# Antipsychotic-Induced Weight Gain and Metabolic Abnormalities: Implications for Increased Mortality in Patients With Schizophrenia

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Patients with schizophrenia have increased rates of morbidity and mortality due primarily to cardiovascular disease, compared with the general population. Case reports, case series, observational analytic epidemiologic studies, and randomized trials raise the possibility that some antipsychotic drugs add to this increased risk, likely due to drug-induced weight gain and associated metabolic abnormalities including hyperglycemia, diabetes mellitus, and dyslipidemia. This constellation of risk factors, referred to as the "metabolic syndrome" leads to greater than additive risks and affects about 1 in 4 adult Americans, approximately 60% of obese adults,[1,2] and perhaps 1 in 2 patients with schizophrenia.

At the time of initiating treatment in their patients with schizophrenia, psychiatrists should be aware of metabolic and cardiovascular risk factors, as well as subsequent treatment-induced changes in risk status. Awareness of established risk factors for major morbidity and mortality should influence choice of antipsychotic medications, based on differences in the potential effect of individual medications on weight and related metabolic and cardiovascular risk. Strategies recommended include identifying high-risk patients, promoting healthy lifestyle/behavioral habits, selecting antipsychotic medication regimens with comparable efficacy and fewer metabolic side effects, and monitoring weight, glucose, and lipid profiles during treatment.

## Epidemiology of Cardiovascular Disease and Major Metabolic Risk Factors

Cardiovascular disease, which includes coronary heart disease, cerebrovascular disease, and peripheral vascular disease, is far and away the leading cause of death in the United States and most developed countries, accounting for about 1 in 2 fatalities.[3] The World Health Organization (WHO) has estimated that cardiovascular disease will become the leading cause of death in the world by 2020.[4] Among the major risk factors for cardiovascular disease are obesity, dyslipidemia, hypertension, and hyperglycemia. These multiple metabolic risk factors are key elements defining the metabolic syndrome, which is a leading clinical and public health problem in the United States. The relationship among these variables is not clear, and likely not simple, but insulin resistance appears to be a central element. The clinical problem derives from the fact that risks are greater than additive so that global risk for a patient with 5 risk factors, each of which causes a doubling of coronary heart disease, may be 15- to 30-fold higher than for patients without any of the risk factors. Table 1 shows the components of the metabolic syndrome.

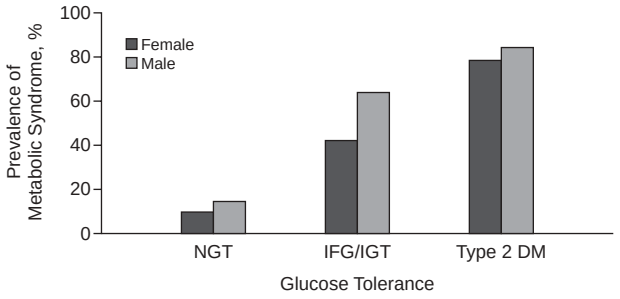
The public health importance of the metabolic syndrome derives from the fact that 24.0% of men and 23.4% of women in the United States over age 20 are affected, and the prevalence is even higher in African American females and Hispanics.[1] Park et al.[2] have reported that 22% of overweight men and 60% of obese men have the metabolic syndrome, with similar rates in women. While the diagnostic criteria for the metabolic syndrome vary, the Adult Treatment Panel III (ATP III) guidelines from the U.S. National Heart, Lung, and Blood Institute (NHLBI) describe the metabolic syndrome as consisting of 3 or more of the following conditions: waist circumference > 102 cm (40 inches) for men and > 88 cm (35 inches) for women, triglycerides ≥ 1.70 mmol/L (150 mg/dL), high-density lipoprotein (HDL) cholesterol < 1.04 mmol/L (40 mg/dL) for men and < 1.30 mmol/L (50 mg/dL) for women, blood

**Table 1. "The Metabolic Syndrome" According to the Adult Treatment Panel III[a]**

| Risk Factor | Defining Level |
|---|---|
| Abdominal obesity (waist) | |
| Men | > 102 cm (> 40 in) |
| Women | > 88 cm (> 35 in) |
| Triglycerides | ≥ 150 mg/dL |
| HDL cholesterol | |
| Men | < 40 mg/dL |
| Women | < 50 mg/dL |
| Blood pressure | ≥ 130/ ≥ 85 mm Hg |
| Fasting glucose | ≥ 110 mg/dL |

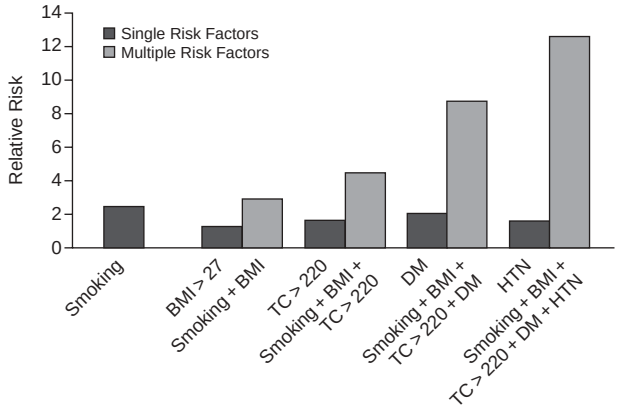
[a]From the National Cholesterol Education Program.[5] The metabolic syndrome is defined as ≥ 3 risk factors.
Abbreviation: HDL = high-density lipoprotein.

**Figure 1. Prevalence of Metabolic Syndrome (Botnia study: subjects aged 35–70 years)[a]**



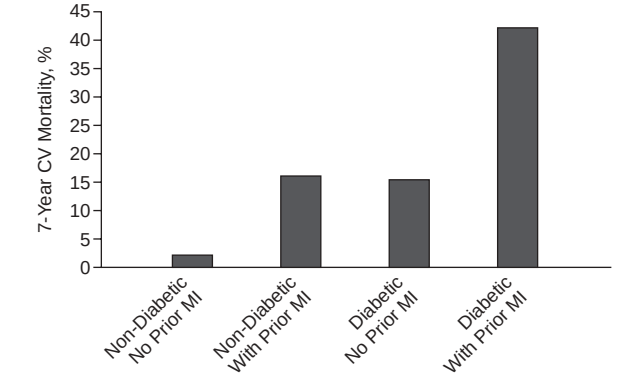

[a]Data from Isomaa et al.[9]
Abbreviations: DM = diabetes mellitus, IFG/IGT = impaired fasting glucose/impaired glucose tolerance, NGT = normal glucose tolerance.

**Figure 2. Relative Risk of Coronary Heart Disease for Multiple Risk Factors (Framingham Heart Study)[a]**




[a]Data from Wilson et al.[12]
Abbreviations: BMI = body mass index, DM = diabetes mellitus, HTN = hypertension, TC = total cholesterol.

**Figure 3. Diabetes Increases Death Rate From Myocardial Infarction (MI)[a]**




[a]Data from Haffner et al.[17]
Abbreviation: CV = cardiovascular.

pressure ≥ 130/85 mm Hg, fasting glucose ≥ 6.1 mmol/L (110 mg/dL).[5]

In the Framingham Heart Study,[6] the initial presentation of coronary heart disease is often sudden death, especially in men. Even among patients who reach the hospital alive with myocardial infarction, their mortality rate is 7% to 10%. In a study of approximately 88,000 Medicare patients admitted to the hospital for the treatment of myocardial infarction, the presence of any mental disorder increased mortality by almost 20%, while the presence of schizophrenia increased mortality by 34%.[7] These considerations reinforce the need for efforts at primary prevention through favorable alteration of modifiable risk factors. The major risk factors for coronary heart disease include age, smoking, body mass index (BMI) > 25 kg/m$^2$, total cholesterol > 200 mg/dL, diabetes mellitus, and hypertension.[5,8] Patients with schizophrenia often have higher prevalence rates of 1 or more of these risk factors (see below).

### Insulin Resistance and Diabetes

In a Scandinavian study using the WHO-proposed definition of metabolic syndrome, Isomaa et al.[9] reported the prevalence to be 10% in women and 15% in men with normal glucose tolerance. As shown in Figure 1, the prevalence rose dramatically to 42% (women) and 64% (men) in those with impaired fasting glucose/impaired glucose tolerance, and 78% (women) and 84% (men) in those with type 2 diabetes mellitus.[9] Consistent with these findings, Hanley et al.[10] showed that the degree of insulin resistance was negatively correlated with HDL cholesterol and positively correlated with low-density lipoprotein (LDL) cholesterol, total cholesterol, triglycerides, and blood pressure, further supporting a positive relationship between insulin resistance and metabolic abnormalities. In patients with the metabolic syndrome, the risks for coronary heart disease and stroke were found to be 3 times higher, and cardiovascular mortality was increased by nearly 6 times (12% vs. 2.2%, $p < .001$).[9]

The U.S. National Cholesterol Education Program (NCEP) III has elevated diabetes from a major risk factor to a coronary heart disease risk equivalent, with the metabolic syndrome that includes insulin resistance, hyperglycemia, and dyslipidemia now identified as a major risk factor for coronary heart disease.[5] Data from young adults in the Bogalusa Heart Study indicate that the more risk factors (i.e., elevated BMI, systolic blood pressure, triglycerides, LDL cholesterol) an individual has, the more likely it is that precursors to coronary artery disease (fatty streaks or fibrous plaques) will be found.[11] As Figure 2 illustrates, risk factors are more than additive as the total risk is higher than just the sum of the individual risk factors.[12] However, the probability of developing coronary heart disease can be decreased by favorable alteration of modifiable risk factors.[4]

Type 2 diabetes mellitus increases morbidity and mortality due in part to acute metabolic complications such as diabetic ketoacidosis but in large measure due to chronic microvascular and macrovascular complications. Microvascular disease accounts for much of the chronic morbidity of type 2 diabetes mellitus, in the form of nephropathy, neuropathy, and retinopathy.[13] For example, diabetic nephropathy currently accounts for approximately 25% of cases of end stage renal failure in the United States.[14] Macrovascular or atherosclerotic disease also accounts for increased morbidity and mortality in type 2 diabetes mellitus, including myocardial infarction, stroke, and cardiovascular death.

### Obesity

There has been extensive research into the cardiovascular consequences of increased adiposity. Obesity is associated with atherogenic dyslipidemia (i.e., elevated triglycerides, elevated small LDL particles, and low HDL), diabetes, and proinflammatory and prothrombotic conditions,[15] which increase vulnerability to acute cardiac events. A positive linear relationship exists between BMI and mortality rate as well as relative risks of developing cholelithiasis, hypertension, coronary heart disease, and especially type 2 diabetes mellitus.[16] On the basis of the elevation of diabetes from a major risk factor to a coronary heart disease risk equivalent in the ATP III from the NHLBI,[5] all diabetic patients should be treated just as aggressively as survivors of a prior coronary heart disease event. This recommendation is based, in part, on data from a Finnish cohort study that demonstrated that the probability of a coronary heart disease event among non-diabetics with prior myocardial infarction was about equal to that of the type 2 diabetics free from prior myocardial infarction as shown in Figure 3.[17]

In general, increased central adiposity particularly in the form of intra-abdominal or visceral fat is strongly related to decreased insulin sensitivity.[18] Decreased insulin sensitivity is an important step in the progression toward type 2 diabetes mellitus in many individuals. Notably, at the high end of BMI, white men have a somewhat greater risk of diabetes than white women.[19] This observation may be related to the tendency for men to develop central obesity and for women to develop gluteal-femoral obesity, since central obesity more strongly contributes to the risk of diabetes.[20] Particularly in the elderly, it is important to bear in mind that up to 20% of diabetic individuals may not be obese based on BMI. Unfortunately, increases in insulin resistance and plasma glucose levels, analogous to the situation with lipids, are associated with increases in the risk of cardiovascular disease.

Increased adiposity also increases proinflammatory factors that predict increased risks of coronary heart disease.[21,22] C-reactive protein (CRP) is an acute-phase reactant produced by the liver that is secreted in response to increased circulating levels of the proinflammatory cytokine, interleukin 6, which in turn is produced by adipose tissue.[23] The high-sensitivity CRP (hsCRP) assay allows measurement of the very low basal levels of CRP that remain in the absence of acute inflammatory processes. Both hsCRP level and lipid levels are independent predictors of future cardiovascular events.[24] In addition, elevated hsCRP levels can predict future development of diabetes in normoglycemic individuals.[25] Increases in hsCRP levels are reported in association with increased adiposity during antipsychotic treatment.[26]

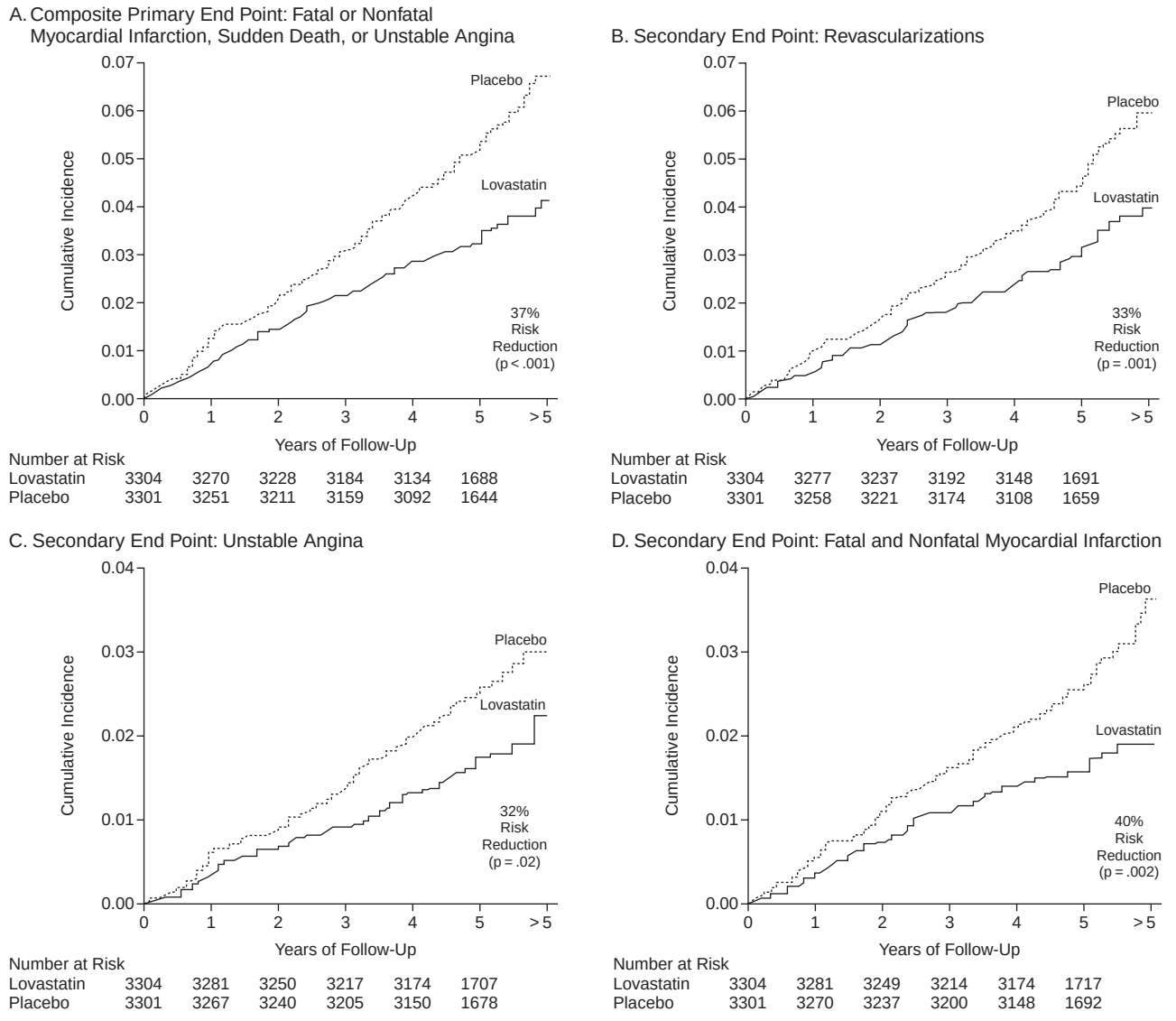
In addition to weight gain, ethnicity is another major risk factor for the development of type 2 diabetes mellitus. Compared with Caucasians, nearly every other ethnic population is at higher risk for developing type 2 diabetes mellitus, even when calculations are adjusted for weight.[27,28] In fact, while U.S. public health officials recommend that people maintain a BMI of $< 25$ kg/m$^2$, the WHO recommends that Asians maintain a BMI of $< 23$ kg/m$^2$, as the morbidity and mortality associated with a BMI of $> 27$ kg/m$^2$ in Caucasians is already present at a BMI of 25 kg/m$^2$ in Asians.[29]

### Dyslipidemia

Increases in insulin resistance can lead to progressive increases in glucose and lipid levels, both of which increase risks of cardiovascular disease. Decreased insulin sensitivity at adipose tissue tends to occur early in the course of naturally occurring diabetes, characterized by an impaired ability to decrease lipolysis with corresponding increases in the release of free fatty acids (FFAs) into circulation.[30] The increased FFAs are usually detected clinically as an elevation in plasma triglyceride. Increased adiposity, especially increased visceral abdominal adiposity, is also associated with increased small, dense LDL particles and decreased HDL cholesterol.[31–33] Since LDL comprises 60% to 70% of the total cholesterol, total cholesterol can be used as an accurate marker for increased LDL as well as coronary heart disease. In the National Health and Nutrition Examination Study III (NHANES III), hypercholesterolemia (total cholesterol $\geq 240$ mg/dL) increased with increasing BMI in men.[34] A similar relationship was observed in women, although BMIs greater than 27 kg/m$^2$ were not associated with further increases in cholesterol levels. These increases in cholesterol are strongly associated with increased cardiovascular risk.[35,36]

Epidemiologic studies, including the Framingham Heart Study,[6] have shown a linear relationship of LDL cholesterol level with risk of coronary heart disease. Randomized trials, including the Lipid Research Clinics Coronary Primary Prevention Trials[37,38] and the Multiple Risk Factor Intervention Trial,[39] have demonstrated that lowering LDL will decrease risks of coronary heart disease. Most recently, numerous landmark randomized trials of statin drugs, which lower LDL by about 30%, and their meta-analyses[40] demonstrate conclusive reductions in myocardial infarction, stroke, cardiovascular death, and

**Figure 4. Cumulative Incidence of Primary End Points and Secondary End Points by Treatment Group[a]**




[a]Reprinted with permission from Downs et al.[45]

total mortality. These findings have been demonstrated in secondary as well as primary prevention.[41–45] In the West of Scotland Coronary Prevention Study, moderately hypercholesterolemic people without evidence of cardiovascular disease who had their LDL levels lowered with statin therapy had a 30% reduction in cardiovascular events and death.[42] Similarly, the Air Force/Texas Coronary Atherosclerosis Prevention Study showed a > 30% reduction in risk for first fatal or nonfatal coronary event in people who underwent aggressive LDL reduction with lovastatin therapy (Figure 4).[45] Lipid-lowering therapy with statins may decrease risk by reducing LDL cholesterol, as well as by depleting and stabilizing the lipid core, strengthening atherosclerotic fibrous caps, improving endothelial function, reducing inflammation, and decreasing platelet-thrombus formation and deposition. On the basis of an extensive body of clinical and preclinical research, the National Cholesterol Education Program ATP III has identified LDL cholesterol as the primary target for reducing risk of cardiovascular disease in both secondary and primary prevention.[5]

Hypertriglyceridemia is emerging as an independent risk factor for cardiovascular disease in observational analytic epidemiologic studies[46,47] and their meta-analyses.[48,49] The ATP III guidelines emphasize that an optimal level of triglyceride is less than or equal to 150 mg/dL.[5] Additionally, obesity is associated with hypertriglyceridemia, but pharmacologic therapy of hypertriglyceridemia can be difficult in the absence of weight control.

## Schizophrenia, Metabolic Disorders, and Cardiovascular Disease

Patients with schizophrenia often have poor health and unhealthy life styles and consequently are at risk for common physical illnesses and increased mortality. In fact, life expectancy for patients with schizophrenia is 57 years for men and 65 years for women, 20% shorter than that for the general population.[50,51] While factors contributing to this lower life expectancy for schizophrenia patients include markedly increased risks for suicide as well as infectious and respiratory diseases, cardiovascular mortality is the major contributor to excess mortality in schizophrenia.[52] In addition, schizophrenia patients suffer from impaired insight, lack of resources (i.e., access to medical care), lower medication and treatment compliance, and more psychosocial stress, all of which can compound medical problems.

The number of excess deaths in the schizophrenia population is 1.6 to 3.0 times the expected number of deaths compared to the general population, with 38% of the excess deaths associated with suicide and homicide, while the other 62% are due to natural causes.[51] Moreover, schizophrenia patients are about twice as likely to die of cardiovascular disease compared to the general population.[53–55] Such high risks of death from cardiovascular disease are likely to be due to higher rates of obesity,[56] lipid abnormalities,[57,58] diabetes,[59,60] hypertension,[61] physical inactivity, and smoking[62] in schizophrenia patients. As a result of these factors, schizophrenia patients would also be expected to have higher rates of the metabolic syndrome, a view that is supported by current data.[63,64] Further, primary prevention efforts in patients with schizophrenia are even more crucial than in the general population, and clinicians should use careful strategies to manage risk factors in their patients, including the choice of antipsychotic medication and monitoring of side effects.

While the risk factors for cardiovascular disease are well documented and are significant public health issues, the ability of antipsychotic drugs to prolong the cardiac QT interval (reported as QTc after heart rate correction) has also been a concern of regulatory authorities. Two types of drugs have raised concerns. The first class of drugs comprises those that produce large prolongations of the QT. Second is the class of drugs, such as terfenadine, that produce modest prolongations of the QT that increase markedly in the presence of metabolic inhibitors. Clinicians should be reassured, however, that in several large prospective cohort studies and their overview, modest prolongation of QTc intervals with most antipsychotic drugs is not a significant risk factor for cardiovascular mortality or sudden death.[65] The exceptions are thioridazine, chlorpromazine, and pimozide.

## The Impact of Atypical Antipsychotics on Weight Gain

The introduction of atypical antipsychotic medications has been a major advance in the treatment of schizophrenia. Besides a significantly lower risk for tardive dyskinesia and extrapyramidal side effects, they may have superior efficacy in treating negative symptoms, improving mood and cognition, and preventing relapse. However, these drugs can also cause some adverse effects, including weight gain and metabolic disturbances, which may increase risks of cardiovascular disease. Adverse effects associated with antipsychotic treatment range from acute complications such as diabetic ketoacidosis, to intermediate-term complications such as weight gain, glucose intolerance, and insulin resistance (pre-diabetes), and dyslipidemia, as well as long-term complications such as diabetes mellitus, hypertension, and the potential development of cardiovascular disease.

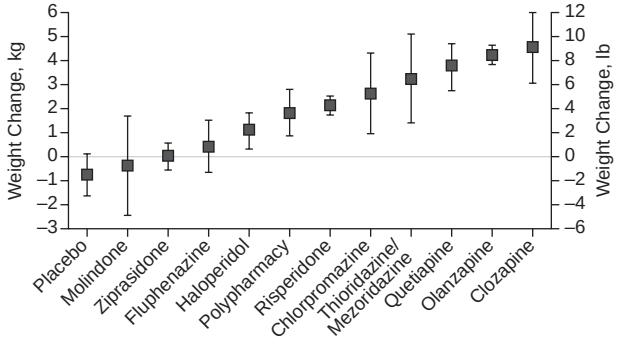
The importance of including these effects in the selection of antipsychotic drug treatment is underscored by a recent analysis of the risks and benefits of clozapine treatment. Using Framingham Heart Study data (Table 2), Fontaine et al.[66] estimated that while clozapine may decrease suicidal behavior in 492 of 100,000 schizophrenia patients over a 10-year period, the weight gain induced by clozapine would be expected to result in 416 additional deaths. While atypical antipsychotic medications are crucial for the effective

**Table 2. Excess Deaths Associated With Weight Gain (per 100,000 people)[a]**

| Data Set | All Subjects | Baseline BMI < 23 | Baseline BMI 23–27 | Baseline BMI > 27 |
|---|---|---|---|---|
| 1948 Framingham distribution | | | | |
| 2.5 kg gain | 26 | –168 | –28 | 258 |
| 5 kg gain | 103 | –299 | –15 | 591 |
| 7.5 kg gain | 232 | –394 | 39 | 1004 |
| 10 kg gain | 416 | –455 | 136 | 1508 |
| 12.5 kg gain | 662 | –486 | 280 | 2117 |
| 1999 US population distribution | | | | |
| 2.5 kg gain | 30 | –263 | –32 | 257 |
| 5 kg gain | 117 | –471 | –20 | 589 |
| 7.5 kg gain | 264 | –625 | 35 | 1001 |
| 10 kg gain | 473 | –729 | 136 | 1504 |
| 12.5 kg gain | 751 | –787 | 287 | 2112 |

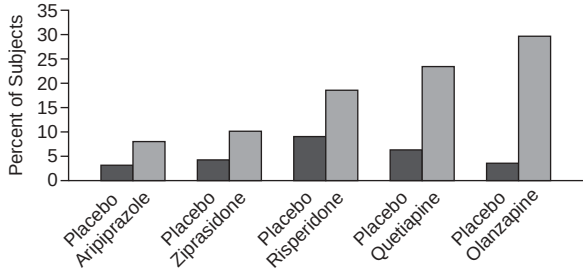
[a]Adapted with permission from Fontaine et al.[66]
Abbreviation: BMI = body mass index.

**Figure 5. Antipsychotics and Weight Gain: Short-Term (10-weeks) Treatment[a]**




[a]Reprinted with permission from Allison et al.[68]

**Figure 6. Amount of Weight Gain Reported in U.S. Package Inserts for Short-Term Studies[a]**




[a]Data from U.S. package inserts.[69–73] Clinically significant weight gain defined by U.S. Food and Drug Administration as ≥ 7% of baseline weight.

treatment of schizophrenia, clinicians must also try to achieve the most favorable benefit-to-risk ratio for their patients with schizophrenia.

### Antipsychotic Drugs and Weight Gain

Obesity is associated with elevated triglycerides, hypertension, and diabetes mellitus, all of which, if sustained, impart significant increased risk for cardiovascular disease. It is well established that as adiposity increases, often measured indirectly by BMI, insulin sensitivity decreases (increase in insulin resistance) and plasma glucose and lipid levels rise. These interrelationships play a key role in the genesis of various medical problems such as diabetes and cardiovascular disease, ultimately leading to higher mortality rates. As a result, antipsychotic drug–induced weight gain among patients with schizophrenia is a well-established and growing concern in the psychiatric community. Data indicate that patients with schizophrenia are as obese as or more obese than those without schizophrenia.[56]

Certain atypical antipsychotics are associated with greater weight gain liability than the high-potency typical antipsychotics. In a recent meta-analysis,[56,67] all antipsychotic drugs with the exceptions of molindone and ziprasidone were associated with some degree of weight gain after 10 weeks of treatment, as illustrated in Figure 5.[68]

In this analysis, certain atypicals such as clozapine and olanzapine were found to have the greatest potential to induce weight gain and ziprasidone the least. Short-term weight gain data supplied by manufacturers in U.S. package inserts[69–73] indicate that all the first-line atypical antipsychotic medications tested (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone) cause substantially different rates of clinically significant weight gain (defined by the U.S. Food and Drug Administration [FDA] as ≥ 7% of baseline weight) compared to placebo (Figure 6). Aripiprazole, risperidone, and ziprasidone treatment are associated with approximately 2 times the placebo-induced incidence of weight gain in short-term clinical trials, and quetiapine with approximately 4 times the placebo-induced incidence, while olanzapine treatment is associated with approximately 10 times the placebo-induced incidence of weight gain during short-term trials.

Long-term data indicate that ziprasidone- and aripiprazole-induced weight gain remains limited to approximately 1 kg over the first year of treatment. Quetiapine and risperidone produce approximately 2 to 3 kg over the same 1-year period, while mean weight gain induced by olanzapine treatment at commonly used doses exceeds 10 kg during the first year of exposure.[69–76] It is also important to note that the change in weight may very much depend on the BMI of a patient at the start of treatment with a particular drug. Studies with ziprasidone and aripiprazole indicate that patients with low BMIs (< 23 kg/m$^2$) gain weight, patients with moderate BMIs (> 23–27 kg/m$^2$) do not change weight much, and patients with higher BMIs (> 27 kg/m$^2$) lose weight.[67,68] In contrast, patients in all BMI groups gain weight with olanzapine.[77] Data from switching studies[67,68] indicated that switching patients to ziprasidone or aripiprazole may be associated with weight loss, particularly in those patients with BMIs greater than 27 kg/m$^2$.

## Antipsychotic Drugs, Insulin Resistance, Hyperglycemia, and Diabetes Mellitus

A range of evidence spanning case reports and case series, prospective observational studies, retrospective database analyses, and controlled analytic studies including randomized clinical trials suggests that treatment with certain antipsychotic medications, in comparison to no treatment or treatment with alternative antipsychotics, is associated with increased risk of insulin resistance, hyperglycemia, and type 2 diabetes mellitus.[78] Interpretation of these studies has been complicated by the fact that abnormalities in glucose regulation were first reported in schizo-

phrenia prior to the introduction of antipsychotic medications, with early reports indicating a pattern of insulin resistance in untreated patients.[79,80] Despite failure to control for age, weight, adiposity, ethnicity, or diet in these early studies, the evidence suggests that patients with schizophrenia may have a higher risk of impaired glucose metabolism compared to the general population, with likely contributions from factors such as diet and activity level. An additional complication is that the criteria for defining diabetes have changed over the years.

In case reports and case series, hyperglycemia, exacerbation of existing type 1 diabetes mellitus and type 2 diabetes mellitus, new-onset type 2 diabetes mellitus, and diabetic ketoacidosis have more frequently been associated with treatment using clozapine and olanzapine. Relatively fewer reports have described similar events in association with quetiapine or risperidone treatment, with little evidence for ziprasidone and the most recently launched drug, aripiprazole.[78,81] In general, case reports can be difficult to interpret due to the lack of control data, such as the number of treated patients who did not experience the event, as well as potential reporting bias.

The most common reporting bias is underreporting; for example, only 1% to 10% of adverse events are reported to the FDA postmarketing surveillance program, MedWatch, with most reports in the first 2 years of market experience. With respect to the number of patients who had to be exposed to a given drug in order to observe the reported adverse events, the higher number of adverse events reported for clozapine and olanzapine in comparison to risperidone, for example, cannot be explained by a larger number of patient-years of drug exposure with either of the former agents. Henderson et al.[82] conducted a longitudinal observational study of clozapine-treated patients and reported that 30 (36.6%) of 82 clozapine-treated patients had developed type 2 diabetes mellitus over the 60-month study period. The development of diabetes was correlated with changes in plasma triglycerides but not BMI or weight gain. Retrospective analyses of clozapine-, olanzapine-, and risperidone-associated cases of new-onset diabetes in the FDA MedWatch database revealed that most new-onset cases occurred within the first 6 months of treatment initiation, about a quarter were not associated with substantial weight gain or obesity, almost one half involved no family history of diabetes, and some cases demonstrated a close temporal relationship between treatment initiation, discontinuation, and the development and/or resolution of the adverse event.[83–85] It should be noted, however, that case reports and case series are useful to formulate but not to test hypotheses.[86] Consistent with this view, the distribution and characteristics of reported cases led the FDA to interpret these data as a "safety signal" requiring further evaluation.

There are several analyses that aim to test the strength of the association between treatment with specific medications and the presence of diabetes mellitus using large administrative or health plan databases, a few of which have been published in indexed journals.[59,60,87–91] While certain aspects of methodology have been highly variable, the common underlying approach has been to measure the association within an existing database between use of specific antipsychotic medications and the presence of 1 or more surrogate indicators of diabetes mellitus (e.g., prescription of hypoglycemic agent or relevant International Classification of Diseases [ICD]-9 codes). None of these analyses have involved prospective testing of validated plasma glucose indicators of diagnoses or insulin resistance. Most of these studies indicate that drugs that induce more weight gain (e.g., olanzapine) are associated with increased risk of diabetes mellitus in comparison to no treatment, conventional treatment, or a drug producing less weight gain (e.g., risperidone).[60,88,90,91]

Limitations on the interpretation and generalizability of these retrospective database analyses include variable methodology, use of insurance or health plan versus population-based datasets in many but not all cases, uncontrolled cohort effects without access to relevant clinical parameters that might allow statistical controls (e.g., baseline and treatment-related weights, diet, family history, prior treatment history, and laboratory values), variable numbers of subjects exposed to comparison drugs for different periods of time leading to unequal sample sizes, limited comparability or exclusion of certain drugs, and, importantly, a limited history of prior antipsychotic and other drug exposures that makes it difficult to control for critical prior treatment effects (e.g., a 20-kg weight gain on prior treatment can impact current risk of type 2 diabetes mellitus). The most important problem with retrospective database analyses involves the use of insensitive, unreliable, surrogate diagnostic indicators for diabetes mellitus (e.g., prescription of hypoglycemic drug, ICD-9 codes). The ADA estimates that approximately 33% of individuals with type 2 diabetes mellitus are undiagnosed, so that these individuals will have no associated hypoglycemic prescription or diabetes-related ICD-9 code to be detected in this type of analysis. Given that antipsychotic-related differences in diabetes mellitus prevalence are probably less than 33%, the measurement error with this approach may be larger than the target signal. This problem with signal-to-noise ratio in studies of this type suggests that variable results, including potential failure to detect the target signal, can be expected.

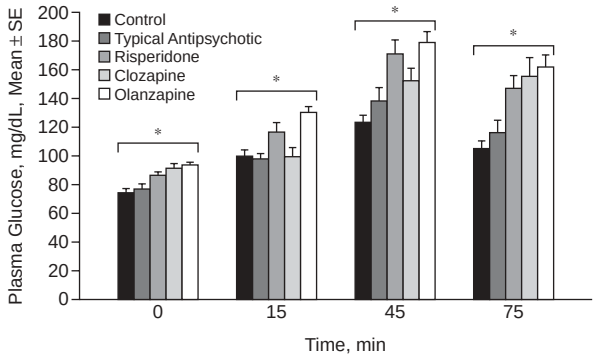
Providing an example of one of the studies from the Veterans Administration, Sernyak et al.[59] studied a total of 38,632 patients who received either conventional neuroleptics or atypical antipsychotics. They found that those who received atypical agents were 9% more likely to have diabetes than those treated with typical neuroleptics when the effects of age were controlled, suggesting that atypicals are associated with increased prevalence of diabetes.

**Table 3. Comparison of Patients Using Olanzapine and Risperidone Within 3 Months of Index Date With Patients Not Using Antipsychotics or Those Using Conventional Antipsychotics[a]**

| Antipsychotic[b] | Cases (N = 451) | Controls (N = 2696) | Adjusted Odds Ratio (95% CI)[c] | p Value |
|---|---|---|---|---|
| No antipsychotic (reference) | 168 | 1228 | | |
| Conventional antipsychotic | 263 | 1404 | 1.4 (1.1 to 1.7) | .004 |
| Olanzapine | 7 | 11 | 5.8 (2.0 to 16.7) | .001 |
| Risperidone | 7 | 26 | 2.2 (0.9 to 5.2) | .079 |
| Other newer agents | 1 | 3 | 1.6 (0.2 to 17.1) | .699 |
| Conventional antipsychotics (reference) | 263 | 1404 | | |
| Olanzapine | 7 | 11 | 4.2 (1.5 to 12.2) | .008 |
| Risperidone | 7 | 26 | 1.6 (0.7 to 3.8) | .290 |
| Other newer agents | 1 | 3 | 1.2 (0.1 to 12.4 | .900 |

[a]Reprinted with permission from Koro et al.[60]
[b]Categories mutually exclusive. Results not shown for patients using more than one antipsychotic, included in model.
[c]Adjusted for age, sex, index year, duration of follow-up, and use of either α-blocker, β-blocker, β-blocker and thiazide diuretic, corticosteroid, thiazide diuretic, lithium, oral contraceptives containing norgesterol, or valproate.

**Figure 7. Plasma Glucose Values at Fasting and Postglucose Time Points During a Modified Oral Glucose Tolerance Test in Patients With Schizophrenia (N = 48) Treated With Typical Antipsychotic Medication (N = 17), Clozapine (N = 9), Olanzapine (N = 12), or Risperidone (N = 10) and Untreated Healthy Control Subjects (N = 31)[a]**



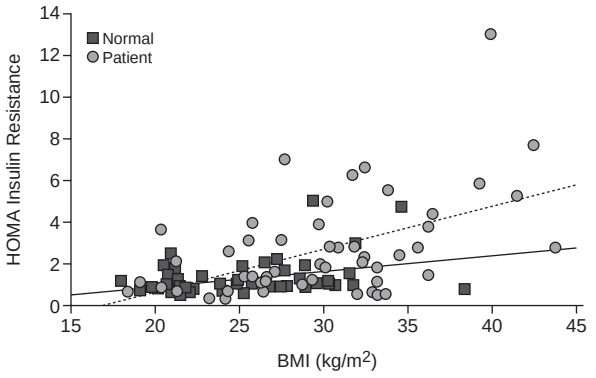

[a]Reprinted with permission from Newcomer et al.[92]
*p < .05.

Using a case-control design and a population-based sample, Koro et al.[60] reported that olanzapine-treated patients had a significantly greater risk of developing diabetes (odds ratio = 5.8, 95% confidence interval = 2.0 to 16.7) in comparison to healthy controls, as well as a significantly greater risk in comparison to risperidone-treated patients (Table 3). In the absence of population-based epidemiologic studies using validated plasma indicators of diabetes mellitus, insulin resistance, impaired glucose control, and other measures of metabolic syndrome, readers might make cautious use of these retrospective database analyses, for hypothesis generation rather than hypothesis testing, based on a thorough understanding of their limitations.

The final area of evidence involves controlled analytic studies, including randomized clinical trials that make use of sensitive and validated measures of glucose metabolism, with results that can be used for hypothesis testing rather than just hypothesis generation. Two initial studies in this area were motivated by the case report literature, including FDA MedWatch analyses, suggesting that approximately 25% of reported new-onset cases of type 2 diabetes mellitus occur in the absence of substantial weight gain or obesity.[78] These reports stimulated interest in whether treatment-related disturbances in glucose metabolism, which could be expected in the setting of weight gain, might also occur without weight gain or obesity, and whether different medications were associated with more or less risk for adiposity-independent effects on glucose regulation. In order to begin to address this question, investigators have studied patients chronically treated with different antipsychotic medications, experimentally controlling key nonmedication variables like adiposity, age, and ethnicity by carefully matching treatment groups for BMI, as well as age and ethnicity.

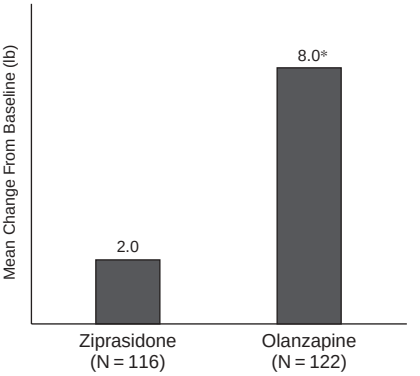
Newcomer et al.[92] measured effects of conventional and atypical antipsychotics on glucose regulation in nondiabetic patients with schizophrenia compared to untreated healthy controls, with all patient and control groups matched for adiposity and age (Figure 7). Based on a modified oral glucose tolerance test, significantly higher fasting and after-load plasma glucose values were found in patients who were taking olanzapine or clozapine compared to those taking conventional antipsychotics or untreated healthy controls. The risperidone-treated group did not differ from the conventional antipsychotic group, but had higher postload glucose levels than the controls. The authors calculated that both olanzapine- and clozapine-treated patients had higher insulin resistance in comparison to those treated with conventional agents, while risperidone- and typical antipsychotic–treated patients did not differ from the controls. Newcomer et al.[26] used homeostasis model assessment to measure insulin resistance in 72 schizophrenia patients chronically treated with olanzapine (N = 28), risperidone (N = 21), or typical antipsychotics (N = 22) in comparison to 61 healthy controls. A significant interaction between subject group (pooled treated patients vs. untreated

**Figure 8. Effect of BMI and Disease/Treatment on HOMA Insulin Resistance[a]**




[a]Data from Newcomer et al.[26] BMI × subject group interaction on HOMA insulin resistance: F = 5.29, df = 1,105; p = .024.
Abbreviations: BMI = body mass index, HOMA = homeostasis model assessment.

**Figure 9. Mean Weight Change for Ziprasidone vs. Olanzapine: 6-Week Acute Study[a]**




[a]Reprinted with permission from Glick et al.[96]
*p < .0001 ziprasidone vs. olanzapine.

controls) and BMI on insulin resistance was observed (Figure 8), with treated schizophrenia patients having higher levels of insulin resistance even at low levels of BMI, compared to healthy controls. A significant interaction between treatment group (olanzapine vs. risperidone vs. typicals vs. controls) and BMI was also seen, with olanzapine-treated patients demonstrating significantly more pronounced increases in insulin resistance with increasing BMI, in comparison to healthy controls. These data suggest that the use of some atypical antipsychotics is associated with adverse effects on glucose metabolism, but for most patients the magnitude of these effects depends largely on changes in weight induced by antipsychotic treatment. Of concern, however, is the apparently smaller number of patients who experience hyperglycemia, new-onset diabetes, or diabetic ketoacidosis in the absence of weight gain.

Comparing 10 subjects treated with clozapine, 9 with olanzapine, and 6 with risperidone, all matched for age, gender, ethnicity, and BMI (kg/m$^2$), Henderson et al.[93] reported higher postload plasma glucose values in clozapine- and olanzapine-treated subjects compared to those taking risperidone. Insulin sensitivity measured by intravenous glucose tolerance testing was significantly reduced in the clozapine- and olanzapine-treated subjects, compared to those treated with risperidone.

Several prospective, randomized studies assessing the effects of atypical antipsychotic drugs on measures of glucose and lipid metabolism are ongoing. Given the well-established differences between antipsychotic medications with respect to weight gain, it is expected that weight gain during prospective assignment to antipsychotic treatment will be consistent with these differences in weight gain liability. Similarly, results to date are consistently showing greater metabolic disturbance associated with atypical antipsychotics that cause greater weight gain. Lindenmayer et al.[94] analyzed plasma glucose and cholesterol levels in 101 schizophrenia patients randomized to 14 weeks of clozapine, olanzapine, risperidone, or haloperidol treatment. Unfortunately, neither weight nor BMI calculations were included in this analysis. Clozapine, olanzapine, and haloperidol were associated with increases in plasma glucose, and clozapine and olanzapine were associated with increases in cholesterol levels. Fourteen of the 101 subjects developed glucose levels diagnostic for type 2 diabetes mellitus (> 125 mg/dL) during the trial. In spite of significant weight gain for the clozapine and olanzapine groups, there was no treatment interaction for the relationship between glucose change and weight gain during the 14-week treatment.[94] However, the relatively short duration of these trials may contribute to the lack of interrelationships in this study.

A post hoc analysis of pooled data from 602 patients randomized to 26 weeks of treatment with placebo, aripiprazole, or olanzapine was performed by L'Italien[95] to calculate the incidence of treatment-emergent metabolic syndrome associated with each treatment group. ATP III guidelines for diagnosis of the metabolic syndrome were modified by substituting a BMI criteria for the ATP III waist circumference criteria. Using a log rank comparison, significant (p = .006) differences were seen among treatment groups, with a nearly 20% incidence of the metabolic syndrome in the olanzapine group, compared to approximately 12% incidence in the placebo group and a 6% incidence in the aripiprazole group. Glick et al.[96] recently reported the results of another such study, using fasting plasma glucose and lipid measures, as well as homeostasis model assessment of insulin resistance to measure changes in insulin resistance in olanzapine- and ziprasidone-treated patients. In a trial of 269 acutely hospitalized schizophrenia patients who were randomized to treatment with olanzapine or ziprasidone, Glick et al.[96] observed significant increases in weight (Figure 9), BMI,

**Table 4. Change in Fasting Triglyceride Levels (Pfizer 054 Study)[a]**

| Triglycerides (mg/dL) | Ziprasidone (N = 34) | Risperidone (N = 28) | Olanzapine (N = 27) | Quetiapine (N = 29) | Thioridazine (N = 31) | Haloperidol (N = 29) |
|---|---|---|---|---|---|---|
| Median baseline | 141.0 | 158.0 | 148.0 | 124.0 | 120.0 | 118.0 |
| Median change | –37.0* | –17.0 | 43.0* | 25.0* | 9.0 | –18.0† |
| Median % change | –28.0* | –6.7 | 31.0* | 18.3* | 7.9 | –18.0† |

[a]From FDA Psychopharmacological Drugs Advisory Committee.[103]
*p < .001, †p < .01.

fasting insulin, fasting lipids, and insulin resistance in patients treated with olanzapine, but not ziprasidone, after 6 weeks of treatment.

### Antipsychotic Drugs and Diabetic Ketoacidosis

Diabetic ketoacidosis is an acute, life-threatening complication most often associated with type 1 diabetes. However, high rates of diabetic ketoacidosis in type 2 diabetes mellitus have been reported in various ethnic groups.[97] Diabetic ketoacidosis may be more common in type 2 diabetes than previously thought, and this complication may not be limited to higher risk groups. In a multiethnic population, Balasubramanyam et al.[98] observed that nearly 40% of cases of diabetic ketoacidosis were associated with type 2 diabetes mellitus and that almost half of the patients with type 2 diabetes mellitus who presented with diabetic ketoacidosis had not been previously diagnosed. In addition, of patients with type 2 diabetes who present with diabetic ketoacidosis, 50% have no identifiable stressor associated with the onset of diabetic ketoacidosis.[98] A variant of diabetes called "Flatbush diabetes" has been described that is characterized by discrete periods of beta cell failure leading to diabetic ketoacidosis, followed by recovery of beta cell function.[99] Mechanisms associated with Flatbush diabetes may be applicable to reported cases of diabetic ketoacidosis in antipsychotic-treated schizophrenia patients in the absence of significant weight gain.

An important feature of diabetic ketoacidosis is acute onset of hyperglycemia associated with loss of pancreatic beta cell function requiring emergent inpatient insulin treatment. Diabetic ketoacidosis can occur in those with normal BMI, but appears to be closely tied with visceral body fat accumulation. Diabetic ketoacidosis is increasingly observed in type 2 diabetes and is of significant concern since the mortality rate is 6% to 10% or higher if not identified and treated early.[100–102] The mortality rate of diabetic ketoacidosis may be even higher in schizophrenia since these patients may not be as likely as the general population to seek medical treatment either as promptly or at all, and these individuals may experience delays in the initiation of care or reductions in the level of care.[7]

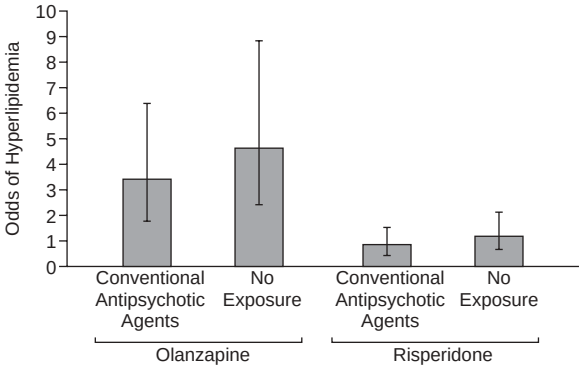
### Antipsychotic Drugs and Dyslipidemia

Some atypical antipsychotic drugs are also associated with changes in fasting serum lipid levels. In Pfizer's Study 054, a randomized trial of patients with schizophrenia assigned to different antipsychotic medications, statistically significant changes in triglyceride levels were observed after approximately 3 weeks.[103] Although the variable of adiposity was not controlled, the degree to which different antipsychotic drugs altered fasting lipid levels appeared to vary from one drug to another. As shown in Table 4, olanzapine treatment (+31%) and quetiapine treatment (+18%) were associated with a significant increase in fasting plasma triglyceride levels compared to baseline, whereas ziprasidone treatment (–28%) and haloperidol treatment (–18%) were associated with a significant decrease in fasting plasma triglyceride levels, with risperidone treatment inducing nonsignificant decrease. This was a very short study so long-term effects of different atypicals on triglyceride levels remains to be evaluated. Nonetheless, the observed acute elevation caused by olanzapine is noteworthy. Similar results were observed in fasting total cholesterol (olanzapine and thioridazine causing significant elevation from baseline and ziprasidone and haloperidol causing significant decline) and LDL cholesterol levels (thioridazine causing significant increase and quetiapine and haloperidol causing decrease).[103]

In a 4-week prospective study by Casey et al.,[104] total cholesterol increased 26 mg/dL with olanzapine and 13 mg/dL with risperidone. Interestingly these increases were significantly mitigated in patients who also received divalproex sodium along with these antipsychotics.[104] In the same prospective randomized 14-week study cited previously comparing clozapine, olanzapine, risperidone, and haloperidol, [94] a significant elevation from normal baseline cholesterol levels was found for the clozapine group (14.7 mg/dL; SD = 30.5) and the olanzapine group (20.1 mg/dL; SD = 26.8). There also was a significant association between cholesterol increase and weight increase for the clozapine group.[94]

In a retrospective study of inpatients at the Oregon State Hospital in Salem,[105] fasting lipid levels were measured before and after 1 year of treatment with olanzapine or risperidone. Significant differences were observed, with olanzapine-treated patients experiencing average increases in triglycerides of 104.8 mg/dL versus 31.7 mg/dL in risperidone-treated patients. Cholesterol levels increased by an average of 30.7 mg/dL during olanzapine treatment versus 7.2 mg/dL during risperidone treatment.[105] In a case control study involving approximately 18,000 subjects who had plasma lipid sampling, Koro et al.[91] observed a nearly 5-fold increase in risk of diagnosis of hyperlipidemia during olanzapine treatment compared to non-antipsychotic treatment, and a greater than 3-fold increased risk of hyperlipidemia compared to typical antipsychotic treatment (Figure 10). Risperidone treatment was not associated with statistically signifi-

**Figure 10. Adjusted Odds of Hyperlipidemia in Patients Exposed to Olanzapine and Risperidone Relative to Different Comparison Groups[a]**




[a]Reprinted with permission from Koro et al.[91]

**Table 5. Criteria for the Diagnosis of Diabetes Mellitus[a]**

1. Symptoms of diabetes plus casual plasma glucose concentration ≥ 200 mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

   or

2. Fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours

   or

3. 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

[a]Reprinted with permission from the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.[14] In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use.

cant increases in hyperlipidemia compared to non-antipsychotic treatment.[91] In data from a 6-week prospective, randomized trial, olanzapine but not ziprasidone was associated with increases in total and LDL cholesterol and triglyceride.[96]

Overall, available data suggest that clozapine, olanzapine, and possibly quetiapine are associated with statistically significant adverse effects on several lipids, including total and LDL cholesterol as well as triglyceride, whereas risperidone, ziprasidone, and aripiprazole are much less likely to be associated with these effects. The potential clinical significance of these lipid changes is substantial as both elevated cholesterol and triglyceride are independent risk factors for cardiovascular disease. Additionally, elevated triglyceride is associated with increased rates of pancreatitis.

## Monitoring Metabolic Side Effects

While precise mechanisms underlying the glucose dysregulation and dyslipidemia during antipsychotic treatment are not yet fully elucidated, available data underscore the need for clinicians to be informed about weight, glucose, and lipid levels in patients taking atypical antipsychotics.

Glucose and insulin metabolism in humans can be assessed by several different methods, which can be listed in an approximate rank order ranging from least to most sensitive: random plasma glucose, glycated hemoglobin (A1C), fasting plasma glucose, homeostasis model assessment insulin resistance, postprandial glucose, oral glucose tolerance test (OGTT) and intravenous glucose tolerance test (IVGTT), frequently sampled IVGTT with Minimal Model analysis, and hyperinsulinemic-euglycemic and hyperglycemic clamps. Random plasma glucose offers limited sensitivity and may be falsely reassuring. In addition, no American Diabetes Association (ADA) or WHO criteria exist to diagnose impairments in glucose metabolism based on random plasma glucose levels in otherwise asymptomatic patients. In contrast, fasting plasma glucose and OGTT have higher sensitivity and do correlate to ADA criteria for diagnosis of diabetes, with established reliability and validity.

Tests used to diagnose diabetes include the casual or random plasma glucose (PG) test, the fasting glucose (FG) test, postprandial glucose following a mixed meal, and the OGTT. Recently revised diagnostic criteria from the ADA provide 3 different ways to diagnose diabetes: (1) symptoms of diabetes and casual PG ≥ 200 mg/dL, (2) FG ≥ 126 mg/dL, or (3) 2-hour PG > 200 mg/dL during OGTT.[14] These criteria are shown in Table 5. A positive result must be confirmed on a subsequent day by any of the 3 methods. For many patients with psychotic disorders, it is very difficult to obtain fasting glucose levels. Thus, it may be more practical to use the finger stick approach in the office or clinic to obtain a postprandial or random glucose level as a screening tool. When checking random or postprandial glucose levels, clinicians should bear in mind that the American College of Endocrinology considers a 2-hour postprandial glucose level of ≥ 140 mg/dL following a mixed meal to be abnormally elevated.[106]

Current ATP III guidelines for monitoring lipids recommend collection of a complete fasting lipoprotein profile, which includes total, LDL, and HDL cholesterol and triglyceride levels. In ATP III guidelines, it is recommended that patients with a 10-year risk of 20% or greater as well as all diabetics should achieve LDL levels of less than 100 mg/dL. Total cholesterol levels less than 200 mg/dL and triglyceride levels less than 150 mg/dL are described as "desirable."[5] These criteria are summarized in Table 6.

**Table 6. Adult Treatment Panel III Classification of LDL, Total, and HDL Cholesterol (mg/dL)[a]**

| | |
|---|---|
| LDL cholesterol | |
| < 100 | Optimal |
| 100–129 | Near or above optimal |
| 130–159 | Borderline high |
| 160–189 | High |
| ≥ 190 | Very high |
| Total cholesterol | |
| < 200 | Desirable |
| 200–239 | Borderline high |
| ≥ 240 | High |
| HDL cholesterol | |
| < 40 | Low |
| ≥ 60 | High |

[a]From the National Cholesterol Education Program.[5]
Abbreviations: LDL = low-density lipoprotein, HDL = high-density lipoprotein.

**Table 7. Treatment Recommendations**

(1) Identification of High-Risk Patients
*Obtain a risk profile for each patient:*
Medical factors (obesity, dyslipidemia, hypertension, hyperglycemia, diabetes)
Behavioral/life style factors (poor diet, smoking, physical inactivity, high stress)
Genetic factors (ethnicity, family history or metabolic or cardiovascular illnesses)

(2) Treatment Selection
*Select an antipsychotic medication based on the patient risk profile:*
Discuss risk factors and side effects with the patient and family
For a high-risk patient, choose an agent with fewer metabolic side effects

(3) Baseline Assessment and Monitoring
*Obtain baseline values and monitor them regularly:*
Blood pressure, weight, body mass index (BMI), waist circumference
Serum lipids, fasting plasma glucose

(4) Management
*When treatment-emergent metabolic abnormalities are observed:*
Change medication regimen or switch to another agent
Initiate behavioral and/or medical intervention
Refer to a specialist for further evaluation

## Treatment Recommendations for Psychiatrists

Patients with schizophrenia suffer elevated rates of diabetes, cardiovascular morbidity, and mortality due to multiple risk factors including obesity and unhealthy lifestyle habits. Further, treatment with certain atypical antipsychotic medications can worsen these already elevated independent risk factors for cardiovascular disease. Clinicians should make every effort to prevent and lower all these risks when treating schizophrenia patients. Of all the independent risk factors for heart disease, those associated with weight gain (hyperlipidemia, hyperglycemia, hypertension) may be the easiest to modify since the clinician has the ability to modify these risk factors for the patient by prescribing medications that are less likely to be associated with weight gain.

The metabolic syndrome is a recognized constellation of weight, glucose, and lipid abnormalities that causes significant morbidity and mortality often due to diabetes and cardiovascular disease. While increases in obesity and type 2 diabetes have become significant health concerns for the population in general, they are of even greater concern for patients suffering from schizophrenia. The underlying mechanisms that mediate the development of type 2 diabetes are complex, but weight gain along with increased visceral abdominal adiposity appears to be at the core of the metabolic impairment. Insulin resistance may be the result of chronic exposure of the liver to fatty acids derived from visceral adiposity. There is also a less understood risk of sudden onset diabetic ketoacidosis, a potentially fatal disorder that can occur in the setting of either type 1 or type 2 diabetes.

While most antipsychotic drugs cause weight gain, not all atypical antipsychotic medications are associated with the same degree of weight gain liability. In general, aripiprazole, quetiapine, risperidone, and ziprasidone appear to be associated with clinically significantly less weight gain in comparison to clozapine and olanzapine. While clinically significant differences in weight gain have been demonstrated among atypical antipsychotic medications, no significant differences in efficacy have been consistently demonstrated, with the exception of clozapine use in less commonly encountered treatment-refractory patients.[107] Considering the chronic nature of schizophrenia, it is critical that clinicians minimize antipsychotic-associated increases in risk factors for cardiovascular disease in patients suffering from schizophrenia. Below, and summarized in Table 7, are some principles for addressing this growing problem in the clinical setting.

### Identification of High Risk Patients

Identifying the patients who currently have or are at high risk for cardiovascular disease and related metabolic disorders is the initial goal for clinicians. It is important to stress that patients with persisting mental illness carry a high overall risk of common medical diseases. Initial risk assessment should include comorbid medical conditions (e.g., obesity, dyslipidemia, hypertension, hyperglycemia/diabetes), behavioral/lifestyle factors (e.g., diet, smoking, exercise habits, psychosocial stressors), and genetic predisposition (e.g., ethnicity, family history). Identifying individuals with increased risk of developing these disorders should prompt the clinician to be more vigilant for changes in weight, glucose, and lipids. Moreover, clinicians should provide patient education, promote healthier life style (e.g., smoking cessation, appropriate diet, increased levels of activity), and implement medical/behavioral interventions if necessary.

### Treatment Selection (Customizing Treatment)

On the basis of the profiles obtained through the process mentioned above, clinicians should carefully select an antipsychotic medication regimen. It is very important to inform and discuss risk factors and side effects with the patients and their families for early detection of symptoms that may be asso-

ciated with the medication-induced adverse effects. Clinicians should weigh the benefits and risks of antipsychotic agents for each individual patient in order to minimize unwanted and potentially serious complications. In patients already at high risk for cardiovascular morbidity and mortality (e.g., patients with diabetes or the metabolic syndrome), medications associated with greater severity of metabolic side effects should be considered only as a last resort treatment. Selection of an atypical antipsychotic medication with fewer metabolic side effects (aripiprazole, risperidone, and ziprasidone) will avoid adding further risk to the already high-risk patient. At the same time, selecting antipsychotic medications with fewer metabolic side effects will help patients without risk factors for heart disease maintain their low-risk status.

**Baseline Assessment and Monitoring**

Obtaining baseline values of the relevant physical and laboratory parameters including blood pressure, weight, height, BMI, waist circumference, serum lipids (total, LDL, and HDL cholesterol along with triglycerides), and a fasting, postprandial or postload plasma glucose level is critical prior to initiating antipsychotic medications. During the initiation of antipsychotic treatment, patients should have these values monitored regularly, although frequency must be dictated by the individual patient's level of risk. For example, an obese schizophrenia patient with a family history of diabetes who has gained 30 pounds on his current antipsychotic demands more intensive monitoring than a slender patient with no family history of diabetes who is not gaining weight during antipsychotic treatment. However, it should not be assumed that patients who do not gain weight have not had adverse changes in their lipid or glucose parameters. In general, assessments should be made more frequently during the initial phase of treatment. Nevertheless, all schizophrenia patients treated with antipsychotic medication should have at least a yearly assessment of fasting lipids and glucose. Similarly, vital signs, weight, and waist circumference should be measured at every visit since these are simple measures to monitor that have a high yield of alerting clinicians to adverse metabolic side effects.

**Management**

When treatment-emergent weight gain, hyperlipidemia, hyperglycemia, and/or diabetes are observed, switching to another agent should be considered. Concerted efforts should be made to discontinue the potential offending agent, prior to the institution of additional therapy for a metabolic side effect. However, a clear response to a particular medicine, combined with a patient's preference for this medicine, suggests that the benefit-to-risk ratio must be periodically reassessed. These patients should also be referred to a specialist for further medical consultation and potential collaboration to comanage the psychiatric and medical problems. Finally, clinicians need to be aware of the signs and symptoms of acute metabolic deterioration (e.g., diabetic ketoacidosis, hyperosmolar coma). Confusion, psychomotor retardation, abdominal pain, nausea, polyuria, and polydipsia can be indicative of life-threatening complications, and these symptoms should prompt emergent evaluation and treatment.

## Conclusions

Among patients with schizophrenia, substantial evidence exists that metabolic risk factors for as well as risks of cardiovascular disease are far higher than in the general population. Accumulating evidence also suggests that certain atypical antipsychotic treatments are associated with metabolic disturbances that can further increase risks for developing metabolic/cardiovascular illnesses in patients with schizophrenia. Although precise mechanisms of antipsychotic agent–induced metabolic disturbances are not yet fully elucidated, insulin resistance and weight gain as well as their interrelationships appear to play crucial roles. Clinicians who are treating schizophrenia patients should make every effort to minimize risks of developing serious and long-term complications through careful monitoring, patient education, appropriate use of medical specialists, and careful selection of antipsychotic treatment.

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*Drug names:* aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), divalproex sodium (Depakote), fluphenazine (Prolixin and others), haloperidol (Haldol and others), lovastatin (Mevacor and others), mesoridazine (Serentil), molindone (Moban), olanzapine (Zyprexa), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).