Chapter 58: Obesity

INTRODUCTION

- *Obesity* occurs when there is an imbalance between energy intake and energy expenditure over time, resulting in increased energy storage.

PATHOPHYSIOLOGY

- The etiology of obesity is usually unknown, but it is likely multifactorial and related to varying contributions from genetic, environmental, and physiologic factors.
- Genetic factors appear to be the primary determinants of obesity in some individuals, determining both obesity and distribution of fat, whereas environmental factors are more important in others. The total number and identity of contributing genes are still being determined.
- Environmental factors include reduced physical activity or work, abundant food supply, relatively sedentary lifestyles, increased availability of high-fat foods, and cultural factors and religious beliefs.
- Medical conditions including Cushing disease, growth hormone deficiency, insulinoma, leptin deficiency, and psychiatric disorders such as depression, binge-eating disorder, and schizophrenia and genetic syndromes such as Prader–Willi syndrome can be associated with weight gain.
- Medications associated with unintended weight gain include insulin, corticosteroids, some antidepressants, conventional antipsychotics, and several anticonvulsants.
- Many neurotransmitters and neuropeptides stimulate or depress the brain's appetite network, impacting total calorie intake.
- The degree of obesity is determined by the net balance of energy ingested relative to energy expended over time. The single largest determinant of energy expenditure is metabolic rate, which is expressed as *resting energy expenditure* or *basal metabolic rate*. Physical activity is the other major factor that affects total energy expenditure and is the most variable component.
- Major types of adipose tissue are: (1) white adipose tissue, which manufactures, stores, and releases lipid; and (2) brown adipose tissue, which dissipates energy via uncoupled mitochondrial respiration. Adrenergic stimulation activates lipolysis in fat cells and increases energy expenditure in adipose tissue and skeletal muscle.

CLINICAL PRESENTATION

- Obesity is associated with serious health risks and increased risk of all-cause mortality. Central obesity reflects high levels of intra-abdominal or visceral fat that is associated with the development of hypertension, dyslipidemia, type 2 diabetes, and cardiovascular disease (sometimes referred to as the "metabolic syndrome").
- Body mass index (BMI) and waist circumference (WC) are recognized, acceptable markers of excess body fat that independently predict disease risk (**Table 58-1**).
- BMI is calculated as weight (kg) divided by the square of the height (m^2).
- WC, the most practical method of characterizing central adiposity, is the narrowest circumference between the last rib and the top of the iliac crest.

TABLE 58-1

Classification of Overweight and Obesity by Body Mass Index, Comorbidity Risk, Waist Circumference, and Associated Disease Risk

				Disease Risk[a] (Relative to Normal Weight and Waist Circumference)	
				Men	
				≤40 in. (102 cm)	>40 in. (102 cm)
				Women	
	BMI (kg/m^2)	Obesity Class	Comorbidity Risk	≤35 in. (89 cm)	>35 in. (89 cm)
Underweight	<18.5		Low but other problems	—	—
Normal weight[b]	18.5–24.9		Average	—	High
Overweight	25.0–29.9		Increased	Increased	High
Obesity	30.0–34.9	I	Moderate	High	Very high
	35.0–39.9	II	Severe	Very high	Very high
Extreme obesity	≥40	III	Very severe	Extremely high	Extremely high

[a]Disease risk for type 2 diabetes, hypertension, and cardiovascular disease.

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

BMI, body mass index.

Adapted from Preventing and Managing the Global Epidemic of Obesity. Report of the World Health Organization Consultation on Obesity. Geneva: World Health Organization, 1997. Reprinted with permission from National Institutes of Health, National Heart, Lung, and Blood Institutes. 1997, http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm.

TREATMENT

- Goals of Treatment: Current clinical practice guidelines recommend a “complication-centric approach” to assess for the presence and severity of weight-related complications to determine appropriate treatment and intensity of weight loss therapy in individuals with overweight and obesity. The primary goal is to ameliorate weight-related complications and ultimately improve health and quality of life rather than a preset decrease in body weight.

GENERAL APPROACH

- Nonpharmacologic therapy, including reduced caloric intake, increased physical activity, and behavior modification, is the mainstay of obesity management. Set goals based on factors including initial body weight, patient motivation and desire, presence of obesity-related comorbid conditions, and age.
- Current adult practice guidelines recommend reduced caloric intake through adherence to a low-calorie diet. Adherence to this type of diet with increased exercise, and in-person behavioral counseling sessions have been reported to result in an average weight loss of 8 kg (17.6 lb) over 6 months.
- Bariatric surgery, which reduces the stomach volume or absorptive surface of the alimentary tract, remains the most effective intervention for obesity. Surgery should be reserved for those with extreme obesity (BMI ≥40 kg/m^2) or BMI >35 kg/m^2 with significant comorbidities such as hypertension, type 2 diabetes, or obstructive sleep apnea.
- Implantable medical devices are an option for individuals who do not qualify for bariatric surgery or choose to not undergo the procedure. These devices are designed to work in conjunction with prescribed diet and exercise programs.

PHARMACOLOGIC THERAPY

- Pharmacotherapy is an adjunct to comprehensive lifestyle intervention in adults who are motivated to lose weight, have failed to achieve or sustain weight loss with lifestyle change alone, and have a BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least one weight-related comorbidity (**Table 58-2**).
- Long-term pharmacotherapy may have a role for patients who have no contraindications to approved drug therapy (**Table 58-3**).
- **Orlistat** (180 or 360 mg in three divided doses/day) is a lipase inhibitor that induces weight loss by lowering dietary fat absorption; it also improves lipid profiles, glucose control, and other metabolic markers. Soft stools, abdominal pain or colic, flatulence, fecal urgency, and/or incontinence occur in 80% of individuals using prescription strength, are mild to moderate in severity, and improve after 1–2 months of therapy. Orlistat is approved for long-term use. It interferes with the absorption of fat-soluble vitamins, **cyclosporine**, **levothyroxine**, and **oral contraceptives**. A nonprescription formulation is also available.
- **Phentermine** in combination with **topiramate extended release** is indicated for chronic weight management. Doses are gradually titrated from phentermine 3.75 to 15 mg and topiramate 23–92 mg over 4 months, but the drug should be stopped after 12 weeks if 5% weight loss is not achieved. Common adverse effects include constipation, dry mouth, paraesthesia, dysgeusia, and insomnia.
- **Naltrexone** in combination with **bupropion extended release** is indicated for chronic weight management. Doses are gradually increased over 4 weeks, starting with one tablet daily (8 mg naltrexone/90 mg bupropion) to a maintenance dose of two tablets twice daily. Patients should avoid taking their dose with a high-fat meal. Common adverse effects include nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea. Discontinue treatment if 5% weight loss is not achieved after 12 weeks.
- **Liraglutide** is a glucagon-like peptide-1 receptor agonist indicated for chronic weight management at a dose of 3 mg daily. It is administered subcutaneously and is available in prefilled, multidose pens. A 5-week dose escalation schedule is recommended to improve tolerability of GI adverse events, beginning with 0.6 mg daily and increasing weekly by 0.6 mg increments to a maintenance dose of 3 mg daily. Common adverse effects include nausea, diarrhea, constipation, vomiting, dyspepsia, hypoglycemia, and abdominal pain. Discontinue liraglutide if weight loss of at least 4% is not achieved after 16 weeks of therapy.
- **Amphetamines** should generally be avoided because of their powerful stimulant effects and addictive potential.
- **Lorcaserin** is a selective serotonin receptor agonist (5-HT_{2C}) that was removed from the market in February 2020.
- Many complementary and alternative therapy products are promoted for weight loss. Regulation of dietary supplements is less rigorous than that of prescription and over-the-counter drug products; manufacturers do not have to prove safety and effectiveness prior to marketing.

TABLE 58-2

FDA-Approved Pharmacotherapeutic Agents for Weight Loss

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comment
Gastrointestinal lipase inhibitor					
Orlistat	Xenical	120 mg three times daily with each main meal containing fat	120 mg three times daily with each main meal containing fat		Approved for long-term use Take during or up to 1 hour after the meal Omit dose if meal is occasionally missed or contains no fat
Orlistat	Alli[a]	60 mg three times daily with each main meal containing fat	60 mg three times daily with each main meal containing fat		Same as Xenical
Phentermine–topiramate combination					
Phentermine and topiramate extended-release	Qsymia	3.75 mg of phentermine and 23 mg of topiramate once daily for 14 days; then increase to 7.5 mg of phentermine and 46 mg of topiramate once daily	7.5 mg of phentermine and 46 mg of topiramate once daily to a maximum dose of phentermine 15 mg and topiramate 92 mg once daily	Maximum dose for patients with moderate or severe renal impairment or patients with moderate hepatic impairment is 7.5 mg of phentermine and 46 mg of topiramate	Approved for long-term use Take dose in the morning to avoid insomnia Controlled substance: C–IV
Naltrexone–bupropion combination					
Bupropion and naltrexone extended-release	Contrave	8 mg naltrexone/90 mg bupropion (1 tablet) once daily in the morning for 1 week; then 8 mg naltrexone/90 mg bupropion twice daily (morning and evening) for 1 week; then 16 mg naltrexone/180 mg bupropion in the morning and 8 mg naltrexone/90 mg bupropion in the evening for 1 week; then 16 mg naltrexone/180 mg bupropion twice daily (morning and evening)	16 mg naltrexone and 180 mg bupropion (2 tablets) twice daily	Maximum dose for patients with moderate or severe renal impairment is 8 mg naltrexone/90 mg bupropion (1 tablet) twice daily Maximum dose for patients with hepatic impairment is 8 mg naltrexone/90 mg bupropion (1 tablet)	Approved for long-term use Do not take dose with high-fat meal

				once daily in the morning	
Glucagon-like peptide-1 agonist					
Liraglutide	Saxenda	0.6 mg once daily for 1 week 1.2 mg once daily for 1 week 1.8 mg once daily for 1 week 2.4 mg once daily for 1 week 3.0 mg once daily for 1 week[a] administered by subcutaneous injection	3 mg once daily	Use with caution in mild, moderate, and severe renal and hepatic impairment	Approved for long-term use Inject subcutaneously in the abdomen, thigh, or upper arm Administer at any time of day without regard to the timing of meals
Noradrenergic agents					
Phendimetrazine	Bontril PDM; Bontril slow-release	Conventional tablet: start at 17.5 mg two or three times daily, given 1 hour before meals Extended-release capsule: 105 mg once daily 30–60 minutes before morning meal	70–105 mg/day	Use caution in patients with renal impairment	Approved for short-term monotherapy Controlled substance: C–III Prescriptions should be written for the smallest quantity to minimize possibility of overdose
Phentermine	Lomaira Adipex-P	8 mg three times daily, given half hour before meal Orally disintegrating tablet: 15 or 30 mg once every morning Phentermine hydrochloride: 15–37.5 mg/day given in one or two divided doses; administer before breakfast or 1–2 hours after breakfast	8 mg three times daily, given half hour before meal Orally disintegrating tablet: 15 or 30 mg once every morning Phentermine hydrochloride: 15–37.5 mg/day given in one or two divided doses; administer before breakfast or 1–2	Use with caution in patients with renal impairment	Approved for short-term monotherapy Controlled substance: C–IV Prescriptions should be written for the smallest quantity to minimize possibility of overdose Individualize to achieve

			hours after breakfast		adequate response with lowest effective dose
Diethylpropion	Tenuate, Tenuate Dospan	Immediate release: 25 mg three times daily administered 1 hour before meals Controlled release: 75 mg once daily administered at midmorning	75 mg/day	Use with caution in patients with renal impairment	Approved for short-term monotherapy Dose should not be administered in the evening or at bedtime Controlled substance: C–IV

[a]Available without a prescription.

TABLE 58-3

Clinical and Economic Considerations for Long-Term Pharmacotherapy Options

Drug	Brand Name	Weight Loss Above Diet and Exercise Alone (1 year)	Cost for 30 days of Therapy[a]	Comments
Orlistat	Xenical	2.9–3.4 kg (6.5–7.5 lb)	$685.81	Use may be limited by GI intolerance
Phentermine and topiramate extended-release	Qsymia	6.6–8.6 kg (14.5–18.9 lb)	$186.00, 7.5–46 mg $199.50, 15–92 mg	Limited distribution under FDA Risk Evaluation Mitigation Strategy (REMS)
Bupropion and naltrexone extended-release	Contrave	4.9 kg (10.8 lb)	$277.99	Lowers seizure threshold (bupropion) Rare reports of hepatotoxicity (naltrexone) Drug interactions with opioids, CYP2B6 inducers, and CYP2D6 substrates
Liraglutide	Saxenda	5.8 kg (12.8 lb)	$1242.00	Injectable Reduces A1C and fasting glucose Risk of medullary thyroid carcinoma and multiple endocrine neoplasia syndrome type 2 Rare reports of pancreatitis, gall bladder disease, and suicidal ideation

[a]Cost of therapy based on maintenance dose using wholesaler acquisition cost (WAC) as of January 9, 2018.

EVALUATION OF THERAPEUTIC OUTCOMES

- Assess progress once or twice monthly for 1–2 months, then monthly. Each encounter should document weight, WC, BMI, blood pressure, medical history, and patient assessment of tolerability of drug therapy.
- Discontinue medication therapy after 3 months if the patient has failed to demonstrate weight loss or maintenance of prior weight.
- Diabetic patients require more intense medical monitoring and self-monitoring of blood glucose. Weekly healthcare visits for 1–2 months may be necessary until the effects of diet, exercise, and weight loss medication become more predictable.
- Monitor patients with hyperlipidemia or hypertension to assess effects of weight loss on appropriate end points.

See Chapter 161, Obesity, authored by Amy Heck Sheehan, Judy T. Chen, and Jack A. Yanovski, for a more detailed discussion of this topic.