Weight Gain With Atypical Antipsychotics: Evidence and Insights

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Weight gain associated with antipsychotic medication can be a barrier to the overall improvement of mental health patients due to a discontinuation of treatment. The goal of this article is to establish a better understanding regarding the mechanisms of antipsychotic medications and their associated risk of weight gain, obesity, and subsequent mortality and morbidity. Additionally, the need to closely monitor patients' lifestyles and homeostatic components in order to prevent weight gain or facilitate weight loss is emphasized. *(J Clin Psychiatry 2007;68[suppl 12]:18–26)*

The cause of antipsychotic-induced weight gain is the subject of extensive research. Some researchers have suggested that antipsychotic-induced weight gain occurs largely due to an increase in appetite. Weight gain and obesity occur when there is an imbalance over time between energy (food) intake and energy expenditure (mainly resting metabolism and physical activity). Homeostatic mechanisms keep the difference between energy intake and energy expenditure close to zero. However, small imbalances over long periods of time can have a large cumulative effect on body mass index (BMI).

To illustrate this, consider that most U.S. adults consume approximately 900,000 kcal of food each year or approximately 2500 kcal/day. If energy intake exceeds energy expenditure by as little as 0.5% (12 kcal/day), then 0.6 kg (1.3 lb) of fat is gained over the course of 1 year (Figure 1). By the same calculation, a daily 5% excess intake (125 kcal/day or a small candy bar) could result in the accumulation of approximately 6 kg (13 lb) of adipose tissue in 1 year.[1]

An anonymous survey of treatment and health issues was mailed to local chapters of the National Alliance for the Mentally Ill and the National Mental Health Association, who then distributed them to people with schizophrenia.[2] Noncompliance was defined as a self-report of missing any antipsychotic medication in the previous month. The primary independent variables were (1) BMI (weight [kg]/height [m^2]) categorized as normal (< 25, N = 73), overweight (25–30, N = 104), or obese (> 30, N = 100) and (2) subjective distress over weight gain. Other independent variables included demographics, medication attitudes, and treatment satisfaction. The results showed that BMI status and subjective distress from weight gain were predictors of noncompliance. In addition, obese persons were more than twice as likely as those with a normal BMI to report missing their medication. A comprehensive model suggested that the foremost mediator of noncompliance was patient distress over weight gain. There is a significant, positive association between obesity and subjective distress from weight gain and medication noncompliance, even when accounting for other possible confounding factors.[2]

The treatment outcome of a group of 175 patients with bipolar I disorder who were being treated for an acute affective episode and subsequently followed through a period of maintenance treatment was measured.[3] Not surprisingly, obesity was closely correlated with a poorer overall outcome in patients with bipolar I disorder (Figure 2). Preventing and treating obesity in bipolar disorder patients could greatly improve outcomes. Weight-control interventions tailored to patients with bipolar illness should be developed and tested. Further, these interventions should then be integrated into the routine care provided for these patients.[3]

In an effort to place the weight gain–inducing effects of antipsychotic drugs into context, a study was done to estimate and compare the distributions of BMI in individuals with and without schizophrenia.[4] Data sources included the mental health supplement of the 1989 National Health Interview Survey (N = 80,130 nonschizophrenic and 150

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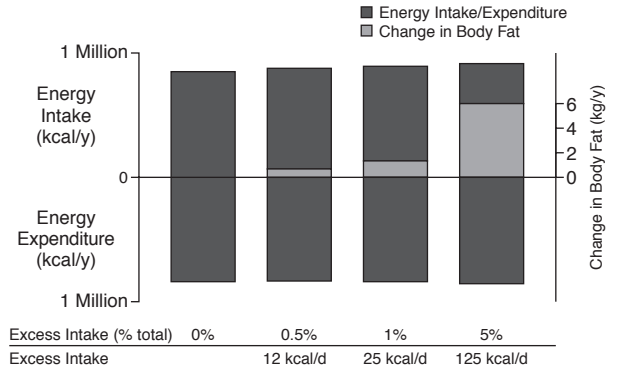
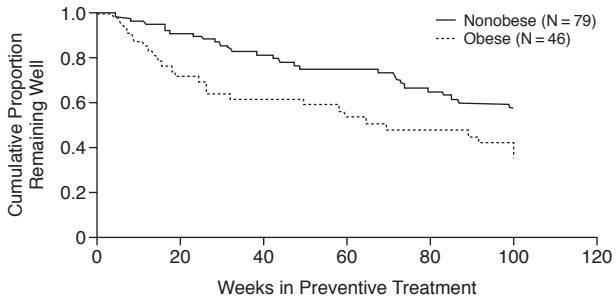
Figure 1. Cumulative Effect of Small Daily Errors in Energy Balance[a]



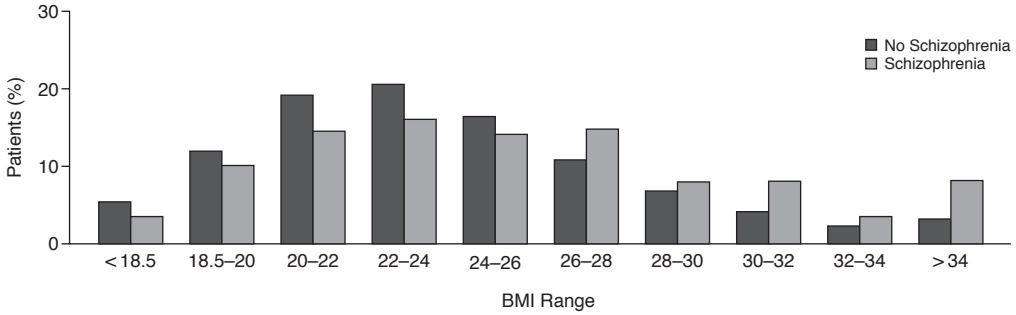
[a]Data from Rosenbaum et al.[1]

Figure 2. Impact of Obesity on Recurrence in Bipolar Disorder[a]



[a]Reprinted with permission from Fagiolini et al.[3] Obese patients had shorter time to recurrence of depression than nonobese patients. Log-rank $\chi^2 = 5.54$; df = 1; $p < .02$.

Figure 3. Body Mass Index (BMI) Distributions for the General Population and Those With Schizophrenia[a]



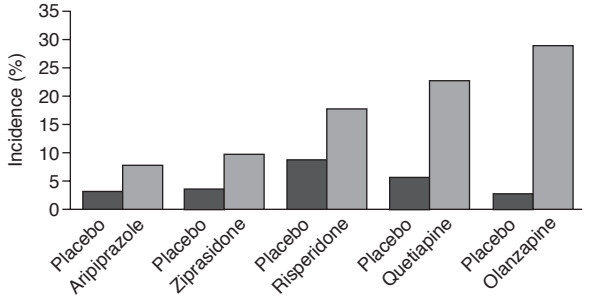
[a]Data from Allison et al.[4] Underweight = BMI < 18.5, acceptable weight = BMI 18.5 to < 25, overweight = BMI 25 to < 30, obese = BMI ≥ 30.

self-reported schizophrenic individuals), baseline BMI data from a drug trial of the antipsychotic ziprasidone supplied by Pfizer Inc (420 noninstitutionalized individuals with chronic psychotic disorders [DSM-IV schizophrenia or schizoaffective disorder]), and, finally, data from the National Health and Nutrition Examination Survey III (NHANES III; N = 17,689 nonschizophrenic individuals) to act as a control group for the ziprasidone trial data. Results of the study showed that although there may be a small percentage of schizophrenic individuals who are underweight, individuals with schizophrenia were overall as obese as or more obese than persons without schizophrenia (Figure 3). These data suggest that weight gain induced by antipsychotic agents is an important issue for many patients that could lead to nonadherence and consequent relapse in some individuals.[4]

Weight gain was first reported as an effect of conventional antipsychotic drugs (e.g., chlorpromazine) and subsequently observed for all antipsychotic agents to a variable degree. The causal effect of drugs (e.g., clozapine) on weight regulation is strongly supported by large-scale pivotal clinical trials using placebo-controlled randomized treatment. In one study,[5] the average weight gain during 6 months of clozapine treatment was 16.9 lb. In the same study, 75% of the patients gained at least 10 lb. These results have been confirmed in numerous follow-up studies.[6,7] Some antipsychotic agents can induce significant weight gain (e.g., low-potency phenothiazines, clozapine, and olanzapine).[8] A reasonable balance between energy intake and energy expenditure is necessary in patients on treatment with antipsychotic medications.

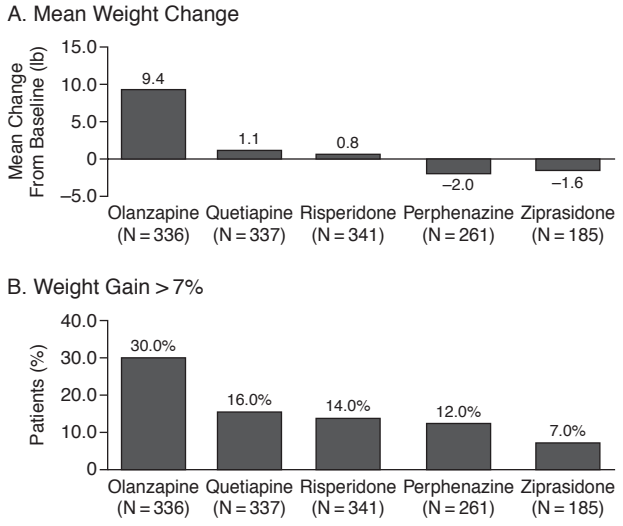
The U.S. Food and Drug Administration defines clinically significant weight gain as an increase in body weight greater than or equal to 7% above baseline during a clinical trial. Figure 4 shows clinically significant weight gain in short-term clinical trial data for individual atypical antipsychotic agents. These data are based on the U.S. package insert for each drug. It is important that each agent be compared with a placebo control rather than against another drug, as failure to do so may compromise meaningful results. Aripiprazole and ziprasidone produced twice the placebo rate of weight gain. Risperidone, with somewhat higher absolute numbers, also produced twice the placebo rate of weight gain. Quetiapine produced 3 to 4

Figure 4. Clinically Significant (≥ 7%) Weight Gain During Antipsychotic Treatment[a]



[a]Data from the package inserts for the drugs listed.[9–13]

Figure 5. Weight Change and Weight Gain > 7% in the Clinical Antipsychotic Trials of Intervention Effectiveness Schizophrenia Study[a]

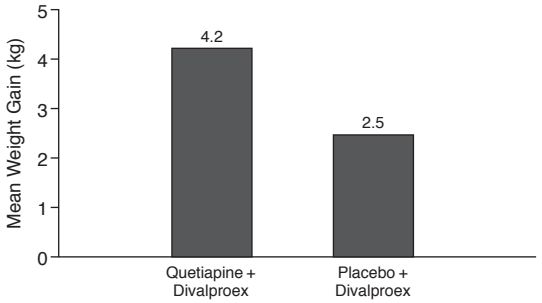


[a]Data from Lieberman et al.[15]

times and olanzapine approximately 10 times the placebo rate of weight gain (see Figure 4).

Antipsychotic therapy is associated with a differential risk of weight gain, depending on the individual agent. A meta-analysis of standardized 10-week exposure to different antipsychotic agents compared mean weight change in kilograms and pounds.[14] Both the older high-potency antipsychotics as well as some of the newer agents were associated with relatively minimal weight gain. Haloperidol, fluphenazine, ziprasidone, and aripiprazole induced a minimal weight change (under 1 kg) during this short-term exposure. Agents such as risperidone and quetiapine showed intermediate increases in weight (2–3 kg), while some of the older antipsychotics, including low-potency phenothiazines such as chlorpromazine, and some of the newer agents, such as olanzapine and clozapine, were

Figure 6. Weight Gain With Quetiapine and Divalproex Combination Treatment[a]



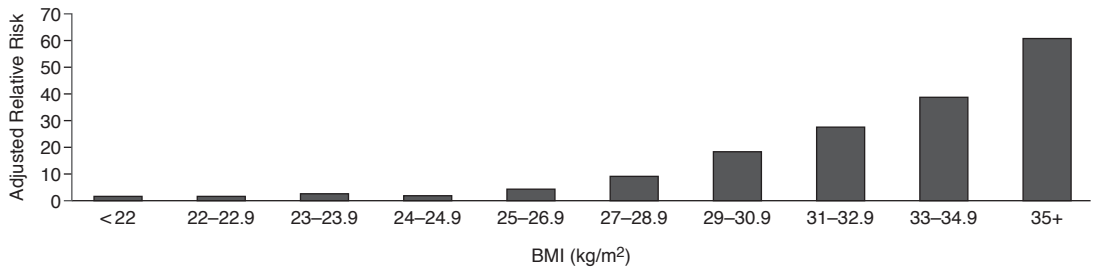
[a]Data from DelBello et al.[16] Six-week, double-blind, randomized comparison of quetiapine plus divalproex versus divalproex alone in 30 adolescents with bipolar mania.

associated with larger increases in weight (up to and exceeding 4 kg, or approximately 9 lb) during short-term periods.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) also show significant problems with weight gain and antipsychotic medications. In the CATIE study, 74% of patients discontinued the study medication before 18 months.[15] Discontinuation results were as follows: 64% of those assigned to olanzapine, 75% of those assigned to perphenazine, 82% of those assigned to quetiapine, 74% of those assigned to risperidone, and 79% of those assigned to ziprasidone. The time to the discontinuation of treatment for any cause was significantly longer in the olanzapine group than in the quetiapine ($p < .001$) or risperidone ($p = .002$) group, but not in the perphenazine ($p = .021$) or ziprasidone ($p = .028$) group. The times to discontinuation because of intolerable side effects were similar among the groups, but the rates differed ($p = .04$). Olanzapine was associated with greater weight gain than other treatments (Figure 5) and with more discontinuation for weight gain or metabolic effects, and perphenazine was associated with more discontinuation for extrapyramidal effects.[15]

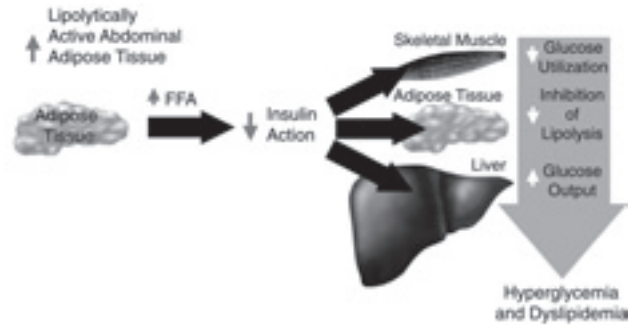
It is obvious that weight gain is one of the major side effects of most antimanic monotherapies. In 2 studies examining the efficacy and tolerability of combination therapy (quetiapine and divalproex in one study[16] and a mood stabilizer [lithium or divalproex] and placebo, risperidone, or haloperidol in another[17]), weight gain was again associated with these drug regimens. Although the combination of quetiapine and divalproex resulted in a larger weight gain than divalproex alone, the addition of quetiapine did not significantly increase the amount of weight gained (Figure 6).[16] Nevertheless, studies examining the weight gain changes associated with combination therapy are necessary, as minimizing the weight gain associated with most antipsychotic treatments might increase

Figure 7. Body Mass Index (BMI) and Relative Risk of Type 2 Diabetes[a]



[a]Data from Colditz et al.[18] In women aged 35–55 years in 1976; data adjusted for age.

Figure 8. Obesity and Insulin Resistance[a]



[a]Based on Caballero et al.,[19] Steinberg et al.,[20] and Reaven.[21]
Abbreviation: FFA = free fatty acid.

medication compliance in patients and decrease the long-term risks associated with significant weight gain, such as hyperglycemia, metabolic syndrome, and type 2 diabetes.[16,17]

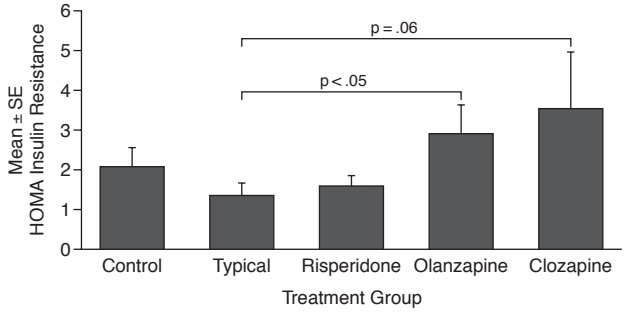
As previously discussed, BMI relates to an individual's proportion of height and weight, or more precisely, weight/height^2. In one study, BMI was examined in regard to the risk of clinical non–insulin-dependent diabetes.[18] The study analyzed data from a cohort of 113,861 U.S. women aged 30 to 55 years in 1976. During 8 years of follow-up, 873 definite cases were identified among women initially free from diagnosed diabetes. In women with an average BMI of 23 to 23.9 kg/m^2, the relative risk was 3.6 times that of women with a BMI of less than 22 kg/m^2 (Figure 7). The risk continued to increase above this level of BMI. There was a much weaker positive association with weight at age 18, and this association was eliminated after adjustment for current BMI, making weight gain after age 18 a major determinant of risk. For an increase of 20 to 35 kg, the relative risk was 11.3, and for an increase of more than 35 kg, the relative risk was 17.3. Although adjustments were made for family history, this did not appreciably alter the strong relation observed among women at average levels of BMI. These data indicate that, even at average weight, women are at increased risk of clinical non–insulin-dependent diabetes and that the relation between BMI and risk of diabetes is continuous.[18] Clearly then, the risk of diabetes in relation to a patient's BMI should be taken seriously by the clinician.

OBESITY, INSULIN RESISTANCE, AND ENDOTHELIAL DYSFUNCTION

Mechanisms through which obesity, insulin resistance, and endothelial dysfunction are closely associated exist in the human body. Obesity leads to insulin resistance and endothelial dysfunction. Insulin resistance leads to endothelial dysfunction and may also contribute to obesity itself. Insulin resistance is frequently associated with other abnormalities that can affect endothelial function, such as hyperglycemia, hypertension, dyslipidemia, and altered coagulation/fibrinolysis. Further, it has been shown that endothelial dysfunction may also favor insulin resistance.[19] Therefore, insulin itself, in addition to its metabolic actions, directly affects vascular endothelium and smooth muscle. All of these findings have added a new dimension to the association of obesity, insulin resistance, and endothelial dysfunction that may become a key target in the prevention of type 2 diabetes and cardiovascular disease.[20] Abdominal adipose tissue, in particular, leads to insulin resistance and endothelial dysfunction through fat-derived metabolic products, hormones, and cytokines (Figure 8).[19]

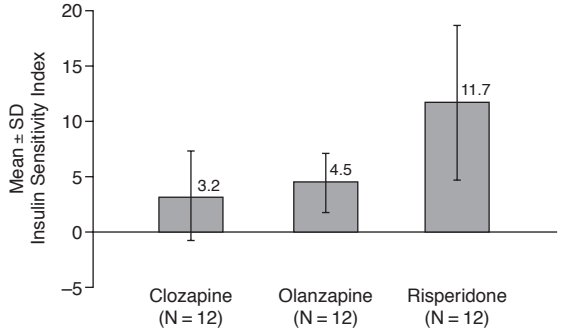
Glucoregulatory abnormalities have been linked with the use of antipsychotic drugs themselves, independent of the possible gains in adipose tissue. In one study,[22] 48 patients matching in age and adiposity were treated with clozapine, olanzapine, risperidone, typical antipsychotics, or no treatment and were given modified oral glucose tolerance tests. Olanzapine-treated patients showed marked glucose elevations at all timepoints (fasting and 15-, 45-, and 75-minute intervals) compared with subjects treated with typical antipsychotics. Clozapine and risperidone also showed glucose elevations, although risperidone to a lesser extent. Healthy, untreated subjects and subjects given typical antipsychotics showed no significant differ-

Figure 9. HOMA Insulin Resistance in Treated Patients With Schizophrenia[a]



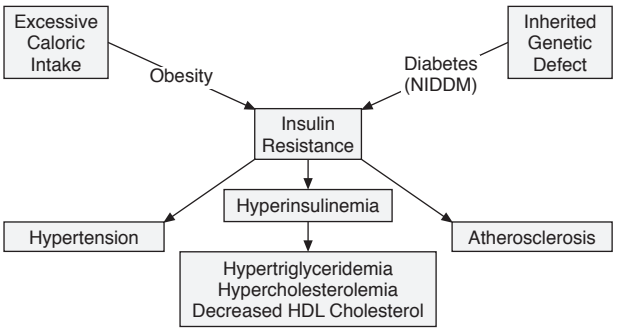
[a]Reprinted with permission from Newcomer et al.[22]
Abbreviation: HOMA = homeostasis model assessment.

Figure 10. Insulin Sensitivity Index in Antipsychotic-Treated Patients With Schizophrenia[a]



[a]Data from Henderson et al.[23]

Figure 11. Insulin Resistance Syndrome[a]



[a]Based on Despres et al.[24]
Abbreviations: HDL = high-density lipoprotein, NIDDM = non–insulin-dependent diabetes mellitus.

ences in glucose elevations (Figure 9). This study may indicate that treatment of nondiabetic patients with newer antipsychotic drugs may have adverse effects on glucose regulation, independent of weight, and consequently could put patients in jeopardy of long-term cardiovascular risk.[22]

Two commonly used antipsychotics are olanzapine and clozapine. A study was conducted in an effort to discern whether atypical agents are directly affecting glucose metabolism or simply increasing known risk factors for diabetes.[23] Thirty-six nonobese subjects with schizophrenia or schizoaffective disorder, matched by BMI and treated with clozapine, olanzapine, or risperidone, were included in this analysis. The main outcome measures included fasting plasma glucose and fasting serum insulin levels, insulin sensitivity index, homeostasis model assessment of insulin resistance, and glucose effectiveness. There was a significant difference in insulin sensitivity index among the groups, with the clozapine and olanzapine groups exhibiting significant insulin resistance compared with subjects who were treated with risperidone. The homeostasis model assessment of insulin resistance differed significantly among the groups as well, with clozapine and olanzapine performing worst and risperidone showing the best homeostasis. Glucose effectiveness was also poor in both the clozapine and olanzapine groups, while subjects in the risperidone group fared far better, especially when compared to the atypical drug groups. This study indicates that patients taking the atypical antipsychotics clozapine and olanzapine must be examined for insulin resistance and its sizable health consequences (Figure 10).[23]

EPIDEMIOLOGY

Of increasing interest in regard to this discussion are the epidemiologic and metabolic studies conducted over the past 15 years. These studies have noted that complications frequently found in obese patients appear to be associated with the location of excess fat rather than to excess weight per se; specifically, abdominally distributed obesity. Patients with abdominal obesity, excess visceral adipose tissue, or metabolic syndrome are at high risk for coronary artery disease, type 2 diabetes, and related mortality. In addition, individuals who are obese and have a high concentration of visceral adipose tissue tend to have dyslipidemia in the form of elevated levels of triglycerides and decreased levels of high-density lipoprotein cholesterol (HDL-C). This places them at higher risk for cardiovascular disease. Because obesity is a major factor in metabolic syndrome, the relevance of managing obesity to treat metabolic syndrome in order to prevent or ameliorate chronic diseases such as cardiovascular disease and type 2 diabetes is undeniable (Figure 11). A simple and practical screening tool such as a measurement of the waist circumference with a tape measure can be used to assess risk by monitoring the accumulation or loss of visceral fat in between office visits. The waist should be measured at the iliac crest, while the patient gently exhales.[24]

Table 1. The Metabolic Syndrome[a]

Risk Factor	Defining Level
Abdominal obesity (waist)	
Men	> 102 cm (> 40 in)
Women	> 88 cm (> 35 in)
Triglycerides	≥ 150 mg/dL
High-density lipoprotein cholesterol	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	≥ 130/≥ 85 mm Hg
Fasting glucose	≥ 100 mg/dL

[a]Reprinted with permission from the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.[25] Diagnosis is established when ≥ 3 of these risk factors are present.

The Adult Treatment Panel III defines the metabolic syndrome as a high-risk constellation of lipid and nonlipid risk factors to be targeted for intensified therapy.[25] These risk factors are closely linked with insulin resistance, in which the normal actions of insulin are impaired. The risk factors of the metabolic syndrome are highly concordant, and in aggregate, they enhance risk for coronary heart disease at any given low-density lipoprotein level. Risk factors include abdominal obesity, high triglycerides, low HDL-C, hypertension, and elevated blood glucose. The diagnosis of metabolic syndrome can be made when 3 or more of the risk factors are present (Table 1). Management of the metabolic syndrome has 2 objectives: to reduce underlying causes, including obesity and physical inactivity, and to treat the associated lipid and nonlipid risk factors.[25]

Using baseline data from CATIE, assessment of the prevalence of the metabolic syndrome was performed using National Cholesterol Education Program criteria, and also a fasting glucose threshold of 100 mg/dL (American Heart Association).[26] Subjects with sufficient anthropometric data; data on use of antihypertensives, hypoglycemic medications, or insulin; and fasting glucose and lipid values > 8 hours from last meal were included in the analysis. Comparative analyses were performed using a randomly selected sample from NHANES III matched 1:1 on the basis of age, gender, race, and ethnicity. Subjects in CATIE had extremely high rates of the metabolic syndrome as well as of the concomitant risk factors. These data represent an enormous source of cardiovascular risk, especially for women (Table 2). Clinicians must monitor schizophrenic patients for this syndrome and attempt to minimize metabolic risks associated with antipsychotic treatment.[26]

There are several potential mechanisms of weight gain. Some of these mechanisms include antihistaminic considerations, sedation, decreased physical activity, serotonin antagonism (5-HT_{2C} genetic variability), increased appetite (including loss of control of satiety), and a possible role of the hypothalamus. It is crucial to understand the mechanisms involved in weight gain if it is to be effectively addressed. There are multiple clinical issues regarding weight gain and the use of second-generation antipsychotics (SGAs). First, not everyone gains weight. To add to the confusion is the fact that weight gain is thought to be associated with clinical response in some studies, but not in others. Second, it is very difficult to predict which patients will be prone to weight gain. In addition, weight gain is not associated with dose. Finally, weight gain begins early in treatment and may plateau at 3 months to a year, depending on the study consulted. Once weight is gained, it is very difficult for patients to lose and has negative implications regarding health, self-esteem, and compliance. This broad array of issues serves to complicate the treatment of patients taking SGAs.

Weight gain interventions should be used to ameliorate the health risks associated with weight increases. The best results to date have been seen with switching of medications.[27–29] Patient education should be instituted from the onset of treatment and should include diet and nutrition programs as well as exercise programs (e.g., walking). Pharmacologic agents may be of use; however, whether these drugs should be prescribed as a preventive measure or following weight gain is unclear. Current drugs that may assist in weight loss include sibutramine, orlistat, antihistaminic agents (e.g., nizatidine), amantadine, topiramate, bupropion, and metformin.

INTERVENTION DATA AND STUDIES

A systematic search was conducted of major databases in addition to citation searches to assess the efficacy of multiple weight loss/weight control medications in 8 pharmacologic intervention studies.[30] Five of the 8 studies showed small reductions in weight (< 5% baseline body weight). Behavioral interventions, including diet and/or exercise, also reported small reductions in, or maintenance of, weight. Authors of this study could not recommend the widespread use of pharmacologic interventions given the inconsistent results, and they concluded that both dietary and exercise counseling within a behavior modification program was necessary for sustained weight control. However, a study[31] on the use of metformin as a weight management medication in children and adolescents taking atypical antipsychotics rendered different conclusions when these patients were compared to subjects taking placebo. Metformin was seen as safe and effective and, further, decreased insulin sensitivity and abnormal glucose metabolism in these patients.

When considering pharmacologic interventions regarding weight gain with the use of antipsychotics, it is necessary to find a good balance between the clinical imperatives of management of the psychiatric condition and management of obesity and comorbid conditions. The management of weight gain involves a multidisciplinary approach to treatment through not only behavior and lifestyle changes, but also pharmacologic interventions, which

Table 2. Comparison of Metabolic Syndrome and Individual Criterion Prevalence in Fasting CATIE Subjects and Matched NHANES III Subjects[a]

	Males (%)			Females (%)		
Variable	CATIE (N = 509)	NHANES (N = 509)	p	CATIE (N = 180)	NHANES (N = 180)	p
Metabolic syndrome prevalence	36.0	19.7	.0001	51.6	25.1	.0001
Waist circumference criterion	35.5	24.8	.0001	76.3	57.0	.0001
Triglyceride criterion	50.7	32.1	.0001	42.3	19.6	.0001
High-density lipoprotein criterion	48.9	31.9	.0001	63.3	36.3	.0001
Blood pressure criterion	47.2	31.1	.0001	46.9	26.8	.0001
Glucose criterion	14.1	14.2	.9635	21.7	11.2	.0075

[a]Reprinted with permission from McEvoy et al.[26]
Abbreviations: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness, NHANES = National Health and Nutrition Examination Survey.

Table 3. Medications Indicated for Treating Obesity[a]

Drug/Mechanism	Indication/Dosage	Evidence of Efficacy, Safety	Comment
Sibutramine (sympathomimetic; serotonergic, noradrenergic reuptake inhibitor)	Obesity (5–20 mg/d)	↓10% to 15% of body weight in 1 y; safety, efficacy beyond 1 y undetermined	↓Triglycerides, total cholesterol, LDL cholesterol ↑HDL cholesterol. Monitor for serotonin syndrome when used with serotonergic psychotropics
Orlistat (inhibits gastric and pancreatic lipases by binding to these enzymes in the gut)	Obesity (120 mg tid with meals; take other drugs 1 h pre- or post-orlistat)	↓9% to 10% of body weight in 1 y; safety, efficacy beyond 2 y undetermined	↓Triglycerides, total cholesterol, LDL cholesterol ↑HDL cholesterol. Lower risk of drug interactions than with sibutramine; GI side effects; multivitamin required
Rimonabant (investigational, pending FDA approval; selective type 1 cannabinoid receptor blocker)	Obesity (20 mg/d) (pending approval)	Reduced weight, improved heart disease risk factors in obese patients with metabolic syndrome or > 1 cardiovascular risk factors (1–2 y)	Generally well-tolerated; mild nausea most common side effect

[a]Reprinted with permission from Schwartz et al.[32] Many studies in this table were conducted in patients taking second-generation antipsychotics for schizophrenia or bipolar disorder. Results may not apply to antidepressant-induced weight gain.
Abbreviations: FDA = U.S. Food and Drug Administration, GI = gastrointestinal, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

may provide a benefit not available through lifestyle changes alone.

A variety of options are available for use as part of a balanced attempt to control weight gain with antipsychotic drug use, ranging from medications indicated specifically for use in treating obesity, such as sibutramine (indicated in Table 3), to medications used off-label for treatment, including metformin. In clinical trials, it was demonstrated that metformin may safely assist olanzapine-treated patients in body weight and carbohydrate metabolism control (Table 4).[32,33]

To date, there have been at least 11 trials focused on a range of pharmacologic adjuncts for attenuating weight gain, including amantadine, *d*-fenfluramine, dextroamphetamine sulfate, fluoxetine, nizatidine, phenylpropanolamine, sibutramine, and topiramate.[33]

In a study[34] measuring the effectiveness of sibutramine, an approved weight loss agent, in 37 overweight and obese subjects taking olanzapine for schizophrenia or schizoaffective disorder, results were also encouraging. At week 12, the sibutramine group had significantly greater losses than the placebo group in weight (mean = 8.3 lb, SD = 2.4 vs. mean = 1.8 lb, SD = 1.6), waist circumference, and BMI, as well as hemoglobin A1c (Figure 12). There were no significant differences regarding most side effects, although the sibutramine group exhibited a mean increase in systolic blood pressure, and anticholinergic side effects and sleep disturbances were at least twice as common in the sibutramine group. As an adjunct to behavior modification, sibutramine was effective and well tolerated.

CONSENSUS STATEMENT

Recently, a consensus statement issued by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity concluded that despite shortcomings in many of the studies examining the relationship between atypical antipsychotics and obesity or diabetes, there is varying propensity for weight gain among the atypical agents as well as risk for diabetes and dyslipidemia.[35]

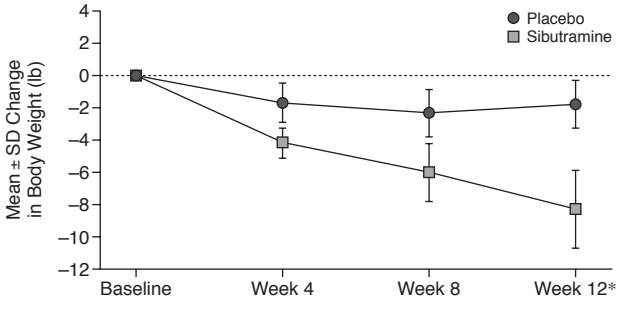
Clozapine and olanzapine have a fairly high potential for causing weight gain and have the highest risk potential for diabetes and dyslipidemia. To a lesser extent, risperidone and quetiapine have some potential to cause weight

Table 4. Medications Used "Off-Label" for Treating Obesity[a]

Drug/Mechanism	Indication/Dosage	Evidence of Efficacy, Safety	Comment
Amantadine (antiviral agent; may potentiate dopaminergic function)	Influenza A prophylaxis and Parkinson's disease (300 mg/d, with olanzapine)	↓3.5 kg over 3 to 6 mo (study of 12 patients)	Patients had gained a mean 7.3 kg during olanzapine treatment
Nizatidine (histamine-2 receptor antagonist)	Duodenal ulcer; GERD (600 mg/d as prophylaxis with olanzapine)	↓2.5 kg with nizatidine; ↑5.5 kg with placebo (16-week RCT)	Unknown effectiveness when used as prophylaxis with antidepressants; can cause delirium, especially in older patients
Naltrexone (opioid antagonist; decreases craving for sweet, fatty foods caused by TCAs and lithium)	Alcohol, narcotics addiction (50 mg/d)	TCA-induced weight gain reversed, then resumed after drug was stopped (8-patient trial)	Small mean weight loss compared with previous drug-induced weight gain; no adverse effects seen on depressive symptoms
Topiramate (anticonvulsant)	Epilepsy, migraine (100–400 mg/d as adjunct to antipsychotics)	↓10 to 15 lb in 33% to 55% of bipolar disorder patients	May serve dual purpose in treating obese patients with affective disorders; fatigue, cognitive dulling, ataxia, glaucoma, oligohydrosis, acidosis are possible
Metformin (biguanide antihyperglycemic)	Type 2 diabetes (500 mg tid as adjunct to antipsychotics)	15 of 19 patients who gained 10% in body weight taking SGAs lost weight with add-on metformin (12-week, open-label trial)	Sporadic diarrhea in some patients; risk of lactic acidosis (tests unremarkable in this small trial)

[a]Reprinted with permission from Schwartz et al.[32] Many studies in this table were conducted in patients taking second-generation antipsychotics for schizophrenia or bipolar disorder. Results may not apply to antidepressant-induced weight gain.
Abbreviations: GERD = gastroesophageal reflux disease, RCT = randomized, double-blind, placebo-controlled trial, SGAs = second-generation antipsychotics, TCAs = tricyclic antidepressants.

Figure 12. Change in Body Weight From Baseline in 37 Obese Olanzapine-Treated Patients Receiving Sibutramine or Placebo[a]



[a]Reprinted with permission from Henderson et al.[34]
*p = .009.

Table 5. American Diabetes Association Consensus on Antipsychotic Drugs and Obesity and Diabetes[a]

Drug	Weight Gain	Diabetes Risk	Dyslipidemia
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	0	0
Quetiapine	++	0	0
Aripiprazole[b]	+/–	–	–
Ziprasidone[b]	+/–	–	–

[a]Reprinted with permission from the American Diabetes Association.[35]
[b]Newer drugs with limited long-term data.
Symbols: + = increased effect, – = no effect, 0 = discrepant results.

gain.[35] However, aripiprazole and ziprasidone appear to have more favorable weight-gain profiles (Table 5).

The consensus statement also includes a monitoring schedule for the periodic assessment of glucose, lipid, and blood pressure levels over the long term. Clinicians who prescribe atypical antipsychotic agents should monitor key indicators of patients' baseline risk for the development of metabolic adverse effects. This includes a thorough family history and baseline values for BMI, waist circumference, blood pressure, fasting plasma glucose level, and fasting lipid profile for patients regardless of their level of risk. Patients' weight should be reassessed at 4, 8, and 12 weeks after starting or switching atypical antipsychotics and quarterly thereafter. Blood pressure, fasting plasma glucose level, and fasting lipid profile should be repeated at 12 weeks for all patients. Thereafter, blood pressure and plasma glucose values should be obtained annually or more frequently in those with a higher baseline risk of developing diabetes or hypertension. The presence of symptoms of diabetic ketoacidosis requires immediate evaluation and treatment. If a patient gains more than 5% of his or her initial weight at any time during therapy, the clinician should consider switching the SGA.[35]

CONCLUSION

In conclusion, atypical antipsychotic drugs vary in both risk for weight gain and mechanism for causing weight gain. The physician should routinely consider the health consequences of antipsychotic treatment and base the choice of antipsychotic on its perceived efficacy as well as short-term and long-term safety and tolerability.

Based on patients' history of treatment, their medical history, and the population-based risk, the medication with the least potential for weight gain should be chosen for the

individual patient. Physicians should be cognizant of the fact that there is a very low threshold for switching to medications with less potential for weight gain (> 5% of total body weight). Prevention of weight gain is the best approach. Routine discussions regarding potential for weight gain should take place for as long as the patient is on treatment with the drug. It is also important to assess for lifestyle changes, as a change in housing may lead to change in diet. It is critical to routinely monitor weight, BMI, and waist measurements as well. Regular monitoring of glucose and lipids should also be part of regular treatment, and it must be remembered that these abnormalities may occur even in the absence of significant weight gain. It is imperative to routinely discuss components of a healthy lifestyle, as patients with severe mental illness are often unaware of the real components of such a lifestyle. Finally, interventions or referrals to address weight issues should be proactive in nature. The risks associated with weight gain are too dire to be reacted to only after the weight gain has occurred.

Drug names: amantadine (Symmetrel and others), aripiprazole (Abilify), bupropion (Wellbutrin and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo, Clozaril, and others), dextroamphetamine (Dexedrine, Dextrostat, and others), divalproex (Depakote), fluoxetine (Prozac and others), haloperidol (Haldol and others), metformin (Riomet, Fortamet, and others), naltrexone (ReVia and others), nizatidine (Axid and others), olanzapine (Zyprexa), orlistat (Xenical), sibutramine (Meridia), topiramate (Topamax and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, amantadine, metformin, nizatidine, and topiramate are not approved by the U.S. Food and Drug Administration for weight loss.

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