Comparing the Safety and Efficacy of Atypical Antipsychotics in Psychiatric Patients With Comorbid Medical Illnesses

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Patients with severe mental illnesses have a higher risk of premature mortality than the general US population. Illnesses such as schizophrenia and bipolar disorder are frequently complicated by physical comorbidities such as diabetes and cardiovascular disease, including both coronary heart disease and cerebrovascular disease, which are associated with increased mortality and morbidity. Coronary heart disease is the leading cause of death among individuals with severe mental illnesses. Modifiable risk factors such as dyslipidemia, hyperglycemia, hypertension, smoking, and obesity are common in this population and contribute to risk for both diabetes and coronary heart disease. While many psychotropic medications used in the treatment of schizophrenia or bipolar disorder have similar efficacy, some medications are associated with more metabolic side effects than others, and clinicians should consider these risks when choosing among these medications. Patients with severe mental illnesses tend to have reduced access to health care and treatment for medical comorbidities compared with the general population. Therefore, clinicians involved in the care of this patient population should screen and monitor carefully for cardiometabolic side effects and risk factors.

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Comorbid medical illnesses are common in patients with major mental disorders such as schizophrenia and bipolar disorders. These individuals tend to have a high prevalence of cardiovascular disease (CVD) risk factors but typically receive less screening, less preventive health care, and less medical treatment than the general population. When selecting psychotropic medications, including antipsychotics, for this clinical population and monitoring ongoing treatment, clinicians should consider safety and tolerability, as well as efficacy, as some psychotropic medications are associated with potential adverse metabolic effects that can contribute to long-term risk for mortality and morbidity.

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MORTALITY AND MORBIDITY IN PATIENTS WITH MAJOR PSYCHIATRIC DISORDERS

Compared with the general population, patients with major mental disorders have a higher risk of premature mortality. Data from a multistate survey indicated that public hospital and mental health center patients with major mental disorders lose about 25 to 30 years of potential life.[1,2] While many psychiatrists have been trained to consider suicide as the leading potential contributor to premature mortality in this patient population, leading causes of death are similar to those in the general population, including heart disease, cancer, and cerebrovascular, respiratory, and lung diseases.[1,2] A state-by-state calculation of the percentages of deaths from different causes indicates that CVD, in the form of coronary heart disease (CHD), is the leading cause of death in the mentally ill population.[1] Three of the major causes of death,[1] CHD, cerebrovascular disease, and diabetes, share some elements of common underlying pathophysiology and common risk factors.

Risk Factors for Increased Morbidity and Premature Mortality

Individuals with major mental disorders have an increased prevalence of risk factors that contribute to in-

FOR CLINICAL USE

- Screen and monitor for adverse cardiometabolic risk factors.
- When risks are identified, intervene with therapeutic lifestyle changes and remove secondary causes of weight gain or dyslipidemia.
- Treat risk factors like hypertension, diabetes, and dyslipidemia with appropriate pharmacotherapies, and oversee referral to primary care or specialists as needed.
- Select psychotropic regimens, including antipsychotics, with lower cardiometabolic risk profiles whenever possible.

creased morbidity and premature mortality. Key modifiable risk factors for CVD, including CHD and cerebrovascular disease, are more prevalent in patients with severe mental illness compared with the general US population, including dyslipidemia, hyperglycemia, hypertension, smoking, physical inactivity, and obesity.[3] The increased prevalence of modifiable risk factors is related to relative failures in primary and secondary prevention in this patient population.[3]

The usual public health approach to prevention is to apply a screening and intervention plan for the general population, targeting high-risk populations with additional primary and secondary prevention efforts. However, patients with major mental disorders are less likely to receive screening and preventive measures compared with the general population. People with major mental disorders have less access to medical care, receive less preventive care and fewer medications for the treatment of risk factors, and have decreased adherence to medical pharmacotherapies relative to their adherence to psychotropic medications.[3] In the United States, for example, individuals with mental disorders are less likely to be screened for dyslipidemia, hyperglycemia, and hypertension; less likely to be diagnosed; and less likely to receive interventions of proven benefit than the general population.[3] An important large study[4] of Medicare patients over 65 years of age who had suffered acute myocardial infarctions indicated that patients with mental disorders were less likely than those without mental disorders to subsequently receive appropriate treatments like reperfusion, aspirin, β-blockers, or ACE inhibitors, and the presence of any mental disorder was associated with a 19% increased risk of mortality within a year.

Psychotropic medications can cause or contribute to the presence or severity of all of the modifiable risk factors discussed above, with the exception of smoking. Within an individual, the choice of psychotropic medications can beneficially or adversely impact the level of modifiable risk factors. It is now well understood that psychotropic medications—some antipsychotic medications, in particular—can influence risk factors like weight gain, obesity, insulin resistance, diabetes, hyperglycemia, dyslipidemia, and hypertension.[5] Clinicians should consider the patient's current medical illness risk factors, as well as potential drug effects on those factors, when they weigh efficacy and tolerability profiles of psychotropic medications for this patient group.

EFFICACY OF ANTIPSYCHOTIC MEDICATIONS

Psychotropic medications have substantially different patterns of efficacy within major mental illness populations. In patients with schizophrenia or bipolar mania, different antipsychotics have a similar magnitude of effect. For example, a meta-analysis[6] of 24 studies found the second-generation antipsychotics aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone to be similarly effective for acute mania. Data for the efficacy of antipsychotic medications for these disorders are reviewed here.

Schizophrenia

A number of studies and meta-analyses have examined differences in efficacy across second-generation antipsychotic medications in patients with schizophrenia. In short-term (4- to 8-week) studies[7–9] of atypical antipsychotics in patients with schizophrenia, with haloperidol sometimes included as an active comparator, mean reductions in global symptom severity, as measured by the reduction in the Positive and Negative Syndrome Scale (PANSS) total score from baseline to endpoint, were generally similar for all active drugs, with some notable variability across individual studies. The most common sources of differences in the magnitude of effect between agents across trials were drug dose and rate of dose escalation, study entry criteria and study populations, statistics and methods, and how the results were reported and the findings worded. This conclusion is supported by a recent analysis of results of head-to-head studies of second-generation antipsychotics funded by pharmaceutical companies.[10] Of 33 studies that received funding from industry, 90% reported overall outcome in favor of the supporter's drug, resulting in contradictory conclusions across studies when the findings of studies with the same drug, but with different supporters, were compared. From this perspective, it is useful to consider the registration trials leading to US Food and Drug Administration (FDA) regulatory

approval for the second-generation antipsychotics, in which the FDA had an opportunity to comment on trial design and analysis. Those registration trials indicated that all currently approved non-clozapine second-generation agents were equivalent to haloperidol in the acute treatment of schizophrenia (with the exception of a North American trial in which risperidone was statistically superior to haloperidol at some doses[11]), as measured by planned primary analyses of PANSS total and positive symptom ratings.

In the treatment of schizophrenia, atypical antipsychotics also have generally similar discontinuation rates, a putative measure of treatment effectiveness. For example, phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study,[12] a large head-to-head comparator trial of atypical antipsychotics for schizophrenia, found the following all-cause discontinuation rates: quetiapine (82%), ziprasidone (79%), perphenazine (75%), risperidone (74%), and olanzapine (64%). Substantial rates of discontinuation were found for all of the drugs, and, although some individual statistical differences across treatment arms were detected in the primary analysis, a variety of critiques subsequently cast doubt on the clinical significance of any differences. For example, dosing may not have been equivalent across all study arms with respect to equipotency for occupancy of the dopamine-2 receptor. "All-cause discontinuation" in the context of the CATIE design meant subjects discontinuing generally were choosing to go on to the next promising phase of the study, which may or may not be the best measure of effectiveness. Most importantly, the phase 1 rule that allowed subjects to be randomly assigned to a drug that they were already taking allowed the high prevalence of olanzapine use in subjects entering the study to influence study outcomes.

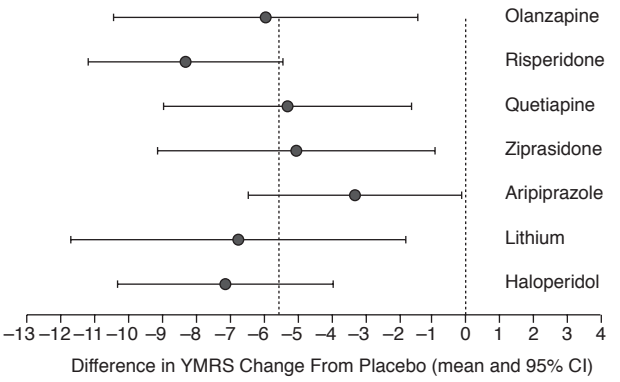
A recent post hoc analysis[13] of CATIE phase 1 results indicated that, in general, subjects who stayed on olanzapine or risperidone (stayers) had lower rates of all-cause discontinuation than subjects who switched (switchers). Therefore, the high prevalence of olanzapine treatment at study entry would give the olanzapine arm an advantage.[13] Indeed, statistical differences across phase 1 study arms were no longer detected when the analysis was restricted to only those participants who actually made a switch in their phase 1 randomized treatment assignment.[13]

Other head-to-head comparisons[14–17] of treatments for schizophrenia have shown a largely similar pattern of efficacy across individual atypical antipsychotic medications. Within any study, a variety of effects can contribute to results favoring one medication over another, but efficacy among antipsychotic agents in head-to-head trials has tended to be very similar.

Bipolar Mania

In the treatment of bipolar disorder, the efficacy of second-generation antipsychotics for bipolar mania shows a similar pattern to that seen in schizophrenia studies. As shown in Figure 1, a meta-analysis[18] of 12 randomized, placebo-controlled, monotherapy trials in patients with acute bipolar mania found all 5 of the atypical antipsychotics examined to be superior to placebo as measured by reductions in Young Mania Rating Scale scores, and no significant differences in efficacy were found among the atypical antipsychotics.

Figure 1. Atypical Antipsychotic Monotherapy Efficacy Relative to Placebo in the Treatment of Bipolar Mania: Pooled Trial Effects (Random-Effects Model)[a]



[a]Reprinted with permission from Perlis et al.[18] Bars represent 95% CI. The dotted line on the left indicates the pooled difference from placebo among all monotherapy and combination trials.
Abbreviation: YMRS = Young Mania Rating Scale.

TOLERABILITY OF ANTIPSYCHOTIC MEDICATIONS

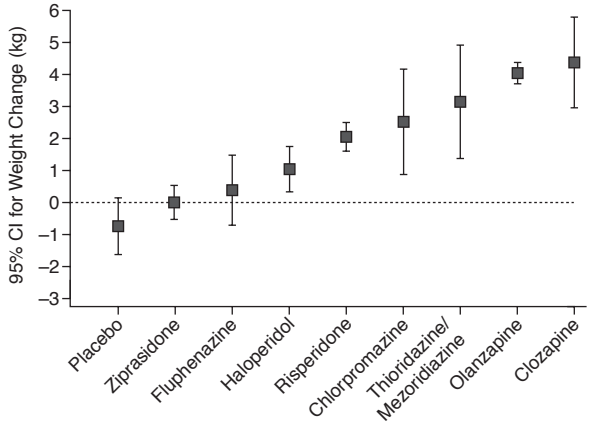
While the efficacy of the different antipsychotics is largely similar for the treatment of schizophrenia and bipolar mania, individual medications have different profiles with respect to safety and tolerability. Adverse events associated with individual medications can impact modifiable risk factors for CVD. In particular, metabolic adverse events can affect body weight, adiposity, insulin sensitivity, and circulating lipid levels, along with other changes.

Weight and Adiposity

Individual antipsychotic medications are associated with different levels of risk for adverse effects on body weight and body fat, or adiposity. In general, as adiposity increases, so does risk for dyslipidemia, hypertension, and hyperglycemia,[5] conditions that all contribute to the risk of CVD.

A meta-analysis[19] estimated the 10-week weight change for a variety of first- and second-generation antipsychotics using data from studies that measured weight at time points ranging from 1 week to 104 weeks (Figure 2). A wide spectrum of effect on weight change was found. Drugs capable of producing substantial weight gain were found in both the first- and second-generation antipsy-

Figure 2. Estimated Weight Change After 10 Weeks of Standard-Dose Antipsychotic Treatment[a]



[a]Adapted with permission from Allison et al.[19] 95% CI estimated from a randomized effects model.

chotic classes. Low-potency phenothiazines, such as chlorpromazine, thioridazine, and mesoridazine, and some second-generation antipsychotics, specifically olanzapine and clozapine (the gold standard agent for treatment-resistant patients with schizophrenia), can all produce substantial weight increases. Conversely, other first- and second-generation drugs, including ziprasidone, fluphenazine, and haloperidol, are associated with relatively low risk of weight gain. A review[20] of aripiprazole studies lasting 4 to 6 weeks similarly found relatively low risk of weight gain.

Head-to-head comparisons of estimated monthly changes in body weight for patients treated with antipsychotics were made in the 3 phases of the CATIE trial.[12,21,22] It is important to note that the CATIE sample was a chronically treated sample of patients with schizophrenia, and the most common single antipsychotic agent being taken at study baseline was olanzapine. Weight change during a specific course of treatment is a function of the current medication being used but also the prior treatment conditions. For example, if patients discontinue a medication that is associated with substantial weight gain and switch to an agent with less risk of weight gain, clinicians may see a mean reduction in the patients' body weight; this phenomenon may explain the results in the CATIE sample.

In all 3 phases of the CATIE trial, patients who were randomly assigned to olanzapine gained weight. Patients who discontinued their phase 1 atypical antipsychotic and switched to ziprasidone lost weight in phase 2T. In phase 3, patients who chose clozapine gained the most weight, followed by olanzapine. Although some degree of weight loss was associated with all the other second-generation antipsychotics, the greatest monthly weight losses were associated with aripiprazole and ziprasidone, medications chosen by patients with the highest body mass index (BMI).

Weight change after switching to a low weight gain agent has been examined in several other studies. For example, Weiden and colleagues[23] described a group of 185 patients who began treatment with a high potency conventional antipsychotic, risperidone, or olanzapine, and were then all switched to ziprasidone, which they continued to take for a maximum of 58 weeks. The patients previously treated with high-potency conventional antipsychotics like haloperidol experienced nonsignificant change in body weight after switching to ziprasidone, consistent with a switch from low-risk to low-risk medications with respect to weight gain. The patients previously treated with risperidone who were switched to ziprasidone experienced a mean weight decrease of about 15 lb ($P < .005$). Patients previously treated with olanzapine experienced a mean weight loss with ziprasidone of nearly 22 lb ($P < .001$) after 1 year of treatment.

The effects of treatment switch on weight change and psychiatric status were formally tested in a 16-week, multicenter, double-blind, randomized study of overweight patients initially taking olanzapine (N = 173). Patients were randomly assigned to continue olanzapine or switch to aripiprazole.[24] Even though many of the olanzapine-treated patients had received less than 3 months of treatment with that agent, the patients who switched to aripiprazole still experienced a significant mean weight decrease (–4.0 lb) compared with those who continued olanzapine (+3.1 lb; $P < .001$). In addition, while there was statistical advantage for stayers compared with switchers in Clinical Global Impressions-Improvement (CGI-I) scale scores ($P = .020$), CGI-I ratings for both groups remained in the range of "minimal improvement" to "no change."

A recent post hoc analysis[25] of CATIE phase 1 results also confirmed that switching from olanzapine to another antipsychotic resulted in weight loss, whereas continued use of olanzapine was associated with weight gain. This analysis confirms the weight gain described by Weiden and colleagues[23] for subjects switching from olanzapine to ziprasidone. Weight changes in these studies approximate 10% reductions in body weight in these samples, a weight reducing effect that matches or betters well-studied best-available behavioral or pharmacologic weight loss approaches in large nonpsychiatric obese patient samples.

All these results[25] suggest that switching from an antipsychotic with high weight-gain risk like olanzapine to a lower risk agent can help with weight loss, with some small increased risk of treatment dissatisfaction, but no large or readily measured group differences in psychiatric outcome. The Comparison of Antipsychotics for Metabolic Problems (CAMP) study,[26] currently underway, should help to further clarify the utility of switching antipsychotics for the treatment of weight gain and other metabolic problems in schizophrenia. Also, see the article "Obesity in Patients With Severe Mental Illness: Overview and Management" elsewhere in this supplement.[27]

Insulin Resistance, Glucose Homeostasis, and Dyslipidemia

Treatment with antipsychotic medications can decrease insulin sensitivity and increase plasma triglyceride, along with changes in other lipid fractions. In general, medications with the greatest effect on body weight are also associated with increased risk for insulin resistance, elevated plasma triglycerides, and failures in glucose homeostasis, which leads initially to reductions in glucose tolerance and eventually to elevations in fasting plasma glucose. These effects increase risk for CVD and type 2 diabetes mellitus, both leading causes of death in those with major psychiatric disorders. The magnitude of risk varies across individual medications.

Data[28] from the Framingham Heart Study were used to calculate the number of excess cases of diabetes that could be anticipated over the next 10 years based on initial BMI and weight gain over the observation period. The group that at baseline had a BMI < 23 and gained 22 lb, for example, were estimated to develop 610 excess cases of diabetes per 100,000 people. Those with baseline BMIs between 23 and 27 and a 22 lb weight gain were estimated to develop 1,403 excess cases, and those with a baseline BMI > 27 were estimated to develop 3,166 excess cases of diabetes per 100,000 over 10 years. The last group is probably most representative of patients with schizophrenia or bipolar disorder who take antipsychotics, many of whom are overweight or obese at the start of a treatment trial.

Decreases in insulin sensitivity are a necessary early step in the development of the various changes in lipid metabolism, blood pressure, and glucose homeostasis that constitute conditions like the insulin resistance syndrome and the related metabolic syndrome. A study[29] by our group demonstrates that adiposity levels achieved during antipsychotic treatment are highly predictive of the level of insulin sensitivity. Measures of adiposity that include waist circumference and BMI significantly ($P < .0001$) predicted insulin sensitivity measured during frequently sampled intravenous glucose tolerance tests in antipsychotic-treated patients with schizophrenia as well as in untreated healthy controls. The greater the adiposity, the lower insulin sensitivity tends to be, with adiposity explaining more than 30% of the variance in insulin sensitivity.

Relative to the other lipid fractions, plasma triglyceride level can be a useful marker of insulin resistance. Elevated fasting triglyceride levels have been incorporated into the definition of the metabolic syndrome, a well-described risk factor for CHD and diabetes. The effect of different antipsychotic medications on plasma triglyceride levels was examined in the CATIE trial as part of a larger effort to measure safety and tolerability.[12,21,22] Changes in plasma triglyceride, total cholesterol, and glycosylated hemoglobin were measured for all treatment groups.

In phase 1,[12] patients randomly assigned to receive olanzapine experienced the greatest increase in mean plasma triglyceride levels during treatment; patients treated with quetiapine experienced about half the increase of the olanzapine group. A decrease in mean plasma triglyceride levels occurred in patients treated with ziprasidone, presumably as a result of the lower risk for weight gain, insulin resistance, and triglyceride elevation with ziprasidone compared with medications patients were taking before being switched into this treatment arm. In this phase, patients could be randomly assigned to a medication they were already taking.

In phase 2,[21] patients could not be randomly assigned to a medication that they were already taking. Since all patients had a "new" exposure to their assigned antipsychotic, clinicians should note that the triglyceride elevation observed in the olanzapine and quetiapine treatment arms was approximately double that observed in phase 1. In phase 3,[22] decreases in triglyceride levels were noted in patients who chose ziprasidone and fluphenazine decanoate while levels rose to varying degrees in those taking the other medications.

Further definitive evidence of differing antipsychotic drug effects on triglyceride levels was provided in the 16-week study discussed above[24] in which overweight patients taking olanzapine were randomly assigned in a double-blind manner to stay on olanzapine therapy or switch to aripiprazole treatment, with planned primary endpoint analysis of changes in weight and triglyceride levels. Plasma triglyceride levels decreased from baseline in the aripiprazole group and increased from baseline in the olanzapine group ($P = .002$).

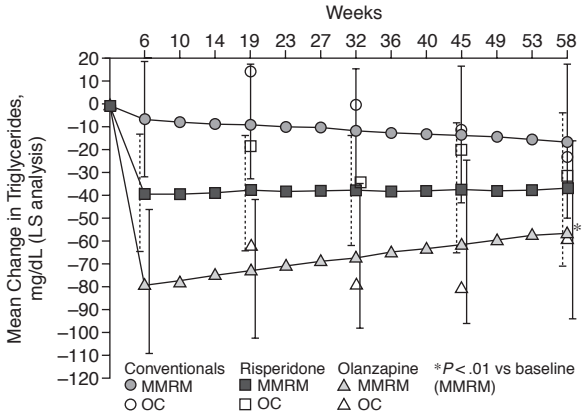
In Weiden and colleagues' 58-week study[23] of patients who were previously treated with high-potency conventional antipsychotics, risperidone, or olanzapine who were all switched to ziprasidone, a temporal dissociation was evident between the changes in weight and the changes in triglyceride levels. In contrast to the gradual weight reductions after the switch from risperidone or olanzapine, decreases in triglycerides occurred over the first 6 weeks (olanzapine, –78.0 mg/dL [$P < .0001$] and risperidone, –39.2 mg/dL [$P < .01$]) and then were largely sustained over the course of treatment (olanzapine, –76.5 ± 176.6 mg/dL [$P < .01$] and risperidone, –35.1 ± 115.2 mg/dL [$P = .052$]; Figure 3).

Analyses of the overall risk profile for weight gain, diabetes, or dyslipidemia associated with different antipsychotics are available to help clinicians predict the clinical risks associated with different medications, but clinicians should also monitor these risk factors in their patients during treatment courses.[30]

REDUCTION OF MEDICAL ILLNESS RISKS

Several groups have made recommendations about tracking body weight, lipid levels, and blood glucose level in patients taking antipsychotics. However, little change

Figure 3. Estimated Change in Triglyceride Levels From Baseline Over 58 Weeks After Switch to Ziprasidone[a]



[a]Reprinted with permission from Weiden et al.[23]
Abbreviations: LS = least-squares, MMRM = mixed-model repeated measures analysis, OC = observed cases analysis.

has taken place in the behavior pattern of physicians since these risks first became apparent. For example, in the United States, although the likelihood of glucose testing increased 2-fold between 1998 and 2003, in a large Medicaid patient population who received index prescriptions of a second-generation antipsychotic, the percentage of patients who received testing was still small.[31] Over the period examined, less than 20% of patients received baseline glucose testing and less than 10% received baseline lipid testing. With medication initiation, the rates increased slightly (glucose testing increased 7% to 11%; lipids, 2% to 3%). Patients with pre-existing diabetes or dyslipidemia were about 2 to 3 times more likely to receive baseline testing than those without these conditions, but only a small percentage were tested within 14 days before or 28 days after starting antipsychotic medication.

Since the 2004 American Diabetes Association (ADA) report[30] and the FDA recommendation[32] to modify package inserts for atypical antipsychotics with a warning about hyperglycemia and diabetes risk, the awareness of need for glucose and lipid testing has increased. Ketter and Haupt[33] conducted a survey in 2005 and 2006 of psychiatrists who treat patients with bipolar disorder. They found that 80% of physicians who responded reported regularly monitoring patients' weight, fasting glucose, and fasting lipid profile after starting a new medication. Waist circumference was reportedly monitored by only 20% of respondents. Unfortunately, quantification of actual screening and monitoring rates for glucose and lipids in the years before and after the ADA and FDA warnings and recommendations to monitor have indicated only very limited improvement in testing rates.[34,35] This represents a lost opportunity. Compared with secondary prevention, early screening and identification of risk offer the greatest opportunity to impact the course of cardiometabolic diseases for the largest number of patients.[36]

Even modest reductions in any one of the modifiable risk factors for cardiometabolic diseases can lead to substantial payoffs over the long term. For example, trials have found that a 10% reduction in blood cholesterol results in a 30% decrease in risk of CHD; a 6 mm Hg decrease in diastolic pressures > 90 mm Hg results in a 16% decrease in CHD and a 42% reduction in stroke.[37] Smoking cessation leads to about a 50% reduction in risk of CHD, regardless of the patient's age.[37] Maintaining an ideal BMI of 18.5 to 25 and maintaining an active lifestyle by walking about 30 minutes per day reduced the risk of CHD between 35% and 55%.[38]

A range of strategies are available to manage cardiovascular risk. Behavioral interventions such as healthy food choices, physical activity increases, and smoking cessation are standard approaches that are appropriate for patients with major mental disorders.[39] Smoking cessation is particularly important in this patient population.

CONCLUSION

Patients with severe mental illness are at elevated risk for overall medical morbidity and mortality, particularly CVD-related mortality. Modifiable cardiometabolic risk factors are prevalent in patients with major mental disorders. Various psychotropic agents, particularly antipsychotics, which are often used to treat severe mental illnesses such as schizophrenia and bipolar disorder, are associated with different levels of risk for weight gain, dyslipidemia, and hyperglycemia. Clinicians can beneficially modify patient risk through medication choice, regular monitoring of weight, BMI, waist circumference, fasting plasma glucose level, and lipid profiles, with active interventions for identified risk, including ongoing encouragement of healthy lifestyle choices.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), 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 US Food and Drug Administration–approved labeling has been presented in this article.

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