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/m^2), 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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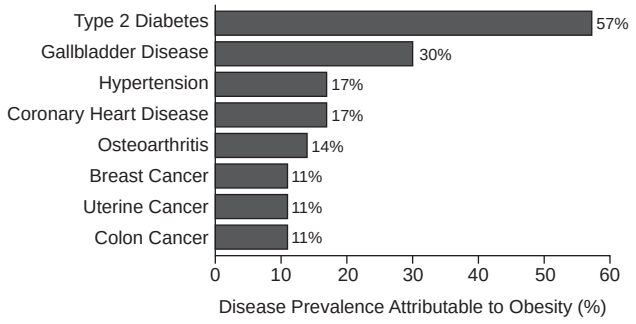
A commonly used term to define obesity is *body mass index*. This term takes into account a person's body weight relative to his or her height and is determined by dividing the individual's weight in kg by his or her height in meters squared (the conversion is 703 × lb/in^2). A BMI greater than or equal to 25 kg/m^2 is currently used as the cutoff of overweight. A BMI greater than or equal to 30 kg/m^2 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/m^2 who have no obesity-related problems and can prescribe anti-obesity medications to patients with a BMI of 27 kg/m^2 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/m^2. 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/m^2). 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]



[a]Data from Wolf and Colditz.[154]

at BMIs greater than 25.0 kg/m^2 in women and 26.5 kg/m^2 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. Thakore[18] 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 colleagues[40] 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 $\geq$ 30 kg/m^2, 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 weight[44] and decreases with age.[45] The thermic effect of food is controlled in part by the sympathetic nervous system[46] 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/m^2), 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 Study[61] found a greater risk for diabetes with increasing BMI, and at a BMI of ≥ 31 kg/m^2, 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 HDL_2 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 Sacks[162] 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/m^2) and that about 28% of adults are obese (BMI ≥ 30 kg/m^2).[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-naive 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 colleagues[17] 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

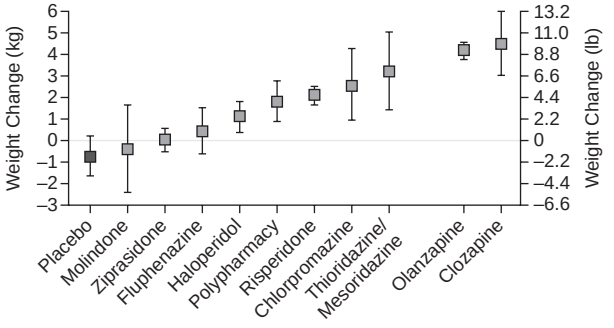
Clozapine, olanzapine, and risperidone. Although clozapine, the first "atypical" (novel or second-generation) antipsychotic medication, showed promise as an alternative to the conventional antipsychotics because of its low incidence of extrapyramidal effects and its beneficial effect on the negative 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 analysis[73] 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]



[a]Reprinted with permission from Allison et al.[90]
[b]Bars 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 trials[83–85] and found this consistent finding. Additionally, nonpharmaceutical company research[86] 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 medication[87] (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 study[89] 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/m^2 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, Peuskens[91] 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 studies[95] 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 studies[97–99] 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 quetiapine[97–99] 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 ≥ 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 study[98] 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 (≥ 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 (≥ 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.

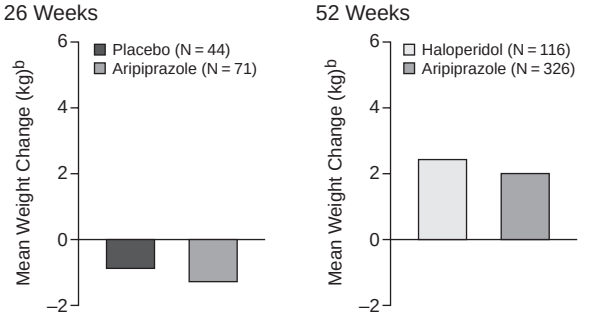
In another randomized, double-blind study by Daniel et al.,[102] patients with an acute exacerbation of schizophrenia or schizoaffective disorder received either 80 mg/day or 160 mg/day of ziprasidone for 6 weeks. There was a median increase in body weight of 1 kg (2.2 lb) for the ziprasidone 80-mg/day 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]



[a]Data from Pigott et al.[109] and Kasper et al.[155]
[b]Observed 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 (≥ 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]

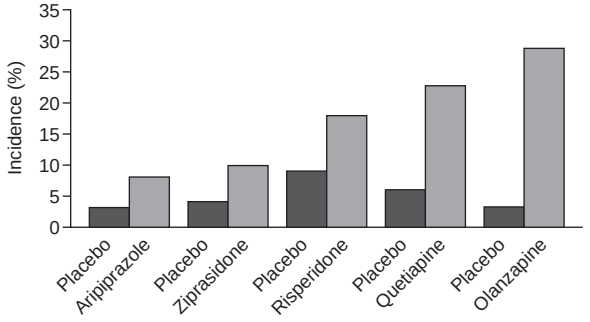
Marder et al.[108] reported on the safety and tolerability of aripiprazole using pooled data from 5 short-term, placebo-controlled trials in schizophrenia including over 1500 patients. At endpoint, aripiprazole patients showed minimal (< 1 kg [< 2.2 lb]) mean weight gain at doses from 2 to 30 mg/day, 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 study[110] 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 (≥ 7%) Weight Gain During Antipsychotic Treatment[a]



[a]Data 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 ≥ 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 ≥ 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 colleagues[114] 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 ± SD age = 10.2 ± 3.7 years), there was a range of weight gain in 12 individuals of 10 to 35 lb (5–16 kg) and a mean ± SD weight gain of 17.8 ± 7.5 lb (8.0 ± 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.

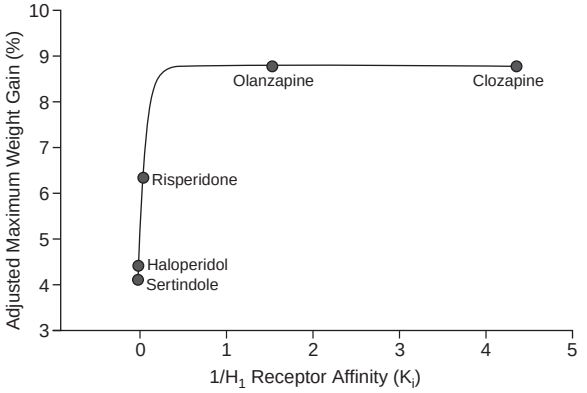
Children and adolescents have also been shown to gain substantial weight on quetiapine. Martin et al.[118] reported on a 16-week, open-label trial of 6 male patients with a mean ± SD age of 10.9 ± 3.3 years, treated with quetiapine. The 2 patients who completed the trial had significant weight gains 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 antipsychotics.[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).

Figure 5. Weight Gain as a Function of Histamine H_1 Receptor Affinity[a,b]



[a]Reprinted 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_i).

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

H_1 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 study[140] 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 study[141] 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 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.

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 $703 \times lb/in^2$)
Preventive maneuvers
Encourage healthy lifestyles
Educate caregivers

[a]Data from Wirshing et al.[73] and the American Diabetes Association consensus statement.[142]
Abbreviation: BMI = body mass index.

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 colleagues[143] 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	✓			✓			✓

[a]Based on the American Diabetes Association consensus statement.[142]
[b]More 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), molindone (Moban), nizatidine (Axid and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), quetiapine (Seroquel), risperidone (Risperdal), sibutramine (Meridia), topiramate (Topamax), ziprasidone (Geodon).

REFERENCES

1. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 2003;289:76–79
2. Mokdad AH, Bowman BA, Ford ES, et al. The continuing epidemics of obesity and diabetes in the United States. JAMA 2001;286:1195–1200
3. National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. Obes Res 1998;6(suppl 2):51S–209S
4. Allison DB, Fontaine KR, Manson JE, et al. Annual deaths attributable to obesity in the United States. JAMA 1999;282:1530–1538
5. Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of US adults. N Engl J Med 1999;341:1097–1105
6. McCreadie RG. Diet, smoking and cardiovascular risk in people with schizophrenia: descriptive study. Br J Psychiatry 2003;183:534–539
7. Schlosser E. Fast Food Nation: The Dark Side of the All-American Meal. New York, NY: Houghton Mifflin; 2001
8. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999–2000. JAMA 2002;288:1723–1727
9. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. J Clin Psychiatry 2001;62(suppl 7):22–31
10. Silverstone T, Smith G, Goodall E. Prevalence of obesity in patients receiving depot antipsychotics. Br J Psychiatry 1988;153:214–217
11. Stedman T, Welham J. The distribution of adipose tissue in female inpatients receiving psychotropic drugs. Br J Psychiatry 1993;162:249–250
12. Kendrick T. Cardiovascular and respiratory risk factors and symptoms among general practice patients with long-term mental illness. Br J Psychiatry 1996;169:733–739
13. Centorrino F, Baldessarini RJ, Kando JC, et al. Clozapine and metabolites: concentrations in serum and clinical findings during treatment of chronically psychotic patients. J Clin Psychopharmacol 1994;14:119–125
14. Druss BG, Bradford DW, Rosenheck RA, et al. Mental disorders and use of cardiovascular procedures after myocardial infarction. JAMA 2000; 283:506–511
15. Dixon L, Weiden P, Delahanty J, et al. Prevalence and correlates of diabetes in national schizophrenia samples. Schizophr Bull 2000;26:903–912
16. Allison DB, Fontaine KR, Heo M, et al. The distribution of body mass index among individuals with and without schizophrenia. J Clin Psychiatry 1999;60:215–220
17. Homel P, Casey D, Allison DB. Changes in body mass index for individuals with and without schizophrenia, 1987–1996. Schizophr Res 2002;55: 277–284
18. Thakore JH. Metabolic disturbance in first-episode schizophrenia. Br J Psychiatry Suppl 2004;47:S76–S79
19. Leucht S, Pitschel-Walz G, Abraham D, et al. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo: a meta-analysis of randomized controlled trials. Schizophr Res 1999; 35:51–68
20. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2003;60:553–564
21. Fontaine KR, Heo M, Harrigan EP, et al. Estimating the consequences of anti-psychotic induced weight gain on health and mortality rate. Psychiatry Res 2001;101:277–288
22. Ho B-C, Andreasen N, Flaum M. Dependence on public financial support early in the course of schizophrenia. Psychiatr Serv 1997;48:948–950
23. McGlashan TH. A selective review of recent North American long-term followup studies of schizophrenia. Schizophr Bull 1988;14:515–542
24. Kenny JT, Meltzer HY. Attention and higher cortical functions in schizophrenia. J Neuropsychiatry Clin Neurosci 1991;3:269–275
25. Saykin AJ, Gur RC, Gur RE, et al. Neuropsychological function in schizophrenia: selective impairment in memory and learning. Arch Gen Psychiatry 1991;48:618–624
26. Seidman LJ, Oscar-Berman M, Kalinowski AG, et al. Experimental and clinical neuropsychological measures of prefrontal dysfunction in schizophrenia. Neuropsychology 1995;9:481–490
27. Bellack AS. Cognitive rehabilitation for schizophrenia: is it possible? is it necessary? Schizophr Bull 1992;18:43–50
28. Jaeger J, Berns S, Tigner A, et al. Remediation of neuropsychological deficits in psychiatric populations: rationale and methodological considerations. Psychopharmacol Bull 1992;28:367–390
29. Harris EC, Barraclough B. Excess mortality of mental disorder. Br J Psychiatry 1998;173:11–53
30. Newman SC, Bland RC. Mortality in a cohort of patients with schizophrenia: a record linkage study. Can J Psychiatry 1991;36:239–245
31. Goff DC, Heckers S, Freudenreich O. Schizophrenia. Med Clin North Am 2001;85:663–689
32. Cohen LJ, Test MA, Brown RL. Suicide and schizophrenia: data from a prospective community treatment study. Am J Psychiatry 1990;147: 602–607
33. Osby U, Correia N, Brandt L, et al. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. Schizophr Res 2000;45: 21–28
34. Ziedonis D, Williams JM, Smelson D. Serious mental illness and tobacco addiction: a model program to address this common but neglected issue. Am J Med Sci 2003;326:223–230
35. Kurzthaler I, Fleischhacker WW. The clinical implications of weight gain in schizophrenia. J Clin Psychiatry 2001;62(suppl 7):32–37
36. Robinson D, Woerner MG, Alvir JM, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 1999;56:241–247
37. Perkins DO. Predictors of noncompliance in patients with schizophrenia. J Clin Psychiatry 2002;63:1121–1128
38. Masand PS. Weight gain and antipsychotic medications [letter]. J Clin Psychiatry 1999;60:336–337
39. Young JL, Zonana HV, Shepler L. Medication noncompliance in schizophrenia: codification and update. Bull Am Acad Psychiatry Law 1986;14:105–122
40. Weiden PJ, Allison DB, Mackell JA, et al. Obesity as a Risk Factor for Antipsychotic Noncompliance. Arlington, Va: American Psychiatric Association; 2000
41. Fairburn CG, Brownell KD, eds. Eating Disorders and Obesity: A Comprehensive Handbook. 2nd ed. New York, NY: The Guilford Press; 2002
42. Ravussin E, Lillioja S, Anderson TE, et al. Determinants of 24-hour energy expenditure in man: methods and results using a respiratory chamber. J Clin Invest 1986;78:1568–1578
43. Ravussin E, Lillioja S, Knowler WC, et al. Reduced rate of energy expenditure as a risk factor for body-weight gain. N Engl J Med 1988;318: 467–472
44. Bray G. Drug treatment of obesity: don't throw the baby out with the bath water. Am J Clin Nutr 1998;67:1–2
45. Centers for Disease Control and Prevention. Physical Activity and Health: A Report of the Surgeon General. Atlanta, Ga: US Dept Health Human Services; 1996:1–278
46. de Jonge L, Bray GA. The thermic effect of food and obesity: a critical review. Obes Res 1997;5:622–631
47. Bray GA. Contemporary Diagnosis and Management of Obesity. Newtown, Pa: Handbooks in Health Care Co; 1998
48. Gibbs J, Smith GP. Peptides of digestive system and brain: model of the cholecystokinin [in French]. Ann Endocrinol (Paris) 1988;49:113–120
49. Flint A, Raben A, Astrup A, et al. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest 1998;101:

515–520
50. Heymsfield SB, Greenberg AS, Fujioka K, et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. JAMA 1999;282:1568–1575
51. Bray GA, York DA. The MONA LISA hypothesis in the time of leptin. Recent Prog Horm Res 1998;53:95–117
52. Bray GA, Tartaglia LA. Medicinal strategies in the treatment of obesity. Nature 2000;404:672–677
53. Smith BK, York DA, Bray GA. Activation of hypothalamic serotonin receptors reduced intake of dietary fat and protein but not carbohydrate. Am J Physiol 1999;277:R802–R811
54. Leibowitz SF. Reciprocal hunger-regulating circuits involving alpha- and beta-adrenergic receptors located, respectively, in the ventromedial and lateral hypothalamus. Proc Natl Acad Sci U S A 1970;67:1063–1070
55. Bray GA. Contemporary Diagnosis and Management of Obesity. 2nd ed. Newtown, Pa: Handbooks in Health Care Co; 2003
56. Astrup A, Breum L, Toubro S, et al. The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine and placebo in obese subjects on an energy restricted diet: a double blind trial. Int J Obes Relat Metab Disord 1992;16:269–277
57. Bjorntorp P. Body fat distribution, insulin resistance, and metabolic diseases. Nutrition 1997;13:795–803
58. Agras WS. Treatment of binge-eating disorder. In: Gabbard GO, ed. Treatments of Psychiatric Disorders, vol 2. 3rd ed. Washington, DC: American Psychiatric Publishing, Inc; 2001:2209–2219
59. Aronne LJ. Epidemiology, morbidity, and treatment of overweight and obesity. J Clin Psychiatry 2001;62(suppl 23):13–22
60. Field AE, Byers T, Hunter DJ, et al. Weight cycling, weight gain, and risk of hypertension in women. Am J Epidemiol 1999;150:573–579
61. Colditz GA, Willett WC, Rotnitzky A, et al. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 1995;122:481–486
62. Despres J-P. Dyslipidaemia and obesity. Baillieres Clin Endocrinol Metab 1994;8:629–660
63. Despres J-P, Nadeau A, Tremblay A, et al. Role of deep abdominal fat in the association between regional adipose tissue distribution and glucose tolerance in obese women. Diabetes 1989;38:304–309
64. Bjorntorp P. Visceral obesity: a "civilization syndrome." Obes Res 1993;1:206–222
65. Reaven GM. Banting lecture 1988: role of insulin resistance in human disease. Diabetes 1988;37:1595–1607
66. Mokdad AH, Serdula MK, Dietz WH, et al. The spread of the obesity epidemic in the United States, 1991–1998. JAMA 1999;282:1519–1522
67. Kraepelin E. Dementia Praecox and Paraphrenia. Edinburgh, Scotland: E&S Livingston; 1919
68. Planansky K. Changes in weight in patients receiving a "tranquilizing" drug. Psychiatr Q 1958;32:289–303
69. Kuczmarski RJ, Flegal KM, Campbell SM, et al. Increasing prevalence of overweight among US adults: the national health and nutrition examination surveys, 1960 to 1991. JAMA 1994;272:205–211
70. Tsuang MT, Perkins K, Simpson JC. Physical diseases in schizophrenia and affective disorder. J Clin Psychiatry 1983;44:42–46
71. Koran LM, Sox HC Jr, Marton KI, et al. Medical evaluation of psychiatric patients, 1: results in a state mental health system. Arch Gen Psychiatry 1989;46:733–740
72. Baptista T. Body weight gain induced by antipsychotic drugs: mechanisms and management. Acta Psychiatr Scand 1999;100:3–16
73. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. J Clin Psychiatry 1999;60:358–363
74. Bagnall A, Fenton M, Lewis R, et al. Molindone for schizophrenia and severe mental illness. Cochrane Database Syst Rev 2000;CD002083
75. Hummer M, Kemmler G, Kurz M, et al. Weight gain induced by clozapine. Eur Neuropsychopharmacol 1995;5:437–440
76. Stanton JM. Weight gain associated with neuroleptic medication: a review. Schizophr Bull 1995;21:463–472
77. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. Am J Psychiatry 2000;157:975–981
78. Eaton WW, Mortensen PB, Herrman H, et al. Long-term course of hospitalization for schizophrenia, pt 1: risk for rehospitalization. Schizophr Bull 1992;18:217–228
79. Umbricht DSG, Pollack S, Kane JM. Clozapine and weight gain. J Clin Psychiatry 1994;55(suppl B):157–160
80. Beasley CM Jr, Sanger T, Satterlee W, et al. Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacology (Berl) 1996;124:159–167
81. Osser DN, Najarian DM, Dufresne RL. Olanzapine increases weight and serum triglyceride levels. J Clin Psychiatry 1999;60:767–770
82. Tollefson GD, Beasley CM Jr, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997;154:457–465
83. Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997;17:407–418
84. Tran PV, Dellva MA, Tollefson GD, et al. Oral olanzapine versus oral haloperidol in the maintenance treatment of schizophrenia and related psychoses. Br J Psychiatry 1998;172:499–505
85. Conley RR, Mahmoud R. A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. Am J Psychiatry 2001;158:765–774
86. Lindenmayer JP, Czobor P, Volavka J, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. Am J Psychiatry 2003;160:290–296
87. Beasley CM Jr, Hamilton SH, Crawford AM, et al. Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. Eur Neuropsychopharmacol 1997;7:125–137
88. Gupta S, Droney T, Al Samarrai S, et al. Olanzapine: weight gain and therapeutic efficacy. J Clin Psychopharmacol 1999;19:273–275
89. Ried LD, Renner BT, Bengtson MA, et al. Weight change after an atypical antipsychotic switch. Ann Pharmacother 2003;37:1381–1386
90. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686–1696
91. Peuskens J. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Br J Psychiatry 1995;166:712–726
92. Claus A, Bollen J, De Cuyper H, et al. Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients: a multicentre double-blind comparative study. Acta Psychiatr Scand 1992;85:295–305
93. Hoyberg OJ, Fensbo C, Remvig J, et al. Risperidone versus perphenazine in the treatment of chronic schizophrenic patients with acute exacerbations. Acta Psychiatr Scand 1993;88:395–402
94. Emsley RA. Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. Risperidone Working Group. Schizophr Bull 1999;25:721–729
95. Song F. Risperidone in the treatment of schizophrenia: a meta-analysis of randomized controlled trials. J Psychopharmacol 1997;11:65–71
96. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825–835
97. Borison RL, Arvanitis LA, Miller BG. ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. J Clin Psychopharmacol 1996;16:158–169
98. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biol Psychiatry 1997;42:233–246
99. Small JG, Hirsch SR, Arvanitis LA, et al. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. Arch Gen Psychiatry 1997;54:549–557
100. Rak IW, Jones AM, Raniwalla J, et al. Weight changes in patients treated with Seroquel (quetiapine) [abstract]. Schizophr Res 2000;41:206
101. Keck P Jr, Buffenstein A, Ferguson J, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. Psychopharmacology (Berl) 1998;140:173–184
102. Daniel DG, Zimbroff DL, Potkin SG, et al. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Ziprasidone Study Group. Neuropsychopharmacology 1999;20:491–505
103. Arato M, O'Connor R, Meltzer HY. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. Int Clin Psychopharmacol 2002;17:207–215
104. Cohen S, Fitzgerald B, Okos A, et al. Weight, lipids, glucose, and behavioral measures with ziprasidone treatment in a population with mental retardation. J Clin Psychiatry 2003;64:60–62
105. Daniel DG. Tolerability of ziprasidone: an expanding perspective. J Clin Psychiatry 2003;64(suppl 19):40–49
106. Casey DE, Carson WH, Saha AR, et al. Switching patients to aripiprazole from other antipsychotic agents: a multicenter randomized study. Psychopharmacology (Berl) 2003;166:391–399
107. Potkin SG, Saha AR, Kujawa MJ, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. Arch Gen Psychiatry

2003;60:681–690
108. Marder SR, McQuade RD, Stock E, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. Schizophr Res 2003;61:123–136
109. Pigott TA, Carson WH, Saha AR, et al. Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study. J Clin Psychiatry 2003;64:1048–1056
110. Cornblatt B, Kern RS, Carson WH, et al. Neurocognitive effects of aripiprazole versus olanzapine in stable psychosis [abstract]. Int J Neuropsychopharmacol 2002;5(suppl 1):S185
111. Wirshing DA, Boyd JA, Pierre JM, et al. Delusions associated with quetiapine-related weight redistribution [letter]. J Clin Psychiatry 2002;63:247–248
112. Tandon R, Harrigan E, Zorn SH. Ziprasidone: a novel antipsychotic with unique pharmacology and therapeutic potential. J Serotonin Res 1997;4:159–177
113. Casey DE, Daniel DG, Wassef AA, et al. Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. Neuropsychopharmacology 2003;28:182–192
114. Theisen FM, Linden A, Geller F, et al. Prevalence of obesity in adolescent and young adult patients with and without schizophrenia and in relationship to antipsychotic medication. J Psychiatr Res 2001;35: 339–345
115. Findling RL, Maxwell K, Wiznitzer M. An open clinical trial of risperidone monotherapy in young children with autistic disorder. Psychopharmacol Bull 1997;33:155–159
116. McDougle CJ, Holmes JP, Bronson MR, et al. Risperidone treatment of children and adolescents with pervasive developmental disorders: a prospective open-label study. J Am Acad Child Adolesc Psychiatry 1997;36:685–693
117. Martin A, Landau J, Leebens P, et al. Risperidone-associated weight gain in children and adolescents: a retrospective chart review. J Child Adolesc Psychopharmacol 2000;10:259–268
118. Martin A, Koenig K, Scahill L, et al. Open-label quetiapine in the treatment of children and adolescents with autistic disorder. J Child Adolesc Psychopharmacol 1999;9:99–107
119. Shaw JA, Lewis JE, Pascal S, et al. A study of quetiapine: efficacy and tolerability in psychotic adolescents. J Child Adolesc Psychopharmacol 2001;11:415–424
120. Jones AM, Rak IW, Raniwalla J, et al. Weight changes in patients treated with Seroquel (quetiapine). Presented at the 38th annual meeting of the American College of Neuropsychopharmacology; Dec 12–16, 1999; Acapulco, Mexico
121. Brecher M, Rak IW, Melvin K, et al. The long-term effect of quetiapine (Seroquel) monotherapy on weight in patients with schizophrenia. Int J Psychiatry Clin Pract 2000;4:287–291
122. Woods SC, Seeley RJ, Porte D Jr, et al. Signals that regulate food intake and energy homeostasis. Science 1998;280:1378–1383
123. Halford JC, Blundell JE. Pharmacology of appetite suppression. Prog Drug Res 2000;54:25–58
124. Casey DE, Zorn SH. The pharmacology of weight gain with antipsychotics. J Clin Psychiatry 2001;62(suppl 7):4–10
125. Richelson E. Receptor pharmacology of neuroleptics: relation to clinical effects. J Clin Psychiatry 1999;60(suppl 10):5–14
126. Richelson E, Souder T. Binding of antipsychotic drugs to human brain receptors focus on newer generation compounds. Life Sci 2000;68: 29–39
127. Shapiro DA, Renock S, Arrington E, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology 2003;28:1400–1411
128. Schmidt AW, Lebel LA, Howard HR Jr, et al. Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. Eur J Pharmacol 2001;425:197–201
129. Sargent PA, Sharpley AL, Williams C, et al. 5-HT2C receptor activation decreases appetite and body weight in obese subjects. Psychopharmacology (Berl) 1997;133:309–312
130. Rauser L, Savage JE, Meltzer HY, et al. Inverse agonist actions of typical and atypical antipsychotic drugs at the human 5-hydroxytryptamine(2C) receptor. J Pharmacol Exp Ther 2001;299: 83–89
131. Coulie B, Tack J, Bouillon R, et al. 5-Hydroxytryptamine-1 receptor activation inhibits endocrine pancreatic secretion in humans. Am J Physiol 1998;274:E317–E320
132. Peschke E, Peschke D, Hammer T, et al. Influence of melatonin and serotonin on glucose-stimulated insulin release from perifused rat pancreatic islets in vitro. J Pineal Res 1997;23:156–163
133. Seeger TF, Seymour PA, Schmidt AW, et al. Ziprasidone (CP-88,059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. J Pharmacol Exp Ther 1995;275:101–113
134. Baptista T, Lacruz A, Meza T, et al. Antipsychotic drugs and obesity: is prolactin involved? Can J Psychiatry 2001;46:829–834
135. Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest 2000;106:473–481
136. Harris RBS. Leptin: much more than a satiety signal. Annu Rev Nutr 2000;20:45–75
137. Melkersson KI, Hulting A-L, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. J Clin Psychiatry 2000;61:742–749
138. Pollmacher T, Haack M, Schuld A, et al. Effects of antipsychotic drugs on cytokine networks. J Psychiatr Res 2000;34:369–382
139. Zhang ZJ, Yao ZJ, Mou XD, et al. Association of –2548G/A functional polymorphism in the promoter region of leptin gene with antipsychotic agent-induced weight gain [in Chinese]. Zhonghua Yi Xue Za Zhi 2003;83:2119–2123
140. Reynolds GP, Zhang ZJ, Zhang XB. Association of antipsychotic drug-induced weight gain with a 5-HT2C receptor gene polymorphism. Lancet 2002;359:2086–2087
141. Pooley EC, Fairburn CG, Cooper Z, et al. A 5-HT2C receptor promoter polymorphism (HTR2C-759C/T) is associated with obesity in women, and with resistance to weight loss in heterozygotes. Am J Med Genet 2004;126B:124–127
142. American Diabetes Association. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. J Clin Psychiatry 2004;65:267–272
143. Reinstein MJ, Sirotovskaya LA, Jones LE, et al. Effect of clozapine-quetiapine combination therapy on weight and glycaemic control: preliminary findings. Clin Drug Invest 1999;18:99–104
144. O'Keefe CD, Noordsy DL, Liss TB, et al. Reversal of antipsychotic-associated weight gain. J Clin Psychiatry 2003;64:907–912
145. Ball MP, Coons VB, Buchanan RW. A program for treating olanzapine-related weight gain. Psychiatr Serv 2001;52:967–969
146. Menza M, Vreeland B, Minsky S, et al. Managing atypical antipsychotic-associated weight gain: 12-month data on a multimodal weight control program. J Clin Psychiatry 2004;65:471–477
147. Levy E, Margolese HC, Chouinard G. Topiramate produced weight loss following olanzapine-induced weight gain in schizophrenia [letter]. J Clin Psychiatry 2002;63:1045
148. Atmaca M, Kuloglu M, Tezcan E, et al. Nizatidine for the treatment of patients with quetiapine-induced weight gain. Hum Psychopharmacol 2004;19:37–40
149. Bahk W-M, Lee KU, Chae JH, et al. Open label study of the effect of amantadine on weight gain induced by olanzapine. Psychiatry Clin Neurosci 2004;58:163–167
150. Appolinario JC, Bacaltchuk J, Sichieri R, et al. A randomized, double-blind, placebo-controlled study of sibutramine in the treatment of binge-eating disorder. Arch Gen Psychiatry 2003;60:1109–1116
151. Hofer A, Fleischhacker WW, Hummer M. Worsening of psychosis after replacement of adjunctive valproate with topiramate in a schizophrenia patient [letter]. J Clin Psychiatry 2003;64:1267–1268
152. Taflinski T, Chojnacka J. Sibutramine-associated psychotic episode. Am J Psychiatry 2000;157:2057–2058
153. Hamoui N, Kingsbury S, Anthone GJ, et al. Surgical treatment of morbid obesity in schizophrenic patients. Obes Surg 2004;14:349–352
154. Wolf AM, Colditz GA. Current estimates of the economic cost of obesity in the United States. Obes Res 1998;6:97–106
155. Kasper S, Lerman MN, McQuade RD, et al. Efficacy and safety of aripiprazole vs haloperidol for long-term maintenance treatment following acute relapse of schizophrenia. Int J Neuropsychopharmacol 2003;6: 325–337
156. Abilify [package insert]. Princeton, NJ: Bristol-Myers Squibb Co; 2002
157. Geodon [package insert]. New York, NY: Pfizer Inc; 2002
158. Risperdal [package insert]. Titusville, NJ: Janssen Pharmaceutica Products, LP; 2002
159. Seroquel [package insert]. Wilmington, Del: AstraZeneca Pharmaceuticals LP; 2001
160. Zyprexa [package insert]. Indianapolis, Ind: Eli Lilly and Company; 2001
161. Conley RR, Buchanan RW. Evaluation of treatment-resistant schizophrenia. Schizophr Bull 1997;23:663–674
162. Sacks FM. Metabolic syndrome: epidemiology and consequences. J Clin Psychiatry 2004;65(suppl 18):3–12
163. McQuade RD, Stock E, Marcus R, et al. A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. J Clin Psychiatry 2004;65(suppl 18):47–56