity, lack of moderate exercise, harmful levels of alcohol consumption, excessive salt intake, and poor diet.[12] Patients with schizophrenia have less access to medical care, are less likely to seek out care, and are less likely to report physical symptoms spontaneously, and patients with schizophrenia have psychiatric symptoms (social isolation, suspicion, cognitive impairment) that impair their ability to adhere to treatment.[13] Approximately 75% of the schizophrenia population are smokers, 40% to 80% have a BMI at least 20% higher than normal, and the symptoms of the disease lead to significant physical inactivity, all increasing the risk of the metabolic syndrome and CVD.[14]

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study reinforces the evidence for metabolic and cardiovascular risk in patients with schizophrenia. Using baseline data from the CATIE schizophrenia study, Goff et al.[15] compared patients with age-, race-, and gender-matched controls from the National Health and Nutrition Examination Survey (NHANES) III. They found that schizophrenia patients had significantly higher rates of smoking (68% vs. 35%), diabetes (13% vs. 3%), hypertension (27% vs. 17%), and lower HDL cholesterol levels (43.7 vs. 49.3 mg/dL) compared with controls. Further, they calculated 10-year risk for CHD using the Framingham CHD risk function for 689 subjects and found that 10-year CHD risk was significantly elevated in male and female schizophrenia patients compared with matched controls (9.4% vs. 7.0% and 6.3% vs. 4.2%, respectively).

In another analysis of baseline CATIE data, McEvoy et al.[16] compared the prevalence of the metabolic syndrome (based on NCEP criteria, modified using a fasting glucose threshold of 100 mg/dL) with that in randomly selected controls from NHANES III matched for age, gender, and ethnicity. They found that patients in the CATIE study had a prevalence of the metabolic syndrome of 42.7% at baseline, approximately twice the prevalence in the general population. Further, they found that both male and female patients entering CATIE were statistically significantly more likely to meet TG, HDL, blood pressure, and waist circumference criteria for the metabolic syndrome than their matched counterparts in the general population. Even after controlling for differences in BMI, CATIE men were 85% more likely to have the metabolic syndrome than the NHANES sample of men, and CATIE women were 137% more likely to have the metabolic syndrome than women in NHANES, suggesting significantly increased risk for T2DM and CVD.

## IMPACT OF ANTIPSYCHOTICS

Crucial to the public health perspective concerning cardiovascular and metabolic risk in patients with schizophrenia is the focus on modifiable risk factors. Outlined above, obesity, hyperglycemia, and dyslipidemia are modifiable risk factors for CVD. Therapeutic lifestyle interventions that might reduce the level of key risk factors are extremely important in this population, and patients should routinely be counseled on proper nutrition, exercise, and smoking cessation. However, medication effects on some of the key modifiable risk factors reviewed above strongly suggest that treatment decisions should incorporate an understanding of the potential metabolic consequences of treatment using different medications.

In addition to the analyses of baseline cardiovascular risk in previously treated patients with schizophrenia, the CATIE study has added to a growing literature showing a significant effect of specific antipsychotic medications on both weight gain and metabolic endpoints.[11]

### Weight Gain

As discussed above, weight gain and obesity have adverse effects on glucose and lipid metabolism and are associated with an increased risk of hypertension, suggesting that potential adverse treatment effects of antipsychotics on weight alone may increase 4 key modifiable risk factors for CVD.[6] Weight gain has been reported in up to 50% of patients receiving antipsychotics, and certain

  

**Table 3. Metabolic Abnormalities With Atypical Antipsychotics[a]**

| Drug | Weight Gain | Risk for Diabetes | Worsening Lipid Profile |
|---|---|---|---|
| Clozapine | +++ | + | + |
| Olanzapine | +++ | + | + |
| Risperidone | ++ | D | D |
| Quetiapine | ++ | D | D |
| Ziprasidone | +/– | – | – |
| Aripiprazole | +/– | – | – |

[a]Adapted with permission from the American Diabetes Association.[19]
Abbreviation: D = discrepant results.
Symbols: + = increased effect, – = no effect.

agents have been associated with higher rates of weight gain and adverse effects on plasma lipids as well as an increased risk of disturbances in glucose regulation (diabetes).

Weight gain during antipsychotic therapy has been evaluated in the short term and the long term. In the short term,[17] treatment with various antipsychotics has been shown to produce a wide range of changes in mean body weight, from < 2.2 lb to > 8.8 lb. Over the long term, using data pooled from multiple clinical trials,[18] aripiprazole and ziprasidone were associated with a mean weight gain of approximately 2.2 lb over 1 year; quetiapine and risperidone with 4.4 to 6.6 lb over 1 year; and olanzapine with a gain of > 13.2 lb over 1 year, with a gain of > 22 lb in patients who received olanzapine at doses between 12.5 and 17.5 mg.

Growing concerns about the impact of antipsychotics on modifiable risk factors for diabetes and CVD prompted the American Diabetes Association (ADA), along with the American Psychiatric Association (APA), the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity, to issue a consensus statement[19] to highlight the relationship between the various atypical antipsychotics and the development of weight gain, diabetes, and hyperlipidemia. As shown in Table 3, the report concluded that clozapine and olanzapine treatment were associated with the greatest weight gain potential among the second-generation antipsychotics, with consistent evidence for increased risk of T2DM and dyslipidemia. Risperidone and quetiapine were noted to produce intermediate weight gain and variable metabolic changes, with discrepant results regarding the risk for diabetes and dyslipidemia. Aripiprazole and ziprasidone were noted to produce the lowest risk of weight gain among currently available atypical agents, with no evidence of an adverse effect on risk for diabetes or dyslipidemia.

Consistent with the ADA Consensus Statement and multiple randomized clinical trials to date, the CATIE phase 1 study showed that patients in the olanzapine group experienced more weight gain than patients in other treatment groups, with an average increase of 2 lb per month.[20] Additionally, a higher percentage of patients in the olanzapine group (30%) gained more than 7% of their baseline weight, as compared with patients taking the other medications in the study, in which between 7% and 16% of patients gained > 7% above their baseline weight.

Furthermore, recent studies suggest that switching from a medication with higher weight gain liability to another with a lower weight gain liability may produce significant reductions in body weight and BMI. While none of the atypical antipsychotics can be considered weight loss drugs, ziprasidone and perphenazine were associated with weight loss in the CATIE 1 study,[20] most likely related to removal of an agent that had been contributing to weight gain or maintenance prior to being started on ziprasidone or perphenazine therapy. For example, patients randomly assigned to ziprasidone experienced statistically significant or mean weight loss of 0.3 lb per month of treatment.[20] Other studies have reported this effect: after a switch from risperidone or olanzapine to aripiprazole or ziprasidone, clinically significant reductions in weight occurred in 6 to 8 weeks.[21] Similar effects (3.0 lb loss after 26 weeks of treatment) have been observed in switching from a medication with higher weight gain liability to aripiprazole.[22]

In the CATIE phase 2 tolerability arm (phase 2T), in which patients who had discontinued their antipsychotic in phase 1 were randomly assigned to double-blind treatment with a different antipsychotic, weight differences between the antipsychotics were also pronounced.[23] Patients randomly assigned to olanzapine gained more weight than patients receiving the other study medications, with a mean increase of 1.3 lb per month, while patients receiving ziprasidone had a mean loss of 1.7 lb per month. Risperidone and quetiapine both demonstrated minimal weight change during phase 2T. Also consistent with previous studies, in CATIE phase 2T, more patients receiving olanzapine gained > 7% of their baseline weight (27%) than patients receiving the other study medications (13% for risperidone and quetiapine; 6% for ziprasidone). During CATIE 2T, ziprasidone was the only medication that no patients discontinued because of weight gain or metabolic side effect—versus discontinuation of risperidone (5%), olanzapine (8%), or quetiapine (10%).

Of those patients who had gained > 7% of their body weight in CATIE phase 1 who were randomly assigned to ziprasidone in phase 2T, 42% lost > 7% of their body weight (mean ziprasidone group loss of 11.3 lb); 20% of those randomly assigned to risperidone were able to lose > 7% of their body weight (mean risperidone loss of 1.4 lb); and 7% of patients randomly assigned to quetiapine were able to lose 7% of their body weight (no significant weight change in quetiapine group).[23] None of the patients who gained > 7% of their body weight in phase 1 who were randomly assigned to olanzapine in CATIE phase 2T lost > 7% of their body weight (mean olanzapine group gain of 2.1 lb).

Table 4. Metabolic Changes Among Patients in CATIE Phase 2 Tolerability Arm[a]

| Assessment | Olanzapine | Risperidone | Quetiapine | Ziprasidone |
|---|---|---|---|---|
| Weight change over course of treatment, mean/median, lb/mo | 1.3/1.1 | –0.2/0.1 | 0.1/0.0 | –1.7/–1.5 |
| Proportion gaining > 7% body weight | 27% | 13% | 13% | 6% |
| Exposure-adjusted blood glucose change, mean (SE), mg/dL | 13.8 (5.9) | 6.9 (5.8) | 1.2 (6.0) | 0.8 (5.6) |
| Exposure-adjusted hemoglobin A1c, mean (SE), % change | 0.97 (0.3) | 0.49 (0.3) | 0.61 (0.3) | 0.46 (0.3) |
| Exposure-adjusted cholesterol change, mean (SE), mg/dL | 17.5 (5.2) | –3.1 (5.2) | 6.5 (5.3) | –10.7 (5.1) |
| Exposure-adjusted triglyceride change, mean (SE), mg/dL | 94.1 (21.8) | –5.2 (21.6) | 39.3 (22.1) | –3.5 (20.9) |

[a]Data from Stroup et al.[23]
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

The clinical significance of weight gain is comparable to the clinical significance of severe psychiatric outcomes. Using data from published clinical trials, Fontaine and colleagues[24] estimated that approximately 492 suicide deaths per 100,000 patients with schizophrenia could be prevented over 10 years with the use of clozapine. However, they also made projections concerning potential CVD-related deaths from the Framingham Heart Study data. On the basis of Framingham risk modeling, weight gain of 22 lb due to antipsychotic treatment could potentially result in an additional 416 deaths per 100,000 over 10 years for those with baseline BMIs of 27. These findings suggest that lives saved during antipsychotic treatment could be offset by additional deaths related to weight gain.

### Metabolic Abnormalities

In addition to the increased incidence of clinically significant weight gain with some antipsychotics, published literature suggests that treatment with certain antipsychotic medications is also associated with an increased risk for insulin resistance, hyperglycemia, and T2DM.[25] Approximately two thirds of the reported observational analyses using large administrative or health plan databases have indicated that second-generation antipsychotic medications associated with greater weight gain (olanzapine and clozapine) are also associated with increased risk for T2DM, compared with no treatment or with first-generation medications associated with less weight gain.[18] However, these studies are fraught with methodological limitations, most importantly their reliance on surrogate markers for the presence of diabetes, without direct measures of metabolism. To clarify these findings, a recent meta-analysis[26] of 14 studies (11 retrospective, 5 case-control) looking at the association of diabetes incidence among patients treated with atypical antipsychotics compared with conventional or no antipsychotic treatment showed that clozapine and olanzapine were consistently associated with increased risk for diabetes (vs. both conventional antipsychotics and no treatment), in contrast to risperidone and quetiapine treatment.

More scientifically rigorous confirmation of the association between certain antipsychotics and metabolic abnormalities comes from short- and long-term randomized controlled trials. At least 5 studies have reported statistically significant increases in plasma insulin levels during olanzapine treatment, suggesting a treatment-related increase in insulin resistance.[18] A 6-month study of patients with schizophrenia or schizoaffective disorder detected a statistically significant increase from baseline in median fasting glucose and insulin levels with olanzapine therapy but no statistically significant changes during ziprasidone treatment.[27] In a 26-week study of patients with schizophrenia comparing weight change and metabolic indices during treatment with olanzapine versus aripiprazole,[22] the treatment groups experienced statistically significant differences in mean changes from baseline in fasting TGs (+79.4 mg/dL vs. +6.5 mg/dL), HDL (–3.39 mg/dL vs. +3.61 mg/dL), and an increase in total cholesterol to > 200 mg/dL at endpoint (38% vs. 19%).

Consistent with this literature, CATIE phase 1 data indicated that random assignment to olanzapine treatment was associated with increased metabolic risk, including increases in plasma TG, glycosylated hemoglobin, and total cholesterol.[20] In this study, olanzapine-treated patients experienced the greatest increase in exposure-adjusted mean plasma TG (mean ± SE = 40.5 ± 8.9 mg/dL), total cholesterol (9.4 ± 2.4 mg/dL), and glycosylated hemoglobin (0.4 ± .07%), with significant differences between treatment groups in each of these indices. Illustrating treatment-related differences in risk, ziprasidone treatment was associated with a decrease in exposure-adjusted mean plasma TG (mean ± SE = –16.5 ± 12.2 mg/dL) and total cholesterol (–8.2 ± 3.2 mg/dL), and with minimal change in glycosylated hemoglobin (0.11 ± 0.09%). In the CATIE phase 1 study, ziprasidone was the only study drug associated with improvement or minimal change in each of these variables.

As shown in Table 4, CATIE phase 2T study results[23] further clarified the metabolic effects of the various tested antipsychotics, when patients leaving phase 1 and opting for the so-called tolerability arm containing ziprasidone were randomly assigned once again to a different antipsychotic treatment than they had received in phase 1. In phase 2T, random assignment to olanzapine treatment was associated with substantial increases in exposure-adjusted mean plasma TG (mean ± SE = 94.1 ± 21.8 mg/dL) and total cholesterol (mean increase of 17.5 ± 5.2 mg/dL),

  

whereas risperidone and ziprasidone treatment were associated with decreases in these parameters (Table 4). Only risperidone treatment was associated with a significant plasma prolactin increase.

Comparison of the CATIE 1[20] and 2T[23] data illustrates an interesting pattern. In phase 1, while patients randomly assigned to olanzapine experienced an exposure-adjusted mean 40.5 mg/dL increase in fasting TG levels, those randomly assigned to ziprasidone had a 16.5 mg/dL decrease in TG levels. However, patients in phase 1 could be randomly assigned to a treatment condition that they had been receiving prior to phase 1 entry, which might limit change in metabolic parameters on phase 1 entry. In contrast, in phase 2T, patients could not be randomly assigned to a treatment they had received in phase 1, so that changes in metabolic parameters observed in phase 2T more consistently reflect the effects of the newly started medication. Notice, for example, that the difference in exposure-adjusted mean TG change between the olanzapine and ziprasidone arms was slightly greater than 50 mg/dL in phase 1 but almost 100 mg/dL in phase 2T.

### Weight Gain and Metabolic Abnormalities

The relative risk for metabolic abnormalities during antipsychotic treatment generally follows the rank order for weight gain among the different agents. Any medication that can cause significant weight gain can potentially increase metabolic risks secondary to changes in adiposity as discussed above. However, a small but significant minority of patients experience metabolic abnormalities in the absence of obesity or substantial weight gain, implying a potential direct mechanism whereby some medications in some patients could impact glucose or lipid metabolism.[18]

Emerging literature supports the hypothesis that, in addition to effects mediated by changes in adiposity, there are additional independent effects of some antipsychotics on metabolic indices. A study using euglycemic hyperinsulinemic clamps in freely running Wistar rats found a highly significant dose-dependent reduction in insulin sensitivity within 2 hours of initial exposure to clozapine or olanzapine but not ziprasidone or risperidone.[28] Similarly, using a modified oral glucose tolerance test in subject groups matched for adiposity and age, patients receiving olanzapine and clozapine had significantly higher fasting and postload plasma glucose values as well as higher calculated insulin resistance compared with patients receiving conventional antipsychotics and controls.[29] In another study involving frequently sampled intravenous glucose tolerance tests in subject groups matched for adiposity and age, patients treated with clozapine and olanzapine had significant insulin resistance compared with those treated with risperidone.[30] Finally, in a recent review by Bergman and Ader,[31] data in a conscious canine model using euglycemic hyperinsulinemic clamps indicated that olanzapine treatment induced preferential visceral fat deposition, a risk factor for insulin resistance. These canine studies also demonstrated that expected beta-cell compensation for insulin resistance may be reduced during olanzapine treatment.

Therefore, while weight gain and abdominal adiposity may mediate most of the effects of antipsychotic treatment on glucose and lipid metabolism, ongoing research suggests there may be a direct effect of some medications on tissue insulin sensitivity or pancreatic beta-cell function. Further research is needed to elucidate the relative contribution of such effects over time and in different patient samples.

## HEALTH CARE IMPACT

Despite increasing data on the high frequency of metabolic abnormalities and cardiovascular disease in patients with schizophrenia, there is increasing evidence that patients with mental illnesses are not getting appropriate medical attention. In a national cross-sectional study of over 300,000 Veterans Health Administration patients with diabetes,[32] patients with mental health conditions (25% of the sample) were found to be more likely to receive substandard care than patients without mental illnesses. Indeed, the odds ratio (OR) for not getting proper monitoring for diabetes significantly increased with the presence of mental illness: unadjusted ORs of 1.24 (95% CI, 1.22 to 1.27) for no hemoglobin testing, of 1.25 (95% CI, 1.23 to 1.28) for no LDL cholesterol testing, and of 1.05 (95% CI, 1.03 to 1.07) for no eye examination. The increased odds of not getting appropriate monitoring was, not unexpectedly, accompanied by an increased OR of poorer outcomes: 1.32 (95% CI, 1.30 to 1.35) for poor glycemic control and 1.17 (95% CI, 1.15 to 1.20) for poor lipemic control. These differences were even more pronounced with certain mental health conditions (psychosis, mania, substance use, and personality disorders). Finally, the study showed that the disparity in care increased in patients with increasing numbers of mental health conditions, indicated by the percentage of patients not meeting diabetes care standards increasing with increasing numbers of psychiatric diagnoses.

These findings were complemented in a recent analysis of the CATIE schizophrenia study. Nasrallah and colleagues[33] analyzed those patients entering the CATIE trial at baseline who met established criteria for diabetes, hyperlipidemia, and hypertension, in comparison to the proportion who were actively receiving treatment for their conditions. They found that, of the 85 patients with diabetes, 45.3% were receiving no treatment with an antidiabetes drug; of the 471 patients with criteria-level elevations of fasting plasma lipids, 89.4% were receiving no lipid-lowering agent; and of the 550 patients who met criteria for hypertension, 62.4% were receiving no antihypertensive medications.

These data are particularly important given the evidence, reinforced by the CATIE study, of differential weight gain and metabolic risk associated with the various antipsychotics. Over the past several years, the ADA/APA Consensus Guidelines,[19] the Mount Sinai Guidelines,[34] and other international efforts have all supported the concept of increased risks of weight gain and metabolic abnormalities associated with certain antipsychotics. However, a recent study[35] examining the change in blood glucose and lipid monitoring of patients receiving antipsychotics before and after the introduction of the ADA Consensus Statement shows the lack of impact of these guidelines: In a national study of a large claims database (N = 30,014), lipid and glucose testing rates (6%–8% and 16%–23%, respectively) were low before and after consensus statement publication. Small increases (on the order of 1%) in testing were seen in the postguideline cohort, but testing still decreased significantly after antipsychotic treatment initiation, both before and after guideline publication. Monitoring was low even in high-risk patient groups, such as older patients and those on treatments known to increase risk for weight gain, diabetes, and worsening lipid profiles.

Thus, there is a need to increase the awareness of metabolic and cardiovascular abnormalities in patients with schizophrenia. The impact of monitoring, recognition, and intervention on these risk factors for CVD in mentally ill patients would be large. A critical review by Hennekens[36] noted that reductions in cholesterol of 10% can result in a 30% decrease in CHD; 4 to 6 mm Hg reductions in blood pressure can effect a 15% decrease in CHD and a 42% decrease in stroke; cigarette smoking cessation causes a 50% to 70% decrease in CHD; maintenance of ideal body weight (BMI = 25) causes a 35% to 55% decrease in CHD; and maintenance of an active lifestyle (20-minute walk daily) can lead to a 33% to 55% decrease in CHD. Thus, small incremental changes in key modifiable risk factors can significantly impact risk for life-threatening diseases that are especially prevalent in this population.

The Institute of Medicine (IOM) of the National Academies recently issued a report, *Improving the Quality of Health Care for Mental and Substance-Use Conditions*, including a section on Health Care Provider and Organization Strategies.[37] These include strong recommendations that clinicians and administrators anticipate medical comorbidities and provide routine screening. The IOM report also recommends that mental health providers collaborate with primary care and relevant specialties and indicates the value of a variety of approaches to the delivery of integrated primary and mental health care. Key research can be used to validate these strategies. For example, a study of 120 patients enrolled in the Veterans Affairs mental health system[38] found that patients treated in an on-site integrated care clinic had improved quality and outcomes of medical care versus those treated in a usual-care setting, with no significant difference in mental health symptoms or overall costs.

Co-localization of services, along with psychiatrists' and primary care physicians' willingness to devote increased attention to the medical care of their psychiatric patients, could all contribute to reductions in adverse medical outcomes in this vulnerable population.

*Drug names:* aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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