Chapter 167: Obesity

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 59, Obesity.

KEY CONCEPTS

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1. Two clinical measures of excess body fat, regardless of sex, are the body mass index (BMI) and the waist circumference (WC). BMI and WC provide a better assessment of total body fat than weight alone and are independent predictors of obesity-related disease risk.

2. Excessive central adiposity increases risk for development of type 2 diabetes mellitus, hypertension, and dyslipidemia.

3. Weight loss goals should be determined based on severity of obesity-related complications. Treatment selection and intensity of obesity intervention varies depending on the phase of prevention and treatment in which the patient resides. Sustained, large weight losses (ie, after bariatric surgery) are associated with a lower risk of cardiovascular events and death and with long-term improvements in many of the complications associated with obesity.

4. Clinicians should consider the weight-altering effects of medications used to treat comorbid conditions (eg, antidepressants, antipsychotics, antiepileptics, and antidiabetics) and select medications that promote weight loss or are weight-neutral.

5. Bariatric surgery is reserved for adolescents with extreme obesity (BMI more than or equal 35 kg/m^2 or more than or equal 120% of the 95th percentile for age, whichever is lower, with a severe comorbidity, or in youth with BMI more than or equal 40 kg/m^2 or more than or equal 140% of the 95th percentile for BMI, whichever is lower, with any obesity-related comorbidity) and adults with extreme obesity (BMI more than or equal 40 kg/m^2 or BMI more than or equal to 35 kg/m^2 with a major comorbidity).

6. Pharmacotherapy may be considered an adjunctive treatment in adolescents age 12 years and older with BMI corresponding to 30 kg/m^2 or greater for adults (more than or equal to the 95th percentile for age) and adults with a BMI more than or equal to 30 kg/m^2 or BMI of 27 to 30 kg/m^2 with a comorbidity if comprehensive lifestyle modifications (eg, diet, exercise, behavioral modification) fail to achieve or sustain weight loss.

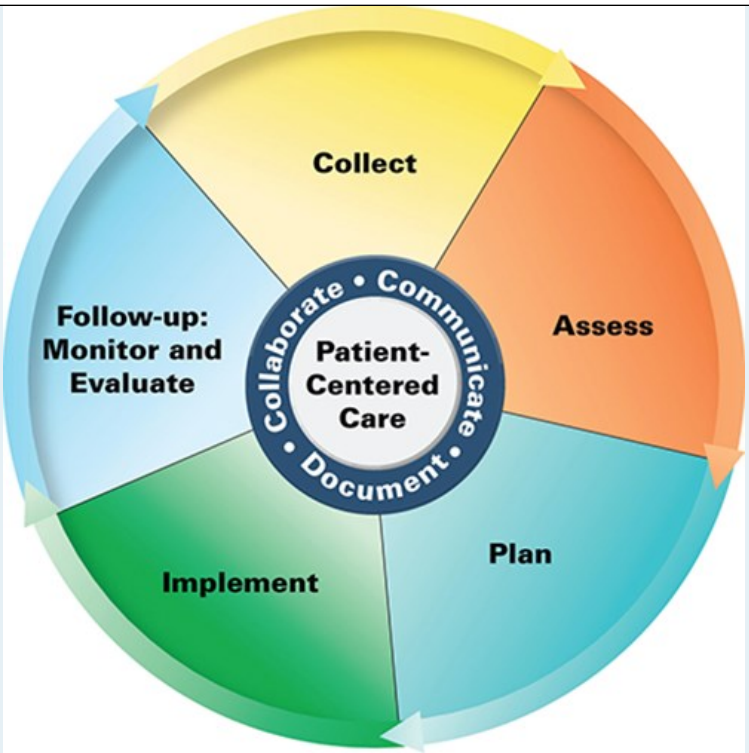
7. Weight regain occurs with a high probability when pharmacotherapy for obesity is discontinued.

8. Pharmacotherapy should be discontinued if weight loss of at least 5% is not achieved after 12 weeks of maximum-dose therapy with phentermine-topiramate, bupropion-naltrexone, or setmelanotide because significant weight loss is unlikely to be achieved despite continued therapy. Liraglutide should be discontinued if weight loss of at least 4% is not achieved after 16 weeks of therapy. There is no recommendation for early discontinuation of semaglutide.

9. The Food and Drug Administration (FDA) does not regulate labeling of herbal and food supplement diet agents, and content is not guaranteed.

PATIENT CARE PROCESS

Patient Care Process for Management of Obesity



Collect

- Patient characteristics (eg, age, race, sex)
- Patient history (past medical, family, social—dietary habits, tobacco use)
- Obesity-related conditions (see Table 167-1)
- Current medications including prescription, non-prescription, and herbal product use
- Weight loss history and prior attempts to lose weight
- Objective data
  - Height, weight, BMI, waist circumference, and blood pressure
  - Labs (eg, fasting glucose, hemoglobin A1c, lipid panel)

Assess

- Causes of secondary obesity (eg, insulinoma, Cushing syndrome)
- Current medications that may contribute to weight gain
- Presence of obesity-related comorbidities (eg, hypertension, dyslipidemia, coronary artery disease, type 2 diabetes mellitus, sleep apnea, increased waist circumference; see Fig. 167-3)
- Class of overweight and obesity determined by BMI, waist circumference, and obesity-related comorbidities (see Table 167-3)
- Readiness to engage in weight loss efforts and potential barriers to success
- Candidacy for treatment with pharmacotherapy, medical devices, or bariatric surgery

Plan*

- Nonpharmacologic lifestyle intervention including low-calorie diet, physical activity, and behavioral modifications
- Determine appropriate weight loss goals based on severity of existing obesity-related complications (see Table 167-4)
- Pharmacotherapy (if appropriate) including specific medication, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Tables 167-6 and 167-8)
- Medical devices (if appropriate) including specific instruction for use, dose, route, duration, and adverse medication reactions (see Table 167-5)
- Monitoring parameters including efficacy (weight loss) and tolerability (medication and/or medical device–specific adverse effects) (see Tables 167-5 and 167-8)
- Bariatric surgery (if appropriate) ensuring specific pre- and post-operative criteria are met
- Patient education (eg, purpose of dietary and lifestyle modification, medication therapy)
- Self-monitoring of weight—when and how to record results
- Referrals to other providers when appropriate (eg, physician, dietitian, psychologist)

Implement*

- Educate patient regarding health risks associated with overweight and obesity
- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule appropriate follow-up (eg, monthly for first 3 months and every 3 months thereafter) based on treatment selected

Follow-Up: Monitor and Evaluate

- Determine weight loss goal attainment
- Presence of adverse medication reactions
- Patient adherence to treatment plan using multiple sources of information

* ***Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

Access the Centers for Disease Control and Prevention (CDC) Overweight & Obesity Website found at https://www.cdc.gov/obesity/index.html. Review the latest obesity statistics and recommended strategies to prevent and manage obesity. This Website is useful to enhance student awareness of the significant public health impact of overweight and obesity and provides tools to assist in the IMPLEMENT step of the patient care process.

INTRODUCTION

Since 1975, the prevalence of obesity worldwide has nearly tripled.[1] It is now estimated that at seven out of every ten adult women and three of every four adult men have overweight or obesity in the United States, and the number of women with obesity outnumbers those who are overweight.[2] While the rise in obesity among young children ages 2 to 5 years appears to have reached a plateau,[3] the prevalence of obesity persistently increased among 6 to 11 year-olds, 12 to 17 year-olds, and adults over the most recent decade between 1999 and 2000 and 2017 and 2018.[2] The presence of obesity and overweight is associated with a dramatically increased risk for the development of many diseases (Table 167-1), poorer outcomes of comorbid disease states, compromise quality of life, and increased healthcare costs.[4-24] As of 2013, it was estimated that obesity accounted for 28.2% of total healthcare spending in non-institutionalized adults in the United States, and the total medical costs of obesity were $342.2 billion annually in 2013.[25] National and global initiatives to stem the obesity epidemic have been established through prevention strategies, consensus guidelines, and best practices.[4-6,22,26-34] This chapter reviews the epidemiology, pathophysiology, and therapeutic approaches for the management of obesity. Although nonpharmacologic treatment modalities are discussed, the pharmacotherapy of obesity is highlighted, and the role of pharmacotherapy relative to the other therapeutic options is critically reviewed.

TABLE 167-1

Conditions More Prevalent Among Patients with Obesity

Cancer	**Genitourinary**
Biliary tract system cancer	Chronic kidney disease
Breast cancer (postmenopausal)	End-stage renal disease
Colorectal cancer	Increased serum urate
Cervical cancer	Nephrolithiasis (kidney stones)
Endometrial cancer (premenopausal)	Obesity-related glomerulopathy
Esophageal cancer	Urinary stress incontinence
Gallbladder cancer	**Immune System**
Gastric cardia cancer	Chronic inflammatory reaction
Leukemia	Immune dysfunction
Liver cancer	**Metabolic**
Multiple myeloma	Diabetes mellitus
Meningioma	Gestational diabetes mellitus
Melanoma	Hyperlipidemia
Non-Hodgkin's lymphoma	Hyperinsulinemia
Ovarian cancer	Hypertriglyceridemia
Pancreatic cancer	Impaired glucose tolerance
Prostate cancer	Low high-density lipoprotein

Rectal cancer	Metabolic syndrome
Renal cell cancer	**Musculoskeletal**
Thyroid cancer	Degenerative joint disease
Cardiovascular	Diffuse idiopathic skeletal hyperostosis
Atrial fibrillation	Disc disease
Cerebral vascular accidents	Fibromyalgia
Chronic heart failure	Flat feet
Coronary artery disease	Gait disturbance
Cor pulmonale	Gout and hyperuricemia
Hypertension	Immobility
Left ventricular hypertrophy	Low back pain/back strain
Myocardial infarction	Osteoarthritis (knee, hips, ankles, feet)
Peripheral vascular disease	Osteoporosis
Peripheral venous insufficiency	Plantar fasciitis
Pulmonary embolism	Sarcopenic obesity
Sudden cardiac death	Total knee arthroplasty (total knee replacement)
Thrombophlebitis	Tendinopathy
Varicose veins	**Neurologic**
Venous thromboembolism	Carpal tunnel syndrome
Ventricular arrhythmias	Idiopathic intracranial hypertension
Dermatologic	Migraines
Acanthosis nigricans	Meralgia paresthetica
Acrochordons (skin tags)	Pseudotumor cerebri
Acne	Stroke
Atopic dermatitis	**Oral Health**
Cellulitis	Dental caries

Hidradenitis suppurativa	Loss of teeth
Intertrigo, carbuncles	Periodontitis
Lymphedema	Xerostomia
Keratosis pilaris	**Psychological**
Panniculitis	Affective disorders
Plantar hyperkeratosis	Anxiety
Psoriasis (women)	Body image disturbance
Status pigmentation of legs	Cognitive dysfunction
Striae distensae (stretch marks)	Depression
Xerosis	Eating disorders
Endocrine and Reproductive	Low self-esteem
Amenorrhea and other menstrual disorders	Social stigmatization
Congenital anomalies	Social isolation
Fetal abnormalities	**Respiratory**
Hirsutism	Asthma
Hyperandrogenism	Chronic obstructive pulmonary disease
Hypogonadism (male)	Dyspnea
Infertility	Hypoventilation syndrome
Precocious thelarche	Obstructive sleep apnea
Polycystic ovary syndrome	Pickwickian syndrome
Pregnancy complications	Pneumonia
Sexual dysfunction	Pulmonary hypertension
Gastrointestinal	Respiratory viral infections (coronavirus, influenza, parainfluenza, metapneumovirus, and rhinovirus)
Altered gut microbiome	
Cholelithiasis	
Gastroesophageal reflux disease	

Hepatic cirrhosis	
Hernias	
Nonalcoholic fatty liver disease	
Pancreatitis	
Nonalcoholic steatohepatitis	
Vitamin deficiencies (fat-soluble and water-soluble vitamins)	

Data from References 4-24.

EPIDEMIOLOGY

One of the global health targets set by the World Health Organization (WHO) is to halt the rise of diabetes mellitus and obesity.[27,35] Obesity in the United States has climbed since the 1960s.[2] The National Health and Nutrition Examination Survey (NHANES) II estimated the prevalence of obesity among adults in the United States was at 15% in 1976 to 1980.[2] By 2017 to 2018, the prevalence of obesity had increased almost threefold and affected 42.4% of the adult population and severe obesity affected 9.2% of the adult population.[2] While the speed with which the prevalence of obesity has increased appears to have somewhat leveled off in recent years, prevention of obesity remains a public health priority due to its high prevalence. If the current trend continues, new projection indicates that by 2030, 78% of the adults in the United States projected will have overweight or obesity and one in every two adults will have obesity.[36] In children, 1 in every 3 children aged 6 to 11 years and 1 in every 2 adolescents aged 12 to 19 years will have overweight or obesity by 2030.[36] Children who are overweight are likely to remain overweight as adults.[37] Furthermore, children and adolescents with overweight or obesity have a higher risk of premature mortality and morbidity as adults.[37] Therefore, childhood and early adulthood are critical intervention periods for prevention of obesity in the next generation and require long-term commitment and investment from all stakeholders.[35] The prevalence of obesity using the 30 kg/m^2 cut point varies by sex and race/ethnicity within the United States. Non-Hispanic Asian men (17.5%) and women (17.2%) have the lowest prevalence of obesity compared to other ethnic groups, though they develop obesity-linked complications at lower BMI than other races/ethnicities.[2] The highest prevalence of obesity is observed among non-Hispanic Black women (56.9%) compared with non-Hispanic Black men (41.1%).[2] This disparity is also associated with the level of education. Black women without a college degree are at greater risk of obesity compared with Black men.[38] Educational achievement, which is linked to socioeconomic status, is also correlated with the fraction of people who have obesity. The prevalence of obesity is greatest in those with high school education or less among non-Hispanic White women and men, non-Hispanic Black women, and Hispanic Women.[38]

ETIOLOGY

Obesity occurs when there is increased energy storage resulting from an imbalance between energy intake and energy expenditure over time. The specific etiology for this imbalance in the vast majority of individuals is multifactorial, with genetic and environmental factors contributing to various degrees. In a small minority of individuals, excess weight may be attributed to an underlying medical condition or an unintended effect of a medication.

Genetic Influences

Genetics plays an important role in determining both obesity and distribution of body fat. In some individuals, genetic factors are the primary determinants of obesity, whereas in others, obesity may be caused primarily by environmental factors. The genetic contribution to the actual variance in BMI and body fat distribution is estimated to be up between 40% and 50%.[39] A number of single-gene mutations producing extreme obesity have been identified, but such mutations are rare and account for a relatively small number of the total cases of obesity.[39] The total number and identity of

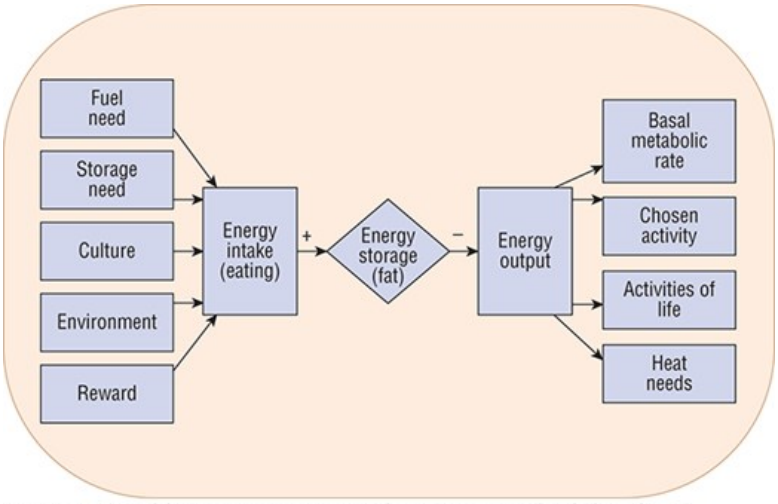
contributing genes are still being determined, as is the means by which the many potential so-called obesity genes interact with each other and with the environment to produce the obese phenotype.

Environmental Factors

Many of the societal changes associated with economic development over the past 50 years have been implicated as potential causes for the increase in the prevalence of obesity.[40] These include an abundant and easily accessible food supply and the material comforts of modern life in Western civilizations, which have contributed to a reduction in physical activity. Advances in technology and automation have resulted in more sedentary lifestyles during both work and leisure time for most individuals. At the same time, there has been a substantial increase in the availability and portion size of high-fat foods, which are aggressively marketed and are often more convenient and less expensive than healthier alternatives. This modern environment has been described by some as "obesogenic" because it is likely to result in a state of positive energy balance in many individuals (Fig. 167-1).[41] Obesity is observed more frequently among individuals within close social networks (eg, siblings, spouses, and friends), with a person's risk of developing obesity increasing dramatically if a friend in their social network has obesity.[42] Cultural factors such as socioeconomic status, and religious beliefs may influence eating habits and body weights. Obesity has also been linked to changes in gut microorganisms and lack of sleep.[40]

FIGURE 167-1

Net energy stores are determined by various inputs and outputs. Simply stated, obesity occurs when there is an imbalance between energy intake and expenditure.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Medical Conditions

Occasionally, patients present with obesity secondary to an identifiable medical condition. Conditions associated with weight gain include iatrogenic and idiopathic Cushing syndrome, growth hormone deficiency, insulinoma, leptin deficiency, and various psychiatric disorders, such as depression, binge-eating disorder, and schizophrenia. Hypothyroidism is often included in this list, but it mostly causes fluid retention (myxedema) and is generally not a cause of obesity. Genetic syndromes that have obesity as a major component are extremely rare and include Prader-Willi, Wilms' tumor, aniridia, genitourinary abnormalities or gonadoblastoma, mental retardation (WAGR), Simpson-Golabi-Behmel, Cohen, Bardet-Biedl, Carpenter, Börjeson, and Wilson-Turner syndromes. The clinician evaluating a patient for obesity needs to be aware of these potential conditions. The physical examination of patients with obesity patients always should include an assessment for secondary causes of obesity, including genetic syndromes.

Medications

An increasing number of medications are associated with unintended weight gain. These include several antiseizure medications (eg, carbamazepine, gabapentin, pregabalin, valproic acid), antidepressants (eg, mirtazapine, tricyclic antidepressants), atypical antipsychotics (eg, clozapine, olanzapine,

quetiapine, risperidone), conventional antipsychotics (eg, haloperidol), lithium, hormones (eg, corticosteroids, insulin, medroxyprogesterone), beta adrenergic blockers, sulfonylureas, thiazolidinediones, and antiretrovirals.[43] Although the pharmacologic mechanism responsible for weight gain is usually medication-specific, in most cases the precise mechanism is unknown.

PATHOPHYSIOLOGY

The pathophysiology of obesity involves numerous factors that regulate appetite and energy balance.[29,44,45] Disturbance of these homeostatic functions results in an imbalance between energy intake and energy expenditure.

Appetite

Human appetite is a complex process that is the net result of many inputs within a neural network involving principally the hypothalamus, limbic system, brainstem, hippocampus, and elements of the cortex.[29,44,45] Within this neural network, many neurotransmitters and neuropeptides have been identified that can stimulate or inhibit the brain's appetite network and thereby affect total caloric intake. The first receptor systems found to alter food intake in animals and humans were the biogenic amines. Serotonin, also known as 5-hydroxytryptamine (5-HT), and cells known to respond to 5-HT are found throughout the central nervous system (CNS) and the periphery. Currently, two major noradrenergic receptor subtypes are recognized (α and β), each with multiple subtypes. Histamine and dopamine also demonstrate multiple receptor subtypes, but their role in the regulation of human eating behaviors and food intake is less well documented. Table 167-2 summarizes the major effects of direct receptor stimulation, inhibition, and changes in synaptic cleft amine concentrations on food intake.

TABLE 167-2

Effects of Various Neurotransmitters, Receptors, and Peptides on Food Intake

Anatomic Region	Increased Eating	Decreased Eating
Arcuate nucleus of hypothalamus	• NPY • AgRP	• α-MSH • CART • Leptin • Insulin • GLP-1 • PYY
Paraventricular nucleus of hypothalamus	• NPY • AgRP	• α-MSH, melanocortin • CRH • CCK
Lateral hypothalamus	• Orexin • MCH	
Hypothalamus	• Norepinephrine α_2 • Serotonin 5-HT_{1A}	• Norepinephrine α_1 and β_2 • Serotonin 5-HT_{1B} and 5-HT_{2C} • Histamine H_1 and H_3
Nucleus accumbens	Dopamine	
Brainstem (hindbrain)	• NPY • AgRP • Opioids (especially μ)	• Leptin • α-MSH, melanocortin • CCK
Vagus nerve	Ghrelin	• Leptin • CCK • GLP-1 • PYY

AgRP, agouti-related protein; CART, cocaine-and-amphetamine-regulated transcript; CCK, cholecystokinin; CRH, corticotropin-releasing hormone; GLP-1, glucagon-like peptide-1; MCH, melanocyte concentration hormone; α-MSH, α-melanocyte-stimulating hormone; NPY, neuropeptide Y; PYY, peptide YY.

Data from References 44,45.

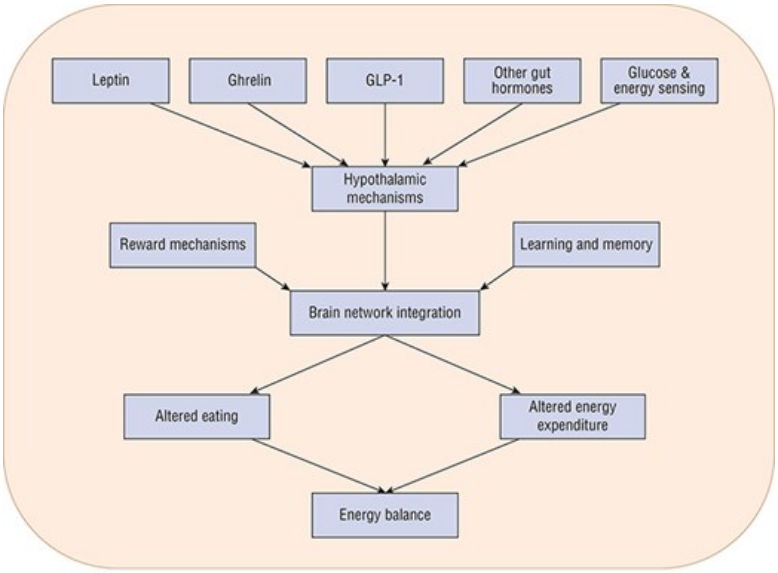
Many neuropeptides also influence appetite within the hypothalamus. Most research has focused on the neural projection between parts of the hypothalamus and the arcuate nucleus with signals to the paraventricular nucleus. The key peptides in this projection are thought to include neuropeptide Y and α-melanocyte–stimulating hormone. Neuropeptide Y is the most potent known stimulator of eating, and α-melanocyte–stimulating hormone action at the melanocortin 3 and 4 receptors is one of the crucial inhibitors of eating.[44] The lateral hypothalamus has been referred to as the "hunger" center within the brain. The most prominent of the lateral hypothalamic peptides, orexin, increases food intake stimuli within the lateral hypothalamus.[40] Another important neuropeptide stimulator of eating that principally originates in the lateral hypothalamus is melanocyte-

concentrating hormone. Neurons in the lateral hypothalamus use orexin and melanocyte-concentrating hormone to communicate with other neurons throughout the brain and thereby affect a number of functions beyond appetite.[44] Table 167-2 summarizes the major effects of various neuropeptides on food intake.[44,45] Although hunger and satiety functions are thought to be primarily regulated by the hypothalamus, humans eat in response to a broad set of stimuli, including reward, pleasure, learning, and memory.

Peripheral appetite signals also dramatically affect food intake.[45] Leptin, a hormone that is secreted by adipose cells, acts on the arcuate nucleus of the hypothalamus and elsewhere in the brain to decrease appetite and increase energy expenditure.[45] Exogenous leptin administration produces considerable weight loss in leptin-deficient patients; however, recombinant leptin replacement therapy in patients with obesity who are not leptin-deficient has not proved successful because most with obesity appear to be leptin resistant.[44] Figure 167-2 shows the peripheral link that leptin appears to provide in signaling the CNS about the status of fat cell mass.

FIGURE 167-2

Intrinsic hypothalamic hunger and satiety mechanisms are modified by input from fat tissue via leptin, and from the gut via ghrelin, glucagon-like peptide-1 (GLP-1), and other hormones. Additional input is derived by direct sensing of prevailing glucose and other energy signals. The hypothalamus generates signals that are integrated within brain networks, which also receive additional signals. The brain network effects change in energy balance by modifying food intake and energy expenditure.



Other peripheral signals important to the brain's processing of appetite include several gut hormones, notably those released by the intestine in response to passage of digesting food such as glucagon-like peptide-1 (GLP-1), oxyntomodulin, and peptide YY.[45] Each of these hormonal signals suppresses eating. GLP-1 has other effects, most importantly as an incretin, which facilitates release of insulin by pancreatic β cells in response to meal-related glucose. Ghrelin, another important gut hormone that is released from the distal stomach and duodenum, stimulates appetite. An understanding of the relationships among the brain, its many neurotransmitters and neuropeptides, environmental stimulation of brain activities, and other hormones is still evolving.

Energy Balance

The net balance of energy ingested relative to energy expended by an individual over time determines the degree of obesity (Fig. 167-1). An individual's metabolic rate is the single largest determinant of energy expenditure. Resting energy expenditure (REE) is defined as the energy expended by a person at rest under conditions of thermal neutrality. Basal metabolic rate (BMR) is defined as the REE measured soon after awakening in the morning at least 12 hours after the last meal. Metabolic rate increases after eating based on the size and composition of the meal. It reaches a maximum approximately 1 hour after the meal is consumed and returns to basal levels 4 hours after the meal. This increase in metabolic rate is known as the *thermogenic effect of*

food. The REE measures the energy costs of the wakeful state and may include the residual thermogenic effect of a previous meal. Physical activity is the other major factor that affects total energy expenditure and is the most variable component. With regard to energy storage, there are two major types of adipose tissue, white adipose tissue (WAT) and brown adipose tissue (BAT). The primary function of WAT is energy storage, whereas BAT is brown because it has much greater mitochondrial density along with high expression of uncoupling proteins that give it the capacity to uncouple oxidative phosphorylation to produce heat and maintain body temperature.[46] BAT is more commonly identified in those who are lean than those with obesity, but its importance for human obesity remains unclear. Both white and brown adipose tissues are highly innervated by the sympathetic nervous system, and adrenergic stimulation via β-adrenergic receptors (β_1, β_2, and β_3) is known to activate lipolysis in fat cells as well as increase energy expenditure in adipose tissue and skeletal muscle.

CLINICAL PRESENTATION

Although obesity is often readily apparent, most patients with obesity seek healthcare only when obesity-associated comorbidities become problematic. The National Institutes of Health (NIH) has established a stratification of weight excess based on associated medical risks.[4,7] These levels of excess weight are defined on the basis of BMI, a measure of total body weight relative to height. Using metric units, BMI (kg/m^2) is defined as weight in kilograms divided by height in meters squared (kg/m^2). Using pounds and inches, BMI (kg/m^2) is estimated as (weight [lb]/height [inches^2]) × 703. Adults with a BMI of 25 to 29.9 kg/m^2 are considered "*overweight*"; the terms *obesity* and *extreme obesity* are reserved for those with a BMI of 30 to 39.9 kg/m^2 and 40 kg/m^2 and over, respectively. The Endocrine Society clinical practice guideline currently classifies children and adolescents older than 2 years of age with a BMI at 120% or above of the 95th percentile or BMI at 35 kg/m^2 or above as having extreme obesity, BMI at the 95th percentile or above as obesity, and those with a BMI between the 85th and 94th percentiles as overweight.[34] Because BMI may overestimate the degree of excess body fat in some clinical situations (eg, edematous states, extreme muscularity, muscle wasting, hydration status, large tumor, short stature), the assessment of body composition in such cases often requires clinical judgment.

1 BMI measurement is the practical method of defining obesity in the clinic and in epidemiologic studies; however, it does not always correspond to excess fat. There are well-established differences in the relationship between BMI and obesity-related risks among disparate racial, sex, and ethnic groups. For example, the standard cut points for BMI underestimates risks among Asian patients and utilizing a lower BMI value of 23 kg/m^2 or above to confirm excess body adiposity in this population is recommended.[6,26,47] Across all ethnic groups, men tend to have higher visceral adipose tissues.[48] Central obesity reflects high levels of intra-abdominal or visceral fat, and this pattern of obesity is associated with an increased propensity for the development of hypertension, dyslipidemia, type 2 diabetes mellitus, and cardiovascular disease (sometimes referred to as the "metabolic syndrome") and have an increased cardiometabolic disease risk.[5] Thus, in addition to the absolute excess fat mass, the distribution of this fat regionally in the body has important clinical effects. Intra-abdominal fat is best estimated by imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) but can be approximated through measurement of waist circumference (WC). Clinically, WC is the narrowest circumference measured in the area between the last rib and the top of the iliac crest. Currently in the United States, Canada, and Europe, the definition for high-risk WC is greater than 40 inches (102 cm) in men and greater than 35 inches (89 cm) in women.[7] Specific region- and ethnicity-specific waist circumference thresholds should be used to assess abdominal obesity and disease risks in other populations.[6] Routine determination of WC should be implemented in those with BMIs between 25 and 34.9 kg/m^2 to assess additional metabolic risk.[5,31-33] However, after a patient's BMI reaches 35 kg/m^2, it is not necessary to measure WC because it will likely be elevated and adds little in terms of risk prediction.[32]

2 Although BMI and WC are related, each measure independently predicts disease risk. Both measurements should be assessed and monitored during therapy for obesity.[5-7] The risks for development of type 2 diabetes mellitus, hypertension, or cardiovascular disease at various stages of obesity based on BMI or WC are outlined in Table 167-3. Note that increased WC confers increased risk even in normal-weight individuals. A higher prevalence of cardiometabolic abnormalities among normal weight individuals is particularly evident in racial/ethnic minority populations.[49]

TABLE 167-3

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

BMI, body mass index.

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

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

Data from WHO Consultation on Obesity (1999: Geneva, Switzerland) & World Health Organization. (2000). Obesity: preventing and managing the global epidemic: report of a WHO consultation. World Health Organization. Available at: https://apps.who.int/iris/handle/10665/42330.

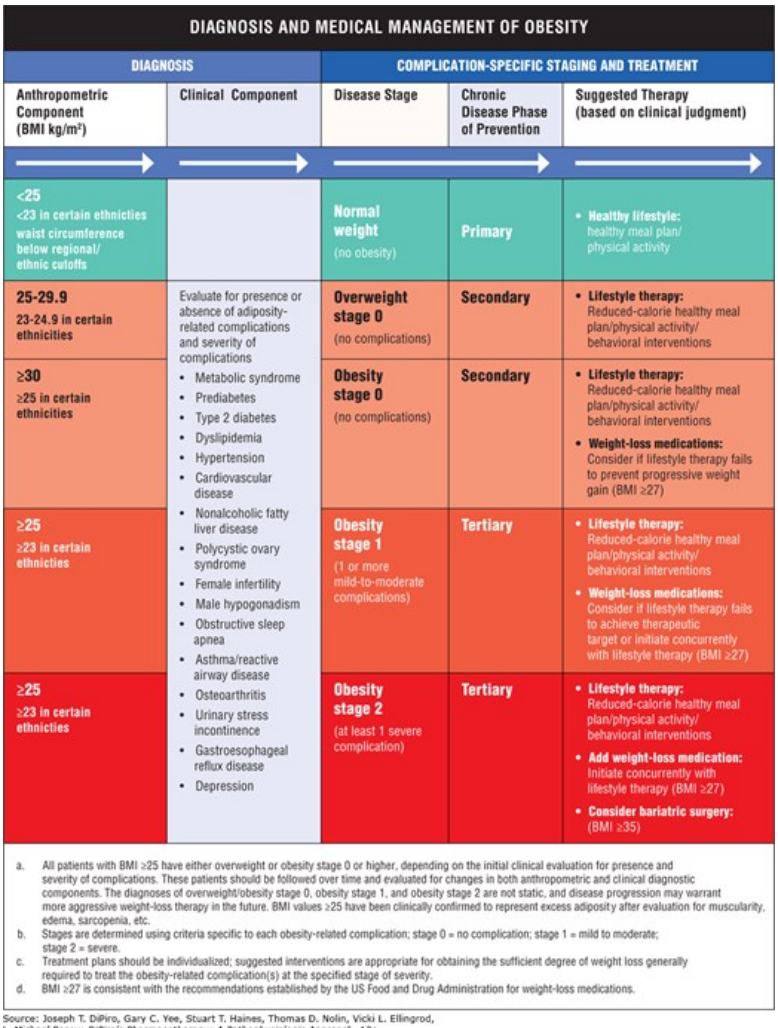
Comorbidities

Obesity and overweight are associated with an increased risk of all-cause mortality and contributed to approximately 7.1% of total death globally.[50] A U-shaped association is noted between BMI and all-cause mortality for patients with diabetes mellitus, hypertension, coronary artery disease, and peripheral artery disease because underweight, obesity, and morbid obesity are all associated with increased risk of cardiovascular diseases (CVD) and mortality.[51] For each standard deviation higher BMI the risk of type 2 diabetes mellitus increases by 67% and coronary artery disease by 20%.[52] While substantial reduction in life expectancy has been predicted in adults with BMIs greater than 35 kg/m^2,[53,54] healthy life-years lost due to obesity is estimated to be two to four times greater than total years of life lost.[53] Excessive body fat affects virtually all organ systems. A plethora of evidence continue to link obesity with numerous disease states and health conditions (Table 167-1).[4-24] Therefore, current clinical practice guidelines

recommend a “complication-centric approach” for management of obesity.[6,29] It is important for clinicians to assess presence and severity of weight-related complications to determine the appropriate treatment and intensity of weight loss therapy in all individuals with overweight and obesity (Fig. 167-3).[6] Because individuals with obesity are also at risk for developing many malignancies, adherence to routine age- and risk-appropriate cancer screening guidelines is recommended.[29] Furthermore, hypertension, hyperlipidemia, coronary heart disease, cerebrovascular accidents, insulin resistance, glucose intolerance, and diabetes mellitus are all known cardiac risk factors that tend to cluster in individuals with obesity. Aggressive management of these comorbid cardiovascular risk factors and other weight-related complications (eg, sleep apnea, major depression, osteoarthritis, nonalcoholic fatty liver disease) is warranted in an individual with obesity regardless of an individual’s weight loss efforts.[6,7,29]

FIGURE 167-3

Diagnosis and Medical Management of Obesity. *(Reprinted from Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologist and American College of Endocrinology Comprehensive Clinical Practice Guidelines for medical care of patients with obesity. Endocr Pract. 2016;3:1–203.)*



DIAGNOSIS AND MEDICAL MANAGEMENT OF OBESITY

DIAGNOSIS		COMPLICATION-SPECIFIC STAGING AND TREATMENT		
Anthropometric Component (BMI kg/m²)	Clinical Component	Disease Stage	Chronic Disease Phase of Prevention	Suggested Therapy (based on clinical judgment)
<25 <23 in certain ethnicities waist circumference below regional/ ethnic cutoffs		Normal weight (no obesity)	Primary	• **Healthy lifestyle:** healthy meal plan/ physical activity
25-29.9 23-24.9 in certain ethnicities	Evaluate for presence or absence of adiposity-related complications and severity of complications • Metabolic syndrome • Prediabetes • Type 2 diabetes • Dyslipidemia • Hypertension • Cardiovascular disease • Nonalcoholic fatty liver disease • Polycystic ovary syndrome • Female infertility • Male hypogonadism • Obstructive sleep apnea • Asthma/reactive airway disease • Osteoarthritis • Urinary stress incontinence • Gastroesophageal reflux disease • Depression	Overweight stage 0 (no complications)	Secondary	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions
≥30 ≥25 in certain ethnicities		Obesity stage 0 (no complications)	Secondary	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Weight-loss medications:** Consider if lifestyle therapy fails to prevent progressive weight gain (BMI ≥27)
≥25 ≥23 in certain ethnicities		Obesity stage 1 (1 or more mild-to-moderate complications)	Tertiary	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Weight-loss medications:** Consider if lifestyle therapy fails to achieve therapeutic target or initiate concurrently with lifestyle therapy (BMI ≥27)
≥25 ≥23 in certain ethnicities		Obesity stage 2 (at least 1 severe complication)	Tertiary	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Add weight-loss medication:** Initiate concurrently with lifestyle therapy (BMI ≥27) • **Consider bariatric surgery:** (BMI ≥35)

a. All patients with BMI ≥25 have either overweight or obesity stage 0 or higher, depending on the initial clinical evaluation for presence and severity of complications. These patients should be followed over time and evaluated for changes in both anthropometric and clinical diagnostic components. The diagnoses of overweight/obesity stage 0, obesity stage 1, and obesity stage 2 are not static, and disease progression may warrant more aggressive weight-loss therapy in the future. BMI values ≥25 have been clinically confirmed to represent excess adiposity after evaluation for muscularity, edema, sarcopenia, etc.
b. Stages are determined using criteria specific to each obesity-related complication; stage 0 = no complication; stage 1 = mild to moderate; stage 2 = severe.
c. Treatment plans should be individualized; suggested interventions are appropriate for obtaining the sufficient degree of weight loss generally required to treat the obesity-related complication(s) at the specified stage of severity.
d. BMI ≥27 is consistent with the recommendations established by the US Food and Drug Administration for weight-loss medications.

Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

TREATMENT

Available treatment options for the chronic management of obesity include reduced caloric intake, comprehensive lifestyle intervention, pharmacotherapy, medical devices, and bariatric surgery.

Desired Outcomes

Weight management is commonly considered successful when a predefined amount of weight has been lost such that a final goal is achieved. However, in the current "complication-centric approach" in obesity management, the primary goal is to ameliorate weight-related complications and ultimately improve patient's health and quality of life rather than a preset decline in body weight.[6] In 2016, comprehensive clinical practice guidelines published by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) outlined intervention and weight loss goals from at least 5% to 40% based on severity of obesity-related complications (see Table 167-4).[6] The AACE/ACE guideline further outlines the three-phase paradigm of chronic disease prevention and treatment: primary, secondary, and tertiary. The goal of primary phase is to prevent overweight and obesity; the goal of secondary phase is to prevent progressive weight gain or achieve weight loss to prevent complications; the goal of tertiary phase is to achieve sufficient weight loss to improve obesity-related complications and prevent further deterioration. Treatment selection and intensity of obesity intervention varies depending on the phase of prevention and treatment in which the patient resides. If improvement in type 2 diabetes mellitus, dyslipidemia, hypertension, and polycystic ovary syndrome are primary goals, then the recommended weight loss goals is at least 5% to 15% or more.[6] For patient with steatohepatitis, the recommended weight loss goal is 10% to 40% in order to reduce inflammation and fibrosis of the liver.[6] Success may also include end points of decreasing the rate of weight gain or maintaining a weight-neutral status. All too often patients expect to lose weight overnight, only to be disappointed. Thus, it is important to set a time course for the plan. Numerous web-based resources for supporting both patient and practitioner weight-management activities are available.[7,55-58]

TABLE 167-4

Tertiary Prevention Treatment Goals Based on Diagnosis in the Medical Management of Patients with Overweight or Obesity[a]

Diagnosis	Weight Loss Goals	Clinical Goals
Urinary stress incontinence	5% to 10% or more	Reduced frequency of incontinence episodes
Metabolic syndrome	10%	Prevention of type 2 diabetes mellitus
Prediabetes	10%	Prevention of type 2 diabetes mellitus
Gastroesophageal reflux disease	10% or more	Reduced symptoms frequency and severity
Female infertility	10% or more	Ovulation, pregnancy, and live birth
Asthma/reactive air way disease	7% to 8% or more	Improved in forced expiratory volume at 1 second (FEV1), improved symptoms
Obstructive sleep apnea	7% to 11% or more	Improved symptoms, decreased apnea-hyponea index
Osteoarthritis	≥10% (5%-10% or more when coupled with exercise)	Improved symptoms, increased function
Type 2 diabetes mellitus	5% to ≥15%	Reduced A1c, reduced number and/or doses of diabetes medications, diabetes remission (if diabetes duration is short)
Dyslipidemia	5% to ≥15%	Lowered triglycerides, raised HDL-C, lowered non-HDL-C
Hypertension	5% to ≥15%	Lowered blood pressure, reduced number and/or doses of antihypertensive medications
Polycystic ovary syndrome	5% to ≥15%	Ovulation, regularization of menses, reduced hirsuitism, enhanced insulin sensitivity, reduced serum androgen levels
Nonalcoholic fatty liver disease		
• Steatosis • Steatohepatitis	• 5% or more • 10% to 40%	• Reduced intrahepatocellular lipid • Reduced inflammation and fibrosis
Depression	Uncertain	Improved depressive symptoms and depression scores

A1c, glycated hemoglobin A1c; HDL-C, high density lipoprotein cholesterol.

[a]Patients with BMI ≥25 kg/m^2 (≥23 kg/m^2 in certain ethnicities).

Adapted from Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologist and American College of Endocrinology Comprehensive Clinical Practice Guidelines for medical care of patients with obesity. Endocr Pract. 2016;3:1–203.

General Approach to Treatment

To achieve meaningful weight loss goals, successful obesity treatment plans require incorporation of comprehensive lifestyle interventions such as healthy diet, adequate physical activity, and behavioral modifications as the cornerstone of weight management.[5,6,26,28,29,31-33] Psychological interventions such as cognitive therapy or stress management to address the emotional relationship with food may help further promote adherence, intrinsic motivation, and treatment success.[32,33] Once the need for weight loss has been determined, the clinician needs to assess a patient's readiness to engage in weight loss efforts and identify any potential barriers to success. They need to initiate a dialogue with each patient who has overweight or obesity to ensure they understand the potential health consequences of excess body weight and benefits of appropriate weight management. Specific weight goals should be established that are consistent with medical needs, weight-related complications, and the patient's personal desire.[6] Patients should not be allowed to attain an abnormally low body weight (ie, less than their estimated ideal body weight).

3 Patients seeking help for obesity do so for many reasons, including improvement in their quality of life, a reduction in associated morbidity, and increased life expectancy. Because weight stigma is prevalent in the western culture, numerous individuals seek therapy for obesity primarily for cosmetic purposes and often have unrealistic goals and expectations. Aggressive marketing of weight loss programs, therapies, and diets—parallel to the fashion industry's standards of desirable body profiles—has led many individuals to set impossible goals and expectations. Often, these individuals will go to extreme measures to achieve weight loss. Consequently, clinicians must be careful to fully discuss the risks of therapies and to clearly define the achievable benefits and magnitude of weight loss. Patients with obesity should be redirected away from trying to achieve an "ideal weight" to the more realistic goal of modest (eg, loss of 5%-10% of body weight) but sustained, medically relevant weight loss. In practice, goals should be set based on many factors, including initial body weight, patient motivation and desire, presence of obesity-related comorbid conditions, and age. The Look Action for Health in Diabetes (AHEAD) study found that patients with diabetes mellitus who maintained weight loss of at least 7% with intensive lifestyle modifications for a period of almost 10 years did not experience a reduced incidence of cardiovascular events, but they did have a reduced need for diabetes mellitus medications and improvement in physical function, lipids, blood pressure, kidney disease, sleep apnea, fitness, and depression.[59] When behavioral-based weight loss intervention is incorporated, with or without medication therapy, patients are able to achieve more weight loss and have a lower risk of developing diabetes mellitus.[60] In patients with overweight and obesity with diabetes mellitus, lifestyle modification with sustained weight loss of greater than 5% improves HbA1c level and ameliorates hyperglycemia, hyperlipidemia, and hypertension within a year.[61] For individuals with obesity who have gastroesophageal reflux disease, a 10% or more weight reduction may be required to improve symptoms.[6] This highlights the importance of defining end points and measures of success in any weight-loss plan.

4 Weight-loss interventions must be founded on lifestyle changes, such as a modification in eating practices; complemented by medication therapy, if indicated; and in some cases, surgery. Before recommending any therapy, the clinician must evaluate the patient for the presence of secondary causes of obesity.[62] If a secondary cause is suspected, then a more complete diagnostic workup and the initiation of appropriate therapy may be warranted. The next step in patient evaluation is to determine the presence and severity of other medical conditions that are either directly associated with obesity (eg, diabetes mellitus, cardiovascular diseases, uncontrolled hypertension) or that have an impact on therapeutic decision making (eg, history of pancreatitis, cardiac arrhythmia, seizure disorders, concurrent medications).[6,29] The Endocrine Society Clinical Practice Guideline for the Pharmacological Management of Obesity emphasizes that clinicians should always consider the potential weight-altering effects of all medications a patient is receiving for the management of comorbid conditions and select medications that are weight-neutral or promote weight loss (strong recommendation with moderate quality evidence).[29] For example, in patients with type 2 diabetes mellitus, antidiabetic agents that promote weight loss (eg, metformin, glucagon-like peptide-1 analogs, sodium-glucose-linked transporter-2 inhibitors) are preferred. Appropriate laboratory tests to exclude or quantify the degree of specific conditions such as diabetes mellitus, liver dysfunction, and nephropathy should be performed as indicated by the history and physical examination. Based on the outcome of this medical evaluation, the patient should be counseled on treatment options, benefits, and risks. Ultimately, lifelong therapeutic goals should consist of maintenance of reduced body weight and prevention of weight gain.

Nonpharmacologic Therapy

Nonpharmacologic therapy, including reduced caloric intake, increased physical activity, and behavioral modification, is the mainstay of obesity management. This combination, also known as lifestyle therapy, is recommended for all patients with overweight and obesity by the ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease,[5] the Endocrine Society Clinical Practice Guidelines for the Pharmacological Management of Obesity (graded as strong recommendation with high quality evidence),[29] and the AACE/ACE Guidelines for the Medical Care of Patients with Obesity

(grade A recommendation with the best level of evidence).[6] Weight loss will require major effort on the part of the patient to change their lifestyle and comply with the management plan. If the patient is not ready to meet these expectations, then early counseling will reduce the chance of frustration for the patient, clinician, and possibly other family members. Providing basic education can lead to a substantial change in motivation and desire to lose weight and improved compliance.

Reduced Caloric Intake

Current adult guidelines recommend reduced energy intake through adherence to a low-calorie diet (LCD).[5,6] The LCD should provide a daily energy deficit of 500 to 750 kcal (2,100-3,150 kJ), which generally correlates to a total intake of 1,200 to 1,500 kcal/day (5,000-6,300 kJ/day) for women and 1,500 to 1,800 kcal/day (6,300-7,550 kJ/day) for men. Individuals with severe obesity will require more energy, at least at the start of dietary restriction. Adherence to the LCD results in an average weight loss of 8% after 6 months.[7]

Numerous diet and nutrition plans are available to aid patients in their pursuit of weight loss, and current guidelines allow for choice among many potential evidence-based diet plans.[6,7,63] Popular diets include moderate energy-deficient plans (eg, DASH [Dietary approaches to Stop Hypertension], Mediterranean, Weight Watchers, LEARN [Lifestyle, Exercise, Attitude, Relationships, Nutrition], Jenny Craig), vegetarian-based plans (eg, Ornish), and low carbohydrate plans (eg, Zone, Atkins). Short-term weight loss is considerable for almost all diet plans. However, long-term weight loss and maintenance of weight loss are less promising, primarily because of difficulty with adherence. Therefore, the choice of diet plan should be determined based on patient-specific preferences, health status, and ability to consistently adhere to the specific recommendations of the diet.[6] A meta-analysis of 121 clinical trials assessing the efficacy of various diets concluded that differences in weight loss among popular named diets are not clinically significant,[64] highlighting the general consensus that macronutrient composition of the diet may not be as important as consistent adherence to reduced energy consumption. Time restricted eating (TRE), defined as consuming all calories within a restricted time window (eg, 6-8 hours) and fasting during the rest of the day, has recently become a popular diet intervention for weight loss and other health benefits. Although short-term weight loss data are promising, long-term data on the sustained efficacy, ability for patients to adhere to the required lifestyle changes, and safety in patients with obesity-related comorbidities are limited.[65]

Very-low-calorie diets, providing less than 800 kcal/day (3,350 kJ/day), are generally not recommended.[7] Although very-low-calorie diets can often result in substantial early weight loss, long-term results have been disappointing because it is difficult for individuals to maintain compliance. Additionally, very-low-calorie diets require intensive medical monitoring and should only be used in certain situations under the supervision of an experienced clinician. Regardless of the diet program, it is clear that energy consumption must be less than energy expenditure to achieve weight loss (see Fig. 167-1). The challenge is to develop a diet plan that leads to consistent adherence by the patient and sustained weight loss and maintenance.

Comprehensive Lifestyle Intervention

Comprehensive lifestyle intervention encompasses the combination of reduced energy intake, increased physical activity, and behavioral modification. Increased physical activity is an important component in achieving the state of greater energy expenditure than energy intake that is necessary to lose weight and maintain weight loss. Weight loss is modest when increased physical activity is attempted as monotherapy. However, when it is combined with reduced energy intake and behavior modification, it can augment weight loss and improve obesity-related comorbidities and cardiovascular risk factors.[5,7] Aerobic physical activity for at least 150 minutes per week, completed over 3 to 5 days is recommended for adults.[6,66] Greater levels (ie, 200-300 min/wk) may be required to augment weight loss and maintain lost weight. Patients should be advised to start slowly and gradually increase intensity. All patients with obesity should receive a medical examination before embarking on a physical activity program.

Current adult guidelines recommend initiation of a comprehensive lifestyle program to help patients with overweight and obesity adhere to the prescribed LDC and increased physical activity per week (NHLBI Grade A; strong recommendation).[5,6] For patients who have successfully lost weight during the first 6 months, long-term participation in a comprehensive lifestyle program is recommended. The primary aim is to help patients choose lifestyles that are conducive to safe and sustained weight loss. Most such programs use self-monitoring of diet and exercise to increase patient awareness of behavior and as a tool for the clinician to determine patient compliance as well as patient motivation. High-intensity comprehensive lifestyle interventions that include a reduced-calorie diet, increased exercise, and in-person behavioral counseling sessions result in an average weight loss of 8 kg (17.6 lb) after 6 months.[7]

Bariatric Surgery

Consistent with the growing obesity epidemic, the demand for bariatric surgery has increased drastically over the past two decades. Surgery currently remains the most powerful and effective intervention for the treatment of obesity.[67,68] Current clinical practice guidelines recommend that surgical intervention be reserved for adults with extreme obesity (BMI ≥40 kg/m^2 or BMI >37.5 kg/m^2 in Asian Americans) without other comorbidity, or BMI at 35 kg/m^2 or above (BMI 32.5-37.4 kg/m^2 in Asian Americans) with at least one or more major comorbidity such as hypertension, type 2 diabetes mellitus, or obstructive sleep apnea (NHLBI Grade A; strong recommendation).[6,26,29,68] Surgery may also be advocated to adults with BMI between 30 kg/m^2 and 34.9 kg/m^2 (27.5-32.4 kg/m^2 in Asian Americans) with diabetes mellitus or metabolic syndrome, as a similar efficacy and safety profile for improving type 2 diabetes mellitus and metabolic disorders is observed among bariatric patients with a BMI below or above 35 kg/m^2.[26,69] This has led to use of the term "metabolic surgery" with focus on treating metabolic diseases independent of body weight.[68] Bariatric surgery is also endorsed by the American Academy of Pediatrics for severe obesity. For adolescents, the American Society for Metabolic and Bariatric Surgery recommends bariatric surgery can be considered in youth (ages 13 to 18) with BMI ≥35 kg/m^2 or ≥120% of the 95th percentile for age, whichever is lower, with a severe comorbidity, or in youth with BMI ≥40 kg/m^2 or ≥140% of the 95th percentile for BMI, whichever is lower, with any obesity-related comorbidity.[69]

Surgical weight loss options should only be considered in patients who have met the eligibility criteria and have failed other recommended methods for weight loss. It is critical for bariatric surgical candidates to fully understand the surgical risks and be able to commit fully to the extensive postoperative care plan, follow-ups, and necessary lifelong vitamin supplementation, medical monitoring (including costs required), dietary, lifestyle, and behavioral adjustments to ensure the long-term success of the procedure.[68]

Appropriate selection of a bariatric procedure should be individualized based on goals of therapies, available expertise, patient preferences, and inherent risks. The four available surgical procedures currently endorsed by the American Society of Metabolic and Bariatric Surgery are (1) adjustable gastric banding, (2) sleeve gastrectomy, (3) biliopancreatic diversion with duodenal switch, and (4) conventional Roux-en-Y gastric bypass. The adjustable gastric banding and sleeve gastrectomy are designed to reduce the volume of the stomach and thus restrict the rate of nutrient intake. The biliopancreatic diversion with duodenal switch is primarily malabsorptive in nature, and the length of the diversion determines the extent of nutrient malabsorption. This hybrid procedure combines a restrictive approach with a degree of malabsorption induced by reducing the size of the stomach pouch and causing food to bypass parts of the small intestine. Techniques that involve redirection of the flow of nutrients so as to have humoral and malabsorptive effects generally yield greater and longer lasting weight loss than the purely restrictive methods.[67] The sleeve gastrectomy has increased in its popularity worldwide and is currently the most common procedure performed in the United States.[68] Resection of the gastric segment from sleeve gastrectomy also removes the endocrine cells, which alters neuro-humoral activity and results in earlier satiety and improvements in glucose metabolism. The amount of total body weight loss and remission of comorbidities is proportional to intestinal bypass, which is expected from the metabolic effect of the surgery [eg, adjustable gastric banding (20%-25%) < sleeve gastrectomy (25%-30%) < Roux-en-Y gastric bypass (30%-35%) < duodenal switch (35%-45%)].[68] Patients usually achieve the lowest post-bariatric weight from 1 to 2 years after bariatric surgery.

After 5 years, patients with type 2 diabetes mellitus with BMI of 27 to 43 kg/m^2 who undergo gastric bypass surgery lose more (23%) of their initial body weight compared to patients who receive sleeve gastrectomy (19%) and patients who receive intensive medical therapy (5%).[70] Results from gastric bypass appear at least as promising among adolescents, for whom the likelihood for, and durability of remission from comorbid conditions is often greater than observed in adults.[71,72] The extent of weight loss and the potential for weight regain after bariatric surgery is multifactorial as metabolic, anatomic, and lifestyle changes can all impact the outcome of the procedure. Bariatric surgeries are now considered among the safest abdominal surgical procedures performed in the United States today; the operative 30-day mortality rates for gastric bypass and sleeve gastrectomy are 0.2% and 0.1%, respectively.[67] Some of the most common early surgical complications are gastric and anastomotic leaks, bleeding, wound infections, and pulmonary emboli. Due to the disruption of the normal gastric anatomy and physiology, postsurgical patients are often at risk for severe micronutrient deficiencies (eg, vitamin B_{12}, vitamin B_1, vitamin K, zinc, copper, folate, iron, calcium) as well as deficiencies in fat soluble vitamins such as vitamins A, D, E, and K due to fat malabsorption.[68] Therefore, empiric supplementation with daily adult multivitamin plus minerals, elemental calcium, vitamin D, folic acid, thiamine, elemental iron, and vitamin B_{12} is essential to prevent nutritional deficiencies in bariatric patients.[68] Because many commercial dietary supplements products are adulterated with compounds that are not included in the original manufacturer's label, use of supplements verified by the US Pharmacopeia (https://www.quality-supplements.org/verified-products), or other brands that have been safely and effectively tested in clinical

trials are recommended.[68] All bariatric surgical patients should undergo life-long monitoring of nutritional deficiencies after the procedure. Profound weight loss resulting from bariatric surgery provide multitude of health benefits, which are often accompanied by dramatic improvements, and sometimes complete resolution, of many obesity-related complications.[67,68]

Significant reduction in risks of myocardial infarction, cardiovascular deaths, as well as the incidence of type 2 diabetes mellitus, hypertension, dyslipidemia, and cancer occur after adult's bariatric surgery.[14,67,70,73,74] It has long been known that bariatric surgery improves microvascular diseases,[75] and substantially reduces macrovascular disease and mortality in patients with type 2 diabetes mellitus and severe obesity.[73] Patients who undergo Roux-en-Y gastric bypass surgery are expected to have a 40% decrease in all-cause mortality, 60% decrease in mortality due to cancer, 92% decrease in mortality due to diabetes mellitus, and 56% decrease in mortality due to coronary artery disease at 12 years.[74] An increase in life expectancy is also expected after bariatric surgery, regardless of the type of bariatric procedure.[76] Metabolic surgery can prolong median life expectancy by 6.1 years and substantial survival benefit is seen in patients with preexisting diabetes mellitus than those without after surgery (9.3 years vs 5.1 years gain in median life expectancy).[76] Every 1% increase in metabolic surgery utilization rate is estimated to yield 5.1 million to 6.6 million potential life-years saved.[76] Despite the expenses of the bariatric procedure, bariatric surgery is a cost-saving alternative to conventional management over the lifetime for patients who suffer from severe obesity.[77]

After experiencing weight loss, many gastric surgery patients are able to discontinue pharmacotherapy for glucose lowering, dyslipidemia, hypertension, and reduce medication costs.[67,68,70] However, the need for use of proton-pump inhibitors are often increased as a prophylactic therapy for anastomotic ulcers.[68,78] It is imperative for clinicians to recognize that bariatric interventions not only alter nutrient absorption but also may impede medication absorption and can cause potential serious consequences.[78] Achlorhydria, reduced contact time with digestive enzymes, reduced surface area for intestinal and gastric absorption, reduced bile acid exposure after bariatric surgery can lead to altered absorption, distribution, metabolism, and/or elimination of many medications.[78] Use of direct oral anticoagulant (eg, apixaban, rivaroxaban) and nonsteroidal anti-inflammatory drugs (eg, ibuprofen) should be avoided after surgery.[78] Reduced serum concentrations may be observed for some antimicrobials, antidepressants, selective serotonin reuptake inhibitors (SSRIs), antipsychotics, and tamoxifene.[78] Furthermore, concurrent administration of proton-pump inhibitors may also alter bioavailability of weak basic medications such as antifungals (eg, posaconzale),[78] certain antibiotics and some cardiovascular medications (eg, digoxin) as well as hinder the absorption of micronutrients.[78] Therefore, clinicians need to recognize that the standard dosage regimens recommended for presurgical patients may need to be adjusted. Switching from solid medications to opened capsules or liquid formulations (without high sugar loads) for post-surgical patients may be beneficial when inadequate clinical response is observed.[78] Long-term close therapeutic monitoring of all orally administered medications after surgery, particularly those with narrow therapeutic ranges (eg, warfarin, levothyroxine, lithium) is highly recommended because dosage form selection, dose conversion, or therapeutic interchange may be necessary to avoid or minimize absorption problems and ensure optimal patient outcomes.[68,78] Controlled-release formulations may be used after surgery but close monitoring is needed.[78] With increased fertility rate and decreased absorption of oral contraceptives after bariatric surgery, alternative non-oral contraceptive is recommended for all reproductive-aged women who have undergone surgery.[68,78] Women who desire to conceive should wait at least 12 to 18 months after bariatric surgery to ensure stable weight and balance nutrition is achieved.[68]

Implantable Medical Devices

Despite meeting the medical necessity for bariatric surgery, some individuals may not qualify as surgical candidates or may choose to not undergo the procedure. Medical devices may fill the existing treatment gap in obesity management and may address the unmet needs in these individuals. Currently, there are six FDA-approved medical devices for weight reduction involving electrical stimulation, gastric emptying, gastric balloon systems, or superabsorbent hydrogel (Table 167-5).[79-84] Each of these devices is fully reversible and are designed to work in conjunction with prescribed diet and exercises programs. A patient's ability to provide appropriate follow-up is essential to enhance the safety and to avoid complications related to the devices. Unfortunately, once the device is removed, patients will often regain the lost weight.

TABLE 167-5

FDA-Approved Medical Devices for Weight Loss

Device	Mechanism of Action	BMI Indication	Contraindications	Weight Loss	Adverse	Comments

				Outcomes	Medication Reactions	
Gastric Emptying System						
AspireAssist®[79,80]	An implanted percutaneous gastrostomy aspiration tube removes approximately 25%-30% of the meal from stomach 20-30 minutes after ingestion	Adult age ≥22 with BMI 35-55 kg/m^2	- Uncontrolled hypertension - Bulimia - Binge eating disorder - Night-eating syndrome - Previous abdominal surgery - Esophageal stricture, gastric obstruction, gastroparesis - Inflammatory bowel disease - Stomach ulcer - History of serious pulmonary or cardiovascular disease - Coagulation disorders - Anemia - Chronic abdominal pain - Pregnancy or lactation, or desire to become pregnant	%TBWL across trials demonstrated 17.8%, 18.3%, 19.1%, and 18.6% after 1 year, 2 years, 3 years, and 4 years, respectively/[80]	- Abdominal pain - Indigestion - Nausea - Vomiting - Constipation - Diarrhea - Peristomal granulation tissue - Peristomal irritation and inflammation	• Patient must take extra time to chew thoroughly and drink sufficient liquid with each meal to ensure proper aspiration • Frequent medical visits are also necessary to monitor device use and weight loss and to provide counseling on lifestyle therapies • The device contains a safety feature to keep track the number of times the drain tube is connected to the port and automatically stops working after 115 cycles (approximately 5-6 weeks of therapy) to ensure proper use
Electrical Stimulation System						
Maestro® Rechargeable System[79]	A neurometabolic therapy, deliver via a pacemaker-like device that is implanted on the vagal trunk. The device	• Age ≥18 with BMI 40-45 kg/m^2 • OR • Age ≥18 with	- Liver cirrhosis - Portal hypertension - Esophageal varices	%TBWL after 1 year of therapy is 9.2% and excess body	- Neuroregulator site pain - Nausea - Abdominal	• The implanted neuroregulatory is controlled by the clinician with an external

	is designed to intermittently block the communication with the vagus nerve (vBloc) through the delivery of electrical impulse to increase satiety and improve food-related cognitive restraints	BMI 35-39.9 kg/m^2 with at least 1 comorbidity	- Hiatal hernia - Planned MRI or diathermy - Permanently implanted, electrical-powered medical device (ie, pacemaker, defibrillator, neurostimulator)	weight is 24.4%.	pain - Heartburn - Dyspepsia	programming device to deliver 12 to 15 hours of intermittent nerve block. Battery is recharged daily for 30 minutes • Once the device is turn-off, patient often will regain the weight lost
Gastric Balloon System						
Orbera Intragastric Balloon[79,81-83]	Endoscopically placed intragastric balloon device designed to occupy space in the stomach to reduce hunger and improve appetite control	• Orbera® • Adult age ≥22 with BMI 30-40 kg/m^2 • Orbera365™ • Adults with BMI >40 kg/m^2 • OR • Adult with BMI ≥35 kg/m^2 with comorbidities • OR • Adults with BMI between 27 and 50 kg/m^2 who failed to achieve and maintain weight loss with a supervised weight-controlled program	- Previous gastric surgery - Hiatal hernia - Coagulation disorder - A potential bleeding lesion of the upper gastrointestinal tract - Alcohol or drug misuse - Severe liver disease - Pregnancy or lactation, or desire to become pregnant - Any contraindication to endoscopy	%TBWL after 1 year of therapy is 11.3%.[81]	- Abdominal pain - Nausea - Vomiting - Dysphagia - Heartburn - Early explantation - Gastric ulcer - Deflation - Migration - Perforation - Hyperinflation of balloon - Acute pancreatitis	• The device placement is intended to be temporarily. After 6 months (Orbera®) or 12 months (Orbera365™), the balloon is punctured and removed through the mouth via a grasping device • Patients who fail to remove the device after 6 months (Orbera®) or 12 months (Orbera365™), will be at increased risk of intestinal obstruction due to migration of the deflated balloon • Aggressive symptoms control with triple antiemetic medications in

						the early period after insertion • Use of proton pump inhibitor and avoidance of nonsteroidal anti-inflammatory agents during treatment • Weight regain occurs after device removal
[a]The ReShape Integrated Dual Balloon System[79,82,83]	Endoscopically placed intragastric balloon device designed to occupy space in the stomach to reduce hunger and improve appetite control	Adult age 22-60 with BMI 30-40 kg/m^2 with at least 1 comorbidity	- Prior gastrointestinal or bariatric surgery - Inflammatory intestinal or bowel disease - Large hiatal hernia - Delayed gastric emptying - Upper gastrointestinal bleed - Coagulation disorder - Severe liver disease - Active *Helicobacter pylori* infection - A structural abnormality in the esophagus or pharynx - Use of anticoagulants or anti-inflammatory agents - Pregnancy or lactation, or desire to become pregnant - Any	%TBWL after 6 months of therapy is 15.4%	- Abdominal pain - Nausea - Vomiting - Heartburn - Gastric ulcer - Deflation - Perforation - Dysphagia - Gastric bleeding - Hyperinflation of balloon - Acute pancreatitis	• The device placement is intended to be temporarily and should be removed 6 months after insertion as the device will deflate over time • Patients who fail to remove the device after 6 months will be at increased risk of intestinal obstruction due to migration of the deflated balloon • Aggressive symptoms control with triple antiemetic medications in the early period after insertion • Use of proton pump inhibitor and avoidance of nonsteroidal anti-inflammatory agents during

			contraindication to endoscopy			treatment • Patients currently taking selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs) should use this device with caution due to the potential for balloon rupture and release of methylene blue which with these concurrent therapies can increase risk of developing serotonin syndrome • Weight regain occurs after device removal
Obalon Balloon System™[79,83]	Sequentially swallowed balloon device designed to occupy space in the stomach to reduce hunger and improve appetite control. A total of 3 balloons are placed over 3 months	Adult age ≥22 with BMI 30-40 kg/m^2	- Any structural or functional abnormality in the esophagus, pharynx, stomach, intestines, or any portion of the gastrointestinal tract - Prior bariatric surgery - Inflammatory	%TBWL after 6 months of therapy is 6.8%	- Abdominal pain - Nausea - Vomiting - Heartburn - Bloating - Deflation - Gastric ulcer - Hyperinflation of balloon	• The only intragastric balloon that does not require endoscopic placement. The balloon is encapsulated, attached to a tube, and swallowed under provider supervision

			and other conditions of the gastrointestinal tract - Active *Heliocobacter pylori* infection - Bulimia, binge eating or other eating disorders - Use of gastric irritants such as NSAIDs and aspirin - Use of anti-platelets or anticoagulants - Irritable bowel syndrome or other inflammatory bowel disease - Taking medications on specified hourly intervals that may be affected by changes in gastric emptying (eg, anti-seizure or anti-arrhythmic medications) - Alcohol or drug misuse - Pregnancy or lactation, or desire to become pregnant			• The device placement is intended to be temporarily and should be endoscopically removed after 3 to 6 months • Aggressive symptoms control with triple antiemetic medications in the early period after insertion • Use of proton pump inhibitor and avoidance of non-steroidal anti-inflammatory agents during treatment • Weight regain occurs after device removal
Nonsystemic Oral Superabsorbent Hydrogel						
Plenity®[84]	Oral capsule releases carboxymethylcellulose and citric acid hydrogel when taken with water. The particles rapidly absorb water and mix with ingested food,	Adult with BMI 25-40 kg/m^2	- Allergic reaction to cellulose, citric acid, sodium stearyl fumarate, gelatin, or titanium dioxide	%TBWL demonstrated 6.4% and 9.5% after 6 months and 48 weeks, respectively	- Abdominal pain - Diarrhea - Abdominal distension - Infrequent bowel	Take three capsules (2.25 g total) orally twice daily, administer 20 to 30 minutes before lunch and dinner

	which expands to ¼ of the stomach volume, to create a sensation of satiety to reduce hunger and improve appetite control.		- Pregnancy		movements - Flatulence - Constipation	

BMI: Body Mass Index; TBWL: Total Body Weight Loss.

[a]As of January 2019, ReShape has been voluntary withdrawn from the market due to marketing reasons.

Pharmacologic Therapy

According to current guidelines, 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 changes alone, and have a BMI more than or equal to 30 kg/m^2 or a BMI more than or equal to 27 kg/m^2 with at least one weight-related comorbidity (Graded as a strong recommendation with high quality evidence).[6,29] Furthermore, patients who meet the BMI requirements and have a history of failed attempts to lose weight or maintain weight loss with comprehensive lifestyle intervention alone may also be candidates for pharmacotherapy.[29] Long-term pharmacotherapy may have a place in the treatment of obesity for patients who have no obvious contraindications to approved medication therapy, as the likelihood of weight regain after treatment discontinuation is quite high. Table 167-6 lists FDA-approved pharmacotherapeutic agents currently available for management of overweight and obesity.

TABLE 167-6

FDA-Approved Pharmacotherapeutic Agents for Weight Loss

Medication	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
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	120 mg three times daily is approved for adolescents ages 12 or greater with BMI for age equivalent to 30 kg/m^2 in adults	• 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	Qsymia®	3.75 mg of phentermine and 23 mg of	7.5 mg of	Maximum dose for	• Approved for

and topiramate extended release		topiramate once daily for 14 days; then increase to 7.5 mg of phentermine and 46 mg of topiramate once daily	phentermine and 46 mg of topiramate once daily to a maximum dose of phentermine 15 mg and topiramate 92 mg once daily	patients with moderate or severe kidney impairment or patients with moderate hepatic impairment is 7.5 mg of phentermine and 46 mg of topiramate	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 kidney 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) once daily in the morning	• Approved for long-term use • Do not take dose with high-fat meal
Glucagon-Like Peptide-1 Agonists					
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	3 mg once daily	Use with caution in mild, moderate, and severe kidney and hepatic impairment. Dose escalation to 3.0 mg once daily is approved for adolescents ages 12 or greater with weight 60 kg (132 lb) or greater and BMI for age equivalent to 30 kg/m^2 in adults	• Approved for long-term use • Inject subcutaneously in the abdomen, thigh, or upper arm
		Administered by subcutaneous injection			Administer at any time of day without regard to the timing of meals
Semaglutide	Wegovy™	• 0.25 mg once weekly for 4 weeks	2.4 mg once weekly		• Approved for

		• 0.5 mg once weekly for 4 weeks • 1 mg once weekly for 4 weeks • 1.7 mg once weekly for 4 weeks • 2.4 mg once weekly • Administered by subcutaneous injection			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
Melanocortin 4 (MC4) Receptor Agonist					
Setmelanotide	**Imcivree™**	• Adults and adolescents > 12 years: • 2 mg once daily for 2 weeks, then increase to 3 mg once daily if tolerated and additional weight loss is desired (or decrease to 1 mg once daily based on tolerability) • Children aged 6 to <12 years: • 1 mg once daily for 2 weeks, then increase to 2 mg once daily if tolerated (or decrease to 0.5 mg once daily based on tolerability), then increase to 3 mg once daily if tolerated and additional weight loss is desired • Administered by subcutaneous injection	2-3 mg once daily	Not recommended for patients with moderate to severe kidney impairment	• Approved for long-term use in patients aged 6 years and above with genetically confirmed or suspected deficiency of POMC, PCSK1, or LEPR. • Inject subcutaneously in the abdomen, thigh, or upper arm rotating sites each day • Administer at the beginning of the day without regard to 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 kidney 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 ½ 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 ½ 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	Use with caution in patients with kidney 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 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 kidney 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.

A multidisciplinary team approach to the management of obesity is necessary to ensure long-term success. It is common for patients to use a combination of nonprescription, prescription, and other complementary and alternative therapies to attain the desired weight loss goal. Therefore, clinicians should maintain a high degree of sensitivity toward the potential polypharmacy practices of patients with obesity. Finally, it is prudent to consider specific patient factors and characteristics along with the efficacy and safety profiles of individual therapies when determining if use of a pharmacologic intervention is warranted.

Agents Approved for Long-Term Use

There are currently six products approved in the United States for the chronic management of obesity. These include the lipase inhibitor orlistat (Xenical®, Genentech USA, South San Francisco, CA; Alli®, GlaxoSmithKline, Middlesex, UK), the combination product phentermine–topiramate extended release (Qsymia®, Vivus, Inc, Mountain View, CA), the combination product naltrexone-bupropion extended-release tablets (Contrave®, Takeda Pharmaceuticals America Inc, Cambridge, MA), the GLP-1 receptor agonists liraglutide (Saxenda®, Novo Nordisk Inc, Plainsboro, NJ) and semaglutide (Wegovy™, Novo Nordisk Inc, Plainsboro, NJ), and the melanocortin 4 (MC4) receptor agonist, setmelanotide (Imcivree™, Rhythm Pharmaceuticals Inc, Boston, MA). Pharmacotherapy management guidelines recommend discontinuation of medication therapy in patients who fail to lose sufficient amounts of body weight after 3 months and in patients who experience significant adverse medication reactions, with consideration given to potential alternative weight loss agents (strong recommendation with high-quality evidence).[29] Table 167-7 lists clinical and economic considerations for use of the products approved for long-term use.

TABLE 167-7

Clinical and Economic Considerations for Long-Term Pharmacotherapy Options

Medication	Brand Name	Weight Loss Above Diet and Exercise Alone (1 year)[85-88]	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 mg-46 mg • $199.50, 15 mg-92 mg	- Limited distribution under FDA Risk Evaluation Mitigation Strategy (REMS)
Bupropion and naltrexone extended release	Contrave®	4.9 kg (10.8 lb)	$303.60	- Lowers seizure threshold (bupropion) - Rare reports of hepatotoxicity (naltrexone) - Drug interactions with opioids, CYP2B6 inducers and CYP2D6 substrates
Liraglutide	Saxenda®	5.2 kg (11.4 lb)	$1,349.00	- Injectable (daily dosing) - Available as pre-filled dosing pen - Reduces HbA1c and fasting glucose - Risk of medullary thyroid carcinoma and multiple endocrine neoplasia syndrome type 2 - Rare reports of pancreatitis, gallbladder disease, and suicidal ideation
Semaglutide	Wegovy™	15.5 kg (34.1 lb)[b]	$1,349.00	- Injectable (weekly dosing) - Available as pre-filled dosing pen - Reduces HbA1c and fasting glucose - Risk of medullary thyroid carcinoma and multiple endocrine neoplasia syndrome type 2 - Rare reports of pancreatitis, gallbladder disease, and suicidal ideation
Setmelanotide	Imcivree™	23.1% (patients with POMC or PCSK1 deficiency) 9.7% (patients with LEPR deficiency)	$19,800	- Injectable (daily dosing) - Available as multiple-dose vial (10 mg/mL) - Indicated for genetically confirmed or suspected deficiency POMC, PCSK1, or LEPR

[a]Cost of therapy based on maintenance dose using wholesaler acquisition cost (WAC) as of September 29, 2021.

[b]Data from 68-week trial.

Lipase Inhibitor: Orlistat

Excessive intake of dietary fat is one of the contributing factors in the development of obesity. GI (gastric, pancreatic, and carboxyl ester) lipases are essential in the absorption of the long-chain triglycerides. Additionally, lipase is known to play a role in facilitating gastric emptying and secretion of other pancreaticobiliary substances. Orlistat (Xenical®) is a synthetic derivative of lipstatin, a natural lipase inhibitor produced by *Streptomyces toxytricini*. The medication is minimally absorbed and induces weight loss by persistent lowering of dietary fat absorption through selective inhibition of the GI lipase. Furthermore, lower luminal free fatty acid concentrations result in malabsorption of cholesterol. Up to 30% reduction in fat absorption occurs with daily doses of 120 mg three times daily with meals.[89] A nonprescription formulation of orlistat (Alli®) is approved in the United States at a reduced daily dose of 60 mg three times daily.[89] The medication must be taken within 1 hour of consuming foods that contain fat in order to exert its effect. If a meal is skipped or contains no fat, the dose of orlistat can be omitted.

As an adjunct to diet therapy, orlistat results in dose-dependent reductions in fat absorption. Orlistat modestly increases the amount of weight lost and decreases the amount of weight regained during medically supervised weight loss programs.[89] Improved glycemic control can be attained in patients with type 2 diabetes mellitus by inducing or increasing weight loss with orlistat in addition to diet management.[89] In some cases, dosages or the number of antidiabetic medications may be reduced or discontinued. Improvements in the lipid profile (reduction in total and low-density lipoprotein [LDL] cholesterol), glucose control, and other markers of metabolism are seen when using orlistat in addition to the diet.[89,90] Orlistat is approved for the chronic treatment of obesity in adults and adolescents between ages 12 and 16 years. The recommended dose is 120 mg three times daily taken within 1 hour of consuming a fat-containing meal.

At least one GI complaint (soft stools, abdominal pain or colic, flatulence, fecal urgency, or incontinence) has been reported in up to 80% of individuals using prescription-strength orlistat. These complaints are most common in the first 1 to 2 months of therapy, are mild to moderate in severity, and tend to improve with continued orlistat use. Limiting dietary fat before initiation of orlistat therapy may be beneficial in decreasing initial GI complaints. Severe diarrhea secondary to orlistat use can affect the absorption of orally administered medications, such as oral contraceptives, fat-soluble vitamins (A, D, E, and K), and β-carotene. Therefore, supplementation with a multivitamin should be considered during therapy. In the presence of severe diarrhea, women receiving oral contraceptives should be advised of the need to use alternative backup methods because absorption of oral contraceptive may be reduced. Reduced fat absorption can potentially affect the absorption of lipophilic medications, such as lamotrigine, valproic acid, gabapentin, and amiodarone.[91,92] Decreased vitamin K absorption has also been noted and can alter the patient's warfarin dosage needs. Clinicians should also be aware that orlistat may directly interfere with the absorption of other narrow therapeutic range medications, such as cyclosporine, levothyroxine, and antiretrovirals.[92] In patients requiring concomitant therapies with orlistat, close monitoring is warranted to ensure an adequate therapeutic response. Separation of the administration times of the medications may minimize these potential drug interactions. Finally, there have been rare postmarketing reports of liver damage with the use of orlistat.[92] Although causality has not been definitively linked to orlistat, patients are advised to notify their healthcare providers if they notice signs and symptoms of liver injury, such as development of itching, yellow eyes or skin, dark urine, loss of appetite, or light-colored stools.

Phentermine–Topiramate Extended Release

A combination product containing phentermine and topiramate extended release (Qsymia®) is approved for chronic weight management in patients who have obesity (BMI of greater than or equal to 30 kg/m^2) or overweight (BMI of greater than 27 kg/m^2) with at least one weight-related comorbidity.[93] Phentermine is structurally similar to amphetamine, but it has less severe CNS stimulation and a lower misuse potential. Its mechanism of action centers on its ability to enhance norepinephrine (NE) and dopamine neurotransmission, resulting in appetite suppressing effects. Topiramate is an antiseizure medication. Although the exact mechanism for its efficacy in weight management is unknown, it may decrease appetite and increase satiety through multiple pathways, including effects on γ-aminobutyrate, voltage-gated ion channels, excitatory glutamate receptors, or carbonic anhydrase.[93] The doses of phentermine (3.75-15 mg) and topiramate (23-92 mg) in this combination are lower than the therapeutic doses of each separate product when used as monotherapy for obesity (37.5 mg) and seizures (400 mg), respectively. The recommended dosing strategy for phentermine–topiramate extended release involves gradual titration, staring with 3.75 mg of phentermine and 23 mg of topiramate once daily for 14 days and then increasing the dose to 7.5 mg of phentermine and 46 mg of topiramate once daily.[93] After 12 weeks of therapy, the dose may be increased again to 11.25 mg of

phentermine and 69 mg of topiramate for 14 days and then to a maximum dose of 15 mg of phentermine and 92 mg of topiramate daily. Likewise, when discontinuing therapy, the dose should be gradually decreased by taking a dose every other day for at least 1 week to prevent the possible precipitation of seizures.

When used as an adjunct to a reduced-calorie diet and lifestyle changes, phentermine–topiramate leads to dose-dependent weight loss and reductions in blood pressure, total cholesterol, LDL cholesterol, triglycerides, fasting glucose, and HbA_{1c}.[85] Mean weight loss after 1 year of treatment is 8.1 kg (17.8 lb) for the 7.5-mg phentermine and 46-mg topiramate dose and 10.2 kg (22.4 lb) for the 15-mg phentermine and 92-mg topiramate group. The efficacy of phentermine–topiramate has also been documented in patients with class II and class III obesity (mean BMI, 42 kg/m^2), with a mean weight loss of 10.9% after 1 year of treatment.[85]

The most common adverse medication reactions associated with the use of phentermine–topiramate are constipation, dry mouth, paraesthesia, dysgeusia, and insomnia.[85,93] Because topiramate is a known teratogen, this medication is contraindicated in pregnancy because fetal exposure in the first trimester increases the risk of cleft lip or cleft palate. To manage the potential risk of teratogenicity, the medication is only available through a limited distribution process under a risk evaluation and mitigation strategy (REMS).[93] All women of childbearing age must have a documented negative pregnancy test result before beginning treatment and then monthly to continue therapy. Topiramate has been associated with acute myopia associated with secondary angle-closure glaucoma, and phentermine can cause mydriasis from adrenergic stimulation. Therefore, this product is also contraindicated in patients with glaucoma. The potential for hypertensive crisis with coadministration of phentermine and monoamine oxidase inhibitors (MAOIs) exists; therefore, patients should have stopped an MAOI for at least 14 days before use of any adrenergic agent. Phentermine–topiramate is also contraindicated in patients with untreated hyperthyroidism.

Monitoring parameters and drug interactions that clinicians should be aware of include known issues related to both components of the formulation. Of note, increases in heart rate greater than 10 beats/min are observed in approximately 50% of patients receiving phentermine–topiramate.[93] In patients receiving the highest dose, 19% experience increases in heart rate that are greater than 20 beats/min. Therefore, heart rate should be monitored in all patients, particularly those with preexisting CVD. Decreases in serum bicarbonate are generally mild, but peak after 4 weeks of therapy. Decreases in serum potassium and increases in serum creatinine are also seen. Therefore, monitoring of serum electrolytes and creatinine is recommended at baseline and during therapy. Clinicians should be aware that concomitant use of non–potassium-sparing diuretics may potentiate the risk for hypokalemia. Although pregnancy risk is not expected, use of phentermine–topiramate concomitantly with oral contraceptives may result in breakthrough bleeding because of increased exposure to progestin and decreases exposure to estrogen. Phentermine–topiramate is classified as a controlled substance in schedule IV because of the misuse potential of phentermine. Therapy should be discontinued if 5% weight loss is not achieved after 12 weeks with the 7.5-mg phentermine and 46-mg topiramate dose.[93]

Naltrexone–Bupropion Extended Release

A combination product containing naltrexone and bupropion extended release (Contrave®) is approved for chronic weight management in patients who have obesity (BMI of more than or equal to 30 kg/m^2) or overweight (of more than or equal to 27 kg/m^2) with at least one weight-related comorbidity.[94] Naltrexone and bupropion are both approved separately for treatment of alcohol and opioid physical dependence, and depression and smoking cessation, respectively.[95] Bupropion is a dopamine and norepinephrine reuptake inhibitor, and naltrexone is an opioid antagonist. Although the exact weight-loss mechanism of action is not known for this medication combination, stimulation of release of α-MSH in hypothalamus by bupropion and inhibition of endogenous opioids by naltrexone are thought to contribute to a decrease in appetite.[95] The recommended dosing strategy for naltrexone-bupropion extended-release involves gradual titration, starting with one tablet (8-mg naltrexone/90-mg bupropion) per day and slowly increasing the dose over a period of 4 weeks to a maintenance dose of two tablets twice daily. Doses greater than 32 mg of naltrexone and 360 mg of bupropion (ie, 4 tablets) per day are not recommended. Patients should be advised to not take their dose with a high-fat meal as this would result in increased systemic exposure to both naltrexone and bupropion.

When used in combination with a reduced-calorie diet and lifestyle changes, naltrexone/bupropion is associated with improvements in high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, and insulin.[85,95] Average total weight loss is 7.3 kg (16.1 lb) following 1 year of treatment,[95] with the greatest weight loss (9.7 kg [21.3 lb]) seen in patients without diabetes mellitus also receiving intensive behavior modification therapy.[85]

The most common adverse medication reactions associated with the use of naltrexone/bupropion are nausea, constipation, headache, vomiting,

dizziness, insomnia, dry mouth, and diarrhea.[94] Approximately 24% of patients who receive naltrexone-bupropion discontinue treatment due to adverse medication reactions, with nausea being the most frequent reason.[94] Statistically significant increases in heart rate (2.1 beats/min) and blood pressure (1.8-2.3 mm Hg systolic and 1.7-2.1 mm Hg diastolic) occur in patients receiving naltrexone-bupropion during the first 3 months of therapy, but the clinical significance of these increases is unknown. Blood pressure and pulse should be monitored at baseline and at regular intervals following initiation of therapy. Naltrexone-bupropion should not be used in patients with uncontrolled hypertension.[94] Naltrexone monotherapy is associated with rare reports of hepatotoxicity, and patients receiving naltrexone-bupropion should be advised of the signs and symptoms of acute hepatitis. Bupropion lowers the seizure threshold in a dose-dependent manner and has been associated with serious neuropsychiatric reactions and an increased risk of suicidal thoughts and behavior when used for smoking cessation and treatment of depression. Bupropion may also be associated with activation of mania, serious allergic reaction, and angle-closure glaucoma.

Clinicians should also be aware of potential drug interactions with naltrexone-bupropion. Because of the opioid antagonist effects of naltrexone, naltrexone-bupropion is contraindicated in patients receiving chronic opioid or opiate agonist therapy, and also in patients undergoing abrupt withdrawal of chronic alcohol, benzodiazepine, barbiturate or antiseizure medications. Bupropion is metabolized by cytochrome P450 2B6 (CYP2B6) and inhibits cytochrome P450 2D6 (CYP2D6). Therefore, any medication that induces CYP2B6 (eg, rifampin, carbamazepine) could potentially reduce the effects of bupropion, and bupropion could increase the effects of medications that are CYP2D6 substrates (eg, SSRIs, tricyclic antidepressants, antipsychotics). Bupropion is also contraindicated with concomitant use of MAOIs. As with other long-term pharmacologic treatments for obesity, weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus receiving antidiabetic medications. Finally, treatment with naltrexone-bupropion should be discontinued if 5% weight loss is not achieved after 12 weeks.[94]

Glucagon-Like Peptide-1 Receptor Agonists

Liraglutide

Liraglutide (Saxenda®), an analog of GLP-1, is approved in the United States for chronic weight management in adult patients who have obesity (BMI of more than or equal to 30 kg/m^2) or overweight (BMI of more than 27 kg/m^2) with at least one weight-related comorbidity and in adolescents age 12 years and older with body weight above 60 kg (132 lb) and an initial BMI corresponding to obesity according to international cut-offs for age and sex.[96] Endogenous GLP-1 is released in response to food digestion and stimulates GLP-1 receptors in the brain to reduce appetite. GLP-1 also stimulates insulin secretion and reduces glucagon secretion. For that reason, several GLP-1 receptor agonists, including liraglutide, are currently approved for the treatment of type 2 diabetes mellitus at recommended doses of 1.2 mg or 1.8 mg daily far less than the maintenance dose for weight loss of 3 mg daily. Liraglutide is administered subcutaneously and is available in prefilled, multidose pens. When used for weight loss, a 5-week dose escalation schedule is recommended to improve tolerability of GI adverse medication reactions. It should be initiated at a dose of 0.6 mg daily, and increased weekly by 0.6-mg increments to a final maintenance dose of 3 mg daily. If the patient cannot tolerate the GI adverse medication reactions at any point during the dose escalation phase, a dose increase may be delayed by a week. Patients should be instructed on the proper technique for subcutaneous injection into the abdomen, thigh, or upper arm.

The efficacy of liraglutide for the management of overweight and obesity has been studied in patients with and without diabetes mellitus. A mean weight loss of 5.2 kg (11.4 lb) more than placebo is observed after 1 year of treatment with liraglutide[86]; slightly less weight loss is reported for adolescents.[97] As expected, patients who receive liraglutide also experience improvements in HbA_{1c}, fasting glucose and insulin, and had a lower prevalence of prediabetes. Similarly, patients with diabetes mellitus experience a 6% average weight loss after 1 year of treatment.[93] Improvements in fasting glucose and the number of subjects achieving HbA_{1c} targets are also observed. The most common adverse medication reactions associated with the use of liraglutide are nausea, diarrhea, constipation, vomiting, dyspepsia, hypoglycemia, and abdominal pain.[96] GI complaints are the most common reason for premature discontinuation of therapy, underscoring the importance of the slow dose-escalation schedule with initiation of therapy. Rare cases of acute pancreatitis (0.3%), potentially leading to fatal hemorrhagic or necrotizing pancreatitis, may occur with the use of liraglutide.[93] Resting heart rate increases an average of 2 to 3 beats/min with liraglutide; however, increases as high as 20 beats/min may be seen. Although the clinical significance of these increases is unknown, heart rate should be regularly monitored in all patients receiving liraglutide. Cholelithiasis (1.5%), cholecystitis (0.6%), and suicidal ideation (0.2%) are also observed.[96] Liraglutide carries a boxed-warning about the risk of thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), and is contraindicated in patients with a personal or family history of MTC or multiple endocrine neoplasia syndrome type 2 (MEN2). Hypoglycemia may occur when liraglutide is used in combination with other antidiabetic agents

(particularly sulfonylureas and insulin) in patients with type 2 diabetes mellitus. Therefore, dose adjustments of antidiabetic medications may be necessary. Because liraglutide increases gastric emptying time, clinicians also should be aware that absorption of concomitantly administered oral medications may be altered. Liraglutide should be discontinued if weight loss of at least 4% is not achieved after 16 weeks of therapy.

Semaglutide

Semaglutide (Wegovy™) is the most recent medication approved in the United States for chronic weight management in patients who have obesity (BMI of more than or equal to 30 kg/m^2) or overweight (BMI of more than 27 kg/m^2) with at least one weight-related comorbidity.[98] Similar to liraglutide, semaglutide stimulates GLP-1 receptors in the brain to reduce appetite. Semaglutide (Ozempic®) is also approved for the treatment of type 2 diabetes mellitus and to reduce the risk of major cardiovascular events in adults with type 2 diabetes mellitus and cardiovascular disease as a subcutaneous injection at a dose of 1 mg once weekly.[99] When used for weight loss, the starting of semaglutide is 0.25 mg once weekly for 4 weeks, followed by monthly dose escalation to improve tolerability of GI adverse medication reactions, to a maintenance dose of 2.4 mg weekly. If the patient cannot tolerate the GI adverse medication reactions at any point during the dose escalation phase, a dose increase may be delayed by a month. If a patient cannot tolerate the 2.4 mg weekly dose, the dose may be decreased to 1.7 mg weekly for 1 month before increasing the dose back to 2.4 mg weekly. Patients should be instructed on the proper technique for subcutaneous injection into the abdomen, thigh, or upper arm.

The efficacy of semaglutide for the management of overweight and obesity has been studied in patients with and without diabetes mellitus and has been associated with the greatest amount of weight loss when compared to all other approved weight loss medications.[87,100] Patients receiving semaglutide 2.4 mg weekly lose an average of 14.9% of their original body weight (15.5 kg [34.1 lb]) after 68 weeks of treatment and experience considerable improvements in systolic blood pressure, LDL cholesterol, and HbA1C measurements.[87] Notably, 50% of subjects receiving semaglutide achieve >15% reduction in body weight. In patients with type 2 diabetes mellitus, average weight loss is 9.6% after 68 weeks of therapy.[100]

Adverse medication reactions associated with the use of semaglutide are similar to those observed with liraglutide and include nausea, diarrhea, constipation, vomiting, dyspepsia, and abdominal pain.[87,98,100] Semaglutide is also associated with rare cases of acute pancreatitis, acute gall bladder disease, acute kidney injury, diabetic retinopathy, and small increases in resting heart rate.[98] Semaglutide carries a boxed-warning about the risk of thyroid C-cell tumors, including MTC, and is contraindicated in patients with a personal or family history of MTC or multiple endocrine neoplasia syndrome type 2 (MEN2). As with liraglutide, hypoglycemia may occur when semaglutide is used in combination with other antidiabetic agents in patients with type 2 diabetes mellitus. Therefore, dose adjustments of antidiabetic medications may be necessary.

Melanocortin 4 (MC4) Receptor Agonist

Setmelanotide

Setmelanotide (Imcivree™) is a peptide analog of endogenous alpha-melanocyte stimulating hormone (α-MSH) approved for chronic weight management in patients with genetically confirmed or suspected proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency.[101] Patients with variants in POMC, PCSK1, or LEPR genes are thought to have obesity due to insufficient activation of MC4 receptors in the brain. Setmelanotide is an MC4 receptor agonist that results in reduced hunger and promotes weight loss through decreased energy intake and slightly increased energy expenditure. Setmelanotide is indicated in adults and children aged 6 years and older. It is administered once daily as a subcutaneous injection with a starting dose of 2 mg daily for those 12 years and older and 1 mg daily for children aged 6 to less than 12 years.[101] Depending on tolerability the dose can be gradually increased to a maximum of 3 mg daily. In patients with LEPR or POMC deficiency, setmelanotide is associated with >10% weight loss after 1 year of treatment in 45% and 80% of subjects, respectively.[88] The most common adverse medication reactions associated with setmelanotide include injection site reactions (96%), skin hyperpigmentation (78%), nausea (56%), headache (41%), diarrhea (37%), and abdominal pain (33%).[101] Sexual adverse medication reactions such as spontaneous penile erections may occur. Male patients should be advised to seek medical treatment for an erection lasting longer than 4 hours. It is also advised to monitor for the potential of new or worsening depression and suicidal ideation. According to the manufacturer, if a patient fails to lose at least 5% of baseline body weight (or 5% of baseline BMI) after 12 to 16 weeks of treatment, it is recommended to discontinue setmelanotide due to a low potential for a meaningful weight loss with continued treatment.[101]

Agents Approved for Short-Term Use

Several noradrenergic agents are currently approved by the FDA for short-term weight loss. Because short-term therapy is not consistent with current national guidelines for the chronic management of obesity, these agents have limited clinical utility in practice.[6,7]

Phentermine

Phentermine is available in both immediate-release and sustained-release formulations. However, the value of sustained-release formulations is questionable based on the phentermine plasma half-life of 12 to 24 hours. Phentermine is an effective adjunct to diet, exercise, and behavior modification for producing weight loss.[102] Intermittent phentermine therapy appears to elicit comparable weight loss as that seen with continuous use. However, most individuals experience weight regains during therapy and generally always after discontinuing use.[102] A single dose of 30 mg once daily in the morning provides effective appetite suppression throughout the day. Divided doses of 8 mg immediately before meals, however, are common.[103] Evening or nighttime dosing should be avoided because of insomnia. Large increases in blood pressure, palpitations, and arrhythmias can occur with phentermine administration. Use is not advisable in hypertensive patients. Pharmacotherapy management guidelines recommend against the use of sympathomimetic agents in patients with uncontrolled hypertension or a history of CVD (strong recommendation with high-quality evidence).[29]

The potential for hypertensive crisis with coadministration of phentermine and MAOIs is noted in the product labeling of each agent; therefore, patients should be off an MAOI for at least 14 days before use of any adrenergic agent to avoid excessive adrenergic stimulation syndromes.[104] Phentermine use is contraindicated in patients with hyperthyroidism or agitated states and in those who misuse substances such as cocaine, phencyclidine, and methamphetamine, again because of the potential for excessive adrenergic stimulation syndromes and misuse potential. Mydriasis from adrenergic stimulation can worsen glaucoma, and patients diagnosed with glaucoma should not receive phentermine. Patients with diabetes mellitus may experience altered insulin or oral hypoglycemic dosage requirements soon after beginning therapy and before any substantial weight loss. Phentermine remains the most widely prescribed weight management medication by obesity specialists despite product labeling that indicates short-term (a few weeks), monotherapy use only.[102] This usage pattern deviates from the current national recommendations that promote only long-term medication intervention when obesity pharmacotherapy is appropriate.[7] Some clinicians consider use of long-term phentermine to be reasonable in select patients given the low cost and a lack of serious long-term adverse medication reactions reported over the past 20 years. Select patients include those without CVD, psychiatric disease, or substance misuse; without clinically significant increases in blood pressure or heart rate while receiving phentermine; and documentation of weight loss while receiving phentermine.

Diethylpropion

Diethylpropion stimulates NE release from presynaptic storage granules. Increased adrenergic neurotransmitter concentrations activate hypothalamic centers, which result in decreased appetite and food intake. Diethylpropion can be taken in divided daily doses, generally 25 mg three times daily before meals. An extended-release formulation is also used by some clinicians, usually as 75 mg taken once daily in the morning or midmorning.[102] Both dosing regimens are effective in achieving short-term weight loss. Complaints of insomnia increase if late afternoon dosing is used. Diethylpropion causes less stimulation of the CNS than mazindol and generally causes less insomnia than phentermine. Patients with severe hypertension or CVD should not receive diethylpropion. Patients with diabetes mellitus may experience decreased insulin or oral hypoglycemic dosage requirements soon after beginning therapy and before any substantial weight loss. In patients with diabetes mellitus, more frequent blood glucose self-monitoring and medical follow-up are warranted when treating patients with diethylpropion.

Amphetamines

Appetite suppressant effects of the amphetamines were well recognized in the 1930s. Amphetamines activate central noradrenergic receptor systems as well as dopaminergic pathways at higher doses by stimulating neurotransmitter release. Increases in blood pressure and mild bronchodilation are attributed to peripheral α- and β-receptor activation. Amphetamines are no longer widely used for the treatment of obesity because of their powerful stimulant effects and addictive potential.

Complementary and Alternative Therapies

Many complementary and alternative therapy products are currently promoted for weight loss. A nationwide survey of US consumers reported that about 15.2% of adults had used “dietary supplements” specifically for the purposes of weight loss.[105] It is important for clinicians to be aware that the

regulation of dietary supplements is less rigorous than that of prescription and over-the-counter medications. As such, a manufacturer of a dietary supplement does not have to prove the safety or effectiveness of the product before it is marketed. Of concern, some herbal and food supplement diet agents contain pharmacologically active substances that should be used with caution or avoided in patients who have obesity who also have conditions such as diabetes mellitus, hypertension, and CVD. In addition, many marketed products lack consistency in labeling versus actual product content, and a number of dietary supplements have been found to contain undeclared prescription medications. Common herbal and natural products that have been used for weight loss include hoodia, green tea, citrus aurantium, forskolin, caffeine, glucomannan, yohimbine, chitosan, guar gum, hydroxycitric acid, and garcinia cambogia.[105,106]

EVALUATION OF THERAPEUTIC OUTCOMES

The evaluation and management of a patient with obesity requires careful clinical; biochemical; and, if necessary, psychological evaluation. This evaluation should include an assessment of the patient's current medical condition and medication regimen. A multidisciplinary team including, but not limited to, a physician, dietitian, psychologist, behavioral expert, and pharmacist should ideally be involved in the care of individuals with obesity.

Monitoring the Pharmaceutical Care Plan

Assessment of patient progress should be documented frequently.[6] Each encounter should document weight, WC, BMI, blood pressure, medical history, and patient assessment of obesity medication tolerability.[6] Chronic use of obesity medications should be consistent with the approved product labeling. According to current pharmacologic management guidelines, efficacy and tolerability of the medication should be assessed monthly for the first 3 months, followed by visits every 3 months thereafter (weak recommendation with low quality evidence).[29] If the patient has failed to demonstrate weight loss or maintenance of prior weight, medication therapy should be discontinued after 3 months (strong recommendation with high quality evidence).[29]

To achieve optimal weight loss, patients should be instructed about the importance of adherence to prescribed medication and lifestyle changes. The Short Form 36 (SF-36) is used as a quality-of-life evaluation tool for patients with obesity undergoing programmatic weight loss. Quarterly assessments of well-being and quality of life using validated assessment tools can be helpful in objectively quantifying the effectiveness of therapy. Table 167-8 provides monitoring parameters and potential adverse medication reactions of agents used for long-term management of overweight and obesity.

TABLE 167-8

Adverse Medication Reactions and Monitoring Parameters

Medication	Brand Name	Adverse Medication Reactions	Monitoring Parameters	Comments
Gastrointestinal Lipase Inhibitor				
Orlistat	Xenical®, Alli®[a]	Soft stools, diarrhea, abdominal pain or colic, flatulence, fecal urgency, incontinence, liver damage (rare)	BMI; calorie and fat intake; serum glucose in patients with diabetes; thyroid function in patients with thyroid disease; liver function tests in patients exhibiting symptoms of hepatic dysfunction	Supplement with a multivitamin during therapy to prevent vitamin deficiency
Phentermine–Topiramate Combination				
Phentermine and topiramate extended release	Qsymia®	Constipation, dry mouth, paresthesia, dysgeusia, insomnia, hypoglycemia in patients with diabetes	BMI; calorie and fat intake; serum glucose in patients with diabetes; pregnancy; depression or suicidal thoughts; mood or sleep disorders; heart rate; serum electrolytes and creatinine at baseline and during	• Discontinue or escalate dose if 3% weight loss not achieved by week 12 on phentermine 7.5 mg and topiramate 46 mg • Discontinue if 5% weight

			treatment	loss not achieved by week 12 on phentermine 15 mg and topiramate 92 mg • Gradually discontinue phentermine 15 mg and topiramate 92 mg to prevent possible seizure
Bupropion-Naltrexone Combination				
Bupropion and naltrexone extended release	Contrave®	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea	BMI; calorie and fat intake; serum glucose in patients with diabetes; heart rate and blood pressure; signs and symptoms of hepatotoxicity, neuropsychiatric reactions, and suicidal thoughts or behavior	Discontinue if 5% weight loss not achieved by week 12
Glucagon-Like Peptide-1 Antagonists				
• Liraglutide • Semaglutide	• Saxenda® • Wegovi™	Nausea, diarrhea, constipation, vomiting, dyspepsia, hypoglycemia, and abdominal pain	BMI; calorie and fat intake; serum glucose in patients with diabetes; signs and symptoms of pancreatitis; heart rate; signs and symptoms of gallbladder disease and suicidal ideation	Discontinue liraglutide if 4% weight loss not achieved by week 16. At present, there is no recommendation to discontinue semaglutide therapy for inadequate weight loss at week 16.
Melanocortin 4 Receptor Agonist				
Setmelanotide	Imcivree™	Injection site reactions, skin hyperpigmentation, nausea, headache, diarrhea, and abdominal pain	BMI; calorie and fat intake; serum glucose in patients with diabetes, sexual adverse medication reactions, new or worsening depression, and suicidal ideation	• Approved for patients with genetically confirmed or suspected deficiency of POMC, PCSK1, or LEPR • Discontinue if 5% weight loss (or 5% decrease in BMI) not achieved after 12 to 16 weeks
Noradrenergic Agents				
• Phendimetrazine • Phentermine • Diethylpropion	• Bontril® PDM; Bontril® Slow-Release	Increased blood pressure, ischemic events, palpitations, tachycardia, valvular disease, urticaria, agitation, dizziness, headache, insomnia, overstimulation, psychosis,	Baseline cardiac evaluation (for preexisting valvular heart disease, pulmonary hypertension); echocardiogram during therapy; weight, waist circumference; blood	• Approved as monotherapies only for short-term use (a few weeks) • Discontinue if

	• Adipex-P®, Suprenza™ • Tenuate®, Tenuate Dospan	restlessness, dry mouth, constipation, thirst, diarrhea	pressure	satisfactory weight loss has not occurred within the first 4 weeks of treatment or if tolerance develops • Abrupt discontinuation after prolonged high doses may be associated with extreme fatigue and depression

BMI, body mass index.

[a]Available without a prescription.

Patients with diabetes mellitus receiving weight loss medication require more intense medical monitoring and self-monitoring of blood glucose to minimize the risk for hypoglycemia. Insulin therapy may need to be reduced with the start of obesity medication therapy. Some patients with diabetes mellitus may require daily telephone contact with a healthcare provider to assist in adjusting their hypoglycemic therapy. Weekly patient visits to a healthcare setting may be necessary for 1 to 2 months until the effects of diet, exercise, and weight loss medication become more predictable. As frequent as quarterly assessment of HbA_{1c} may be appropriate in patients with type 2 diabetes mellitus who lose weight to aid in adjustment of hypoglycemic therapy. Lipid profiles can normalize or improve with weight loss. Lipid status should be assessed semiannually or annually in patients with hyperlipidemia to determine the need for continued hyperlipidemia therapies. Weight loss also can result in normalization of blood pressure in hypertensive patients who have obesity. Assessment of appropriateness of antihypertensive therapy should occur with each follow-up visit.

CONCLUSION

Obesity is a complex chronic disease with a prevalence that has increased dramatically over the past 50 years. Increased body weight is a consequence of increased energy storage resulting from an imbalance between energy intake and energy expenditure over time, which is influenced by many factors, including genetics and the environment. Nonpharmacologic therapy, including reduced caloric intake, increased physical activity, and behavioral modification, is currently the mainstay of obesity management. Medication therapy may be considered as an adjunct for patients who fail to achieve adequate weight loss with comprehensive lifestyle modifications. Currently, six products—orlistat, phentermine–topiramate extended release, naltrexone-bupropion extended release, liraglutide, semaglutide, and setmelanotide—are approved by the FDA for the long-term treatment of overweight and obesity. Bariatric procedures have long-term efficacy for weight reduction, but they also introduce surgical comorbidities and, for the most efficacious procedures, may cause nutritional deficiencies. For patients who are not able to undergo bariatric surgery, medical devices may also be considered. Treatment of obesity should be individualized, considering factors such as patient desires, age, degree and duration of obesity, and the presence and severity of medical conditions both directly related to obesity and those that may have an impact on the therapeutic decisions. Regardless of the chosen treatment plan, the management of obesity is a lifelong process requiring patient support and careful monitoring for safety and efficacy.

ABBREVIATIONS

5-HT	5-hydroxytryptamine (serotonin)
α-MSH	alpha-melanocyte stimulating hormone
AACE	American Association of Clinical Endocrinologists
ACE	American College of Endocrinology

AHEAD	Action for Health in Diabetes
BAT	brown adipose tissue
BMI	body mass index
BMR	basal metabolic rate
CDC	Centers for Disease Control and Prevention
CNS	central nervous system
CT	computed tomography
CVD	cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
FDA	Food and Drug Administration
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
HbA_{1c}	hemoglobin A_{1c}
HDL	high-density lipoprotein
LCD	low-calorie diet
LDL	low-density lipoprotein
LEPR	leptin receptor
MAOI	monoamine oxidase inhibitor
MC4	melanocortin 4
MEN2	multiple endocrine neoplasia syndrome type 2
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
NE	norepinephrine
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
REE	resting energy expenditure

REMS	risk evaluation and mitigation strategy
POMC	proopiomelanocortin
PCSK1	proprotein convertase subtilisin/kexin type 1
SF-36	Short Form 36
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TRE	time-restricted eating
WAT	white adipose tissue
WAGR	Wilms' tumor, aniridia, genitourinary abnormalities or gonadoblastoma, and mental retardation
WC	waist circumference

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SELF-ASSESSMENT QUESTIONS

1. According to the National Institutes of Health (NIH) guideline, which category *best* describes a 45-year-old Hispanic male who is 5 ft 11 in. (180 cm) tall and weighs 302 lb (135 kg)?

   A. Normal weight

   B. Overweight

   C. Obesity

   D. Extreme obesity

2. Which one of the following is the *best* management approach after determining a patient needs to lose weight?

   A. Prescribe a FDA-approved pharmacotherapy to lose weight

   B. Assess the patient's readiness to lose weight

   C. Refer to a high-intensity comprehensive lifestyle intervention program to lose weight

   D. Set a weight lose goal of 10% weight loss over the next month

3. The Look Action for Health in Diabetes (AHEAD) study found that patients with diabetes mellitus who maintained weight loss of at least 7% with intensive lifestyle modifications for almost 10 years were able to demonstrate which of the following?

A. Did not experience an increased incidence of cardiovascular events, but they did have an increased need for diabetes mellitus medications and improvement in physical function

B. Did not experience a reduced incidence of cardiovascular events, but they did have an increased need for diabetes mellitus medications and improvement in physical function

C. Did not experience a reduced incidence of cardiovascular events, but they did have a reduced need for diabetes mellitus medications and improvement in physical function

D. Experienced an increased incidence of cardiovascular events, but they did have a reduced need for diabetes medications an improvement in physical function

4. Which one of the following weight loss goals is recommended for a White female with BMI of 32 kg/m^2 who also has type 2 diabetes mellitus requiring weight-loss intervention?

A. 5%

B. 7% to 8%

C. 5% to 15% or more

D. Uncertain

5. Which one of the following interventions represents the mainstay of weight loss therapy?

A. Conventional Roux-en-Y gastric bypass

B. Neurometabolic therapy

C. Locaserin 10 mg orally twice daily

D. Reduced-calorie diet, exercise, and behavioral modification

6. A 35-year-old White female weighs 163 lbs (74 kg), height of 5'4" (163 cm) with BMI of 28 kg/m^2. She is interested in losing weight in the next few months so she can wear summer clothes comfortably. She has uncontrolled hypertension and polycystic ovary syndrome. Which of the following is the *most appropriate* weight-loss recommendation for this patient?

A. Lifestyle modification only

B. Weight-loss medication and lifestyle modifications

C. AspireAssist and lifestyle modifications

D. Bariatric surgery and lifestyle modifications

7. Which BMI classification *does not* meet the appropriate criteria for consideration of metabolic and bariatric surgery?

A. Extreme obesity with BMI ≥ 40 kg/m^2

B. Obesity with BMI ≥ 35 kg/m^2 with obstructive sleep apnea

C. Obesity with BMI between 30 and 34.9 kg/m^2 with diabetes or metabolic syndrome

D. Obesity with BMI between 30 and 34.9 kg/m^2 after failed diet and exercise without metabolic abnormalities

8. All of the following supplements are required to prevent nutritional deficiencies in metabolic and bariatric surgery patients, *except*:

A. Niacin

B. Iron

C. Vitamin B_{12}

D. Multivitamin

9. Which of the following postoperative considerations is important in patients after bariatric surgery?

A. Altered nutrient absorption

B. Altered medication absorption

C. Increased adverse medication reactions

D. All of the above

10. Bariatric surgery has been demonstrated to reduce the following obesity-related problems, *except*:

A. Cardiovascular death

B. Type 2 diabetes mellitus

C. Cancer

D. Crohn's disease

11. Acceptable weight management option for a 40-year-old obese woman with uncontrolled hypertension include all of the following, *except*:

A. Liraglutide

B. Lorcaserin

C. Phentermine

D. Orlistat

12. Which effect would *most likely* be experienced by a patient taking semaglutide?

A. Paraesthesia

B. Nausea

C. Headache

D. Dysgeusia

13. Pharmacotherapy with liraglutide should be discontinued if a patient fails to lose 4% of their initial body weight after:

A. 8 weeks

B. 12 weeks

C. 16 weeks

D. 20 weeks

14. Which effect would *most likely* be experienced by a patient taking phentermine/topiramate extended release?

A. Increased heart rate

B. Dumping syndrome

C. Headache

D. Priapism

15. All of the following antidiabetic medications promote weight loss, *except*:

A. Metformin

B. Glucagon-like peptide-1 analogs (GLP-1)

C. Dipeptidyl peptidase-4 inhibitors (DPP-4)

D. Sodium-Glucose-linked transporter-2 inhibitors (SGLT2)

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** The calculated BMI is 42 kg/m^2 for this patient. Using pounds and inches, BMI (kg/m^2) is estimated as (weight [lb]/height [inches^2]) × 703. A BMI of 18.5 to 24.9 kg/m^2 is considered underweight. Adults with a BMI of 25 to 29.9 kg/m^2 are considered "overweight"; the terms obese, and extreme obese are reserved for those with a BMI of 30 to 39.9 kg/m^2, and 40 kg/m^2 and over, respectively (see Table 167-3).

2. **B.** Once the need for weight loss has been determined, the clinician needs to assess a patient's readiness to engage in weight loss efforts and identify any potential barriers to success before recommending any interventions. They need to initiate a dialogue with each patient who is overweight or obese to ensure they understand the potential health consequences of excess body weight and benefits of appropriate weight management. Specific weight goals should be established that are consistent with medical needs and the patient's personal desire (see Table 167-4).

3. **C.** The Look Action for Health in Diabetes (AHEAD) study found that patients with diabetes who maintained weight loss of at least 7% with intensive lifestyle modifications for almost 10 years did not experience a reduced incidence of cardiovascular events, but they did have a reduced need for diabetes mellitus medications and improvement in physical function and other health benefits.

4. **C.** According to the AACE/ACE Guidelines, the recommended weight loss goal for adult with type 2 diabetes mellitus is 5% to 15% or more with the clinical goal of reducing A1c, reduce number and/or doses of glucose-lowering medications, and improve control of diabetes mellitus (see Table 167-4).

5. **D.** All successful obesity treatment plans require incorporation of comprehensive lifestyle interventions such as healthy diet, adequate physical activity, and behavioral modifications as the cornerstone of weight management.

6. **B.** According to current AACE/ACE guidelines, this patient is currently in obesity Stage 1, tertiary chronic disease phase of prevention based on the presence of one or more mild to moderate weight-related complications, therefore, weight-loss medications is to be initiated concurrently with lifestyle therapy with BMI ≥ 27 kg/m^2.

7. **D.** Bariatric surgery is recommended to individuals with extreme obesity (BMI ≥ 40 kg/m^2) or BMI at 35 kg/m^2 or above with at least one or more major comorbidity such as hypertension, type 2 diabetes mellitus, or obstructive sleep apnea. Surgery may also be advocated to patients with BMI between 30 and 34.9 kg/m^2 with diabetes mellitus or metabolic syndrome as it has a similar efficacy and safety profile for improving type 2 diabetes and metabolic disorders among bariatric patients with a BMI below or above 35 kg/m^2. Patients with BMI between 30 and 34.9 kg/m^2 and failed lifestyle modification would be recommended with pharmacologic weight loss therapy as the next step.

8. **A.** Due to the disruption of the normal gastric anatomy and physiology, postsurgical patients are often at risk for severe micronutrient deficiencies

(eg, vitamin B_{12}, vitamin B_1, vitamin K, zinc, copper, folate, iron, calcium) as well as deficiencies in fat soluble vitamins such as vitamins A, D, E, and K due to fat malabsorption. Therefore, empiric supplementation with daily adult multivitamin plus minerals, elemental calcium, vitamin D, folic acid, thiamine, elemental iron, and vitamin B_{12} is essential to prevent nutritional deficiencies in bariatric patients. The level of niacin is usually not affected after bariatric surgery.

9. **D.** Postoperative bariatric surgery patients are often at risk for severe micronutrient deficiencies such as vitamin B_{12}, vitamin B_1, vitamin K, zinc, copper, folate, iron, and calcium due to the disruption of the normal gastric anatomy and physiology. Bariatric surgery can lead to altered dissolution and/or absorption of many medications due to reduced surface area for intestinal and gastric absorption, and alterations in drug metabolism via the intestinal metabolic pathways.

10. **D.** Significant reduction in risks of myocardial infarction, cardiovascular deaths, incidence of type 2 diabetes mellitus, hypertension, dyslipidemia, and cancer have also been documented after adult bariatric surgery.

11. **D.** The 2015 Endocrine Society Clinical Practice Guideline for the Pharmacological Management of Obesity recommend against the use of sympathomimetic agents, such as phentermine, in patients with uncontrolled hypertension or a history of CVD.

12. **B.** Adverse medication reactions associated with the use of semaglutide are similar to those reported with liraglutide and include nausea, diarrhea, constipation, vomiting, dyspepsia, and abdominal pain. Semaglutide has also been associated with rare cases of acute pancreatitis, acute gall bladder disease, acute kidney injury, diabetic retinopathy, and small increases in resting heart rate.

13. **C.** Based on data from clinical trials, the approved label states that liraglutide therapy should be discontinued if 4% weight loss is not achieved by week 16 because it is unlikely that a benefit will be seen.

14. **A.** Increases in heart rate occurred in approximately 50% of patients receiving phentermine–topiramate during clinical trials. In patients receiving the highest dose, 19% experienced increases in heart rate that were greater than 20 beats/min. Heart rate should be monitored in all patients, particularly those with preexisting CVD.

15. **C.** Based on the 2015 Endocrine Society Clinical Practice Guideline for the Pharmacological Management of Obesity, antidiabetic agents that promote weight loss are metformin, glucagon-like pepetide-1 analogs, or sodium-glucose-linked transporter-2 inhibitors.