

Schizophrenia and Obesity: Impact of Antipsychotic Medications

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Obesity is an epidemic in this country and much of the rest of the developed world. It is a major contributor to a range of metabolic disorders responsible for much of the medical morbidity and mortality that burden our society. The combination of the costs to society of the chronic illness of schizophrenia with the costs of obesity and the chronic illnesses associated with it, e.g., metabolic disorders, diabetes, dyslipidemias, and cardiovascular disease, represents a major public health problem. Obesity in schizophrenia is accentuated even further largely through illness-related factors, like poor dietary conditions and more sedentary lifestyles, and particularly because many of the psychiatric medications (antipsychotics, mood stabilizers, and antidepressants) used to combat this devastating illness themselves result in weight gain that, if untreated, may result in the usual obesity-associated morbidity and mortality. This article is intended to review some of the physiology of obesity and obesity-related metabolic disorders, the risks to schizophrenia patients engendered by obesity, the evidence for weight gain associated with the antipsychotic drugs, and the possible mechanisms involved in antipsychotic medication-associated weight gain. (*J Clin Psychiatry* 2004;65[*suppl* 18]:13–26)

The increasing epidemic of obesity in the general population alone is a paramount world health concern and is clearly associated with increased morbidity and mortality. A recent update of results from the Behavioral Risk Factor Surveillance System concluded that in 2001, approximately 21% of the U.S. population was obese (BMI ≥ 30 kg/m²), an increase of 74% over 1991.¹ In 1991, there were no states with a prevalence rate of obesity greater than 20%; in 2000, 22 states met that criterion. All of the states had a 15% or more prevalence of obesity with the exception of Colorado, where the prevalence was 10% to 14%.² That 15% prevalence rate translates to over 44 million obese adults in the United States. Furthermore, obesity is associated with significantly increased risks for diabetes, hypertension, hyperlipidemia, and osteoarthritis (Figure 1). Not surprisingly, these conditions help contribute to the increased mortality associated with obesity.

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Supported by an unrestricted educational grant from Bristol-Myers Squibb Company.

Dr. Wirshing has received grant/research support from Bristol-Myers Squibb, Pfizer, AstraZeneca, and Janssen and has participated in speakers' or advisory boards for Bristol-Myers Squibb, Janssen, Pfizer, and AstraZeneca.

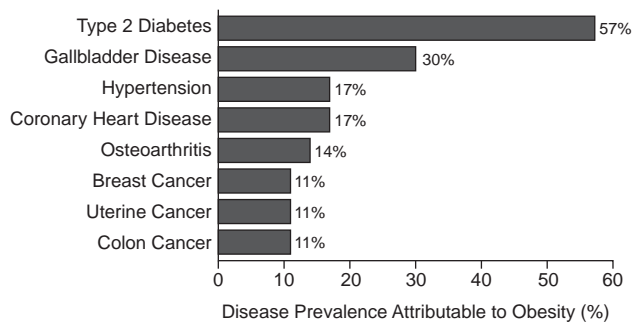
The author thanks William C. Wirshing, M.D., and Brian N. Atkinson, Ph.D., for their editorial assistance.

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A commonly used term to define obesity is *body mass index*. This term takes into account a person's body weight relative to his or her height and is determined by dividing the individual's weight in kg by his or her height in meters squared (the conversion is $703 \times \text{lb/in}^2$). A BMI greater than or equal to 25 kg/m² is currently used as the cutoff of overweight. A BMI greater than or equal to 30 kg/m² is considered obese. These criteria are used, for example, to determine a patient's eligibility for anti-obesity medications. We can prescribe anti-obesity medications to patients with a BMI over 30 kg/m² who have no obesity-related problems and can prescribe anti-obesity medications to patients with a BMI of 27 kg/m² or greater if obesity-related complications exist.³ BMI is a useful parameter to monitor in patients taking atypical antipsychotic medications.

Allison et al.⁴ assessed data from 5 different cohort studies that encompassed almost 1 million subjects. They found that approximately 280,000 deaths annually were attributable to obesity, and that over 80% of obesity-attributable deaths occurred in patients with a BMI of > 30 kg/m². Using a cohort of participants from the Cancer Prevention Study II, Calle et al.⁵ found that the risk of all-cause mortality increased with increasing BMI at all ages. The strongest association between obesity and death from all causes was found in the heaviest men and women (BMI of ≥ 40 kg/m²). The relative risk (RR) of mortality in these heaviest patients was 2.68 among men and 1.89 among women, compared with the reference groups. A high BMI was strongly associated with cardiovascular disease mortality in both men and women, but significantly increased risks of death attributable to cardiovascular disease were found

Figure 1. Proportion of Disease Prevalence Attributable to Obesity^a



^aData from Wolf and Colditz.¹⁵⁴

at BMIs greater than 25.0 kg/m² in women and 26.5 kg/m² in men.

With obesity having reached epidemic proportions in the United States and abroad, we are faced in psychiatry with the challenge of needing to address this problem in patients who suffer from many factors contributing to an unfortunate exacerbation of the problem. Certainly, access to health care can be limited, and financial challenges can lead to patients accessing food that is less than optimal—high in calories and low in nutritional value.⁶ One of the major premises of the book *Fast Food Nation* is that the epidemic of obesity correlates with the growth of the fast food industry.⁷ And of course, following the laws of thermodynamics, people in Westernized societies are obese because we not only eat too much, but we also exercise too little.

Whereas the prevalence of obesity in the United States is estimated to be around 20% to 30% of the general population,^{1,8} the prevalence of obesity in the schizophrenia population, in medicated patients, is reported to be somewhere between 40% and 60%.^{8–17} Most existing data examining the prevalence of obesity in schizophrenia are difficult to interpret because neither valid diagnoses nor anthropometric measurements were utilized in these studies, and often appropriate control groups were not selected. The studies conducted on prevalence of obesity also did not control for medication condition and validity of diagnosis.

Attempts to examine the rates of obesity in drug-naive patients have been made, but the literature is very weak. Thakore¹⁸ recently reviewed the literature on this subject and found that most studies did not control for confounding factors such as previous usage of medication, lifestyle, age, and ethnicity. Very little data regarding the prevalence of obesity in schizophrenia exist from before the advent of antipsychotic medications.

It is an irony of the cruelest sort that the single greatest treatment impact, the very mainstay of our entire arsenal,

appears to actually cause complications that are more difficult to manage than the schizophrenia itself. Although the introduction of the second-generation atypical antipsychotic medications has been associated with decreased neurologic toxicity, some of these antipsychotic medications are associated with greater weight gain and higher incidence of the other metabolic conditions that comprise what is now commonly referred to as the metabolic syndrome.

The notion that there are no differences among the antipsychotic medications is an area of some disagreement. Meta-analyses suggest there appears to be a reasonable uniformity of efficacy among the various antipsychotic medications.^{19,20} However, at this point, clozapine remains the most effective drug for treatment-refractory schizophrenia, and despite its liabilities (e.g., the risks of agranulocytosis, myocarditis, and substantial weight gain), its benefits (e.g., prevention of suicide) may indeed outweigh its risks, although the statistical study of that question—how many suicides are prevented versus lives lost to cardiovascular disease from clozapine-associated weight gain—is debated cogently by Fontaine and colleagues.²¹

PATIENTS' EXPERIENCE WITH DRUG-INDUCED WEIGHT GAIN

Individuals with schizophrenia suffer from one of the most incapacitating of mental illnesses. Schizophrenia usually develops in people in young adulthood and persists the rest of their lives, in most cases causing serious disability as patients are often unable to work due to the interference of their symptoms. Although 2.5% of the U.S. population is diagnosed with schizophrenia, which is characterized by episodes of exacerbation and remission, the course can be chronic and debilitating for 30% of the patients, leading to a cost that exceeds 2.5% of the U.S. gross national product.²² There is no cure for this illness, and although antipsychotic medications that have been available for 50 years can often reduce symptoms of the illness and help patients live outside of institutions, the majority of patients do not achieve a normal level of function in social, educational, and vocational realms. When patients are nonresponsive to medications (the case for approximately a third of patients)¹⁶¹ or nonadherent to medications (the case for 50% of patients),³⁷ however, untreated symptoms of the illness can be devastating. Through its profound effect on cognitive and emotional functioning, schizophrenia often robs individuals of clear thinking, rational decision making, self-direction, self-determination, and the normal range of emotions and social relationships.^{23–28} Schizophrenia has a relative risk of mortality that is 1.6 to 2.6 times greater than that of the general population.^{29,30} The life expectancy of an individual with schizophrenia is 20% shorter than that of the general population, the average age at death being 61 years versus 76 years, respectively.³⁰

Suicide and cardiovascular disease are the 2 most common causes of death in schizophrenia.³¹ The suicide rate of patients with schizophrenia is around 12%,³¹ similar to that in depression.³² Cardiovascular disease is the number one cause of death in schizophrenia patients; in fact, the cardiovascular causes of death in this population are about twice those of the general population.³³ Indeed, the high prevalence of smoking contributes to these statistics.⁶ It is estimated that 75% to 85% of patients with serious mental illness smoke cigarettes.^{6,34}

The threat of weight gain for patients with schizophrenia includes, in addition to the inevitable medical sequelae of obesity, the added stigma of obesity and exacerbation of mental illness through nonadherence to pharmacologic treatment due to the weight gain.³⁵ Nonadherence to treatment is a major cause of relapse and rehospitalization and has been estimated to increase relapse rates by 5-fold.³⁶ It is estimated that the rate of nonadherence is around 50%,³⁷ and, although there are no data from controlled studies on the subject, it is well known that weight gain is the cause of an appreciable noncompliance in schizophrenia patients treated with atypical antipsychotics.^{35,38,39} Weiden et al.⁴⁰ reported that obese schizophrenia patients were 3 times more likely to report missing their medication than patients who were not obese.

All of the above is in addition to the personal burden of being obese in our society, the demoralization of feeling out of control, and the sense of alienation arising from the stigma of being obese. A recent study by Weiden and colleagues⁴⁰ indicated that patients who gained weight on their medications reported lower scores on a quality of life rating scale.

THE PHYSIOLOGY OF OBESITY

Definition of Obesity

Obesity has many definitions (e.g., BMI ≥ 30 kg/m², as discussed earlier), but, simply put, it is the condition of increased adipose masses in the body.⁴¹ The adipose masses are made up of triglyceride-containing fat cells, or adipocytes, whose numbers are determined during several specific time periods in early childhood and adolescence, and also during pregnancy. In the obese individual, the adipocytes are enlarged by excessive deposition of fat.

Adipose Mass as Energy

The purpose of adipose stores is energy storage, as the body has no efficient way of storing protein or carbohydrates. Per the first law of thermodynamics, obesity is the result of an imbalance between energy intake and energy expenditure. The total energy expenditure is determined by resting energy expenditure (the largest component), degree of physical activity, and the energy involved in the metabolism (or the thermic effect) of the food ingested.

The resting energy expenditure is associated mostly with adipose-free body mass.⁴² A low resting energy expenditure has been predictive of future weight gain.⁴³ Food ingested must be oxidized to maintain an energy balance, and the amount of food that the body can oxidize is determined by the type of food, the oxidative capacity of the body, and the rate of energy expenditure. Physical activity expends energy in direct relation to body weight⁴⁴ and decreases with age.⁴⁵ The thermic effect of food is controlled in part by the sympathetic nervous system⁴⁶ and accounts for around 10% of the day's total energy expenditure after food is ingested. Stimulation of thermogenesis has been a method of treating obesity since the first use of thyroid extract,⁴⁷ which, unfortunately, also caused loss of calcium and lean body mass.

Factors Influencing Fat Deposition

Cholecystokinin (CCK), a gastrointestinal peptide, and glucagon, a pancreatic peptide, reduce food intake in animals and humans.^{48,49} Leptin, a cytokine originating mostly from adipose cells, is correlated with the quantity of fat in the body. It reduces food intake, stimulates the thermogenic activity of the sympathetic nervous system,⁴⁴ and is involved in a negative feedback loop with neuropeptide Y, an orexigenic agent. Leptin injections have not yet proven successful in humans as a treatment for obesity. In studies done so far, there was significant discomfort at the injection site, limiting the use of leptin until the route of delivery is improved.⁵⁰

There are also several monoamines and neuropeptides working on the central nervous system to regulate food intake.^{51,52} Serotonin is involved in determining the quantity of food ingested as well as the type of food. Activating the serotonin receptors in the paraventricular nucleus reduces fat intake specifically with minimal effect on protein or carbohydrate intake.⁵³ Stimulation of a particular serotonin receptor (5-HT_{2C}) is the mechanism by which fenfluramine is thought to induce appetite suppression. Conversely, if mice are bred with the 5-HT_{2C} receptor "knocked out," they will become obese. Food intake is also influenced by noradrenergic receptors in the paraventricular hypothalamus. Norepinephrine can either increase or decrease food intake depending on the type of adrenergic receptor involved.⁵⁴ Neuropeptide Y, a strong enhancer of food intake, is controlled by insulin, leptin, and starvation.

Endocrine factors that influence food intake include growth, thyroid, and gonadal hormones; glucocorticoids; and insulin.⁴⁴ Energy expenditure and loss of adipose mass, particularly visceral fat, are increased by growth hormones. Testosterone also causes loss of visceral fat. Adrenal glucocorticoids are important factors in the development of obesity,⁵¹ and their absence can result in loss of adipose mass.⁵⁵ Insulin, through lipogenesis and inhibition of lipolysis, contributes to the development of obesity.

The autonomic nervous system is a primary determinant in the regulation of metabolism.⁵¹ The parasympathetic system controls gastric emptying, hepatic metabolism, and insulin secretion, and the sympathetic system helps to control thermogenesis and insulin secretion. These 2 systems work reciprocally. The combination of ephedrine and caffeine, both thermogenic, has been shown to result in weight loss, over half of which is due to reduced food intake.⁵⁶

The normal amount of fat in adipose tissue is 10 to 15 kg (22–33 lb) (in an individual with a body mass index [BMI] between 18.5 and 24.9 kg/m²), enough to survive on for a month.⁴¹ An obese individual weighing 150 kg (333 lb) has around 80 kg (178 lb) of body fat. If the excess 70 kg (156 lb) of fat were accumulated over 30 to 40 years, the daily overeating would amount to only about half a sandwich per day.⁵⁷ However, for the development of obesity, there clearly would have to be a positive energy balance, and it is important to note that approximately 45% of obese individuals have binge-eating disorder.⁵⁸

Obesity Becomes Risk

An excess of adipose mass increases the risk of a host of medical problems. There is increased incidence of hypertension, coronary heart disease, type 2 diabetes mellitus, stroke, gallbladder disease, osteoarthritis, sleep apnea, a number of cancers (including endometrial, breast, colon, and prostate), infertility, and depression.⁵⁹ The prevalence of hypertension increases progressively as BMI increases in both men and women.⁶⁰ There is also a sensitive relationship between diabetes and weight. The Nurses' Health Study⁶¹ found a greater risk for diabetes with increasing BMI, and at a BMI of ≥ 31 kg/m², the risk for developing diabetes increased more than 40-fold.

The most concerning pattern of fat deposition is visceral abdominal obesity. Obese individuals with abdominal obesity have increased fasting plasma total cholesterol and triglycerides, decreased plasma high-density lipoprotein (HDL) cholesterol, decreased HDL₂ cholesterol, normal or mildly elevated low-density lipoprotein (LDL), increased apoB-carrying lipoproteins, and an increase of smaller, dense LDL particles.⁶² It is this combination of lipid abnormalities that puts the individual with visceral or intra-abdominal obesity at risk for coronary heart disease.⁶²

In addition to the dyslipidemic state being associated with abdominal obesity, individuals with visceral obesity are also at risk for insulin resistance. In fact, the amount of visceral fat correlates well with glucose intolerance, plasma insulin levels, and insulin sensitivity.⁶³ Insulin resistance is the most frequent metabolic abnormality associated with abdominal obesity.⁶⁴ Hypertension and dyslipidemias may result from insulin resistance.⁶⁵ Taken together, this constellation of symptoms comprises the metabolic syndrome, discussed in greater detail in an

accompanying article (see the article by Sacks¹⁶² in this supplement).

THE RISK OF OBESITY IN PATIENTS TREATED WITH ANTIPSYCHOTIC MEDICATION

Prevalence of Obesity in the General Population

The increased prevalence of overweight and obesity in the general U.S. population has been called an epidemic and has enhanced awareness of the seriousness of the problem.² It has been estimated that about 62% of the adult population is overweight (defined as BMI ≥ 25 kg/m²) and that about 28% of adults are obese (BMI ≥ 30 kg/m²).⁸ This represents as much as a 60% increase over the prevalence of obesity in 1991.⁶⁶

Prevalence of Weight Gain and Obesity in the Schizophrenia Population

Weight fluctuations in the schizophrenia population have been observed as far back as Kraepelin,⁶⁷ who described eating behavior among these patients as ranging from "complete refusal to the greatest voracity"^{67(p87)} and "very considerable differences in the body weight."^{67(p87)} Obesity among schizophrenia patients became a concern in the 1950s with the introduction of antipsychotic medication in the form of chlorpromazine accompanied by "obesity on a mass scale" in mental hospitals.⁶⁸ However, the concern about obesity was far outweighed by the antipsychotic medication-induced movement disorders that were devastating and intolerable to patients, leading to physical disability, disfigurement, and high rates of treatment nonadherence. With the advent of the second-generation antipsychotic medications—beginning with clozapine—our patients suffer so few extrapyramidal side effects (EPS) that we actually have the ability to focus on the metabolic side effect of these medications.

Although we do not have sufficient data on the prevalence of obesity in schizophrenia prior to the use of antipsychotic medication or in drug-naïve schizophrenia patients, we know the prevalence of obesity in the medicated schizophrenia population is high, and current estimates range from 40% to 60% of the medicated schizophrenia population versus 30% of the general population,^{8–14,16} putting them at risk for medical conditions such as diabetes mellitus and cardiovascular disease even without further weight gain.^{69,70} Using the National Health and Nutrition Examination Survey (NHANES) data from 1989 (before the advent of "atypical" or novel antipsychotic medications), Allison et al.¹⁶ demonstrated that women with schizophrenia have a considerably greater prevalence of overweight and obesity compared with nonschizophrenia controls. In follow-up work to this original article, Homel and colleagues¹⁷ have demonstrated that in the last decade, women with schizophrenia have had dramatic increases in BMI compared with BMI changes seen in the women in

the control sample. There was a trend in Allison's article suggesting that all schizophrenia patients were overrepresented in the overweight and obese BMI categories, but this difference was not statistically significant.

Complicating the weight gain liability of medications, schizophrenia patients are less likely than the general population to have their medical conditions diagnosed and treated.⁷¹ The negative symptoms of the illness—e.g., social isolation, withdrawal, apathy—can cause patients to lack motivation and insight into the need to maintain a normal body weight, to eat properly and exercise adequately, or even to seek medical attention for such problems. Indeed, even the positive symptoms of the illness—paranoia, for example—may lead people to live in isolation in a sedentary manner. And finally, many patients with schizophrenia are confined by mental institutions and prisons, with little ability to exercise adequately. Acute hospitalizations tend to be on “locked units” as liability issues force hospitals to isolate these patients from other hospital patients and the community, thus forcing sedentary behavior in the inpatient setting.

Weight Gain and First-Generation Antipsychotic Medications

Though dwarfed by the tremendous neurologic toxicity of the first-generation antipsychotic medications—in the form of drug-induced parkinsonism, maddening restlessness (akathisia), and irreversible choreoathetoid movements (tardive dyskinesia)—weight gain associated with antipsychotic medication has been recognized since the introduction of chlorpromazine in 1954.⁷² Among practitioners, it was clear that first-generation antipsychotic medications that were lower potency, e.g., chlorpromazine and thioridazine, had more weight gain than higher potency drugs such as fluphenazine and haloperidol. It was speculated that the histamine receptor blockade of these medications was responsible for the weight gain properties of these medications.⁷³ Among the first-generation antipsychotic medications, molindone was associated with little to no weight gain.⁷⁴ In controlled trials, placebo is associated with weight loss. None of the first- or second-generation antipsychotics are associated with weight loss.

Weight Gain and Second-Generation Antipsychotic Medications

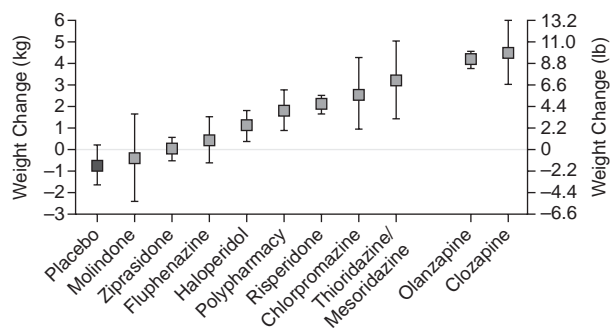
Clozapine, olanzapine, and risperidone. Although clozapine, the first “atypical” (novel or second-generation) antipsychotic medication, showed promise as an alternative to the conventional antipsychotics because of its low incidence of extrapyramidal effects and its beneficial effect on the negative symptoms of schizophrenia, it was also recognized in the earliest and subsequent studies that there was a significant weight gain associated with it—a gain often higher than that associated with the conventional antipsychotics.^{75,76}

Since the advent of clozapine, 5 other drugs have been elaborated that cause mild EPS, but unfortunately most share the problem of weight gain. In our work comparing relative weight gains among patients taking second-generation medications, clozapine was associated with the greatest amount of weight gain.⁷³ We performed a retrospective analysis⁷³ of 92 male patients with schizophrenia who were receiving 5 different antipsychotics (clozapine, olanzapine, risperidone, haloperidol, and sertindole) and found clozapine and olanzapine to be associated with the highest mean weight gain (15.2 lb and 15.0 lb [6.8 kg], respectively, vs. 11.1 lb, 8.2 lb, and 6.8 lb [5.0 kg, 3.7 kg, and 3.1 kg] for risperidone, haloperidol, and sertindole, respectively). We saw the pattern of weight gain for clozapine and olanzapine differ from that of the other medications. Patients taking these drugs had persistent weight gain for up to 30 weeks of treatment. Henderson and colleagues,⁷⁷ in a 5-year naturalistic study, observed weight gain for up to 4 years on average in 82 clozapine-treated patients. Of concern, 37% became diabetic over that 5-year period.

Hummer et al.⁷⁵ described the weight gain patterns seen in 81 patients treated with clozapine. In 35.7% of the clozapine-treated patients, the weight gain exceeded 10% of the initial body weight. Weight gain was apparent within the first 12 weeks of treatment. Five of the 14 patients who gained more than 10% of their initial weight were withdrawn from clozapine. Seven of the remaining 9 patients continued to gain weight, gaining a maximum of 30% of their initial body weight. None of the haloperidol-treated patients gained more than 10% of their initial body weight. The maximum weight gained in a patient treated with clozapine was 9.2 kg (20.4 lb) versus 2.0 kg (4.4 lb) for a haloperidol-treated patient. In several studies,^{73,78} patients' weight did not plateau for 30 weeks. In a retrospective chart review of 68 patients treated with clozapine over 3 to 90 months, Umbricht et al.⁷⁹ found a cumulative incidence of a 10% or more increase in weight reaching 60% within the first 12 months.

Olanzapine, a thienobenzodiazepine that was developed to be like clozapine without agranulocytosis, is also associated with significant, clozapine-like weight gain in controlled studies. Beasley et al.⁸⁰ reviewed and collated data from several studies and found weight gain associated with olanzapine to be significantly greater than the gain associated with patients taking haloperidol or placebo. In a 12-week prospective study of weight and serum triglyceride levels involving 25 inpatients with schizophrenia being treated with olanzapine, Osser et al.⁸¹ found a mean increase in body weight of 12 lb (5 kg). In a large international, multicenter, double-blind study involving 1996 patients at 174 sites in Europe and North America, Tollefson et al.⁸² compared olanzapine and haloperidol in the treatment of patients with schizophrenia. Olanzapine-treated patients experienced a significantly higher average

Figure 2. Estimated Weight Change at 10 Weeks on Placebo or "Standard" Dosages of Antipsychotic Drugs^{a,b}



^aReprinted with permission from Allison et al.⁹⁰

^bBars represent 95% confidence interval.

weight gain than haloperidol-treated patients over 6 weeks, 4.1 kg (9.1 lb) versus 2.3 kg (5.1 lb), respectively ($p = .015$).

In prospective double-blind studies of olanzapine versus risperidone, olanzapine has demonstrated roughly twice the weight gain of risperidone. Both the manufacturers of olanzapine and risperidone conducted head-to-head trials⁸³⁻⁸⁵ and found this consistent finding. Additionally, non-pharmaceutical company research⁸⁶ echoes these findings. Olanzapine-associated weight gain does not appear to be related to dose and appears to persist for up to a year in patients treated with this medication⁸⁷ (and perhaps longer, but we just do not have the data yet).

Gupta et al.⁸⁸ reported that 15 of 16 patients experienced a mean weight gain of 10.05 kg (22.33 lb) over an average of 7 months. A recently published study⁸⁹ investigated change in body weight and BMI upon switching from olanzapine to risperidone and vice versa. Patients who were switched from risperidone (treated > 60 days) to olanzapine (treated > 60 days) gained on average 2.3 kg (5.1 lb) or 2.8% of their baseline weight ($p = .01$) and had an average BMI increase of 0.8 kg/m² or 3.0% ($p = .02$).⁸⁹

Allison et al.⁹⁰ performed an often-quoted meta-analysis of more than 80 studies involving both first- and second-generation antipsychotic medications and over 30,000 patient measurements. Clozapine and olanzapine, the 2 antipsychotic medications associated with the most weight gain, were associated with an average of 4.0 to 4.5 kg (8.9–10.0 lb) of weight gain at 10 weeks of treatment (Figure 2).

It is important to note that data available so far also suggest that the pattern of weight gain differs among the antipsychotic medications. Some long-term studies showed that olanzapine-associated weight gain did not plateau until 30 weeks, whereas risperidone-treated patients gained weight for the initial 8 weeks and then plateaued.⁷³ As discussed below, a pattern of rapid weight gain over a short period of time should be a warning light to physician, patient, and caregivers that an intervention to slow down

and/or reverse the slope of this hill needs to occur to prevent further medical compromise.

In Allison and colleagues' meta-analysis,⁹⁰ weight gain for risperidone appeared intermediate among the antipsychotic medications. Early double-blind studies with risperidone had conflicting results relating to weight gain.⁹¹ Claus et al.,⁹² in a multicenter, 12-week, double-blind trial, studied 44 patients with chronic schizophrenia randomly assigned to treatment with either risperidone or haloperidol. The risperidone-treated patients had a nonsignificant greater increase in weight than the haloperidol-treated patients (2.0 kg [4.4 lb] vs. 1.4 kg [3.1 lb], respectively). In another multicenter double-blind study comparing risperidone with perphenazine,⁹³ the risperidone group experienced weight gain more frequently than the perphenazine group (39% vs. 20%, respectively), but there was no other statistical analysis available.

In a large multinational, double-blind trial, Peuskens⁹¹ studied the comparative effects of risperidone (4 mg, 8 mg, and 12 mg) and haloperidol in 1362 patients with chronic schizophrenia. Patients treated with risperidone experienced a weight increase in all dosage groups that was significantly higher than that in the haloperidol group. The mean increase in weight was 0.3 kg (0.7 lb) for the risperidone 1-mg group and 1.6 kg (3.6 lb) for the 8-mg group. Emsley, in another international multicenter study,⁹⁴ also reported weight gain higher with risperidone than with haloperidol but without a statistical analysis. Song's meta-analysis of 11 double-blind studies⁹⁵ indicated that risperidone was associated with more frequent weight gain than were typical antipsychotics. Risperidone has been found to have an average weight gain of 2 to 3 kg (4.4–6.7 lb) over 8 to 12 weeks.^{83,96} Weight gain with risperidone does appear to correlate with dose.⁹¹

Quetiapine. Double-blind studies⁹⁷⁻⁹⁹ have shown that quetiapine is not free of weight gain liability. Though not included in Allison and colleagues' initial meta-analysis in 1999,⁹⁰ extrapolation of available data on quetiapine⁹⁷⁻⁹⁹ places it somewhere between risperidone and olanzapine in terms of average weight gain expected in 10 weeks of exposure. In a 6-week, multicenter, double-blind study of 109 hospitalized patients with schizophrenia,⁹⁷ 25% of the quetiapine-treated group compared with 4% of the placebo group experienced a clinically significant weight gain (increase of $\geq 7\%$ above baseline weight). The final average weight gain was 5.5 kg (12.2 lb) for the quetiapine group and 0.5 kg (1.1 lb) for the placebo group.

In a large multicenter, double-blind, placebo-controlled study⁹⁸ involving 360 patients with acute exacerbations of schizophrenia from 26 North American centers, Arvanitis and Miller found that quetiapine-treated patients gained significantly more weight than patients treated with haloperidol or placebo. Mean increases of weight for quetiapine daily doses of 75, 150, 300, 600, and 750 mg were 0.9, 2.9, 2.0, 2.6, and 2.3 kg (2.0, 6.4, 4.4, 5.8, and 5.1 lb),

respectively, compared with a 0.3 kg (0.7 lb) increase for haloperidol-treated patients (on 12 mg/day) and a decrease of 0.8 kg (1.8 lb) for the placebo group. Clinically significant weight gain ($\geq 7\%$) was also higher in the quetiapine group regardless of dose (from low to high dose in 11%, 17%, 10%, 16%, and 13% compared with 4% with haloperidol and 6% with placebo).

In another large multicenter, double-blind, placebo-controlled study,⁹⁹ 286 hospitalized individuals with chronic or subchronic schizophrenia were treated with high-dose quetiapine (≤ 750 mg/day), low-dose quetiapine (≤ 250 mg/day), or placebo. There was a clinically significant weight gain ($\geq 7\%$) in 25% of the high-dose compared with 16% of the low-dose group and 5% of the placebo group. Long-term data suggest that the weight gain plateaus at 8 weeks and is approximately 5 lb (2 kg) at the end of 1 year.¹⁰⁰

Ziprasidone. Controlled studies of ziprasidone have indicated that this drug is associated with minimal weight gain for most patients. However, it should be noted that although the average weight gain in the premarketing trials was low, 9% of patients gained more than 7% of their initial body weight according to package insert information.¹⁵⁷ Keck et al.¹⁰¹ report on a double-blind, placebo-controlled, multicenter study of 139 patients with an acute exacerbation of schizophrenia or schizoaffective disorder, randomly assigned to receive 40 mg/day or 120 mg/day of ziprasidone or placebo over 28 days. The only weight change observed was a median increase of 1 kg (2.2 lb) in the 40-mg/day group.

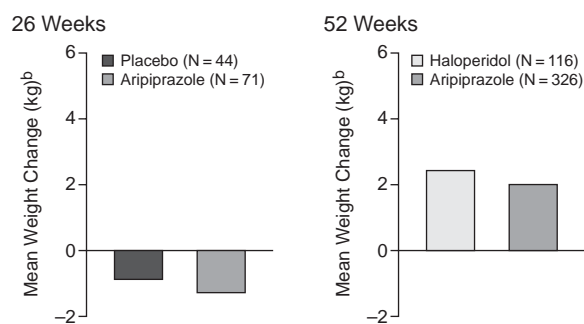
In another randomized, double-blind study by Daniel et al.,¹⁰² patients with an acute exacerbation of schizophrenia or schizoaffective disorder received either 80 mg/day or 160 mg/day of ziprasidone for 6 weeks. There was a median increase in body weight of 1 kg (2.2 lb) for the ziprasidone 80-mg/day group and no change in weight observed in the 160-mg/day group.

Arato et al.¹⁰³ recently reported on a 1-year, double-blind, placebo-controlled study of ziprasidone 40, 80, and 160 mg/day for patients with chronic schizophrenia. There was a decrease in body weight of 2.7, 3.2, and 2.9 kg (6.0, 7.1, and 6.4 lb) associated with the 40-, 80-, and 160-mg doses of ziprasidone, respectively.

Cohen et al.¹⁰⁴ recently studied the effect of ziprasidone on body weight in 40 individuals with maladaptive behavior and mental retardation. There was a mean reduction of body weight associated with ziprasidone of 1 lb (3.6 kg). Long-term data at 1 year in a study with ziprasidone also support little weight gain on average.¹⁰⁵

Aripiprazole. To date, the use of aripiprazole has been associated with minimal weight gain for the majority of patients (Figure 3). Like ziprasidone, average weight gain was low in all premarketing studies. However, 8% of patients gained more than 7% of their initial body weight according to package insert information.¹⁵⁶

Figure 3. Weight Changes With Aripiprazole Therapy Versus Placebo or Haloperidol^a



^aData from Pigott et al.¹⁰⁹ and Kasper et al.¹⁵⁵

^bObserved case analyses.

Potkin et al.,¹⁰⁷ in a 4-week double-blind study assessing the effects of aripiprazole and risperidone in patients with schizophrenia and schizoaffective disorder, found a low incidence of weight gain for both groups. Aripiprazole was associated with a 1.2-kg (2.7-lb) weight increase for the group receiving 20 mg and 0.8 kg (1.8 lb) for the group receiving 30 mg. Risperidone, at a dose of 6 mg/day, was associated with a 1.5-kg (3.3-lb) weight gain. Clinically significant weight gain ($\geq 7\%$ increase from baseline) for the aripiprazole groups was 13% in the group on 20 mg, 9% in the group on 30 mg, and 11% for the risperidone group.¹⁰⁷

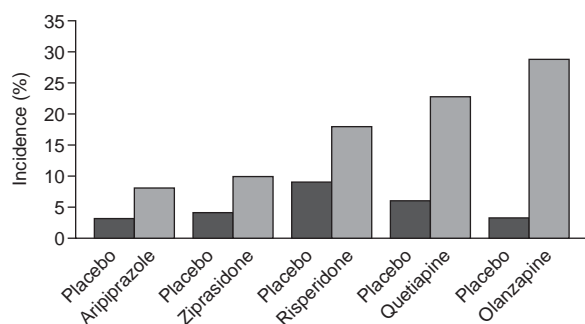
Marder et al.¹⁰⁸ reported on the safety and tolerability of aripiprazole using pooled data from 5 short-term, placebo-controlled trials in schizophrenia including over 1500 patients. At endpoint, aripiprazole patients showed minimal (< 1 kg [< 2.2 lb]) mean weight gain at doses from 2 to 30 mg/day, with a mean weight change of 0.71 kg (1.6 lb) for all doses combined. It should be noted that weight gain for aripiprazole-treated patients did not differ significantly in premarketing trials from haloperidol, though it was statistically meaningful compared with placebo.

Pigott et al.¹⁰⁹ assessed aripiprazole in a 26-week study in 310 patients with clinically stabilized schizophrenia and found that aripiprazole was associated with a mean weight loss of 0.87 kg (1.93 lb), compared with a mean weight loss of 1.26 (2.80 lb) kg for placebo patients.

In a 26-week study¹¹⁰ of the neurocognitive effects of aripiprazole and olanzapine in patients with clinically stable schizophrenia, olanzapine was associated with a greater incidence of weight gain (29%) than aripiprazole (7%). Results from an additional comparative trial of aripiprazole and olanzapine, designed to assess relative weight gain liability of each agent, are presented by Stock et al.¹⁶³ in this supplement and confirm earlier observations.

Casey et al.¹⁰⁶ found that patients switched to aripiprazole experienced weight loss. Patients were switched from

Figure 4. Clinically Significant ($\geq 7\%$) Weight Gain During Antipsychotic Treatment^a



^aData from Abilify [package insert],¹⁵⁶ Geodon [package insert],¹⁵⁷ Risperdal [package insert],¹⁵⁸ Seroquel [package insert],¹⁵⁹ and Zyprexa [package insert].¹⁶⁰

other antipsychotics including olanzapine, risperidone, haloperidol, and thioridazine. The 3 treatment groups, (1) immediate and simultaneous switch to 30 mg of aripiprazole, (2) immediate initiation of 30 mg of aripiprazole and 2-week taper of current antipsychotic, and (3) simultaneous up-titrating of aripiprazole and tapering of current antipsychotic over 2 weeks, were associated with mean changes of weight from baseline of -1.4 , -1.7 , and -1.3 kg (3.1, 3.8, and 2.9 lb), respectively. The incidences of clinically significant weight gain in groups 1, 2, and 3 were 3%, 5%, and 3%, respectively, and the incidences of clinically significant weight loss (a decrease of $\geq 7\%$ from baseline) in groups 1, 2, and 3 were 7%, 15%, and 8%, respectively.

It is important to note that the pattern of weight gain and average amount of weight gained varies between agents (Figure 4). Some medications seem to be associated with longer periods of continued weight gain (e.g., clozapine and olanzapine). In addition, the location of fat deposition is very important. Visceral adiposity is highly associated with the development of diabetes and cardiovascular disease. Abdominal girth exceeding 40 in (102 cm) (males) or 35 in (89 cm) (females) is one of the criteria for metabolic syndrome. Wirshing et al.¹¹¹ reported on 3 patients whose changes in abdominal girth resulted in changes in psychiatric status—2 patients developed delusional thoughts that they were pregnant. We believe it is important, for both medical and psychiatric reasons, to include a measurement of abdominal girth as part of routine monitoring of our patients' physical health. We recommend asking patients if they have noticed a change in belt or pant size.

Drug-induced weight gain information can also be obtained from package insert information, which reports the percentage of patients with $\geq 7\%$ increase of body weight in premarketing trials. A comparison of these package inserts results in an ordering of antipsychotics similar to that found by Allison and Casey,⁹ from most weight gained to least weight gained: olanzapine > quetiapine >

risperidone > ziprasidone > aripiprazole (Figure 4).¹¹² It is important to note that a comparison of package insert information in this manner is not entirely fair, as the populations tested for each drug were different, and it is worthy to note that virtually all of the antipsychotics had twice the weight gain of the placebo comparator.

THE IMPACT OF CONCOMITANT MEDICATIONS

Today, it is not uncommon that patients are treated with multiple classes of medications. Polypharmacy is becoming more the rule than the exception. Mood stabilizers are often given to schizophrenia patients to calm agitated behavior. Antidepressants are given to elevate mood. Both of these classes of psychotropic medication have variable effects on weight gain. A recent study by Casey et al.¹¹³ showed that weight gain when combining risperidone with divalproex sodium was nearly twice the weight gain when patients took risperidone alone. In 4 weeks, patients gained 8 lb (3.6 kg) on average when treated with this medication combination. In the same study, patients treated with olanzapine monotherapy gained 8 lb (3.6 kg) in the 4 weeks and slightly more than 8 lb (3.6 kg) when divalproex sodium was combined with olanzapine.

WEIGHT GAIN, SECOND-GENERATION ANTIPSYCHOTIC MEDICATIONS, AND ADOLESCENTS

Weight gain is more problematic for adolescents than adults, even with medications considered to have little liability for weight gain. In a retrospective chart review study, Theisen and colleagues¹¹⁴ found that the prevalence of obesity in adolescent patients was 64% taking clozapine ($N = 69$) and 56% taking other atypicals (olanzapine, sulpiride, and risperidone) ($N = 27$) compared with 30% for adolescent patients taking first-generation antipsychotic medications ($N = 20$) and 28% for patients taking no medications ($N = 25$).

Findling et al.¹¹⁵ reported on an 8-week, open-label study of 6 children (aged 5–9 years) with autistic disorder treated with risperidone monotherapy. The subjects' weights increased from a mean of 27.6 kg (60.9 lb) at the beginning of this protocol to a mean of 29.2 kg (65.1 lb) at the end of this study (range of gain = 0.5–3.1 kg [1.1–6.8 lb]). In a 12-week, prospective open-label study of 18 individuals (mean \pm SD age = 10.2 \pm 3.7 years), there was a range of weight gain in 12 individuals of 10 to 35 lb (5–16 kg) and a mean \pm SD weight gain of 17.8 \pm 7.5 lb (8.0 \pm 3.4 kg).¹¹⁶ In a retrospective chart review comparing 37 child and adolescent inpatients treated with risperidone for 6 consecutive months with 33 psychiatric inpatients without any experience with atypical antipsychotics, 78% of the risperidone-treated group versus 24% of the control group experienced a clinically significant weight

gain.¹¹⁷ Weight gain for the risperidone group increased at an average of 1.2 kg (2.7 lb)/month and did not plateau during the 6 months. We have speculated that the curious susceptibility of adolescents to weight gain with risperidone (which has a more favorable weight gain profile in adults) may be due to the drug's propensity to increase prolactin; however, this remains only a speculation at this point, and more research is needed to establish a causal link.

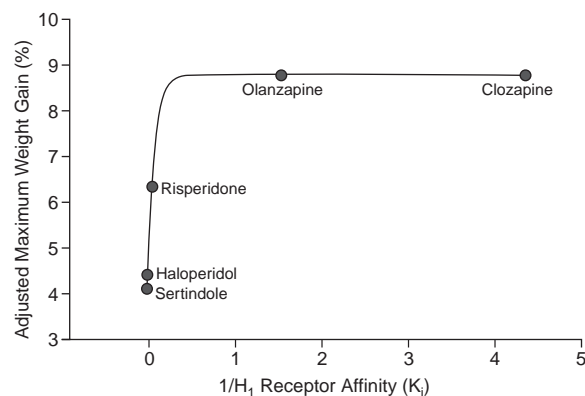
Children and adolescents have also been shown to gain substantial weight on quetiapine. Martin et al.¹¹⁸ reported on a 16-week, open-label trial of 6 male patients with a mean \pm SD age of 10.9 ± 3.3 years, treated with quetiapine. The 2 patients who completed the trial had significant weight gains of 2.3 kg (5.1 lb) and 8.2 kg (18.2 lb). In an 8-week open-label study of 15 adolescents treated with quetiapine, aged 13 to 17 years, there was an average weight gain of 4.1 kg (9.1 lb). After correcting for expected weight gain, the mean weight gain was 3.4 kg (7.6 lb).¹¹⁹ Long-term treatment with quetiapine results in a range of weight gain from 2.0 to 5.6 kg (4.4–12.4 lb).¹²⁰ In 1-year data from Brecher et al.,¹²¹ the pattern of weight gain with quetiapine shows a rapid increase in the first 8 weeks that plateaus over the remainder of the year. No dose-response relationship is seen with weight gain and quetiapine.¹²¹ Quetiapine weight gain does not seem to be dose related. No data exist yet examining the impact of ziprasidone and aripiprazole in children and adolescents. One expects these data will emerge in the near future.

MECHANISM OF ANTIPSYCHOTIC MEDICATION-ASSOCIATED WEIGHT GAIN

The mechanisms by which antipsychotic drugs cause weight gain are not easily determined. Body weight regulation itself involves an interaction of systems having to do with energy intake and expenditure, and determinants of satiety and appetite.^{122,123} Antipsychotic drugs have multiple effects on neurotransmitter systems, which in turn have a range of effects on energy homeostasis.¹²⁴ Virtually all of the antipsychotics work through some amount of dopamine blockade. Thus, a clinical pearl we tell our students: if it increases dopamine activity (e.g., cocaine and methamphetamine), it will make you skinny and crazy, and if it blocks dopamine, chances are the opposite will occur. Of course this is too simplistic: the neurotransmitter systems having potential impact on weight regulation include the serotonergic, histaminergic, adrenergic, and dopaminergic systems,¹²⁴ and antipsychotic drugs target all of these systems in some manner.

Most of the second-generation antipsychotics work through a combination of receptor systems. Many antipsychotics bind to histamine receptors, and affinity for histamine receptor subtypes directly correlates with treatment-associated weight gain.⁷³ Olanzapine has the highest affinity for the H_1 receptor of all the atypical antipsy-

Figure 5. Weight Gain as a Function of Histamine H_1 Receptor Affinity^{a,b}



^aReprinted with permission from Wirshing et al.⁷³

^b $y = 4.7[1 - e^{-12.5x}] + 4.1$ where y = adjusted maximum weight gain (%) and x = $1/H_1$ receptor affinity (K_1).

chotics.^{125,126} This may explain the reduced risk for treatment-associated weight gain with antipsychotics such as aripiprazole and ziprasidone,^{127,128} as they exhibit lower affinity for the same histamine receptor subtypes. Wirshing et al.⁷³ demonstrated a logarithmic relationship between H_1 receptor affinity and weight gain (Figure 5).

In addition, many atypical antipsychotics exhibit activity at several serotonin receptor subtypes, including the $5-HT_{2C}$ subtype, which appears to mediate some effects on appetite.¹²⁹ While most atypical antipsychotics are antagonists at $5-HT_{2A}$ and $5-HT_{2C}$ receptors,¹³⁰ aripiprazole acts as an agonist or partial at the $5-HT_{2A}$ and $5-HT_{2C}$ receptor subtypes, as well as a high-affinity partial agonist at the dopamine D_2 subtype.^{127,131,132}

Clozapine and olanzapine, 2 of the atypical antipsychotics associated with relatively larger weight gains, have similar receptor affinities. Clozapine has particularly high affinity for $5-HT_{2A}$, $5-HT_{2C}$, H_1 -histaminergic, α_1 -adrenergic, and M_1 -muscarinic receptors.¹³³ Olanzapine has the same receptor profile with the exception of a lower affinity for the α_1 -adrenoreceptor.¹³³

Ziprasidone, with a minimal weight gain associated with its use, has more serotonergic and less adrenergic, histaminic, and muscarinic receptor affinity.¹³³ It acts as a full agonist for $5-HT_{1A}$ and has strong affinities for $5-HT_{2C}$ and $5-HT_{1D}$ receptors.¹³³ $5-HT_{2C}$ blockade should, theoretically, increase appetite, as mice bred without $5-HT_{2C}$ receptors are obese and fenfluramine, an appetite suppressant, stimulates these receptors. Ziprasidone has high affinity for the $5-HT_{2C}$ receptor, but is also associated with norepinephrine reuptake inhibition that may account for its relatively low weight gain liability.

Quetiapine, a chemical analogue of clozapine, has relatively high affinity for histamine receptors, which may account for its weight gain profile. Risperidone has modest

H₁ affinity but notable affinity for 5-HT_{2A} and 5-HT_{2C} receptors, which may account for a propensity toward weight gain in certain patients. The distinguishing characteristic of risperidone's weight gain liability is that it varies with the age of the patient, with adults having substantially less gain than children. This distinction suggests that risperidone either exerts its weight gain liability through distinct mechanisms or has additional mechanisms accounting for the heightened liabilities in childhood and adolescence.

There are also endocrine effects of atypical antipsychotics that presumably play a role in weight gain associated with their use. These drugs can induce a hyperprolactinemia, which is associated with weight gain and may be related to insulin resistance and changes in carbohydrate metabolism.¹³⁴ Some studies have suggested hyperinsulinemia occurs in patients being treated with atypical antipsychotics.^{72,135}

Leptin, reflecting the amount of adipose tissue in the body, is increased in about 90% of obese people.¹³⁶ There is some indication in the literature that leptin's role (as well as other cytokines like α -tumor necrosis factor [α -TNF]) might be more than just communicating how much body fat there is, i.e., a causal role in the increased body weight associated with antipsychotic drugs.^{137,138} Melkersson et al.¹³⁷ found that treatment with olanzapine changed the levels of leptin. Pollmacher et al.¹³⁸ reported a rapid increase of both leptin and α -TNF with atypical antipsychotics. Despite high levels of leptin, patients treated with olanzapine continue to gain weight, suggesting that somehow the feedback loop between leptin and neuropeptide Y is disrupted or, more likely, that the impact of these compounds has little or no effect on orexigenic regulators but on feeding behavior per se.

Role of Genetics

Investigators are also interested in the role of genetics and medication-associated obesity. Genetic control of 5-HT_{2C} receptors and leptin is speculated to be predictors of antipsychotic-associated weight gain. The relationship between a functional polymorphism in the promoter region of the leptin gene was studied in acutely treated schizophrenia patients and compared with matched healthy controls, and it was found that a specific genotype (-2548GA) was associated with medication-induced weight gain.¹³⁹

Other studies have focused on genetic polymorphisms affecting serotonin receptor genes. A recent study¹⁴⁰ found that a specific polymorphism in the promoter region for the 5-HT_{2C} receptor gene was associated with significant clozapine-associated weight gain in male schizophrenia patients, but not in females. Another study¹⁴¹ found that the same 5-HT_{2C} polymorphism was associated with obesity in a sample of 120 women, and that among those obese women who participated in a trial of psychological treatments for weight loss, those patients who exhibited a heterozygous profile for the polymorphism lost less weight

Table 1. Suggestions for Combating Obesity in Schizophrenia Patients^a

Screening questions
Have you noticed any weight gain?
Have you noticed a change in your belt or pant size?
Screening procedures
Take thorough family history of cardiovascular disease and diabetes
Measure weight and waist circumference
Calculate BMI (kg/m ² or 703 × lb/in ²)
Preventive maneuvers
Encourage healthy lifestyles
Educate caregivers

^aData from Wirshing et al.⁷³ and the American Diabetes Association consensus statement.¹⁴²

Abbreviation: BMI = body mass index.

than patients who exhibited a homozygous pattern. Thus, genetic polymorphisms for both the 5-HT_{2C} and leptin genes can contribute to body weight and medication-induced weight gain, but other factors (e.g., gender) also may come into play.

INTERVENTIONS FOR ANTIPSYCHOTIC MEDICATION-ASSOCIATED WEIGHT GAIN

Monitoring and Selection of Antipsychotic Medications

Many psychiatrists are the de facto primary care clinicians for patients with schizophrenia. There are many simple things we can do to prevent obesity and its sequelae in our patients. One of the easiest things we can do is to choose a medication with the least weight gain liability when beginning an antipsychotic medication regimen. If a patient has gained weight and is doing well on his or her medication, the risks and benefits of switching medications must be carefully considered. Although statistics suggest no great differences in efficacy among the medications, each patient is an individual and thus may not meet the statistical norm for response for each medication. Thus, switching medications may not be an option for the clinically stable patient but is an excellent option for the patient who is having an acute exacerbation of his or her illness and/or who is chronically symptomatic on the offending drug. Clozapine is clearly indicated in treatment-refractory illness, and patients may not be able to switch; thus, interventions other than switching may need to be embarked upon. Adjunctive treatment with another antipsychotic with less weight gain liability may assist with weight loss. Reinstein and colleagues¹⁴³ examined retrospectively the impact of decreasing the total clozapine medication dose and then adding quetiapine. This intervention helped decrease weight and improve glucose regulation difficulties in many of the patients.

Behavioral Interventions

Behavioral treatments for medication-associated weight gain offer some promise. In a retrospective analysis of data from our clinic,⁷³ we saw that simple maneuvers—

Table 2. Monitoring Protocol for Patients Taking Second-Generation Antipsychotic Medications^{a,b}

Variable	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually	Every 5 Years
Personal/family history	✓					✓	
Weight (BMI)	✓	✓	✓	✓	✓		
Waist circumference	✓					✓	
Blood pressure	✓			✓		✓	
Fasting plasma glucose	✓			✓		✓	
Fasting lipid profile	✓			✓			✓

^aBased on the American Diabetes Association consensus statement.¹⁴²

^bMore frequent assessments may be warranted on the basis of clinical status.

Abbreviation: BMI = body mass index.

e.g., weighing the patients, asking them to provide a food diary, and referring patients to a nutritionist—could be helpful interventions that most clinicians can employ. O’Keefe et al.¹⁴⁴ also did a retrospective analysis of patients in his clinic and found that a multifaceted approach to medication-associated weight gain including nutrition consultation was useful. Several recent investigations that have examined the utility of weight-control support groups and specially designed treatments for patients with schizophrenia show promising preliminary data.^{145,146}

We also recommend providing education and support for healthy lifestyles to our patients. We recently began a series of wellness classes to educate patients about healthy eating behaviors and the merits of exercise. Patients’ families and caregivers should also be educated about the potential weight gain liabilities of currently available antipsychotic medications. Screening questions about weight gain should be asked at each visit so as to prevent this serious problem (Table 1). The American Diabetes Association (ADA) consensus statement published in *Diabetes Care* and *The Journal of Clinical Psychiatry*¹⁴² proposed a number of screening and monitoring guidelines that can serve as an initial template for clinicians who are monitoring schizophrenia patients (Table 2).

Other Interventions

Typical drugs used for weight loss in nonpsychotic patients can potentially exacerbate psychosis, so proceeding with these kinds of treatments should be done with precaution. Adjunctive medications that have been employed have included nizatidine, amantadine, topiramate, and sibutramine in small studies, but with few good randomized clinical trials supporting the use of these agents.^{147–150} Also, somewhat discouragingly, both topiramate and sibutramine may alter mental status and thus worsen symptoms of schizophrenia according to several case reports.^{151,152}

Bariatric surgery for morbid obesity is often contraindicated in psychotic patients as there is concern among the surgical community that schizophrenia patients cannot adhere to dietary and postsurgical instructions. Hamoui et al.¹⁵³ have shown success of bariatric surgery in a small handful of patients, however.

SUMMARY

Obesity presents an ever increasing health threat to millions of Americans, with 62% of the population overweight and 20% to 30% obese. The risks posed by obesity, besides the profound psychosocial consequences, are a range of comorbid medical conditions—hypertension, type 2 diabetes, dyslipidemias, cardiovascular disease, cancer, osteoarthritis, and sleep apnea—as well as premature death. For the population of individuals with schizophrenia, these same burdens of obesity compound a devastating illness with its own morbidity and mortality.

The obese schizophrenia patient’s plight with regard to physical well-being is made worse because the majority of such a person’s treatment regimens will increase the risk of obesity. Iatrogenic weight gain must be at the forefront of concerns regarding the care of the schizophrenia patient and not simply assumed to be an unaddressable challenge beyond the clinician’s concern. When a careful follow-up during the first few weeks of treatment clearly shows weight gain, it is up to the practicing physician when initiating or changing antipsychotic treatment to consider the dissimilar weight gain liabilities of currently available agents. In cases where the risks/benefits are carefully weighed, acute consideration of switching a patient who is rapidly gaining weight on his or her current medication should be made. Prioritizing the patient’s mental condition is essential. A switch should not be made if the risk of exacerbating the mental condition outweighs the potential benefits. We recommend providing education and support for healthy lifestyles to our patients. Patients’ families and caregivers should also be educated about the potential weight gain liabilities of currently available antipsychotic medications.

In a recent consensus conference sponsored by the ADA and its subsequently published monitoring guidelines,¹⁴² we recommended monitoring weight in all patients taking antipsychotic medications. We recommend checking weight and waist circumference at each patient visit, particularly early on in the treatment of a patient with a new antipsychotic medication. A steep slope, e.g., 2 lb (0.9 kg) of weight gain per week in the first 8 weeks of treatment, may predict more serious metabolic conse-

quences for the patient, and intervention will undoubtedly be necessary. Other guidelines will be emerging from various concerned entities, e.g., the American Psychiatric Association.

In addition to the behavioral intervention of weighing a patient, we recommend that patients provide a food and exercise diary to assist with counseling them about healthier food choices. We will often refer patients to a nutritionist and try to coach patients in ways to increase physical activity in their lives. Unfortunately, weight loss medications and bariatric surgery are relatively contraindicated in this patient population, and simple behavioral interventions, at this point, are what we can offer patients, as well as rational choices of medications to minimize weight gain and optimize psychiatric outcomes.¹⁴²

Drug names: amantadine (Symmetrel and others), aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, Fazaclo, and others), divalproex sodium (Depakote), fluphenazine (Prolixin and others), haloperidol (Haldol and others), molidone (Moban), nizatidine (Axid and others), olanzapine (Zyprexa), perphenazine (Trifalon and others), quetiapine (Seroquel), risperidone (Risperdal), sibutramine (Meridia), topiramate (Topamax), ziprasidone (Geodon).

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