Nonpharmacologic and Pharmacologic Management of Weight Gain

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Obesity increases the risk of several serious health problems, including heart disease, type II diabetes mellitus, hypertension, and osteoarthritis. Patients taking certain psychotropic medications may gain a significant amount of weight (as much as a 5% increase in body weight within 1 to 2 months), placing them at risk for obesity. Body weight monitoring and prudent drug selection are the best approaches to preventing weight gain in patients taking psychotropic drugs. When weight gain (> 5% of initial body weight) is unavoidable, intervention counseling should begin. Nonpharmacologic measures for managing weight gain include a balanced deficit diet of 1000 calories and higher, depending on the patient's weight; 30 to 60 minutes of physical activity daily; and behavioral training to restrain excess caloric intake. Each of these measures requires a considerable commitment on the part of the patient and works best with support from the physician and weight-loss support groups. Drug therapy for weight loss is available (at present, sibutramine is the only approved appetite suppressant in the United States); however, for most patients already being treated with a psychotropic agent, the risks (such as drug interactions, adverse events, compliance problems) of adding an antiobesity agent probably outweigh the benefits. Surgical intervention for obesity should be reserved for morbidly obese patients whose disease is intractable to medical therapy. *(J Clin Psychiatry 1999;60[suppl 21]:31–36)*

Use of some psychotropic medications can produce considerable weight gain, so much so that patients who continue treatment and continue to gain weight may ultimately become obese (defined as a body mass index [BMI] of more than 30 kg/m^2). As an adverse effect of psychotropic drug treatment, weight gain of more than 5% of initial body weight within 1 to 2 months often does not receive the attention afforded other serious adverse effects, such as extrapyramidal symptoms and tardive dyskinesia. Yet obesity is a leading cause of preventable death, ranking second only to cigarette smoking.[1] Each year, at least 300,000 people in the United States die of obesity-related causes.[1] Treatment of obesity is never easy, and the challenge is even greater among mentally ill patients whose weight gain is linked to effective, and perhaps life-saving, drug therapy. However, the health risks associated with obesity are significant enough that intervention is always warranted.

Excess body weight increases the risk of syndrome X, or Reaven syndrome, which consists of hypertension, type II diabetes mellitus, hypercholesterolemia, cardiovascular disease, and abnormalities in fibrinolysis.[2] Other medical problems associated with obesity include an increased risk of endometrial, breast, prostate, and colon cancers; sleep apnea; chronic respiratory tract infections; cholelithiasis; osteoarthritis; and menstrual abnormalities.[3]

Early intervention is the key to preventing significant drug-related weight gain and treating obesity if it occurs. We must raise the issue of weight gain as a potential adverse effect before patients begin treatment and monitor their weight as long as they continue taking drugs that may increase weight. Ideally, a diet and exercise plan should be initiated to prevent or treat weight gain before medically significant weight gain occurs.

DEFINING OBESITY

Although insurance companies have developed sex-specific charts showing desirable weight for height, the preferred means of determining a healthy weight is to calculate the BMI or the percentage of ideal body weight. The BMI is calculated as weight in kilograms divided by the square of height in meters, or kg/m^2. The BMI can also be determined by multiplying weight in pounds by 705 and dividing by height in inches squared. Thus the BMI of a person 5'5" tall weighing 185 lb would be 185 lb × 705 ÷ 65 in ÷ 65 in = 31.

The percentage of ideal body weight is calculated by dividing the current weight by the ideal body weight and multiplying by 100. For men, the ideal body weight is esti-

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Table 1. Classification of Obesity by Body Mass Index (BMI) and Percentage of Ideal Body Weight (IBW)[a]

Grade	BMI (kg/m^2)	Classification	Percent IBW Men	Percent IBW Women
0	18.5–24.9	Normal[b]	100	100
I	25.0–29.9	Overweight	110	120
II	30.0–34.9	Obese	135	145
III	35–39.9	Medically significant obesity	160	170
IV	40–44.9	Severe obesity	180	195
V	45–49.9	Super obesity	200	220
VI	> 50	Supermorbid obesity	225	245

[a]Data from reference 5.
[b]Increased waist circumference is a marker for increased health risk even in persons of normal weight.

mated as 106 lb for 5 ft height plus 6 lb for each additional inch.[4] For women, the ideal body weight is estimated as 100 lb for 5 ft height plus 5 lb for each additional inch.[4] Estimated body weight is decreased by 10% for persons with a light frame and increased by 10% for persons with a heavy frame. Classification of obesity by BMI and percentage of ideal body weight is shown in Table 1.[5] Any increase beyond normal weight represents an increase in medical risk.[6]

The increased risk of health problems associated with obesity depends not only on the amount of weight gained but also on where the weight is distributed. Body fat concentrated around the waist places a patient at greater risk for metabolic abnormalities (e.g., hyperinsulinemia, glucose intolerance, dyslipidemia, and hypertension), type II diabetes, breast cancer, cardiovascular disease, and death than does body fat concentrated in the buttocks and thighs.[7] The most widely accepted method of classifying body fat distribution is the waist-to-hip ratio, which is calculated by dividing waist circumference in centimeters by hip circumference in centimeters. A waist-to-hip ratio of more than 0.95 in men and 0.85 in women suggests a body fat distribution that poses an increased health risk.[8] As a simple rule, women whose waist measurement exceeds 35" (88 cm) and men whose waist measurement exceeds 40" (102 cm) are at increased risk for medical problems.[9]

SETTING TREATMENT GOALS

The preferred means of treating weight gain associated with psychotropic drug use is to prevent its occurrence in the first place. Sometimes this can be done through prudent selection of initial drug therapy or a switch to another medication as soon as weight gain becomes a problem. However, even if weight gain is not addressed early, and patients progress from overweight to obesity, later intervention can also be helpful.

One of the first steps in initiating a weight-loss program is to help patients set realistic goals. Many obese patients entering a weight-loss program have high expectations. On average, they expect to lose about 32% of their current body weight, which would be nearly 60 lb for a 180-lb woman. A 25% loss of body weight might be considered acceptable, but most patients consider a loss of only 17% of body weight to be disappointing.[10] Realistically, however, patients can expect to lose no more than 10% to 15% of their body weight over 6 months to 1 year. They need to understand that even such modest weight loss can have significant health benefits. Losing 10% of current body weight and maintaining that loss over time can lower blood pressure and decrease glucose, cholesterol, and triglyceride levels, which consequently decreases the risk of syndrome X or metabolic syndrome (which consists of type II diabetes mellitus, coronary artery disease, gout, and hypertension).[11,12] The incidence of other obesity-related health problems, including sleep apnea and osteoarthritis, also decreases with moderate weight loss.[13]

Once patients achieve a medically significant weight loss, whether they are satisfied with the loss or not, the challenge is to maintain that loss over the long term. Most patients tend to regain weight once they leave a medically supervised or commercial weight-loss program. Only rarely will a patient lose a considerable amount of weight and manage to keep it off. Most patients whose weight gain is associated with psychotropic drug use need considerable support to help maintain their usual adult weight. This requires a decrease in caloric intake or an increase in energy expenditure of 500 to 1000 kcal/day.

NONPHARMACOLOGIC MANAGEMENT

A successful weight-loss program should produce a loss of 0.5% to 1% of the patient's initial body weight per week, a rate of loss considered safe and acceptable.[14] Diet, exercise, and behavior therapy are the principal nonpharmacologic means of producing (and maintaining) weight loss. Thus, a reasonable approach to managing mild-to-moderate obesity is a 500-calorie-restricted diet and 30 minutes of exercise a day. Diet counseling is best provided by a registered dietitian or a graduate-level nutritionist.

Exercise

Exercise is the most important but least addressed component of weight maintenance and appetite control. It is such a powerful predictor of weight control success that patients in our clinic who are unable or unwilling to set time aside for regular exercise on their own usually are referred to an exercise program at a gym. Exercise has both physiologic and psychological benefits, including inhibiting food intake and promoting a sense of self-control. It decreases the risk of heart disease more than does weight loss alone, has a favorable effect on body fat distribution, and decreases the waist-to-hip ratio.[15,16]

Walking is one of the best and easiest exercises for patients to do. We encourage patients at our clinic to walk at least 40 minutes a day. This amount of exercise produces maximal benefit, but requires considerable commitment and

motivation on the part of the patient. Even if patients walk for only 20 minutes 3 times a week, they will still benefit. Weight training to build muscle mass is recommended for motivated patients who have access to the equipment. Weight training is particularly valuable for overweight women, who have a higher percentage of body fat than do men.

Diet

Among patients taking psychotropic drugs, weight gain typically results from eating too many high-fat, high-calorie foods, although in some cases it may be related to a metabolic abnormality in appetite control. Thus, the first step in losing weight is to restrict the number of high-fat and high-calorie foods. Because no calorie-restricted diet will be successful if the patient is noncompliant, any diet selected should reflect the patient's capabilities. Of equal importance for long-term weight control is that the diet be nutritionally sound.

Patients invariably underestimate their food intake, especially portion size and fat content, leading to discrepancies between food diaries and weight loss. Nevertheless, food diaries (a written record of the food a patient eats) can be helpful. Accurate serial food records reveal actual eating habits and patterns, which is valuable information for developing an appropriate diet acceptable to the patient.

Some dietary options. Depending on the population being treated and the degree of obesity, several dietary options can be considered that vary in calories, targeted rate of weight loss, and degree of medical supervision needed. The best diet is an ad libitum (patients eat freely, provided they stay within physician-recommended calorie limits), low-fat, high-fiber diet that is portion controlled and incorporates healthy meals and snack-replacement foods. The diet should restrict fats, oils, and sweets and emphasize fruits, vegetables, and fiber-rich foods. If fresh fruit or vegetables exceed a patient's budget, canned or frozen foods can be substituted.

Low-calorie or very-low-calorie diets provide a quick initial weight loss, which is motivating to patients, but should be attempted only under a physician's supervision. A low-calorie diet provides at least 1000 kcal/day. Very-low-calorie diets usually provide fewer than 800 kcal/day. In clinical trials, approximately 90% of patients following a very-low-calorie diet lose 20 lb or more and 50% lose 40 lb or more in the first 4 to 6 months.[17] Often patients who fail to respond to low-fat diets will be treated with a very-low-calorie diet. Very-low-calorie diets that rely mostly on liquid meal replacements are metabolically similar to semistarvation and can produce fatigue, weakness, lightheadedness, and changes in vital signs, including blood pressure, heart rate, and respiratory rate.[18] Most of the weight loss occurs within the first 12 to 16 weeks, after which an ad libitum, low-fat, high-fiber diet can be used. Low-calorie and very-low-calorie diets are indicated for patients with grade II or higher obesity in whom conservative treatment (i.e., a portion-controlled, low-fat diet) has failed and who are willing to commit to at least 1 year of treatment and major lifestyle changes.

A protein-sparing modified fast is a type of very-low-calorie diet using meat, fish, and fowl.[19] Patients consume an amount equal to 4 to 6 oz of cooked meat, fish, or poultry 3 to 4 times daily. Some physicians add 50 g of carbohydrate per day to decrease ketonemia. In addition, safe use of this diet requires supplementation with salt, calcium, bicarbonate, potassium, magnesium, multivitamins, and minerals.

High-protein diets also can be effective. However, drinking plenty of fluids (at least 1 to 2 L/day) is essential during this semistarvation diet to replenish the large amount of fluid lost, particularly during the first week, and to decrease the uric acid concentration. Low-calorie diets that restrict carbohydrate intake can cause a rapid mobilization of protein and glycogen stores, which can lead to decreased plasma insulin levels and subsequent reduced phosphorylation of the regulatory enzymes used for anabolism. Because 1 g of protein and glycogen is stored with 3 g of water, rapid weight loss (equivalent to 3% to 5% of body weight per week) occurs for the first few days until labile protein and glycogen stores are depleted.[20] Fat stores are lost much more slowly, however.

High-protein, low-carbohydrate diets are acidic and ketogenic. Ketones are produced in the liver as acetoacetic acid and β-hydroxybutyric acid. These acids are eventually excreted in the urine as sodium or potassium salts, resulting in a net loss of sodium and potassium. Thus, these diets can lead to calcium loss from bone, hyperuricemia, and hyperuricuria, which increase the risk of osteoporosis, gout, and uric acid kidney stones, respectively. Low-protein diets (< 1 g of protein per kilogram of body weight) can lead to sarcopenia and potentially life-threatening cardiac arrhythmias.[21] Sodium bicarbonate can be used as an acid-base buffer, and sodium, magnesium, and potassium supplements are required for any patient on a low-protein diet.

Many patients benefit from the structured approach to weight loss provided by commercial weight-loss programs (Table 2), but the likelihood of regaining weight once patients discontinue the program is high. All commercial weight-loss programs include nutrition education and exercise advice. They typically recommend a 1200-kcal/day diet for women and an 1800-kcal/day diet for men, with 55% of calories from carbohydrates, about 25% to 35% from protein, and 10% to 25% from fat.

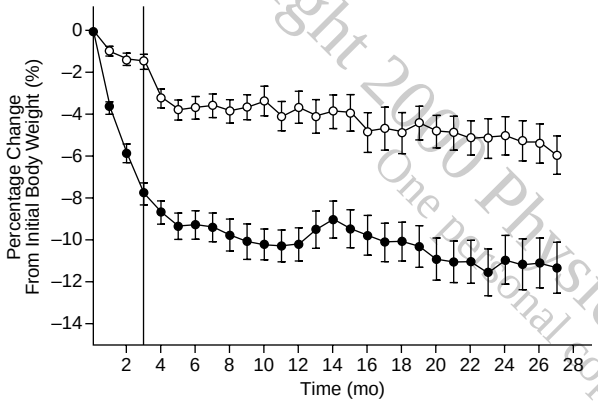
For most patients, the simpler the diet regimen the better. A diet consisting of meal replacements once or twice daily plus one sensible low-fat meal can provide sustained weight loss while removing many choices regarding food intake. In one study of 100 patients,[22] those on a diet of 2 liquid meal replacements per day plus snacks and 1 low-fat meal (approximately 1200 to 1500 kcal/day) lost a considerable amount of weight during the first 3 months

Table 2. Summary of Commercial Medical Weight-Loss Programs[a]

Characteristic	Weight Watchers	Jenny Craig	Diet Center	Slim-Fast Meal Replacement	Optifast/HMR
Diet[b]	Balanced	Balanced	Balanced	Low-calorie diet	Very-low-calorie diet with medical monitoring
Food supply	Prepared food optional	Prepared food	Prepackaged	Prepackaged	Prepackaged
Food availability	Supermarket	Center	Supermarket	Supermarket, drug store	Medical offices, obesity center
Peer support	Yes	Yes	Yes	Self-help	Yes
Weight monitoring	Weekly	Weekly	Weekly	Self	Periodic
Cost	Low	Moderate	Low	Low	High
Physical activity	Emphasized	Emphasized	Emphasized	Emphasized	Emphasized
Appetite suppressant	No	No	No	No	Clinical study optional

[a]Abbreviations: HMR = Health Management Resources.
[b]Balanced diet = 25% to 35% protein, 50% to 55% carbohydrate, 10% to 25% fat.

Figure 1. Weight Loss in Patients Using 1 or 2 Liquid Meal Replacements per Day Plus Low-Fat Foods[a]



[a]Reprinted from reference 22, with permission. During the first 3 mo (phase 1), patients were randomly assigned to receive the energy-restricted diet only (o) or to receive the energy-restricted diet with 2 meals and 2 snacks replaced by energy-controlled, nutrient-dense meal-replacement products (●). During the next 24 mo (phase 2), all patients received the energy-restricted diet, and 1 meal and 1 snack were replaced by energy-controlled, nutrient-dense meal-replacement products.

(Figure 1). Although patients in this study regained some weight, most were able to maintain the weight loss on a diet of 1 liquid meal replacement per day plus snacks and 2 low-fat meals.

Behavior Modification

Exercise and diet help patients lose weight, but behavior therapy is required to change eating habits. The behavior modification technique involves identifying the eating or related lifestyle behavior to be modified, setting specific goals, modifying determinants of the behavior to be changed, and reinforcing the desired behavior. The goal is gradual but consistent changes in behavior that lead to healthier eating habits. Behavior modification programs are offered in group or individual sessions under the guidance of a professional or trained lay person.

Behavior modification alone (a typical program usually lasts 18 weeks) can generate a weight loss of 1 to 1.5 lb per week. Cessation of binge eating, acceptance of modest weight loss, and satisfaction with body image can lead to greater success in losing weight. Having patients keep a record of food intake and level of activity is essential for long-term weight maintenance. Most successful behavior modification programs have patients monitor body weight daily and compare daily, weekly, and monthly changes in weight.

PHARMACOTHERAPY

Whether to resort to antiobesity medication in a population already being treated with psychotropic drugs is a difficult decision, and one that must be made in conjunction with the patient. In general, drug treatment for obesity should be reserved for patients with a BMI of 30 kg/m^2 or greater and those with a BMI of 27 kg/m^2 or greater and other risk factors for cardiovascular disease, stroke, or diabetes. Antiobesity drugs are appropriate only when nonpharmacologic approaches have failed; they should not be used as primary therapy for obesity.

Patients and physicians should realize that use of a weight-loss drug requires a long-term commitment. Using such medication to achieve a short-term weight loss is inappropriate, because most patients will regain the weight once they discontinue the drug. For most patients who are already being treated with a psychotropic drug, the risks (such as drug interactions, adverse effects, compliance problems) of adding an antiobesity agent to their existing drug regimen probably outweigh the benefits. Nonetheless, pharmacotherapy for weight gain might be appropriate for carefully selected patients.

Mechanisms of Action

Antiobesity drugs produce weight loss and help maintain weight by decreasing appetite, decreasing absorption of fat, or increasing energy expenditure. Drugs that reduce caloric intake, commonly known as anorectic agents or appetite suppressants, do so by decreasing appetite or increasing satiety. Appetite suppressants are classified as centrally acting sympathomimetic agents or serotonergic agents. Sympathomimetic agents include phendimetrazine, phen-

termine, mazindol, diethylpropion (all of which are schedule III and IV controlled substances), amphetamine and related compounds, and phenylpropanolamine (an over-the-counter medication). Because of their high potential for abuse, amphetamines are not recommended for treating obesity,[23] whether or not patients are taking psychotropic drugs.

Serotonergic agents include fenfluramine, dexfenfluramine, fluoxetine, sertraline, and other selective serotonin reuptake inhibitors. Fenfluramine and dexfenfluramine, which stimulate serotonin secretion and inhibit serotonin reuptake, were withdrawn from the market in September 1997 over concerns about valvular heart disease.[24] At present, sibutramine, a mixed serotonergic and noradrenergic reuptake inhibitor, is one of 2 appetite suppressants approved by the Food and Drug Administration (FDA) for treating obesity.[25] Orlistat, a fat blocker, was also recently approved for use in the United States by the FDA. Safety and effectiveness beyond 1 year for sibutramine and 2 years for orlistat have not been determined.

Sibutramine

Sibutramine can help patients achieve a 10% to 15% loss of body weight; greater losses depend on the motivation of the patient.[26–29] However, if patients do not lose at least 4 lb within the first 4 weeks after starting sibutramine, they will probably not respond well in the long term and should discontinue the drug. Sibutramine induces weight loss by increasing satiety, so patients tend to eat less. Its weight-loss effect is mediated by 2 pharmacologically active primary and secondary amine metabolites. In placebo-controlled trials, patients taking sibutramine who lost more than 5% of their body weight had decreased levels of triglycerides, total cholesterol, and low-density lipoprotein cholesterol and increased levels of high-density lipoprotein cholesterol.[30] Waist and hip circumference also decreased significantly with sibutramine treatment.[28]

Because sibutramine can increase blood pressure and heart rate, these vital signs should be routinely monitored. For most patients, increases in blood pressure and heart rate are insignificant. At the recommended starting dosage of 5 to 10 mg/day, the mean increase in systolic and diastolic blood pressure is 2 mm Hg; in patients who lose more than 5% of their initial weight, mean blood pressure is essentially unchanged from baseline.[26] At the maximum recommended dosage of 20 mg/day, mean systolic blood pressure increases by 3.3 mm Hg and diastolic blood pressure by 2.5 mm Hg; patients who lose more than 5% of their body weight have smaller increases.[26] Large, potentially clinically significant increases in blood pressure usually appear within the first 4 weeks of treatment, and sibutramine should be discontinued if this occurs. At dosages of 5 to 20 mg/day, heart rate increases an average of 4 to 5 beats per minute. Aside from increases in blood pressure and heart rate, the most common adverse effects of sibutramine are dry mouth, anorexia, insomnia, irritability, and constipation.[29]

Orlistat

Orlistat may be a better option than sibutramine for patients already taking other drugs. Orlistat does not act systemically, so there is less risk of interaction with centrally acting medications. Orlistat, a chemically synthesized derivative of lipstatin (a natural product of *Streptomyces toxytricini*), selectively limits the intestinal absorption of dietary fat beyond that achievable through changes in diet alone.[25] Specifically, it inhibits gastric and pancreatic lipases by binding covalently to the serine residue of the active site of these enzymes.[31] Pancreatic lipase degrades triglyceride at the 1,3-glycerol backbone, which produces fatty acids. The resultant free fatty acids and monoglycerides are then incorporated into bile acid-phospholipid micelles. These micelles are absorbed at the level of the brush border of the small intestine and eventually enter the peripheral circulation as chylomicrons. Inhibition of gastrointestinal lipases prevents the triglycerides from being broken down into their constituent particles, and the intact triglycerides are excreted with the feces.

The recommended starting dose of orlistat has yet to be determined, but in placebo-controlled clinical trials, only the 120-mg dose given 3 times daily produced a statistically significant weight loss.[32–35] Decreases in triglycerides, total cholesterol, and low-density lipoprotein cholesterol and increases in high-density lipoprotein cholesterol have been noted with orlistat.[33] The drug also improves glycemic control.[33] Orlistat does not significantly interact with other gastrointestinal hormones, pancreatic hormones, thyroid hormones, or catecholamine.[36] The most common adverse effects are gastrointestinal, including increased defecation, soft stools, fatty or oily stools, and vitamin A and E deficiency.[37,38]

SURGICAL TREATMENT

Surgical treatment should be reserved for patients whose BMI exceeds 40 kg/m^2 and who have not responded to more conservative measures to reduce weight. Before undergoing gastric restrictive surgery, patients must understand the risks of the procedure and the need for (and agree to participate in) lifelong surveillance of their weight and health status.

Vertical banded gastroplasty and Roux-en-Y gastric bypass are accepted procedures considered safe and effective by a National Institutes of Health consensus development panel.[39] Patients undergoing either procedure typically lose 40% to 70% of excess body weight,[40] although the gastric bypass may be more effective than gastroplasty alone. Obesity-related health problems, including diabetes, hypertension, hyperlipidemia, arthritis, and sleep apnea, usually improve after gastric restrictive surgery. Seventy-eight percent of patients who undergo such surgery no longer require antihypertensive or antihyperglycemic medication.[41,42] Also, with less weight bearing on joints, symptoms of degenerative arthritis improve significantly in most pa-

tients. Quality of life is enhanced considerably in many patients, and self-image is often much improved.

In most large medical centers with experienced physicians trained in these surgeries, the perioperative mortality rate of gastric restrictive surgery is 0.5%. Surgical risks include anastomosis leaks, wound infections, stomal stenosis, and incisional hernia. Long-term complications include vitamin and mineral deficiencies (particularly iron and vitamin B_{12}), nausea and vomiting, constipation, and dumping syndrome.

CONCLUSION

Losing weight is a challenge, particularly for patients with severe mental illness whose lifesaving medication is making them gain weight. Many of these patients have limited resources, poor diets, and problems with medication compliance. The best approach to weight loss and weight control is a combination of diet, regular exercise, and behavioral modification. Physicians can ease the patient's struggle against obesity through careful selection of psychotropic medication, choosing drugs least likely to cause weight gain whenever possible.

Drug names: amphetamine (Benzadrine), diethylpropion (Tenuate, Tepanil), fluoxetine (Prozac), mazindol (Mazanor, Sanorex), orlistat (Xenical), phendimetrazine (Bontril and others), phentermine (Ionamin), sertraline (Zoloft), sibutramine (Meridia).

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