

CONTINUING EDUCATION

Weighing the complications of obesity

After participating in this activity, pharmacists should be able to:

- Review the epidemiology and etiology of obesity
- Explore the clinical assessment and classification system for obesity
- List medications that may contribute to weight gain
- Identify the sequelae of obesity-related health conditions
- Outline basic nutrition concepts and the role of physical activity in weight loss and maintenance
- Identify patients who are candidates for pharmacist-assisted weight-loss therapies according to the NHLBI guidelines
- Recommend pharmacotherapy as appropriate based on a patient case

A photograph showing a person's feet standing on a black digital scale. The scale's LCD display shows the word "OVERLOAD" in large, black, capital letters. Below the display are three buttons: a left arrow, a downward arrow, and an upward arrow. The person is wearing grey pants. The scale is on a light-colored wooden floor.

OVERLOAD

Obesity is a chronic condition associated with metabolic irregularities conferring risk of mortality. Globally, more than 1.6 billion adults

are overweight and approximately 400 million are obese, according to the World Health Organization. The Centers for Disease Control and Prevention report that more than 67% of our population struggles with being overweight or obese.¹ Obesity is second only to tobacco abuse as a preventable disease associated with high mortality. The National Health and Nutrition Examination Survey 2003-2004 data reveal that approximately 35% of children are overweight or already at risk.²

Obesity is a multifactorial condition involving genetics, socioeconomic, and cultural factors; psychological and behavioral influences; and metabolic, cellular and molecular factors, all leading to irregular energy balance.³ Therefore, secondary causes such as Cushing's syndrome, hypothyroidism, or insulinoma should be identified initially (see Table 1).⁴ Excess calories and poor energy expenditure due to inadequate physical activity will promote weight gain. The National Lung and Blood Institute guidelines (NHLBI) define overweight by a body mass index (BMI) ≥ 25 kg/m²; the categories of obesity begin at a BMI ≥ 30 kg/m².

The sequelae associated with obesity-related diseases are significant and affect nearly every organ system⁵ (see Table 2). Often practitioners treat the end-organ effects of this epidemic with pharmacotherapy, lifestyle and behavior modification, and/or surgery. An analysis of the root cause of obesity for each patient such as excessive caloric intake and lack of activity, needs to be addressed in order to prevent complications from manifesting.

The first step in assessing risk is to calculate the BMI.⁶ Dual X-ray absorptiometry and magnetic resonance imaging are examples of more sophisticated methods that directly assess excess adiposity and distribution of body fat, but these are costly and not commonly used in practice.^{4,5} BMI, also known as Quetelet index, is a simple measurement that can screen for overweight and obese patients.⁶ The BMI is calculated as body weight in kg divided by height in meters squared (kg/m²).

BMI measurement is less accurate in patients if they have edema, are body builders, or have muscle wasting.^{4,5}

The distribution of body fat is assessed through waist-to-hip ratios and waist circumference. Waist circumference provides supplementary information regarding risk until the BMI is above 35 kg/m². Waist circumference may be a better estimation of adiposity in older patients and those ethnic populations that have normal body weight but unfavorable distribution of body fat. A waist-to-hip ratio of ≥ 0.9 in females and ≥ 1.0 in males confers higher cardiovascular disease risk. Patients should also be screened for medical conditions such as thyroid disease and Cushing's disease, which may contribute to weight gain.⁵

Certain medications can cause weight gain and increase body fat, thereby making weight loss more difficult (see Table 3). Several mechanisms alone or in combination are responsible for medication-induced weight gain. It can be due to an increase in appetite and therefore energy intake, as observed with antipsychotics and steroid hormones, or a decrease in energy expenditure, as is the case with beta-adrenergic receptor antagonists. A decrease in energy, for example in patients with decreased glucosuria from diabetes therapy, may also play a role.⁷

Weight-loss therapy can be facilitated by decreasing the dose or substituting the medication with another drug that has less weight gain potential. Pharmacists are uniquely positioned to recommend substitutions, if possible, to reduce the incidence of weight gain.

Weight-loss approaches

The key approach to weight loss should center on the triad of dietary modification, increased physical activity, and behavioral modification. These lifestyle modifications should be considered for all patients with a BMI ≥ 25 kg/m².^{1,2,4,8}

An obese patient with no concomitant risk factors or a patient with a BMI of ≥ 27 kg/m² with concomitant risk factors, including hypertension, dyslipidemia, coronary heart disease, type 2 diabetes, and sleep apnea, is considered at high risk and may be considered a candidate for pharmacotherapy if lifestyle modifications are unsuccessful.^{1,2,5,9}

Pharmacotherapy should be considered only in the patient who has made lifestyle changes for a minimum of 6 months, yet has not achieved a weight loss of at least one pound per week.

At the beginning of weight-loss therapy, the recommended initial weight-loss goal

is a reduction of 10 percent of the baseline weight in the first 6 months, at a rate of 1 to 2 pounds per week.¹ A deficit of 3,500 kcal is necessary to lose one pound of fat. Therefore, establishing an energy deficit of 500 to 1,000 kcal/day translates into the recommended rate of weight loss.

Weight-loss therapy is not appropriate in patients who are pregnant or lactating.⁵ Patients should be assessed and screened for uncontrolled psychiatric illnesses such as major depression or mood disorders, as these patients should also be excluded from therapy. In addition, those with active substance abuse should be referred for specialized care, and patients for whom caloric restriction might exacerbate their illness should not receive therapy.

Dietary modification is categorized by the nature of restriction: very low calorie diet (VLCD) of 400 to 800 kcal/day, low calorie diet (LCD) of 1,000 to 1,200 kcal/d, and meal replacement. VLCDs are primarily liquid or protein-sparing diets.⁵ Candidates are patients with a BMI ≥ 30 who are under medical supervision and who have failed at previous weight-loss attempts. While short-term results may be impressive, amounting to an average 26 kg weight loss at treatment end, results one year after treatment show that the VLCD is no more effective than an LCD. The LCD is more commonly prescribed by a physician and or dietitian aiming for a caloric deficit of 500-1,000 kcal/d for the obese and a more modest 300-500 kcal/d for the overweight. These diets are moderate in fat intake ($<30\%$), high in complex carbohydrates (50 to 60%), and moderate in protein (15 to 20%). Depending on the patient's age, calcium supplementation is recommended at 1,000 to 1,500 mg/d, with 25 to 35g of

TABLE 1

Secondary causes of obesity

Hypothyroidism
Cushing's disease
Cushing's syndrome
Polycystic ovarian syndrome
Insulinoma
Familial obesity
Pseudohypoparathyroidism
Prader-Willi syndrome
Laurence-Moon-Biedl syndrome

fiber also recommended as a goal.⁹

Meal replacements are prepared meals of a milk shake, soup, or bar. Replacement meals usually have approximately 200 calories, 10% fat, 30% protein, and 50 to 60% carbohydrate. Meal replacements spare patients the need to make decisions about food selection and portion control; however, it is difficult to adhere to this diet style long-term. Without modification of poor eating habits, patients usually return to previous lifestyles and regain the weight.

An initial weight-loss goal should be 0.5 lb to 1 lb/week or a 10% weight loss in six months.¹ Patient motivation and commitment are critical for successful weight loss. Knowledge of patient readiness helps determine treatment strategies. Patients who have realistic goals and no life stressors, medical illness preventing weight loss, or psychiatric issues are excellent candidates for weight loss. Work, social engagements, and family environments should be conducive to implementation of weight loss strategies. For patients not ready to commit to weight loss, the prevention of further weight gain and exploration of barriers or myths can be initiated, in the hope of moving the patient to a state of readiness.

One key area to target for patient education is the habit of mindless eating. Mindless eaters tend to fall into these categories: eating too much at meals, grazing throughout the day, overeating at restaurants or special occasions, and eating during work or when driving. An extra 100 calories consumed daily during mindless eating will contribute to a 10-lb weight gain in one year.

Pharmacists can use their unique position in the community to educate patients

on modifying portion sizes. A variety of tools exist online to which patients can be directed (see Online Resources).

The American College of Sports Medicine and the American Heart Association released an update on physical activity guidelines in 2007.¹⁰ The basic recommendations for healthy adults under age 65 who aim to maintain health and reduce their risk of chronic disease are moderate intense aerobic activity 30 minutes a day, five days a week, or vigorous intense activity 20 minutes a day, three days a week; plus 8 to 10 strength-training exercises at 8 to 12 repetitions each, twice a week. An initial activity goal for patients wanting to achieve weight loss should be 20 to 40 minutes, 3 to 5 days of the week, and patients may build up to continuous activity. Short bouts of activity have been shown to result in cardiovascular benefit and weight loss. The level of intensity or duration of activity should be increased as the level of fitness improves and weight is reduced, with an optimal goal of 60 minutes of aerobic activity daily and 60 to 90 minutes of aerobic activity for weight maintenance. Some helpful tips pharmacists can share with patients include: setting a schedule, changing activities and intensities, exercising in short bouts, and encouraging family involvement.^{10,11}

Weight maintenance is defined by the NHLBI guidelines as a gain of less than 3 kg over 24 months or a sustained reduction in waist circumference of 4 cm.⁹ The National Weight Control Registry database includes information from more than 4,000 patients who have kept weight off for at least one year.¹² Some common approaches reported are: lifelong modification of diet and exercise of 60 to 90 minutes most days of the week, self-monitoring through journaling, behavioral modification through support groups, eating breakfast everyday, weighing frequently, and avoiding excessive indulgence in mindless activities such as watching television.

The key weight-loss approach is behavioral modification.^{15,6} While energy balance through proper diet and exercise are fundamental components in achieving weight loss, behavioral modification is also necessary in maintaining healthy weight. A recent systematic review showed that behavioral therapy facilitated weight loss in comparison to placebo (2.5 kg) and facilitated weight loss when added to diet and exercise (5 kg).¹² However, changing a patient's behavioral pattern to decrease calorie consumption and increase energy expenditure may not be an easy task. For patients to achieve sustained behavior modification, both self-discipline and social support are important.

TABLE 2

Obesity Co-morbid Conditions

Cardiovascular disease*	Osteoarthritis
Hypertension*	Sleep apnea*
Dyslipidemia/ Hypercholesterolemia*	Diabetes*
Cholelithiasis	Gout
Fertility complications/PCOS	Stress incontinence
Cancers	Mental health disorders
Hyperandrogenism	Phlebitis

*Highest risk. PCOS: Polycystic ovarian syndrome

TABLE 3

Medications Associated with Weight Gain

Diabetes agents	Miscellaneous
Insulin	Alpha adrenergic blockers
Meglitinides	Antihistamines
Sulfonylureas	Beta blockers
Thiazolidinediones	Centrally acting agents
Neurologic agents	Hormones
Anticonvulsants	TCA depot injections
Psychiatric agents	
SSRIs	MAOIs
Antipsychotics	Phenothiazines

MAOI = Monoamine oxidase inhibitors
SSRI = selective serotonin reuptake inhibitor
TCA = tricyclic antidepressant

Adapted from: Malona M, *Annals of Pharmacotherapy*, 2005

It is also important to discuss with patients the techniques of self-monitoring, stimulus control, problem-solving, cognitive restructuring, stress management, and social support. These techniques add to the benefits of other forms of weight-loss treatment and should be a part of all weight-loss interventions. Several studies have identified substantial weight loss in patients who carefully monitor their energy intake.¹⁴⁻¹⁵ Patients can be encouraged to use hand-held computer-tracking devices to record food intake at the time of consumption vs. recording intake at the end of the day or week.

Stimulus control is necessary to achievement of permanent changes in eating habits. Some ways a patient can take control include using strategies to avoid temptation, such as not going grocery shopping when hungry or reaching for healthy alternatives to high-calorie snacks. It is important to remind patients that building new behavioral strategies and increasing levels of physical activity will take time. Therefore realistic goals are a key component of the achievement of long-lasting lifestyle changes. Patients with a social support system of either family or healthcare providers generally tend to have greater weight loss and less residual weight gain. If and when patients hit a roadblock in achieving their weight-loss goals, clinicians can remind patients that rather than give up, they can use those experiences as stepping stones toward refining their techniques.

Complications

Sixty-one percent of patients with diabetes are obese.¹⁶ In addition, uterine cancer, hypertension, cardiovascular disease (CVD), osteoarthritis, and gallbladder disease are related to obesity.¹⁷ Nearly 325,000 deaths are attributable to obesity indirectly through the incidence and prevalence of hypertension, diabetes, and CVD.^{1,2,5,6}

The Framingham Offspring study revealed a clear relationship between obesity and CVD, including myocardial infarction.¹⁸ Incidence of CVD in men and women followed for 16 years was directly related to the number of heart disease risk factors (diabetes, hypertension, BMI). Small changes in body weight correlated with a change in the coronary heart disease risk. An increase of 2.25 kg or more in 16 years increased the sum of risk factors by 20% in men and 37% in women, while a reduction by 2.25 kg decreased the risk by 48% in men and 40% in women.

Hypertension

Guidelines from the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure state that the impact of a weight loss of 10 kg on systolic blood pressure (SBP) ranges from 5 to 20 mmHg.¹⁹ Weight loss also has an impact on diastolic blood pressure (DBP).

Hypertension Prevention Phase II trials evaluated the effect of weight loss on changes in blood pressure. Approximately 1,200 subjects were randomized to usual care or an intervention of diet and physical activity for three years.²⁰⁻²¹ The results demonstrated a linear relationship between weight loss and blood pressure.²⁰⁻²¹ A 5 mmHg reduction in SBP and 7 mmHg in DBP was seen with an 8.8-kg weight loss. These benefits were lost when patients gained the weight back. The Trial of Antihypertensive Interventions and Management reported a weight loss of 5% from baseline. This contributed to reductions in DBP equivalent to a single dose of an antihypertensive medication.¹² In many cases hypertension resolves or drastically improves in those who undergo bariatric surgery; however, this change may be temporary as some studies have illustrated a gradual increase in blood pressure 3 to 5 years after surgery, often due to fluctuations in weight status.²²

The following mechanisms have been linked with sodium retention and hypertension: sympathetic nervous system activation, renin-angiotensin-aldosterone system activation, and compression of the kidney.¹⁹ There are currently no specific recommendations for the pharmacological treatment of obesity and hypertension. Selection of therapy is often targeted based on the etiology of the disorder.

Diabetes

Obesity-related diabetes mellitus occurs when excessive storage of triglycerides raises plasma insulin concentrations, eventually leading to insulin resistance. Obesity-related diabetes is familial and modest weight loss improves insulin sensitivity and glycemic control dose dependently.²³ Most patients diagnosed with type 2 diabetes are overweight or obese. As discussed, several therapies used to treat diabetes, including insulin, sulfonylureas, and thiazolidinediones (TZD), can contribute to weight gain.³ A 5 to 10% weight loss will have a significant impact on clinical markers such as blood glucose, blood pressure, total cholesterol,

LDL-cholesterol, and triglycerides. Modest improvements can also be seen in HDL-cholesterol.

Studies such as the United Kingdom Prospective Diabetes Study illustrate the impact of dietary modification and physical activity on risk reduction in diabetes, blood pressure, and cholesterol.²⁴⁻²⁵ Agents such as biguanides, TZDs, and incretin mimetics can be used to assist with weight reduction and hyperglycemia.^{3,24}

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is the intermittent cessation of breathing during sleep due to partial or complete upper-airway obstruction, resulting in excessive episodes of apnea and hypopnea. In general, patients with sleep apnea are characterized by a BMI of 30 kg/m² or greater, abdominal fat distribution, and a large neck girth (>16 inches in women and >17 inches in men).²⁶

The principal effects are diminished residual lung volume and poor pulmonary dynamics caused by increased abdominal pressure on the diaphragm. Evidence suggests that fatty infiltration of the accessory muscles of breathing can decrease elasticity of the chest wall. It is evident that fat distribution, independent of total fat, has an influence on pulmonary function in men. This is hypothesized to be through the effects of visceral fat levels.

Approximately 12 to 40% of morbidly obese patients have OSA. Furthermore, sleep apnea is probably underdiagnosed in overweight and obese patients and should be strongly considered in patients with complaints of fatigue, daytime somnolence, snoring, restless sleep, and morning headaches.

Gallbladder Disease

The risk of gallbladder disease increases in linear relation to BMI.²⁷ This is particularly true in women. The Nurses' Health Study found that compared to lean women (BMI <24 kg/m²), obese women with a BMI >30 kg/m² had a twofold excess risk of experiencing symptomatic gallstones, and women with clinically severe obesity (BMI <45 kg/m²) had a sevenfold excess risk.²⁸ One rationale for the increased risk of gallstones is the high cholesterol turnover related to total body fat. The production of cholesterol is linearly related to body fat in that about 20 mg of additional cholesterol are synthesized for each kilogram of extra body fat.²⁹

Interestingly, the risk of developing gallstones increases during weight loss.

This is due to increased bile cholesterol supersaturation, enhanced cholesterol crystal nucleation, and decreased gallbladder contractility. Rapid weight loss is an important predictor of symptomatic gallstones. When the rate of weight loss exceeds 1.5 kg or approximately 1.5% of body weight per week, the risk of gallstone formation increases exponentially.³⁰

Moreover, dietary fat content influences de novo synthesis of gallstones during weight loss induced by a VLCD. Consuming a meal with minimal fat does not stimulate the gallbladder to empty, whereas a meal with a higher amount of fat prompts gallbladder contraction. Furthermore, increasing dietary fat content may not be as important in preventing gallstones in patients consuming an LCD compared with those consuming a VLCD. Moreover, the use of bile acids, such as ursodeoxycholic acid, may be beneficial if the risk of gallstone formation is thought to be increased.

Liver Disease

Obesity is associated with a spectrum of liver abnormalities known as nonalcoholic fatty liver disease (NAFLD).³¹ NAFLD is manifested by alterations in liver histology including steatosis, steatohepatitis, fibrosis, and cirrhosis in addition to hepatomegaly and abnormal liver biochemistry. Available data suggest that steatosis affects approximately 75% of obese patients, whereas 20% experience steatohepatitis, and cirrhosis is prevalent in approximately 2%.³² The reasons NAFLD develops in obese patients are ambiguous. However, it is recognized that NAFLD is associated with abdominal obesity and the metabolic syndrome. Losing excess weight through diet and exercise is the cornerstone of treatment of NAFLD.

Gout

Gout is a type of inflammatory arthritis triggered by the crystallization of uric acid within the joints and is often associated with hyperuricemia. Both hyperuricemia and gout are highly associated with overweight and obesity. A 12-year prospective study done by Choi et al. evaluated the relationship between obesity and weight change and the incidence of gout in men.³³ They determined that a BMI of 25 or more was consistently associated with an increased risk of gout. The degree of the association became larger with increasing BMI. Their finding also suggested that risk of gout is more strongly influenced by current BMI than by BMI earlier in life.

Osteoarthritis

The risk of osteoarthritis, particularly of the weight-bearing joints, is increased in overweight and obese individuals. The knees are most often involved because more weight is exerted on these joints during activity than on others. The excess weight places pressure on the joint and wears away the protective cartilage, resulting in joint pain and stiffness. The relationship between BMI and osteoarthritis is stronger in women than in men, and obesity often precedes osteoarthritis by decades. Even small increases in body weight in women can promote osteoarthritis.³⁴

There is some evidence to suggest that increased load on a joint may not be the only factor associated with joint disease in the obese, and studies have demonstrated an association between obesity and osteoarthritis of the hand.^{35,36}

Cancer

Overweight and obesity are associated with an increased risk of certain forms of cancer.³⁷ The mechanism by which obesity confers risk for cancer is still unclear, though there are several proposed processes. The conventional view considers adipose tissue as an active metabolic entity that may promote the genesis and progression of cancer. A more recent hypothesis suggests adipose tissue as a reservoir for lipophilic environmental carcinogens, which are then released into the bloodstream over time.³⁷

Available data indicate that men are at an increased risk for cancers of the colon, rectum, and prostate.³⁷ In women, a substantial risk for neoplasms of the reproductive system and gallbladder are plausible. The Million Women Study found that increasing BMI is associated with a significant increase in the risk of cancer for 10 out of 17 specific types investigated. The study demonstrated that menopausal status is a key factor in the relationship between BMI and cancer risk for women.³⁸ This is true not only of hormonally related cancers, but also for cancers that are not ordinarily associated with hormone levels, such as colorectal cancer. For endometrial and esophageal cancer, BMI represents a major modifiable risk factor, and about half of all cases in postmenopausal women are attributable to overweight or obesity.

Polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS) is associated with incompletely developed ovarian follicles and irregular menses.

Most often caused by insulin resistance, it is the leading cause of infertility and increases the risk of diabetes development. Nearly half of all women with PCOS have abdominal obesity.³⁹ Medications such as TZDs and biguanides are often employed to restore fertility and treat the hyperinsulinemic-producing hormone dysregulation.⁴⁰

Pharmacotherapy for obesity management

When considering pharmacologic therapy, it is essential to be cautious when recommending treatment to patients. Alternatively, some clinicians are quite hesitant to advocate pharmacotherapy due to the history of weight-loss agents being withdrawn from the market.⁴¹ Fenfluramine and dexfenfluramine, two appetite-suppressant medications, were withdrawn from the market in 1997. These agents were marketed and used individually and in combination with phentermine (often referred to as "fen/phen"). The withdrawal of these drugs was triggered when they were linked to the development of valvular heart disease and primary pulmonary hypertension (PPH).⁴¹

Although the relation between PPH and phentermine use is not definitive, there have been a few case reports, and the possibility that phentermine alone is associated with PPH cannot be overlooked.^{5,6,42}

Prior to 1996, all anti-obesity agents were approved for short-term use (<12 weeks). Medications that are currently approved in the U.S. for managing obesity can be divided into two categories: appetite suppressants and lipase inhibitors. Agents that are approved for short-term use include benzphetamine, phendimetrazine, diethylpropion, mazindol, and phentermine.⁴² The most commonly used of these is phentermine. The other prescription medications mentioned have not been studied as well and have not had the same utility in clinical practice. Consequently, the only short-term agent this article will focus on is phentermine.

Phentermine

Phentermine, a noradrenergic agent, acts as an appetite suppressant.⁴³ Phentermine hydrochloride was approved by the FDA in 1973 for short-term use of a few weeks to a few months by obese patients. Phentermine suppresses the appetite by stimulating the release of norepinephrine and dopamine, thereby causing a decrease in gastric secretion and

an increase in energy levels. It is theorized to cause significant increases in blood pressure, palpitations, and arrhythmias. Consequently, phentermine's use is not advised in hypertensive patients and those with unstable cardiovascular function. Other common adverse effects are constipation, dry mouth, and nervousness. Evening dose administration should be avoided because of the possibility of insomnia. As with all adrenergic agents, a minimum washout period of 14 days is suggested if patients are taking a monoamine oxidase inhibitor (MAOI) to avoid excessive sympathomimetic effects. Dosing is commonly one 37.5 mg capsule in the morning. Use is not advisable in patients with hypertension or in those with a history of drug abuse as phentermine may be physically and psychologically addictive.

Sibutramine

Sibutramine is one of two medications that the FDA has approved for long-term use (typically up to a year and possibly longer) for weight loss.⁴⁴ Sibutramine works by inhibiting the reuptake mainly of norepinephrine and serotonin, and to a lesser extent dopamine.⁴⁵ In addition, its active metabolites also inhibit the reuptake of norepinephrine and serotonin.

Unfortunately, many obese patients possess several conditions that are considered contraindications to the use of sibutramine. Studies have found that compared to those taking placebo, patients treated with sibutramine had a significant increase in SBP and DBP of approximately 1 to 3 mmHg and also experienced an increase in pulse of 4 to 5 beats per minute.⁴⁶ For patients who already have hypertension or borderline high blood pressure, this can be a concern, since it may be difficult to achieve and maintain blood-pressure control.⁴⁶ It is imperative that blood pressure and heart rate be monitored regularly throughout therapy. Patients whose hypertension becomes uncontrolled or who develop hypertension or tachycardia during treatment may need to either decrease their dose or discontinue therapy altogether.

Orlistat

Orlistat is unlike any other weight-loss medication in that its mechanism of action is to inhibit gastrointestinal lipases.⁴⁷ Orlistat is currently available by prescription at a 120 mg dose and over the counter at half the prescription strength. This agent is a chemically synthesized,

hydrogenated derivative of lipstatin, a natural product of *Streptomyces toxytricini*. It binds to gastric and pancreatic lipases in the gut lumen and blocks the digestion of dietary fat by preventing lipase from interacting with its lipid target. This results in about one-third of dietary fat remaining unabsorbed. Orlistat does not affect the action of systemic lipases or lipases located in other organ systems because it is minimally (<1%) absorbed from the gastrointestinal tract.

The longest study to look at orlistat's effect on the prevention of type 2 diabetes in obese patients is the Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study.⁴⁸ This four-year, multicenter, randomized control trial included more than 3,000 obese subjects and compared orlistat therapy plus lifestyle intervention to placebo plus lifestyle intervention in people with either normal glucose tolerance (NGT) or impaired glucose tolerance (IGT). Participants were prescribed a reduced-calorie diet of approximately 800 kcal/day deficit, 30% calories from fat, and less than 300 mg cholesterol/day. The study found that orlistat plus lifestyle changes significantly reduced the incidence of type 2 diabetes and improved weight loss. Orlistat therapy resulted in a 37% reduction in the cumulative incidence of new-onset type 2 diabetes, primarily by preventing the development of diabetes in patients who had impaired glucose tolerance.

Side effects that patients may experience include flatulence with discharge, fecal urgency, fecal incontinence, steatorrhea, diarrhea, and increased defecation.⁴⁷ The adverse effects of orlistat often serve as a motivation for patients to avoid foods high in fat. Minimizing fat intake helps to lessen adverse effects, which generally occur early in treatment and can diminish or disappear as treatment is continued. However, some patients may continue to experience side effects six months or more into treatment. Psyllium has been reported to be an effective fiber adjunct to reduce some of the GI side effects associated with orlistat. Orlistat can interfere with the absorption of lipophilic medications such as cyclosporine; therefore close monitoring and dose adjustment may be required. Because orlistat may block the absorption of vitamin K, an increase in international normalized ratio may occur with warfarin treatment. Patients are also advised to supplement the fat-soluble vitamins A, D, E, and K.

Rimonabant

Rimonabant, the first CB-1 cannabinoid receptor antagonist to reach the market, reduces food intake and increases adiponectin through the CB-1 receptor on fat cells. This is thought to increase insulin sensitivity and reduce risk associated with metabolic syndrome. While initially approved for use in more than 30 European, South American, and Asian countries, rimonabant has not met U.S. approval standards because of concerns about psychiatric side effects (i.e., anxiety, depression, and suicidal ideation).^{49,50}

On October 23, 2008, the European Medicines Agency (EMA) recommended suspending use of rimonabant in the European Union (EU) subsequent to a review by the Committee for Medicinal Products for Human Use (CHMP). CHMP concluded that the benefits of rimonabant no longer outweigh the risks. The risk assessment confirmed that there is a doubling of the risk of psychiatric disorders in obese or overweight patients taking rimonabant. Data from ongoing clinical trials also note that serious psychiatric disorders may be more common than earlier, pre-approval clinical trials had identified.⁵¹

Drugs on the Horizon

Several different types of antiobesity agents are under clinical development.⁵² Some include selective 5-HT_{2C} receptor agonists, selective 5-HT₆ receptor antagonists, leptin analogues, human ciliary neurotrophic factor, neuropeptide Y antagonists, melanin-concentrating hormone antagonists, and selective cholecystokinin receptor A agonists. In addition, cetilistat is another lipase inhibitor that may gain FDA approval but has yet to do so. AOD9604 is a modified fragment of growth hormone and is completing phase 2 clinical trials. It is anticipated that with so many drugs under investigation, we will have better options for treatment in the near future. The hope is that newer medications will have limited adverse effects while providing weight loss safely and effectively.

Surgical Candidacy

Bariatric surgery may be necessary in patients with severe obesity who have failed to lose weight with nonsurgical therapy.⁵³ Surgical procedures are an option for obese patients who have a BMI >40 kg/m² or a BMI >35 kg/m² with concomitant serious obesity-related disease.⁵⁴ Absolute contraindications to bariatric surgery are

psychiatric disorders (i.e. schizophrenia, active suicidal ideation, uncontrolled depression) and active substance abuse. There are no specific age restrictions for these surgical procedures. Although long-term studies are currently unavailable, bariatric procedures have been performed in both children and adolescents.⁵⁵ Patients are evaluated individually to assess candidacy. For patients older than 60 years of age, the main concern is quality of life.

Available procedures include Roux-en-Y gastric bypass, vertical banded gastroplasty, laparoscopic adjustable gastric banding, and biliopancreatic bypass with duodenal switch.⁵⁶

Considered the surgical treatment of choice for most patients with severe clinical obesity, Roux-en-Y gastric bypass is the most popular bariatric surgery in the U.S.⁵⁷ It involves closing off the first 20 to 30 ml of the stomach with staples and anastomosing it to the jejunum, thereby bypassing most of the stomach, all of the duodenum, and the first 15 cm of the jejunum.

Mean excess weight loss is 50 to 60% at five years postoperatively. In addition, studies have found that type 2 diabetes is reversed in approximately 80% of patients after surgery if the procedure is performed early enough in the disease process.⁵³

Deficiencies of iron, calcium, vitamin D, and vitamin B are common in these patients due to malabsorption. Rapid emptying from the gastric pouch into the

jejunum can result in dumping syndrome, with symptoms of nausea, lightheadedness, bloating, and diarrhea. Perioperative mortality is less than 1%.

The remaining three procedures are not performed as often, mainly because in the case of vertical banded gastroplasty and gastric banding they have not been successful in maintaining long-term weight loss, and in the case of biliopancreatic bypass because long-term data are lacking. Nonetheless, regardless of which surgical method is chosen, lifelong monitoring of diet, weight, and surgical complications is an essential component of follow-up in these patients.⁵⁶⁻⁵⁷

Pharmacist's Role

As highly trusted members of the healthcare team, pharmacists can promote healthy behavioral modification through counseling activities, including helping patients achieve and maintain a healthy weight. Pharmacists can build their efforts in this area by collaborating with physicians and other appropriate professionals, identifying target patients who have obtained services at the pharmacy or outpatient clinic, contacting patients in at-risk populations within the pharmacy's patient base and/or the community, and helping patients maintain efforts for sustained time periods. Both community pharmacists and those in outpatient ambulatory care clinics have the potential to expand their involvement

in self-care and affect the overall well-being of patients by taking the initiative to identify and counsel overweight and obese patients. Clinician-initiated discussions on obesity and weight-loss-related benefits should be encouraged, since patients who report receiving weight-loss advice from their healthcare providers are more likely to report trying to lose weight than those who do not receive such advice. In addition, for patients with co-morbidities on therapy, pharmacists can assist in improving adherence to medication, diet, and other lifestyle modifications. Ultimately, improving health outcomes for overweight and obese patients can be achieved through the coordinated efforts of pharmacists and their patients.

References available upon request.

Online resources

National Heart and Lung Institute
BMI calculator
www.nhlbisupport.com/bmi/
Portion Control Tools
<http://www.theportionplate.com/>
<http://www.portiondoctor.com/>
<http://www.portionpal.com/>
<http://www.quakeroatmeal.com/>
<http://hp2010.nhlbihin.net/portion/>

Seena Haines, PharmD, FAACP
Associate Professor

Sonia E Cherian, PharmD
Assistant Professor

Lloyd L. Gregory School of Pharmacy,
Palm Beach Atlantic University

Turn to page 18 for the test questions

PHARMACY.ME EDITORIAL THEMES FOR 2009

APRIL

- Scalp and hair care – anti-dandruff shampoos
- Pain management
- Hayfever

JUNE

- Skin care – moisturising and anti-aging
- Vitamins and diet
- Acne

AUGUST

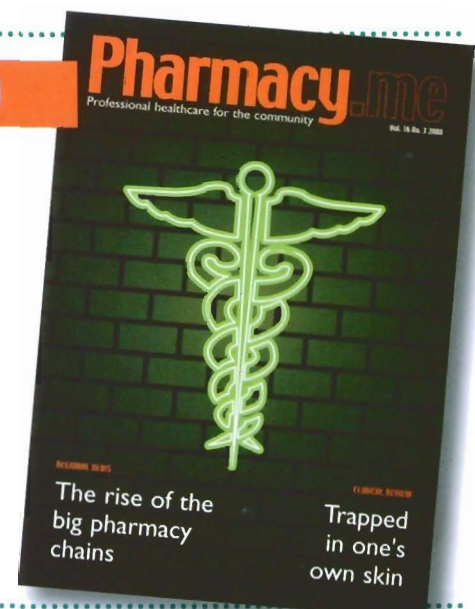
- Infant and child nutrition
- Gastro-intestinal complaints
- Men's health

OCTOBER

- Hair colourants
- Diagnostics
- Women's health

DECEMBER

- First aid – plasters and minor trauma
- Smoking Cessation
- Sore throat



TEST QUESTIONS Mark the most appropriate answer

Questions 1-3 are related to the following patient case:

SH is a 29-year-old black female who presents to your pharmacy with a prescription for sibutramine 10mg once daily. She has a history of hypertension and diabetes, no history of surgeries, and no medication allergies. Upon further review, you find that SH is taking HCTZ 25mg PO daily, glyburide 10 mg PO BID, lisinopril 20mg PO daily, and metformin 1000 mg PO BID. She reports no use of over-the-counter medications or herbal supplements. SH is 5'4" and weighs 180 lbs (BMI 31 kg/m²). After additional questioning, SH reveals that she has been enrolled in "Taking Off the Pounds" (TOPS) weight-loss program for the last six months. She also recently gained 30 lbs after she quit smoking. SH appears android or apple-shaped. She had smoked 1 pack per day for the last 10 years. SH believes losing weight will help her "feel better about how she looks." SH is up to date on her immunizations and has had recent blood pressure readings of: 142/96 and 152/98 this week. When asked, she reported beginning Sibutramine in the last two weeks. SH mentions that she spoke with her doctor about feeling down and depressed. Sertraline is being considered to help "her mood."

- How many obesity-related risk factors does SH have?
a. 0 b. 1 c. 2 d. 3
- How would you classify SH's BMI according to the NHLBI guidelines?
a. Underweight b. Healthy weight c. Overweight d. Obese
- Which of the following medications may contribute to weight gain in SH?
a. Glyburide b. Glucophage
c. Hydrochlorothiazide (HCTZ) d. Lisinopril
- Which of the following factors does not contribute to the etiology of obesity?
a. Cultural influences b. Genetic influences
c. Socioeconomic influences d. Linguistic influences
- Secondary causes of obesity include all of the following except:
a. Cushing syndrome b. Hypertension
c. Hypothyroidism d. Insulinoma
- Which complication associated with obesity can affect fertility and insulin resistance?
a. Gout b. Metabolic syndrome
c. Osteoarthritis d. Polycystic ovarian syndrome (PCOS)
- Healthcare providers should consider recommending lifestyle modifications to patients with a BMI of:
a. 25 kg/m² or greater b. 30 kg/m² or greater
c. 35 kg/m² or greater d. 40 kg/m² or greater
- Which of the following conditions confers the highest obesity-related risk?
a. Diabetes b. Endometrial cancer
c. Gout d. Polycystic ovarian syndrome (PCOS)
- What is the 6-month weight loss recommended for patients?
a. 5% b. 10% c. 15% d. 20%
- According to the Nurses' Health Study, how much greater is the risk of experiencing symptomatic gallstones for women with a BMI of 30 or greater, compared to those with a BMI <24 kg/m²?
a. No greater risk b. Twofold excess risk
c. Threefold excess risk d. Fourfold excess risk
- The risk of gallstones is increased when the rate of weight loss exceeds:
a. 1.0 kg per week b. 1.5 kg per week
c. 2.0 kg per week d. 2.5 kg per week

Questions 12-14 are related to the following patient case:

LB is a 38-year-old Caucasian female who comes into your pharmacy asking for a "magic pill" to help her lose weight. She has a history of glaucoma and sleep apnea. You have known LB for some time now and are aware of her New Year's resolution to lose weight. After counseling LB on diet and exercise and advising her that there is no "magic pill," you decide to recommend orlistat over the counter.

- Which of the following is an appropriate dose of over-the-counter orlistat to recommend to LB?
a. 15 mg TID b. 30 mg TID c. 60 mg TID d. 120 mg TID
- Common adverse effects of orlistat include all of the following except:
a. Flatulence with discharge b. Fecal urgency
c. Increased heart rate d. Steatorrhea
- Which of the following may be a factor related to LB's obesity?
a. Glaucoma b. Osteoarthritis
c. Polycystic ovarian syndrome (PCOS) d. Obstructive sleep apnea
- Which obesity-related medication can block the absorption of fat-soluble vitamins?
a. Mazindol b. Orlistat
c. Phentermine d. Sibutramine
- Patients who may be a candidate for bariatric surgery include those who have a BMI of at least:
a. 30 kg/m² b. 35 kg/m² c. 40 kg/m² d. 45 kg/m²
- Which of the following is the surgical treatment of choice in patients with clinically severe obesity?
a. Biliopancreatic bypass b. Laparoscopic adjustable gastric banding
c. Roux-en-Y gastric bypass d. Vertical banded gastroplasty
- For which of the following disease states is it inappropriate to recommend weight-loss therapy?
a. Diabetes b. Hypertension
c. Major depression d. Obstructive sleep apnea
- Which of the following medications is currently approved by the FDA only for short-term use in obese patients?
a. Orlistat b. Phentermine c. Rimonabant d. Sibutramine
- Which antilipemic agent modifies the CB-1 receptor for the treatment of obesity?
a. Orlistat b. Phentermine c. Rimonabant d. Sibutramine

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