Weight Gain and Antipsychotic Medication

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Antipsychotic-treated patients, who tend to take combinations of psychotropic agents that may cause weight gain, are at special risk for the problems associated with being overweight or obese. Medical and psychiatric examinations should include periodic monitoring for weight change and an obesity assessment for weight-related medical illness. The assessment should involve evaluation of body mass index and waist circumference as well as medical history. Preventative strategies should be undertaken for patients who gain 5 lb (2.3 kg) or more within a 3-year period. A change in antipsychotics may be necessary for overweight patients who are unwilling or unable to lose weight. A treatment plan for overweight or obese patients should include periodic monitoring and recommendations for changes in diet and physical activity. Support groups and adjunct medication may also be helpful. The patient should be reminded of the benefits of even modest weight loss.

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The incidence of obesity in the United States has been increasing steadily for the past several decades. Patients with psychoses who tend to take combinations of psychotropic agents that may cause weight gain are at special risk. A weight gain of 5 lb (2.3 kg) or more within 3 years indicates disruption of the process of appetite control and food ingestion, while continued weight gain with resultant overweight and obesity are associated with increased medical morbidity and mortality. Clinicians should regularly assess antipsychotic-treated patients for changes in weight and use preventative strategies in patients who gain 5 lb (2.3 kg) or more within a 3-year period.

ASSESSMENT OF OBESITY

The risk of morbidity from a wide variety of illnesses as well as mortality from any cause is increased in patients who are overweight or obese. Medical examinations should include periodic monitoring for weight change and, when appropriate, assessment of the individual's risk for conditions commonly associated with weight gain. Health care providers should review medical histories and should measure body mass index (BMI) and waist circumference along with other vital signs when assessing individuals for risks associated with weight gain.

From the Department of Surgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts. BMI, which describes relative weight for height (kg/m²), is significantly correlated with total body fat content and can be used to monitor changes in body weight (Appendix 1). According to the Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults,¹ overweight is defined as a BMI of 25 to 29.9 and obesity as a BMI of 30 or greater. A person with a BMI of 30 is generally about 14 kg (30 lb) overweight (e.g., someone who is 6 feet tall and weighs 221 lb or is 5 6" tall and weighs 186 lb). Obesity can be further subdivided into 3 classes: class I (mild) is a BMI of 30.0 to 34.9, class II (moderate) is a BMI of 35.0 to 39.9, and class III (severe) is a BMI of 40 or more.

An alternative way to assess risks associated with weight gain is to calculate ideal body weight. For men, the ideal body weight is 106 lb for the first 5 feet of height and 6 lb for each additional urch. For women, the ideal body weight is 100 lb for the first 5 feet of height and 5 lb for each additional inch. In this measurement system, an overweight woman is more than 20% above the ideal body weight, and an overweight man is more than 10% above the ideal body weight. Obesity is defined for women as being more than 45% above the ideal body weight and for men as being more than 35% above the ideal body weight.

Under both measurement systems, overweight and obesity are characterized by excess body fat. The presence of excess fat in the abdomen out of proportion to total body fat is an independent predictor of morbidity. Waist circumference provides a clinically acceptable measurement for assessing patient's abdominal fat content. Sex-specific cutoffs can be used to identify increased relative risk for the development of obesity-associated non-insulindependent diabetes mellitus (NIDDM), hypertension, and cardiovascular disease in most adults with a BMI of 25 to 34: a waist circumference of more than 102 cm (> 40 in) in

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men and more than 88 cm (> 35 in) in women. Thus, patients should be routinely queried about changes in clothing or belt size. The relative risk of developing weight-associated diseases increases with BMI and waist circumference in overweight and obese individuals as compared with those of normal weight (Table 1).¹

Adults (age 18 years or older) with a BMI of 25 or more are considered at risk for developing common weight-associated diseases including hypertension, NIDDM, Coronary heart disease, symptomatic gallstones, stroke, and breast cancer. For example, a weight gain of 10 lb or more is associated with an appreciable and statistically significant increase in risk of coronary heart disease. Hypertension is almost 4 times more likely to develop in an obese than a nonobese individual, and about 17% of the cases of hypertension in the United States could be prevented by eliminating obesity. The increased risk for diabetes is very high: obese individuals are 28 times as likely as nonobese individuals to become diabetic, and 61% of the cases of diabetes could be eliminated if obesity could be prevented.

Genotype also factors into the assessment of an individual's risk of developing weight-associated diseases. While obesity is a condition of larger size and excess body fat, it is also a complex and chronic illness that involves an interaction of genotype with the environment. To date, almost 200 genes and other markers have been associated or linked with human obesity phenotypes. An individual's genetic code can determine basal metabolic rate, neurotransmitter levels, regulatory peptide levels, and probably other variables that may create greater risk for weight gain. Some sets of genes interact with a disruption (mediated through alterations in steroid receptors) in the hypothalamic-pituitary-adrenal axis; those genes may ultimately provide a genotype for overweight persons who are at risk for dysfunction and disease.

A family history of syndrome X⁹ or the insulin resistance syndrome¹⁰ increases an individual's risk for developing weight-related illness. Syndrome X is a metabolic condition characterized by glucose intolerance, dyslipidemia, insulin resistance, hypertension, central obesity, and accelerated atherosclerosis. A marker for syndrome X is a weight gain associated with changes in triglyceride and high-density lipoprotein (HDL) levels. A rise in triglyceride levels and a decrease in HDL levels in a patient who has gained more than 5 lb indicate the patient is carrying a series of autosomal recessive genes that place him or her at risk for coronary heart disease, hypertension, NIDDM, and gout. Insulin resistance is characterized by impaired responsiveness to endogenous or exogenous insulin, and hyperinsulinemia is a sensitive and specific biomarker for insulin resistance.

As patients begin to migrate through mild to severe classes of overweight and obesity, their risk of developing cardiovascular disease, atherosclerosis, stroke, fibrinolysin abnormalities, sleep apnea, chronic respiratory infection, cholelithiasis, osteoarthritis, and menstrual abnormalities

Table 1. Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risk^a

			Disease	Risk ^b
			Waist Circumf	erence, cm(in)
	BMI	Obesity	$Men \le 102(40)$	Men > 102(40)
Weight Level	(kg/m^2)	Class	Women $\leq 88(35)$	Women > 88(35)
Underweight	< 18.5			
Normal ^c	18.5-24.9			
Overweight	25.0-29.9		Increased	High
Obesity	30.0-34.9	I	High	Very high
Obesity	35.0-39.9	II	Very high	Very high
Clinically				
significant				
obesity	≥ 40	III	Extremely high	Extremely high

^aReprinted from reference 1. Abbreviation: BMI = body mass index. ^bDisease risk for non-insulin-dependent diabetes mellitus, hypertension, and cardiovascular disease relative to individuals of normal weight and waist circumference.

as well as endometrial, breast, prostate, and colon cancer increases.¹ Patients who are at highest risk for these diseases are those with an adult weight gain of 18 kg (40 lb) or greater, those with a family history of syndrome X or dyslipidemia, and those who have hyperinsulinemia. Other factors that increase the risk of weight-associated illness are smoking, elevated systolic blood pressure, increased blood glucose levels, insulin resistance, and fat accumulation primarily in the upper body.¹¹

Manson et al.¹² investigated the relation between body weight and overall mortality in a cohort of 115,195 U.S. women enrolled in the prospective Nurses' Health Study. They found that body weight and mortality from all causes were directly related in this cohort and that a weight gain of 10 kg (22 lb) or more after the age of 18 years was associated with increased mortality in middle adulthood. The risk of death from coronary heart disease was sevenfold greater in women who had gained 20 kg (44 lb) or more than in those whose weight had remained stable (Table 2).

WEIGHT GAIN IN ANTIPSYCHOTIC-TREATED PATIENTS

Weight gain is a common side effect of many medications, including most antipsychotic agents. Antipsychotictreated patients are often also receiving other concurrent medications to treat psychiatric symptoms, medical illness, or both. When patients are taking multiple agents that cause weight gain, the effects may be additive, leading to obesity in some.

A recent meta-analysis¹³ of 78 studies that included data on weight change during antipsychotic treatment showed a mean weight gain after 10 weeks of 4.5 kg (9.8 lb) with clozapine, 4.2 kg (9.1 lb) with olanzapine, 2.1 kg (4.6 lb) with risperidone, and 0.9 kg (1.9 lb) with ziprasidone (which is not available in the United States). The outliers,

Increased waist circumference can also be a marker for increased risk even in persons of normal weight.

Table 2. Weight Change and Relative Risk of Deatha All Causes, Coronary Heart Disease, Deaths Risk (95% CI)b Risk (95% CI)b Weight Change (N) Loss $\geq 10 \text{ kg}$ 16 0.7 (0.4 to 1.4) 0.3 (0.0 to 4.3) 4-9 kg 54 1.2 (0.9 to 1.6) 0.6 (0.1 to 3.3) 224 Stablec Gain 4-9 kg 269 1.0 (0.8 to 1.2) 0.7 (0.4 to 1.8) 10-19 kg 292 1.2 (1.0 to 1.4) 2.6 (0.7 to 12.8) ≥ 20 kg 204 7.4 (2.4 to 21.7) 1.6 (1.3 to 1.9) < .002 p Value for trend < .001

^aAdapted from reference 12. Abbreviation: CI = confidence interval. ^bRelative risks are for women in specified weight change category as compared with those with stable weight. They have been adjusted for age in 5-year groups and for body-mass index at the age of 18. ^cChange < 4 kg.

those in the top 25%, gained twice as much as the mean. Both clozapine^{14,15} and olanzapine¹⁵ have been associated with significant increases in body weight compared with haloperidol. A weight gain of more than 5 lb (2.3 kg) in a patient being treated with antipsychotics should be a clinical marker for starting preventative efforts against further weight gain. In patients who continue to gain weight and are unwilling or fail to lose weight, a change of antipsychotics would be appropriate since weight gain is a leading cause of medication noncompliance. Of the atypical antipsychotics, risperidone and ziprasidone are less likely than clozapine and olanzapine to cause substantial weight gain. Loxapine and molindone seem to produce the least amount of weight gain among the typical neuroleptics. ¹⁶ Many patients with psychosis smoke, and the risk for developing weight-related disease doubles in patients who smoke.¹¹

Antipsychotic-treated patients often are taking concurrent medications for chronic medical conditions, and many common drugs have the side effect of weight gain. The average weight gain in patients being treated with antineoplastic agents is 2.5 to 6 kg, and weight gains of 10 kg are not unusual. For example, 96% of 237 patients receiving adjuvant chemotherapy for breast cancer gained a mean of 4.3 kg during 12 months of follow-up. ¹⁷ An average of 2 kg was gained during a 6-month daily prednisone course.18 Medications to treat both NIDDM and insulin-dependent diabetes mellitus (IDDM) may also cause weight gain. Patients enrolled in the Diabetes Control and Complications Trial gained a mean of 5.1 kg during the first year of intensive insulin therapy,¹⁹ and those in the United Kingdom Prospective Diabetes Study gained a mean of 2.6 kg with chlorpropamide and 1.7 kg with glibenclamide (glyburide) during 10 years of follow-up.²⁰

Many mood stabilizers and antidepressants, which are commonly administered along with antipsychotics, are linked to weight gain. Lithium maintenance therapy stimulates weight gains of over 10 kg in 20% of patients. ²¹ Anticonvulsants also cause weight gain: a mean gain of 21 kg was reported in women treated long-term with valproate, ²²

and weight gain is induced in a considerable percentage of patients taking carbamazepine.²³ Patients taking tricyclic antidepressants (TCAs) gained a mean of 1.3 to 2.9 lb per month of treatment, which led to an average total weight gain of 3 to 16 lb over 6 months; weight gain was the most common cause of treatment discontinuation, and significant weight loss occurred following discontinuation of the TCAs.²⁴ Weight gain in patients taking monoamine oxidase inhibitors (MAOIs) is less likely than in those taking TCAs,²³ but phenelzine is the MAOI most likely to cause weight gain.²⁵ Some patients taking selective serotonin reuptake inhibitors (SSRIs) may experience an initial weight loss followed by a later gain as the depression improves.

TREATMENT OF OVERWEIGHT AND OBESITY

Even a modest weight loss may improve compliance in antipsychotic-treated patients. Other potential sequelae of modest weight loss include improvement in gynecologic conditions, decrease in severity of sleep apnea, lower cardiovascular risk, reduced blood glucose and insulin levels, decreased blood pressure, decreased low-density lipoprotein (LDL) and triglyceride levels and accompanying increased HDL levels, and fewer and less severe symptoms of degenerative joint disease. Improvements in sleep apnea and cardiovascular risk are particularly important for smokers, and reducing blood glucose levels is a critical preventative strategy for those with an inherited trait for NIDDM. Weight loss of 10% or less has been shown to improve glycemic control in patients with NIDDM, reduce blood pressure in those with hypertension, and lower cholesterol levels in those with hyperlipidemia.²⁶

The first strategy in treating overweight and obesity in patients taking antipsychotics is prevention. Since few patients will be able to maintain a weight loss of more than 10% of their body weight, it is important to monitor and chart weight regularly in antipsychotic-treated patients, who are often at risk for substantial weight gain. A treatment plan should be adopted if a patient gains 5 lb (2.3 kg) or more. Even if weight eventually plateaus, patients are unlikely to lose all the extra weight they have added. A change in weight and the speed of the gain is a sensitive marker for the risk of obesity and its progression through the classes from mild to extreme.

Before devising a treatment plan for an individual patient who has gained 5 lb (2.3 kg) or more, the physician should consider the patient's current medications, tendency toward apathy, cognitive compromise, income level, impaired satiety and hunger cues, and level of sedation. Patients with serious mental illness may be apathetic or cognitively impaired, which could lower their motivation to lose weight. Clinicians may be able to heighten a patient's motivation by enumerating the dangers accompanying persistent obesity and describing a strategy for clinically assisted weight reduction. Medication may affect a

patient's satiety or hunger cues. For example, many antipsychotics act at 5-HT_{2C} and H₁ receptors, which have been implicated in appetite control. Increased 5-HT availability or direct activation of some 5-HT receptors reduces food consumption, while decreasing 5-HT receptor activation increases food consumption. Sedation is also a common side effect of many antipsychotic agents. Patients who are feeling sedated are likely to reduce their activity level and gain weight even without changing their diets. Sedation is often a dose-limiting side effect of clozapine, but risperidone and olanzapine have lower rates of sedation that are similar to or less than those observed with other highpotency compounds such as haloperidol.²⁷ Clinicians should first try lowering the antipsychotic dose in a patient whose level of sedation is impeding physical activity.

A treatment plan for overweight or obese patients should at least include periodic monitoring and recommendations for changes in diet and physical activity. Support groups and adjunct medication may also be useful. For weight loss efforts to be successful, the physician and patient should jointly make the decision to lose weight. The physician can use a simple questionnaire to ascertain the patient's attitude toward low-fat food and dietary control. A patient who doesn't think about dieting may need a different approach than one who has determined that weight loss would be beneficial or one who has unsuccessfully tried to lose weight multiple times. If the patient is reluctant to agree to lose weight, the prevention of further weight gain would be a reasonable goal. Most individuals can attain a loss of 10% of baseline weight at a rate of 1 to 2 lb per week if they are willing to establish an energy deficit of 300 to 500 kcal per day through a combination of dietary changes and increased physical activity. After 6 months, the rate of weight loss usually declines and weight plateaus because of a lesser energy expenditure at the lower weight. Clinicians should generally employ lifestyle therapy for 6 months before considering pharmacotherapy as an adjunct to the patient's dietary modifications and increased physical activity.

Most weight loss occurs because of decreased caloric intake, although sustained physical activity (equivalent to 45 minutes of intense walking at least 5 days/week) is a strong predictor of successful weight maintenance. The weight loss program should include a diet that is individually planned and takes the patient's overweight status into account. Women should choose a diet of 1000 to 1200 kcal per day and men, 1200 to 1500 kcal per day. Reducing the percentage of dietary fat alone will not produce weight loss unless total calories are also reduced. A portion-controlled, plant-based diet that is low in fat and high in fiber should help with weight loss. Patients taking antipsychotics, who often do better with a structured program, may lose weight if they eat portion-controlled products for 1 or 2 meals per day. Ditschuneit et al.²⁸ conducted a 27-month, 2-phase study of the long-term effects of an energy-restricted diet combined with 1 or 2 meal replacements daily. Total

weight loss (as a percentage of initial body weight) was 11.3%, and the patients experienced significant reductions in systolic blood pressure and plasma concentrations of triacylglycerol, glucose, and insulin. However, many patients may need substantial education before they will adopt a low fat, high-fiber, plant-based diet.

While increased physical activity alone is unlikely to lead to substantial weight loss, sustained physical activity is an important component of weight loss therapy because it increases energy expenditure, protects and/or builds lean body mass, and reduces the risk of morbidity and mortality from cardiovascular disease and NIDDM. Physical activity may also suppress appetite and provide a greater sense of psychological well-being. Most obese patients should initiate exercise slowly and increase intensity gradually. The exercise can be done all at one time or intermittently throughout the day. For example, the patient can begin by walking 30 minutes a day for 3 days a week and build to 45 minutes of more intense walking at least 5 days a week to achieve an additional expenditure of 100 to 200 calories per day. Patients should also be encouraged to increase activity during the normal daily routine, e.g., to take the stairs instead of the elevator or to park further away.

Emotional and moral support is another factor in successful weight loss. Frequent contact with the patient during dietary therapy may help to promote dietary changes that lead to weight loss as well as maintenance of a lower weight. Unsupervised weight loss programs can produce significant weight losses, but even minimal physician involvement may enhance outcome. Medical supervision is necessary for patients with health problems including serious mental illness. Behavior strategies that provide tools for overcoming barriers to compliance with dietary therapy and/or increased physical activity can also be helpful in achieving long-term weight loss and weight maintenance goals. Specific strategies include self-monitoring of eating and physical activity, stress management techniques, and cognitive restructuring.²⁹

If obese patients fail to lose weight after 6 months of a combination of lifestyle changes and behavior therapy, pharmacotherapy may be considered and used in conjunction with dietary modifications and increased physical activity. Weight loss drugs such as sibutramine, which has been approved by the Food and Drug Administration (FDA) for long-term use, may enhance weight loss modestly and can help facilitate weight loss maintenance. Sibutramine is a serotonin-norepinephrine reuptake inhibitor, which was found as effective as dexfenfluramine (which has been removed from the market) in achieving weight loss in obese patients.³⁰ Potential side effects include increases in blood pressure and heart rate, and sibutramine should not be used in patients with a history of hypertension, congestive heart failure, arrhythmias or stroke. Another weight loss drug, orlistat, is a lipase inhibitor that has been used in Europe and is now FDA-approved in the

United States. Results of a 2-year study (intent-to-treat population, N=880) indicate that orlistat plus controlled diet significantly promotes weight loss, lessens weight regain, and improves fasting LDL, cholesterol, and insulin levels. Orlistat, which blocks absorption of about one third of consumed fat, has gastrointestinal side effects. Patients should be monitored for these effects as well as compliance. Finally, the drug topiramate can also be used adjunctively to promote weight loss, although it is not approved for the treatment of obesity.

CONCLUSION

Weight is regulated by a complex set of biological and environmental factors, and thus obesity is not simply the result of a lack of willpower. Obesity is a chronic problem requiring lifelong, multidisciplinary management. Patients who are taking antipsychotics are at particular risk for weight gain, which is a side effect of both conventional and atypical antipsychotics. Physicians should monitor antipsychotic-treated patients carefully for weight gain and should choose a medication least likely to cause weight gain in patients who are already overweight A 5-lb (2.3-kg) gain is a clinical marker for preventative intervention, and a 10-lb (4.6 kg) gain increases fisk of common weight-associated illnesses such as NIDDM, cardiovascular disease, and hypertension.

When communicating with patients, physicians should stress the benefits of modest weight loss. Often education is necessary to alter the patient's fundamental thoughts and assumptions about losing weight. Patients should be encouraged to work toward a slow, steady loss of 1 to 2 lb per week for 6 months by modifying diet and increasing physical activity. After 6 months, for most patients, the focus should switch to weight maintenance. A change in medication may be indicated for antipsychotic treatment in patients whose weight gain is a side effect of treatment and who are unable or unwilling to change their diet and increase their activity level.

Drug names: carbamazepine (Tegretol and others), chlorpropamide (Diabenese), clozapine (Clozaril), glyburide (DiaBeta, Glynase, and others), haloperidol (Haldol and others), loxapine (Loxitane and others), molindone (Moban), olanzapine (Zyprexa), orlistat (Xenical), phenelzine (Nardil), prednisone (Deltasone and others), risperidone (Risperdal), sibutramine (Meridia), topiramate (Topamax).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented herein that is outside U.S. Food and Drug Administration—approved labeling.

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Appendix 1: Body Mass Index Charta	xibr	1: Bo	dy N	I sse	ndex	Ch3	r†a																			٠	2									
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69	128	3 135	142	149	155	162	169	176	182	189	196	5 203	209	216	25	230	236	243	250 2	257 2	263 2	270 2	277 2	284 2	291 2	297 3	304 311	1 318	8 324	4 331	1 338	345	351	358	365	
70	132	2 139		146 153		160 167	174	. 181	188	195	202	209	216	222	229	38	243	250	257	264 2	271 2	278 2	285 2	292 2	299 3	306 3	313 32	320 327	7 334	4 341	1 348	355	362	369	376	
71	136	5 143	150	157	165	172	179	186	193	200	208	3 215	23	229	_	236 243	250	257	265	272 2	279 2	286 2	293 3	301 3	308 3	315 33	322 32	329 338	8 343	3 351	1 358	365	372	379	386	
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73	144	151	159	166	174	182	189	197	204	. 212	219	227	235	242	250	257	265	262	280	288 2	295 3	302 3	310 3	318 3	325 3.	333 3	340 348	18 355	5 363	3 371	1 378	386	393	401	408	
74	148	3 155	5 163	171	179	186	194	. 202	210	218	225	233	241	249	256	264	272	280	287	295 3	303 3	311 3	319 3	326 3	334 3	342 3	350 358	365	5 373	3 381	1 389	396	404	412	420	
75	152	2 160	168	160 168 176 184 192	184	. 192	200	208		216 224 232	232		240 248	256	264	272	279	287	295	303 3	311 3	319 3	327 3	335 3	343 3.	351 3	359 367	375	5 383	3 391	1 399	407	415	423	431	
92	156	5 164	172	180	180 189	197	, 205	213	221	230	230 238	246	254	. 263	271	279	287	295	304		320 3	328 3	336 3	344 3	353 3	361 3	369 377	7 385	5 394	4 402	2 410	418	426	435	443	
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