

Classification and Pharmacological Management of Obesity

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Educational Objectives

After reviewing this article, readers should be able to:

- Assess a patient for the degree of obesity and its associated risks to patient health.
- Describe the indications for, complications of, and amount of weight loss achievable with the various types of bariatric surgery.
- Review the mechanism of action, contraindications, and adverse effects of the pharmacological agents used for the treatment of obesity.

Introduction

Despite the overwhelming amount of information regarding the morbidity and mortality associated with being overweight or obese, the number of individuals classified as obese each year continues to rise. According to a 2007 report, the obesity epidemic affects 1.7 billion individuals worldwide and takes the life of 2.5 million people annually.¹

In the U.S., approximately one-third of the adult population is considered to be obese.² The dangers of being either overweight or obese are far more alarming than most people realize. Research indicates that these conditions can significantly increase the risk of diabetes mellitus, coronary artery disease, hypertension, dyslipidemia, stroke, osteoarthritis, gallbladder disease, gastroesophageal reflux disease, lower back pain, sleep apnea, and asthma. Furthermore, obesity has been associated with an increased risk of morbidity from cancers of the colon, endometrium, prostate, and breast.

It is necessary for clinicians to convey the benefits of weight loss to their patients. Weight loss has the potential to reduce heart disease and stroke by decreasing blood pressure and improving cholesterol and triglyceride levels. Diabetic patients have a greater chance of controlling their blood glucose levels by losing weight, which in turn may result in the need for fewer



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glycemic control medications, such as insulin. Many positive outcomes can result from weight loss. This article reviews the assessment and treatment options available to help clinicians identify and care for overweight or obese patients.

Assessment

Patient assessment should begin with a determination of the body mass index (BMI). The patient's weight and height are used to calculate the patient's BMI, which is considered to be an indirect measurement of body fat. After the BMI is known, patients can be further separated into classes. Assessment should also include waist circumference, because excess abdominal fat has been shown to be an independent risk factor for disease. Waist measurements of 40 inches or greater in men and 35 inches or greater in women are associated with an increased risk of type-2 diabetes, hypertension, and cardiovascular disease (Table 1).³

Nonpharmacological Treatment

Diet and Behavior Modification

Obesity management is founded on an integrated program of calorie and fat restriction, exercise, and behavior modification. An initial weight loss goal should be a 5% to 10% reduction from the baseline weight. Dietary counseling may play a vital role in patient compliance, especially during the first year of weight loss.⁴ For a healthy weight loss of one to two pounds per week, a net caloric deficit of 500 to 1,000 kilocalories (kcal) per day must occur. This net deficit can be achieved in two ways: by an intake of fewer calories or by an expenditure of a greater number of calories. The National Heart, Lung, and Blood Institute guidelines suggest 30 to 45 minutes of physical activity

three to five days per week.

Table 2 presents a comparison of physical activities commonly practiced and the average amount of calories a 154-pound individual expends by engaging in each activity for one hour.⁵ Regular exercise is beneficial not only for weight loss goals; it can also have a positive impact on metabolic risk factors such as lowering blood pressure and cholesterol levels.

Surgical Options

Bariatric surgery is an option when diet, exercise, and drug

Table 1 Classification of Overweight and Obesity by Body Mass Index (BMI), Waist Circumference, and Associated Disease Risk

	BMI (kg/m ²)	Obesity Class	Disease Risk (Relative to Normal Weight and Waist Circumference)*	
			Men: ≤40 inches (≤102 cm) Women: ≤35 in (≤88 cm)	> 40 inches (>102 cm) > 35 inches (>88 cm)
Underweight	< 18.5		—	—
Normal weight‡	18.5–24.9		—	—
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9	I	High	Very high
	35.0–39.9	II	Very high	Very high
Extreme obesity	≥ 40	III	Extremely high	Extremely high

* Disease risk for type-2 diabetes, hypertension, and cardiovascular disease.
‡ Increased waist circumference can also be a marker for increased risk even in persons of normal weight.
Adapted from *Obesity: Preventing and Managing the Global Epidemic*. WHO, 1997.³

therapy have not produced satisfactory outcomes. The weight loss achieved with bariatric surgery has been shown to improve a variety of comorbid conditions such as diabetes, hypertension, lipid abnormalities, obstructive sleep apnea, and female urinary stress incontinence.⁶ Patients are eligible for surgery if they have a BMI of 40 kg/m² or higher, and potential benefits of surgery should outweigh the risks. The National

Institutes of Health (NIH) suggests that patients with a BMI of 35 kg/m² or higher with a comorbidity such as severe diabetes, sleep apnea, or joint disease may also be candidates for surgery. In February 2006, the Centers for Medicare and Medicaid Services (CMS) approved reimbursement of weight-loss surgery for patients with a BMI of 35 kg/m² or higher with one comorbidity.

Weight loss as an outcome of surgery can occur by two mechanisms: gastric restriction and malabsorption or a combination of both. Gastric restriction encompasses such procedures as the vertical banded gastroplasty and the laparoscopic adjustable band. Gastric bypass involves both mechanisms to achieve weight loss, whereas the biliopancreatic diversion with duodenal switch involves a technique resulting in malabsorption. The vertical banded gastroplasty that was popular in the 1980s has been replaced by alternatives because of low satisfaction rates.

Adjustable band. The least invasive of the bariatric surgical procedures is the laparoscopic adjustable band. A silicone band is placed around the first portion of the stomach to form a small pouch and stoma. Although the stomach is not permanently altered, risks associated with this procedure include erosion of the band into the stomach, obstruction, infection, and long-term esophageal motility sequelae. The average one-year weight loss is 45% of excess weight.

Gastric bypass. The most commonly used procedure in the U.S. is the Roux-en-Y gastric bypass. The surgeon creates a small pouch, and a portion of the small intestine is bypassed. Patients lose an average of 60% to 70% of their excess weight 9 to 14 months after surgery, and most patients maintain much of the initial weight loss at 10 years.

The Swedish Obesity Study compared more than 2,000 subjects undergoing bariatric surgery (gastric bypass, vertical banded gastroplasty, and banding) with matched controls receiving conventional treatment ranging from sophisticated lifestyle intervention and behavior modification to no treatment at all.⁶ Follow-up visits at 10 years showed that body weight increased in the control group and weight loss had stabilized

Table 2 Average Number of Calories Expended by a 154-Pound Person Engaging in Physical Activity

	Calories/hour* (approx.)
<i>Moderate activity</i>	
Hiking	370
Light gardening/yard work	330
Dancing	330
Golf (walking and carrying clubs)	330
Bicycling (<10 mph)	290
Walking (3.5 mph)	280
Weight lifting (general light workout)	220
Stretching	180
<i>Vigorous activity</i>	
Running/jogging (5 mph)	590
Bicycling (>10 mph)	590
Swimming (slow free-style laps)	510
Aerobics	480
Walking (4.5 mph)	460
Heavy yard work (chopping wood)	440
Weight lifting (vigorous effort)	440
Basketball (vigorous)	440

*The number of calories burned per hour is higher for persons who weigh more than 154 pounds (70 kg) and lower for persons who weigh less than 154 pounds.

Adapted from *The Dietary Guidelines for Americans 2005*. Available at: www.webmd.com.⁵

in all bariatric surgery groups. The most weight loss occurred in the gastric bypass patients. Mortality rates were higher in controls at the 10-year follow-up. The study authors concluded that bariatric surgery not only achieves long-term weight loss but also decreases overall mortality.

As with other weight-loss surgical procedures, gastric bypass is associated with risks, such as infection in the incision; leakage from the stomach into the abdominal cavity or where the intestine is connected, resulting in peritonitis; and nutritional deficiencies of vitamin B₁₂ and iron, which can lead to anemia.⁶

Duodenal switch. Another surgical option that is becoming more popular in the U.S. is the duodenal switch, in which two-thirds of the stomach is removed and most of the small intestine is bypassed. It is the most invasive of the bariatric procedures. The initial weight loss with this procedure is similar to that with gastric bypass, but patients continue to lose weight in the second year after surgery and average weight loss is much higher. The risks associated with the duodenal switch are micronutrient deficiencies, malnutrition, and increased bowel movements. Patients opting for bariatric surgery must be highly motivated and compliant with changes in eating habits and lifestyle.^{1,7}

Pharmacological Treatment

Three drugs have been approved by the FDA for the treatment of obesity in the U.S. Only two of these are approved for long-term use.

Phentermine (Adipex-P, Ionamin)

Phentermine HCl, an appetite suppressant, is approved for short-term monotherapy in patients 16 years of age and older. Phentermine is structurally similar to dextroamphetamine and elicits its effect by stimulating the hypothalamus to result in decreased appetite. These effects are most likely mediated via norepinephrine and dopamine metabolism. Phentermine is available as tablets (Adipex-P, Gate) or as resin capsules (Ionamin, Celltech).

The recommended dose for the tablet is 37.5 mg taken once daily or 18.75 mg taken twice daily. The tablet should be taken before breakfast or one to two hours after breakfast. The resin capsule, at a dose of 15 to 30 mg, is taken before breakfast or 10 to 14 hours before bedtime. Evening administration should be avoided because of the possibility of insomnia, although insomnia appears to be rare with the resin formulation.

The drug is well absorbed and is excreted unchanged in the urine. The elimination half-life is 20 hours. Although phentermine is approved only for short-term therapy (12 weeks), physicians may continue to prescribe it for longer periods of time if it proves to be effective for the patient. Discontinuation of therapy should be considered if significant weight loss has not been achieved during the first four to six weeks.

Anorectic agents should not be used in patients with cardiovascular disease, hyperthyroidism, or moderate-to-severe hypertension. Rare cases of valvular injury, as well as primary pulmonary hypertension (PPH), have been reported. Phentermine may exacerbate behavior and thought disturbances in psychotic patients (Table 3).⁸

Sibutramine (Meridia) and Orlistat (Xenical)

Sibutramine (Meridia, Abbott) and orlistat (Xenical, Roche) are approved for the long-term management of obesity. Long-term therapy is indicated for obese patients with a BMI of 30 kg/m² or greater and for patients with a BMI of 27 kg/m² who also have diabetes, dyslipidemia, or hypertension. The safety and efficacy of these agents have not been established beyond two years.

Sibutramine. Sibutramine is a non-amphetamine appetite suppressant that blocks the neuronal uptake of norepinephrine, serotonin, and dopamine. Sibutramine is labeled as a Schedule IV controlled substance despite its low potential for psychological addiction or drug dependence.

The recommended initial dose is 10 mg orally once daily. This dose may be titrated after four weeks to a maximum of 15 mg once daily and may be decreased to 5 mg daily if intolerance develops. Sibutramine may be given with or without food. It is rapidly absorbed and is highly protein-bound (more than 94%). The parent drug undergoes first-pass metabolism via cytochrome P450 3A4 to form two active metabolites. The half-life of the metabolites is approximately 15 hours. Excretion occurs primarily in the urine.

Side effects include increased systolic and diastolic blood pressure, increased heart rate, tachycardia, palpitations, dry mouth, and constipation (Table 4).⁹ An additional risk associated with sibutramine includes the possibility of the development of a life-threatening adverse drug reaction, known as serotonin syndrome, as a result of excess serotonergic activity at central nervous system (CNS) and peripheral serotonin

Table 3 Contraindications and Adverse Effects Associated with Phentermine (Adipex-P)

Contraindications

- Advanced arteriosclerosis
- Symptomatic cardiovascular disease
- Moderate to severe hypertension (stage II or III)
- Hyperthyroidism
- Glaucoma
- History of drug abuse
- Concomitant monoamine oxidase (MAO) inhibitor use or within 14 days of phentermine use
- Age younger than 16 years
- Hypersensitivity to sympathomimetic amines or any component of the formulation

Adverse effects

- Exacerbation of symptoms of behavior and thought disorder in psychotic patients
- Increased systolic and diastolic blood pressure
- Tachycardia and palpitations
- Euphoria
- Insomnia and restlessness
- Dry mouth
- Diarrhea
- Impotence or changes in libido
- Tremor

From Adipex-P package insert, Teva, 2005.⁸

Table 4 Contraindications and Adverse Effects Associated with Sibutramine (Meridia)**Contraindications**

- Anorexia nervosa or bulimia nervosa
- Concomitant monoamine oxidase (MAO) inhibitor use
- Concomitant use of centrally acting appetite suppressants
- Hypersensitivity to sibutramine

Adverse effects

- Increased systolic and diastolic blood pressure
- Increased heart rate
- Tachycardia and palpitations
- Dry mouth
- Constipation
- Serotonin syndrome

From Meridia package insert, Abbott, 2006.⁹

receptors. This risk is increased significantly if the patient is currently taking other medications that increase serotonin in the CNS, such as selective serotonin reuptake inhibitors (SSRIs) or monoamine oxidase (MAO) inhibitors.

In clinical trials, sibutramine has resulted in weight loss of 4.45 kg or greater, with most patients losing at least 5% of their baseline body weight throughout the course of therapy. Significant weight reduction occurred after two to four weeks of therapy, and patients were able to maintain their original weight loss for up to 18 months by continuing to take the drug. Other possible benefits of weight loss with sibutramine include decreased levels of triglycerides and low-density lipoprotein (LDL) cholesterol and increased high-density lipoprotein (HDL) cholesterol levels.¹⁰

Orlistat. Orlistat (Xenical) is a nonsystemic inhibitor of gastrointestinal (GI) lipases that are necessary for the breakdown of fat in the GI tract. The unabsorbable fat is then excreted. Orlistat is a synthetic derivative of lipostatin isolated from a soil bacterium, *Streptomyces toxytricini*. The recommended dose is 120 mg orally three times daily during or within one hour of each fat-containing meal. If a meal is skipped

Table 5 Contraindications and Adverse Effects Associated with Orlistat (Xenical)**Contraindications**

- Cholestasis
- Chronic malabsorption syndrome
- Hypersensitivity to orlistat products

Adverse effects

- Abdominal pain
- Soft or liquid stools
- Increased defecation and flatulence
- Oily spotting
- Fecal incontinence
- Hemorrhoids

From Xenical package insert, Roche, 2007.¹⁰

or if it contains no fat, the dose of orlistat can be omitted.

Because orlistat can block the absorption of approximately 30% of dietary fat, patients should be counseled to maintain a diet containing 30% or fewer calories from fat. Patients should also supplement their diets with a multivitamin containing fat-soluble vitamins A, D, E, and K as well as beta-carotene, because orlistat reduces the absorption of these components from dietary sources.

Orlistat is now available as a nonprescription product and is marketed as Alli by GlaxoSmithKline. It is taken as a 60-mg dose orally three times daily. The drug itself is only minimally absorbed and excreted as unchanged drug in the feces. It is metabolized within the gut wall to form inactive metabolites.

Side effects of orlistat primarily affect the GI tract and result from the inhibition of fat absorption. These effects may include abdominal pain, soft or liquid stools, increased defecation, and flatulence. Oily spotting, fecal incontinence, and hemorrhoids have also been reported (Table 5).¹⁰ The effects appear to be dose-related, and some effects may decrease over time. Patients should be counseled that increased adverse effects might be related to the amount of fat consumed in the diet.¹¹

Orlistat has been shown to produce weight loss of 2.9 kg greater than placebo when taken for 12 months. When orlistat and sibutramine were compared in clinical trials, sibutramine produced significantly greater weight reduction than orlistat in terms of kilograms lost.

Investigational Therapies

Rimonabant (Acomplia). As a result of the growing population of patients with obesity, there is a wide demand for researchers to examine new safe and effective treatment options. This exploration led to the development of a new medication, rimonabant (Sanofi-Aventis). This drug is distinct because of its novel mechanism of action as a selective cannabinoid-1 (CB-1) receptor antagonist. In the CNS, endocannabinoids are released and stimulate appetite, lipogenesis, and fat accumulation in the periphery. Rimonabant works to block these effects of endocannabinoids.

Studies had shown that rimonabant's blockade of the CB-1 receptor could induce a state similar to melancholic depression as well as increase the risk of suicidal behavior.¹² Patients with a history of psychiatric illness or psychiatric disorders should consider other treatment options before deciding to initiate therapy with rimonabant. Other side effects include nausea, mood alteration, anxiety, and dizziness.

Hepatic CYP 3A and amidohydrolase pathways are involved in the drug's metabolism. The use of tobacco, alcohol consumption, or coadministration of CYP 3A4 inducers, such as phenytoin (Dilantin, Pfizer), phenobarbital, carbamazepine (Carbitrol, Shire; Tegretol, Novartis), and rifampin, may reduce the plasma concentration of rimonabant, just as CYP 3A4 inhibitors like clarithromycin (Biaxin, Abbott), ritonavir (Norvir, Abbott), itraconazole (Sporanox, Janssen), and ketoconazole (Nizoral, Janssen) can cause an increase in serum concentrations of rimonabant.

Rimonabant is absorbed quickly following oral administration and exhibits linear pharmacokinetics. A maximum serum concentration is attained in approximately two hours after oral administration of 20 mg. In a nonobese individual, the termi-

nal half-life ranges from six to nine days, but it is significantly longer, about 16 days, in the obese.¹³

Rimonabant's effectiveness in treating overweight or obese patients was studied during a program consisting of four randomized, controlled trials, known as The Rimonabant in Obesity (RIO) program. Each trial (RIO-Europe, RIO-Lipids, RIO-North America, and RIO-Diabetes) compared rimonabant 5 and 20 mg/day with placebo. In these trials, rimonabant was as effective as sibutramine and orlistat.¹³

Rimonabant was approved in the United Kingdom as Acomplia in 2006. In the summer of 2007, however, the FDA voted against the sale of rimonabant in the U.S., under the brand name Zimulti, because of the medication's psychiatric side effects. In October 2008, Sanofi-Aventis withdrew rimonabant from European markets because of safety concerns. In reviewing postmarketing data, the European Union found that rimonabant doubled the risk of psychiatric disorders in obese or overweight patients taking the drug.

Taranabant. Although the FDA did not approve rimonabant, a drug with a similar mechanism of action—taranabant, a CB-1 receptor inverse agonist—was studied in phase 3 trials. Merck had expected to file for FDA approval; in October 2008, however, the company canceled further investigation into this experimental obesity drug. At more effective dosages, side effects increased excessively.¹⁴

Merck had been aiming for a 5% weight loss, but that goal was achieved only at the highest dose (4 mg). CNS side effects were prominent at this level, twice the rate of the placebo group. The next lower dose, 2 mg, missed the efficacy endpoint and still seemed to show CNS effects. Nearly twice the number of treated patients dropped out of the trial compared with the placebo group, citing neurological effects that included thoughts of suicide.¹⁵

Tesofensine. Another agent undergoing investigational trials is showing potential as an obesity therapy. Tesofensine has shown promising results for weight loss and distinguishes itself from rimonabant and taranabant by its mechanism of action. The serotonin–noradrenaline–dopamine reuptake inhibitor works mainly as an appetite suppressant.

In a phase 2 clinical trial, the average weight loss was 12.8 kg with a 1-mg dose and 11.3 kg with a 0.5-mg dose over a six-month period. Adverse effects caused by the medication are mild, although an increase in blood pressure and heart rate are directly proportionate to the amount of drug administered.

NeuroSearch, a company in Europe, is currently conducting an extension trial in order to determine the efficacy and safety of tesofensine. If the trial proves to be a success, tesofensine could be considered twice as effective as drugs currently available in the U.S.¹⁶

Conclusion

The worsening obesity epidemic has forced health care providers to be more diligent in recognizing and treating patients with weight-management problems. After appropriate assessment of a patient's weight, changes in lifestyle regarding diet and exercise should be implemented. If traditional

methods are unsuccessful, surgery, pharmacological options, or both should be considered.

Phentermine may be used for short-term therapy, and either sibutramine or orlistat may be considered for long-term therapy. Unfortunately, rimonabant and taranabant, as cannabinoid receptor antagonists, were not approved for long-term use. With a multifaceted approach to achieve weight loss in the general population, it is hoped that many chronic diseases resulting from obesity and overweight will decline with the advent of safer drugs and more definitive studies.

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Conflict of Interest (COI) Statement

Dr. Erlanger and Dr. Henson have no relationships to disclose. The article contains discussion of off-label use. The content of this article has been reviewed under Jefferson's Continuing Medical Education COI policy.