

The Clinical Implications of Weight Gain in Schizophrenia

Ilsemarie Kurzthaler, M.D., and W. Wolfgang Fleischhacker, M.D.

© The tendency of most of the second generation antipsychotics to induce weight gain to a larger extent than that of traditional neuroleptics has renewed the interest in weight problems of patients with schizophrenia. Drug-induced weight gain has been identified as a major risk factor for various medical disorders that might be responsible for the increased morbidity and mortality rates of patients suffering from schizophrenia. Also, it has a major impact on compliance. This article focuses on the clinical relevance of increased body weight in schizophrenia. It outlines screening and management options to prevent and/or manage weight gain associated with schizophrenia in everyday clinical practice. The first strategies should be to identify obesity-prone patients at the beginning of treatment and provide information (to patients and caregivers) about the risks of weight gain and its consequences. Additionally, the possibility of weight gain calls for a regular monitoring of weight and weight-related laboratory parameters. The patients should also be offered dietary advice as well as regular exercise and behavior modification programs. Physicians must be aware of the problem of weight gain associated with schizophrenia and choose antipsychotic medication carefully, especially in patients at high risk for weight gain.

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On average, people suffering from schizophrenia are also of poorer physical health than the general population.¹ Thus, the recognition and management of health risk factors resulting either from the illness itself or from prescribed medication are essential parts of caring for these patients. The introduction of antipsychotic drug treatment into clinical psychiatry half a century ago represented a landmark in the management of schizophrenic disorders. Although pharmacotherapy is the basis of the management of patients suffering from schizophrenia, it can produce serious side effects that jeopardize patients' physical health² and can have a negative influence on compliance. For traditional neuroleptics, the main side effect concerns have been extrapyramidal symptoms (EPS).³ Since the development of clozapine and the introduction of other novel antipsychotics, which induce EPS to

a significantly lower extent,⁴ non-EPS-associated side effects, including weight gain, have captured interest in clinical practice and research. This interest is well justified by the fact that body weight gain occurs in up to 50% of patients receiving chronic administration of antipsychotic drugs⁵ and that noncompliance and impairments of quality of life, social reintegration, and physical health are likely consequences.

In this review, we focus on the clinical relevance of weight gain to physical health in schizophrenia as well as its potential influence on treatment outcome and outline management options based on the available evidence.

PREVALENCE OF OBESITY IN PATIENTS WITH SCHIZOPHRENIA

In the early literature on the subject, increased body weight in patients with schizophrenia during long-term treatment with neuroleptics was presented as a definitive fact.^{6,7} More recent evidence about obesity in patients with schizophrenia and in the general population presents a more complicated picture. Diverging results are shown in the study by Allison et al.⁸ that focuses on the distribution of body mass index (BMI) among individuals with and without schizophrenia. This study is based on 3 data sources: (1) the mental health supplement of the 1989 National Health Interview Survey (NHIS; includes 80,130 nonschizophrenic individuals and 150 individuals with self-reported schizophrenia), (2) baseline BMI data from a

From the Department of Biological Psychiatry, Innsbruck University Clinics, Innsbruck, Austria.

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Reprint requests to: Ilsemarie Kurzthaler, M.D., Department of Biological Psychiatry, Innsbruck University Clinics, Anichstrasse 35, A-6020 Innsbruck, Austria (e-mail: birgit.mader@uibk.ac.at).

clinical trial of ziprasidone (420 noninstitutionalized individuals with chronic psychotic disorders), and (3) data from the National Health and Nutrition Examination Survey III (NHANES III; includes 17,689 nonschizophrenic individuals).

The NHIS data revealed a significantly higher mean BMI (age-adjusted) in women with schizophrenia than in women without schizophrenia, but a similar mean BMI in men with and without schizophrenia. In contrast, the results from a comparison of the ziprasidone trial and NHANES III data sets displayed no difference between individuals with and without schizophrenia with respect to being overweight. The reason for the difference in age-adjusted BMI among women in the NHIS data but not the ziprasidone/NHANES III data is unclear. One possible explanation is that NHIS height and weight data were obtained by self-report. In addition, restrictions in entry criteria could have introduced a relative bias into the ziprasidone data set.

Silverstone et al.⁹ reported that the prevalence of clinically relevant obesity¹⁰ among patients (N = 226) suffering from chronic schizophrenia was 4 times that occurring in the greater London area generally¹¹ in the 25- to 64-year-old age group. No difference was found between men and women.

Any interpretation of the data reviewed above must consider the limitations inherent in these studies. In no single case were the samples of individuals with schizophrenia sufficiently large, nationally representative, exactly diagnosed, without selection bias, and inclusive of height and weight data obtained by accurate measurement. However, taken together, these data suggest that body weight is too high in most patients suffering from schizophrenia. Therefore, it is not only a problem in the clinical treatment of an individual patient, but an important issue of broader public health concern.

CAUSES OF WEIGHT GAIN IN SCHIZOPHRENIA

Certain symptoms of schizophrenia may predispose patients to gain weight. These include aspects of the negative syndrome such as apathy and anhedonia, which may impair self-monitoring of eating behavior. A subsequent illness-related increase in body weight will either be unnoticed or will not be a matter of interest or concern. However, positive symptoms may lead to weight loss, for example, in patients who stop eating to "cleanse" themselves or because command hallucinations tell them to do so. In such patients, weight increase may reflect symptom reduction and improvement.

Treatment Conditions

Inpatient treatment may be seen as another factor promoting the increase of body weight in patients with schizophrenia. Hospital admission often leads to reduced activity, causing lower energy output. In addition, meals

are served regularly and, in general, food intake is not limited. The latter, in particular, is difficult to handle in patients who lack the feeling of satiety.

Antipsychotic Treatment

Allison et al.¹² conducted a meta-analysis regarding the amount of weight gain associated with each antipsychotic drug available or undergoing clinical trials in the United States. All antipsychotic drugs, with the exceptions of molidone and pimozide, were associated with weight gain. Among the novel antipsychotics, ziprasidone had the lowest weight increase (0.04 kg after 10 weeks of treatment) followed by risperidone, sertindole, olanzapine, and clozapine, the latter being the drug with the highest weight increase (4.45 kg after 10 weeks of treatment). Several other groups¹³⁻¹⁵ have studied weight gain directly. They also reported increased weight predominantly in patients treated with clozapine, olanzapine, risperidone, and zotepine.

In an ongoing drug monitoring program of novel antipsychotics in our department, we are also investigating antipsychotic drug-induced weight gain. In an initial analysis, 20% (N = 6) of 30 patients treated with olanzapine (mean dose = 14.26 mg/dL) gained more than 10% of their baseline weight within the first 10 weeks of treatment. The maximum weight increase in a patient was 10.5 kg in 4 weeks.¹⁵ It can be assumed that the weight gain will increase in accordance with the length of time patients are treated with antipsychotic medication.¹⁶ This assumption is based on the physics and physiology of weight gain and previous empirical observations from studies for which longer-term data are available.

Presumptive Mechanisms of Weight Gain Associated With Antipsychotics

It is presumed that no single mechanism causes antipsychotics to play a role in increasing body weight. In general, weight can increase only by altering food intake, metabolic activity, or energy output. Until now, the mechanisms of body weight increase with antipsychotic treatment were poorly understood, but several possibilities have been suggested and are discussed in depth in this supplement.¹⁷

Food intake regulation. Weight gain most likely reflects differential pharmacologic action of the novel antipsychotics.¹³ Most of the research in this area has focused on the serotonergic system,¹⁸ which plays an important role in the regulation of food intake. Antagonism of serotonin (5-HT) receptors and the down-regulation of 5-HT₂ sites may explain psychotropic drug-induced appetite stimulation or a reduced feeling of satiety, with a subsequent increase in calorie intake leading to weight gain.¹⁹ Antipsychotics such as clozapine, zotepine, and traditional low-potency neuroleptics also have a high affinity for the histamine H₁ receptor,²⁰ therefore showing sedative effects that may lead to reduced mobility and, consequently, if calorie intake is not reduced, to increased body weight.

Antipsychotics with anticholinergic effects may induce dry mouth and thereby stimulate thirst. Patients suffering from this side effect often drink large amounts of high-caloric drinks, resulting in an increase in body weight.

Endocrine effects. For clozapine and olanzapine, the 2 antipsychotics associated with the highest level of weight gain, increased serum levels of leptin have been described.^{21,22} Leptin is a hormone exclusively expressed and secreted by differentiated adipocytes²³ and may play a role in the pathophysiology of obesity, since leptin levels increase exponentially with BMI or percentage of body fat. Although intriguing, these findings are thought to be secondary to weight gain.

HEALTH RISKS ASSOCIATED WITH WEIGHT GAIN IN SCHIZOPHRENIA

Recent evidence suggests that even if persons remain within the "normal" weight range, weight gain increases the risk of medical illness and premature death.²⁴ In the general population, obesity and weight gain have been associated with hypertension, type 2 diabetes, coronary heart disease, osteoarthritis, sleep apnea, and some types of cancer (endometrial, breast, prostate, and colon cancer).²⁵

Increased insulin secretion is a common feature of obesity. A correlation exists between the degree of obesity and the magnitude of hyperinsulinemia, particularly basal insulin levels. In obese people, insulin resistance is thought to be due to a combination of receptor and postreceptor defects in insulin action. Consequently, obesity is an important contributory factor to the development of diabetes, predominantly through its influence on insulin resistance, which exacerbates the diabetic state.²⁶

Wirshing et al.²⁷ reported 6 cases of new-onset diabetes related to antipsychotic drug treatment. Four of the 6 cases involved clozapine, as did all 9 of the previously reported cases in literature cited in this article, and the remaining 2 cases were treated with olanzapine. In this context, Hägg et al.²⁸ also showed that subjects treated with clozapine were more often diagnosed as suffering from type 2 diabetes or impaired glucose tolerance when compared with subjects treated with conventional depot neuroleptics.

As mentioned above, both clozapine and olanzapine have been shown to induce significant weight gain. Thus, one potential mechanism of diabetes induction in patients treated with antipsychotics may be weight gain, caused by an increase in adipose tissue that in turn leads to insulin insensitivity, glucose intolerance, and, if sufficiently severe, diabetes. In 12 of 15 reported cases, major risk factors for diabetes have been preexistent,²⁷ which indicates that the novel antipsychotics might induce diabetes by exacerbating existing disease or predisease. Until now, no direct relationship between novel antipsychotics and glucose homeostasis could be established.

A strong association also exists between hypertension and obesity. The mechanism by which obesity causes hypertension is uncertain; however, peripheral vascular resistance is usually normal, while blood volume is increased.²⁶ In addition, obesity increases the risk of coronary heart disease and stroke, largely mediated through hypertension, hyperproteinemia, and diabetes. Increased serum triglyceride levels have also been shown to be a significant risk factor.²⁹ In this context, Osser et al.¹⁴ found large triglyceride level elevations in patients taking olanzapine.

Kawachi²⁴ found that people who gain 5.0 to 7.9 kg as adults are 1.9 times more likely to develop type 2 diabetes mellitus and 1.25 times more likely to develop coronary heart disease than those who lose weight or maintain a stable weight after the age of 18 years. Gaining 11 kg or more in adulthood increases the risk of ischemic stroke by 1.69 to 2.52 times.

SOMATIC MORBIDITY/MORTALITY IN SCHIZOPHRENIA PATIENTS

Patients with schizophrenia have increased somatic morbidity and mortality risks compared with the general population.³⁰ Harris and Barraclough³¹ reported an overall death risk in patients suffering from schizophrenia 1.6 times that of the general population. These risks are accentuated in overweight patients. In addition, several studies^{32,33} have reported that patients with schizophrenia have the highest rate of nicotine use. Nicotine use, together with weight gain, plays an important role in cardiovascular morbidity and mortality as well as in the pathogenesis of certain types of cancer.³⁴

All of the issues discussed above add to the risk of morbidity and mortality in patients with schizophrenia, which is higher than that of the general population.^{30,31} It is therefore of utmost importance to keep these problems in mind when taking care of such patients.

Assessment of Physical Health of Psychiatric Patients

Physical examination is an important part in any psychiatric admission, because physical diseases may cause or worsen a mental disorder. However, psychiatric patients show a great deal of undiscovered somatic diseases.³⁵ Physical examination is often neglected, inaccurate, or poorly recorded.^{36,37} Furthermore, large discrepancies exist between psychiatrists in the practice of physical examination.³⁸

The findings of Osborn and Warner,³⁹ concerning the assessment of physical health of psychiatric patients, concur with previous studies^{36,40} that a substantial number of inpatients (29%) are not physically examined. In addition, this study has revealed that among trainees (senior house officers and registrar grade psychiatrists), physical examination is considered more important than taking a somatic health history. However, good evidence indicates that a somatic health history is the most powerful tool in the diagnosis of

somatic disease and that physical examination, when carried out in isolation, gives poor diagnostic information.

The importance of assessing the physical health of psychiatric patients is underlined by a study from Koran et al.⁴¹ showing that 39% of 529 psychiatric patients (269 suffering from schizophrenia) had an active, significant physical disease. Only about half of these diseases were recognized by the mental health system.

OTHER RELEVANT CONSEQUENCES OF ANTIPSYCHOTIC-INDUCED WEIGHT GAIN

Noncompliance

One of the best documented results in psychiatric research is that long-term treatment with antipsychotics is the major factor in preventing relapses and recurrences in schizophrenia. Therefore, almost all patients suffering from schizophrenia, including those with first episodes, are advised to continue medication for a considerable amount of time.⁴² One of the key parameters to ensure successful long-term treatment is compliance. Therefore, next to efficacy, tolerability and subjective acceptance of the drug by the patient are essential factors in a treatment plan. The latter aspects are influenced by antipsychotic side effects to a great extent. Fear of weight gain is one of the main factors contributing to poor compliance found in several other fields of pharmacotherapy (e.g., hormone replacement)⁴³ as well as in antipsychotic treatment.⁴⁴ Since weight gain is a frequently encountered side effect in treatment with novel antipsychotics, one must keep in mind that it may exert a potentially negative influence on compliance in the long-term treatment of schizophrenia.

Impairment of Quality of Life

Several studies examining the role and impact of new antipsychotic medication on quality of life have been reported over the last few years.^{45,46} There are strong indications that novel antipsychotics may help to improve the quality of life of patients with schizophrenia. Since weight gain is a common side effect of novel antipsychotics, it is quite likely to counteract such improvements by diminishing psychological well-being⁴⁷ and impairing physical functioning. A recent patient survey⁴⁸ has also ranked weight gain as the second most frequent negative effect on quality of life.

Social Withdrawal

Social withdrawal is a common and well-known symptom of schizophrenia, but it may also be a possible consequence of obesity. Overweight and obese people are stigmatized and discriminated against in various areas of daily life, including education, employment, and health care.⁴⁹ In a study by Myers and Rosen,⁵⁰ obese people were asked to list stigmatizing situations that they had encountered and their ways of coping with them. One finding was that

Table 1. Clinical Consequences of Antipsychotic-Induced Weight Gain in Patients With Schizophrenia

Health risks
Hypertension
Atherosclerosis
Type 2 diabetes
Cardiovascular diseases
Stroke
Stigmatization
Noncompliance
Impairment of quality of life
Social withdrawal

more frequent exposure to stigmatization was associated with greater psychological distress, more attempts to cope, and more severe obesity.

Patients with schizophrenia often show social, cognitive, and behavioral deficits and a lack of coping strategies to overcome the difficulties and distress of daily life. Thus, social withdrawal is often seen as the only way to manage stigmatization and discrimination evoked by being overweight as well as by the illness itself. Both schizophrenia and higher body weight may lead to a loss of self-esteem and subsequently reinforce social withdrawal.

CLINICAL IMPLICATIONS

An understanding of health behavior as well as a physical history and examination at the beginning of and during treatment are necessary to reduce the risks of morbidity and mortality in patients suffering from schizophrenia. In this review, we restrict the focus to the clinical implications concerning weight gain (Table 1). Screening and management recommendations are summarized in the following paragraphs (Table 2).

Screening

Baseline body weight should be established and recorded before prescribing antipsychotic medication, and monitoring of weight and weight-related laboratory parameters should be undertaken. These include fasting or nonfasting blood glucose and changes in hemoglobin A_{1c}, triglyceride, and total high- and low-density lipoprotein cholesterol levels. In addition, patients who are to be treated with novel antipsychotics should first be screened for risk factors for diabetes and cardiovascular diseases.

Management: Nonpharmacologic Options

Dietary advice is an important component of pretreatment counseling. Patients must be well informed about the risk of body weight increase with antipsychotic therapy. They should be encouraged to avoid high-caloric food and excessive intake of high-caloric drinks as well as to restrict the consumption of fat. Regular weight monitoring including realistic weight targets should be part of long-term management.

Table 2. Clinical Implications of Antipsychotic-Induced Weight Gain in Patients With Schizophrenia

Screening measures
Baseline weight
Weight and weight-related laboratory parameters (glucose, triglycerides, total high- and low-density lipoprotein cholesterol)
Risk factors for diabetes mellitus and cardiovascular diseases
Additional risk factors (smoking, drug and alcohol abuse)
Hemoglobin A _{1c} level
Management strategies
Nonpharmacologic options
Diet
Exercise
Behavioral therapy
Pharmacologic options
Dose reduction
Change of antipsychotic medication
Weight-reduction drugs, in selected cases

In addition, physical activity should be recommended, and patients should be advised to exercise regularly, since exercise has been said to be the most important but least addressed component of weight maintenance and appetite control.⁵¹ To achieve the above goals, behavioral modification programs in group or individual sessions for obesity-prone patients are often helpful.

Management: Pharmacologic Options

Dose adjustment. Intermittent and low-dose antipsychotic treatment in patients with schizophrenia have been suggested in the context of dose adjustment.⁵ However, both treatment options are controversial and cannot be generally recommended.⁵¹⁻⁵³

Change of antipsychotic medication. When clinically significant weight gain occurs during antipsychotic treatment, switching to another drug with a lower risk of inducing weight gain is an important management option. After reviewing the available evidence, we conclude that many of the novel antipsychotics have a higher risk of increasing weight gain than their traditional counterparts, with clozapine and olanzapine presenting the highest risk and ziprasidone possibly being the exception to this rule.¹²

Although the effects of switching antipsychotics have not yet been formally studied, it appears justified to recommend the substitution of drugs that have a lower risk of substantial weight increase for others with a higher risk for this side effect. Clearly, in this case, the decision to switch drugs must take the relative efficacies of the respective antipsychotics as well as the tolerability profiles beyond the effects on body weight into account. As a side note, although we lack robust predictors of drug-induced weight gain, it is self-evident that individuals with a high risk for weight increase or weight-related medical problems should be started on antipsychotics with low weight gain risks.

Weight-reduction drugs. In our opinion, antiobesity drugs should be administered only in selected patients when all other approaches have failed. If such drugs are

deemed to be the treatment of choice, it must be borne in mind that this type of intervention needs a long-term commitment. Using such medication to achieve a short-term weight loss is inappropriate, as most patients will regain weight once they discontinue the drug.⁵⁴

Recently, sibutramine, a mixed serotonergic and noradrenergic reuptake inhibitor, and orlistat were approved in many countries for treating obesity.⁵⁵ Since orlistat does not exert a systemic effect, it has a relatively low risk of interacting with coprescribed, centrally acting medications, such as antipsychotics. However, there are no formal interaction studies for either sibutramine or orlistat with any drugs used to treat schizophrenia. In addition, the antiobesity effects of these drugs have not been studied in patients with antipsychotic-induced weight gain. These facts reinforce the recommendation to use such drugs as last-resort treatment options only until further research has determined the efficacy and safety of these compounds.

CONCLUSION

Clinicians need to be aware of weight gain associated with schizophrenia, since, with the increasing use of novel antipsychotics, it is quite likely to become an increasing problem. In addition, it has a number of far-reaching clinical implications, especially in the long-term management of patients.

Increased body weight has been identified as a major risk factor for various medical disorders that might be responsible for the increased morbidity and mortality rates of patients with schizophrenia. It also has a major impact on compliance.

Therefore, the first strategy to prevent and/or manage excessive weight gain during antipsychotic treatment should be a screening to identify obesity-prone patients and to provide information about the risk of developing weight gain and its consequences to the patient. During the continuing course of treatment, the problem calls for monitoring of weight and weight-related laboratory parameters.

Next to the use of antipsychotics with a low propensity to induce weight gain, the best approach to weight control is a combination of diet, regular exercise, and behavioral modification of eating habits.

Drug names: clozapine (Clozaril and others), molindone (Moban), olanzapine (Zyprexa), orlistat (Xenical), pimozide (Orap), risperidone (Risperdal), sibutramine (Meridia).

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