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414 Evaluation and Management of Obesity

FATTY LIVER DISEASE Obesity is strongly associated with the pres ence of ectopic fat in hepatocytes. In a subset of patients, this can progress to nonalcoholic steatohepatitis (NASH), which can progress to fibrosis, which is a precursor to cirrhosis (Chap. 354). The reported incidence of NASH-related cirrhosis and of hepatocellular carcinoma has increased markedly in step with the increase in the prevalence of obesity in adolescents and adults. TYPE 2 DIABETES The insulin resistance characteristic of the over nourished state strongly predisposes to the development of type 2 diabetes in people who, largely for genetic reasons, are less able to maintain the high levels of insulin secretion over many decades. Impaired glucose tolerance and type 2 diabetes are among the most common complications of obesity (Chap. 415). Endocrine Complications In females, the insulin resistance/ hyperinsulinemia frequently found in obesity strongly predisposes to the development of polycystic ovaries, characterized by irregular men struation, anovulatory infertility, and hirsutism due to hyperandrogen ism. In males, obesity is more often associated with a degree of central hypogonadism, where low circulating testosterone is associated with levels of luteinizing hormone and follicle-stimulating hormone that do not rise appropriately to compensate for the testosterone-deficient state. Dermatologic Complications Obesity can result in problems with excessive skin folds that can cause discomfort through mechanical irritation and can also become infected with fungi. Insulin resistance/ hyperinsulinemia is associated with acanthosis nigricans, where areas such as axilla, groin, and the back of neck develop velvety hyperpig mentation. Hidradenitis suppurativa is a potentially disabling skin con dition strongly associated with obesity. It is characterized by recurrent boils often with chronically draining sinus tracts affecting skin areas containing apocrine sweat glands. Cardiovascular Complications People with obesity, even if they do not have diabetes, have increased morbidity and mortality from atherothrombotic vascular disease, including coronary artery disease and stroke. The factors that result in this are complex and involve increased prevalence of hypertension, dyslipidemia, and insulin resis tance/hyperinsulinemia. The rare condition of thrombotic thrombo cytopenic purpura, which causes microvascular platelet thrombosis, thrombocytopenia, and hemolytic anemia due to the presence of abnormally large von Willebrand factor multimers, is strongly associ ated with obesity. Independent of occlusive arterial disease, people with obesity are also at increased risk of heart failure, particularly characterized primar ily by diastolic dysfunction, and of atrial fibrillation, the most common arrhythmia. Respiratory Complications Exertional dyspnea is common in obesity,

contributed to by the increased work required to move a greater mass as well as impacts of pressure on the diaphragm and tho racic cage on chest wall compliance. Enlargement of soft tissue of the mouth and throat and adipose depots around the airways contribute to the high prevalence of sleep apnea, although other factors such as central nocturnal hypoventilation, also contribute in some people. Gastrointestinal Disorders Reflux esophagitis is the most com mon gastrointestinal complication of obesity, particularly occurring in those with high intraabdominal pressure. Gallstones are also more common in people with obesity, bringing increased risks of biliary colic, cholecystitis, pancreatitis, and gallbladder cancer. Rheumatologic Disorders Osteoarthritis of the knee and gout are the two most common rheumatologic conditions clearly associated with obesity. Interestingly, despite obesity being described as a proin flammatory state, there is no evidence for an increase in rheumatoid arthritis or the seronegative arthritides among people with obesity. Cancers Obesity is a risk factor for a number of common cancers. Indeed, it has recently been calculated that, at least in some countries, obesity has overtaken smoking as the greatest risk factor for developing

cancer. Recent research has found that as the BMI increases by 5 kg/m2, cancer mortality increases by 10%. The largest effects are on colorec tal, kidney, and pancreatic cancer, adenocarcinoma of the esophagus, and, in women, endometrial carcinoma. The recent rapid increase in the prevalence of esophageal adenocarcinoma is likely related to the marked recent increase in reflux esophagitis due to the raised intraab dominal pressure (with or without hiatus hernia) characteristic of central obesity.

Response to Infection The fact that obesity can influence the outcome of some infections has become very apparent with the COVID-19 pandemic. Obese patients have a substantially worse out come if infected by SARS-CoV-2 through mechanisms that are as yet unclear. Obese patients also appear to be more susceptible to bacterial wound infections and postoperative sepsis. Evaluation and Management of Obesity CHAPTER 414 Disorders of the Central Nervous System There is increasing evidence that obesity is a risk factor for dementia in later life, although how that risk is mediated is not clear. Idiopathic intracranial hyperten sion is a rare disorder that is strongly associated with obesity. ■ ■CONCLUSION Obesity is a medical disorder that has been greatly increasing in preva lence due to environmental factors that are ubiquitous in developed and developing countries. However, it is important to bear in mind that it is a highly heterogeneous condition, which in some people is attrib utable entirely to genetic causes, and that underlying genetic variation strongly influences the risk of obesity in all people. It is a serious con dition leading to multiple adverse health outcomes and considerable human suffering. As our understanding of its pathogenesis increases, our duty to treat obese patients with understanding and compassion and to develop new and better options for its treatment and prevention is worthy of emphasis. ■ ■FURTHER READING Farooqi IS, O'Rahilly S: The genetics of obesity in humans, in Endo text. KR Feingold et al (eds). South Dartmouth, MA, 2000. Friedman JM: Leptin and the endocrine control of energy balance. Nat Metab 1:754, 2019. Hall KD et al: The energy balance model of obesity: Beyond calories in, calories out. Am J Clin Nutr 115:1243, 2022. Heymsfield SB, Wadden TA: Mechanisms, pathophysiology, and management of obesity. N Engl J Med 376:1492, 2017. Leibel RL et al: Changes in energy expenditure resulting from altered body weight. N Engl J Med 332:621, 1995. NCD Risk Factor Collaboration (NCD-RISC): Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: A pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet

390:2627, 2017. O’Rahilly S: Harveian Oration 2016: Some observations on the causes and consequences of obesity. Clin Med (Lond) 16:551, 2016. Robert F. Kushner

Evaluation and

Management of Obesity More than 70% of U.S. adults are considered to be overweight or have obesity, and the prevalence of obesity is increasing rapidly in most of the industrialized world. Children and adolescents also are developing greater rates of obesity, indicating that the current trends will accelerate

over time. Obesity is associated with an increased risk of multiple health problems, including hypertension, type 2 diabetes, dyslipidemia, obstructive sleep apnea, metabolic dysfunction-associated steatotic liver disease, degenerative joint disease, and some malignancies. Thus, it is important for health care professionals to identify, evaluate, and treat patients for obesity and associated complications and comorbid conditions.

■ ■EVALUATION Health care professionals should screen all adult patients for obesity and offer intensive lifestyle counseling including behavioral interven tions to promote sustained weight loss. The four main steps in the evaluation of obesity, as described below, are (1) a focused obesityrelated history that includes lifestyle questions about diet, physical activity, sleep, and stress; (2) a physical examination to determine the degree and type of obesity; (3) assessment of complications and comor bid conditions; and (4) assessment of the patient’s readiness to engage in weight management. PART 12 Endocrinology and Metabolism The Obesity-Focused History The first step in taking an obe sity-focused history is to approach the topic in a sensitive manner. The reason for this concern is that the word obesity is a highly charged, emotive term. It has a significant pejorative meaning for many patients, leaving them feeling judged and blamed when labeled as such. This is not the case when patients are told that they have other chronic dis eases such as diabetes or hypertension. Patients prefer that clinicians use more neutral words or terms such as weight, excess weight, body mass index (BMI), or unhealthy weight, versus more perceived stigma tizing terms such as obesity, morbid obesity, or fatness. Information from the history should address the following seven questions: • What factors contribute to the patient’s weight gain and obesity? • How is obesity affecting the patient’s health? • What is the patient’s level of risk from obesity? • What does the patient find difficult about managing weight? • What are the patient’s goals and expectations? • What is the patient’s motivation to begin a weight management program? • What kind of help does the patient need? Although the majority of cases of obesity are promoted by biopsy chosocial and behavioral factors that affect diet and physical activity patterns, the history may suggest secondary causes that merit further evaluation. Disorders to consider include polycystic ovarian syndrome, hypothyroidism, Cushing’s syndrome, and hypothalamic disease. Druginduced weight gain also should be considered. Common causes include medications for diabetes (insulin, sulfonylureas, thiazolidinediones), steroid hormones, antipsychotic agents (clozapine, olanzapine, risperi done), mood stabilizers (lithium), antidepressants (tricyclics, mono amine oxidase inhibitors, paroxetine, mirtazapine), and antiepileptic drugs (valproate, gabapentin, carbamazepine). Other medications, such as nonsteroidal anti-inflammatory drugs and calcium channel blockers, may cause peripheral edema but do not increase body fat. The patient’s current diet and physical activity patterns may reveal factors that contribute to the development of obesity and may identify behaviors to target for treatment. Physical fitness and sedentary lifestyle, in

particular, are important predictors of all-cause mortality rate inde pendent of BMI and body composition, which highlights the importance of taking a physical activity and exercise history during examination as well as emphasizing physical activity as a treatment approach. Inquiring about sleep health that addresses regularity, duration, efficiency, and satisfaction is also important. Although the mechanisms are uncertain, sleep deprivation is associated with metabolic alterations in appetite regulation, sympathetic nervous system overactivity, insulin sensitivity, and changes in circadian rhythm. Stress may also contribute to obesity, in part due to activation of the adrenal cortical axis and elevated cortisol levels and its impact on emotional health and behav iors. This historic information is best obtained by the combination of a questionnaire and an interview.

TABLE 414-1 Classification of Weight Status and Disease Risk BODY MASS INDEX (kg/m2) OBESITY CLASS DISEASE RISK CLASSIFICATION Underweight <18.5 — — Healthy weight 18.5–24.9 — — Overweight 25.0–29.9 — Increased Obesity 30.0–34.9 I High Obesity 35.0–39.9 II Very high Extreme obesity ≥40 III Extremely high Source: Reproduced with permission from WHO Consultation on Obesity (1997): Geneva, Switzerland), World Health Organization; 1997. BMI and Waist Circumference Three key anthropometric mea surements are important in evaluating the degree of obesity: weight, height, and waist circumference. The BMI, calculated as weight (kg)/ height (m)2 or as weight (lb)/height (in)2 × 703, is used to classify weight status and risk of disease (Table 414-1). BMI is correlated with body fat and is related to disease risk. Lower BMI thresholds for overweight and obesity have been proposed for the Asia-Pacific region since this population appears to be at risk for glucose and lipid abnor malities at lower body weights. The problem with BMI is that it only measures the size of an individual. It does not measure body composi tion, distribution of body fat, health, quality of life, or any individual characteristics. BMI has many limitations but is still useful for screen ing and as a population estimate of increased morbidity and mortality. Currently, direct measurement of excess body fat is not universally practical in the clinical setting. Excess abdominal fat, assessed by measurement of waist circumfer ence or waist-to-hip ratio, is independently associated with a higher risk for metabolic syndrome, diabetes mellitus, and cardiovascular dis ease. Measurement of the waist circumference is a surrogate for visceral adipose tissue and should be performed in the horizontal plane above the iliac crest in individuals with a BMI ≤35 kg/m2 (Table 414-2). Obesity-Associated Complications and Comorbid Conditions

The evaluation of complications and comorbid conditions should be based on presentation of symptoms, risk factors, and index of suspicion. For all patients, a fasting lipid profile (total, low-density lipoprotein, and high-density lipoprotein cholesterol and triglyceride levels), chemistry panel, and glycated hemoglobin should be per formed, and blood pressure determined. Symptoms and diseases that are directly or indirectly related to obesity are listed in Table 414-3. TABLE 414-2 Ethnic-Specific Cutpoint Values for Waist Circumference ETHNIC GROUP WAIST CIRCUMFERENCE Europeans Men

> 94 cm (>37 in) Women 80 cm (>31.5 in) South Asians and Chinese Men 90 cm (>35 in) Women 80 cm (>31.5 in) Japanese Men 85 cm (>33.5 in) Women 90 cm (>35 in) Ethnic South and Central Americans Use South Asian recommendations until more specific data are available. Sub-Saharan Africans Use European data

> until more specific data are available. Eastern Mediterranean and Middle Eastern (Arab) populations Use European data until more specific data are available. Source: Reproduced with permission from KG Alberti, P Zimmet, J Shaw; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome-a new worldwide definition. Lancet 366:1059, 2005.

TABLE 414-3 Obesity-Related Organ Systems Review Cardiovascular Respiratory Hypertension Dyspnea Congestive heart failure Obstructive sleep apnea Cor pulmonale Hypoventilation syndrome Varicose veins Pickwickian syndrome Pulmonary embolism Asthma Coronary artery disease Gastrointestinal Endocrine Gastroesophageal reflux disease Metabolic syndrome Nonalcoholic fatty liver disease Type 2 diabetes Cholelithiasis Dyslipidemia Hernias Polycystic ovarian syndrome Colon cancer Musculoskeletal Genitourinary Hyperuricemia and gout Urinary stress incontinence Immobility Obesity-related glomerulopathy Osteoarthritis (knees and hips) Hypogonadism (male) Low back pain Breast and uterine cancer Carpal tunnel syndrome Pregnancy complications Psychological Neurologic Depression/low self-esteem Stroke Body image disturbance Idiopathic intracranial hypertension Social stigmatization Meralgia paresthetica Integument Dementia Striae distensae Stasis pigmentation of legs Lymphedema Cellulitis Intertrigo, carbuncles Acanthosis nigricans Acrochordons (skin tags) Hidradenitis suppurativa Stage 0 No complications BMI ≥25 BMI ≥25 BMI ≥30 BMI 25–29.9 BMI Secondary Tertiary Tertiary Prevent complications Treat complications Treat complications Treatment/ prevention Lifestyle Lifestyle Lifestyle Consider medication Plus medication consider surgery Suggested therapy • Metabolically healthy obese • No biomechanical complications Examples FIGURE 414-1 Staging the severity of obesity using the American Association of Clinical Endocrinology clinical practice guidelines. AHI, apnea-hypopnea index; BMI, body mass index; NASH, nonalcoholic steatohepatitis; OSA, obstructive sleep apnea; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index (a patientreported outcome measure for osteoarthritis registering pain, stiffness, and function). (Data from WT Garvey et al: American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocr Pract 22(Suppl 3):1, 2016.)

Although individuals vary, the number and severity of organ-specific complications and comorbid conditions usually rise with increasing levels of obesity.

Identifying the High-Risk Patient Efforts are under way to develop more practical and useful assessments to identify patients who are at high risk in addition to using BMI alone. Analogous to other staging systems commonly used for congestive heart failure or chronic kidney disease, the American Association of Clinical Endocrinology (AACE) and the American College of Endocrinology (ACE) guide lines advocate a simple and clinically useful obesity disease staging system that is based on ethnic-specific BMI cutoffs in conjunction with assessment for adiposity-related complications (Fig. 414-1). Stage 0 is assigned to individuals who are overweight or have obesity by BMI classification but have no complications, whereas stages 1 and 2 are defined as individuals who are overweight or have obesity by BMI classification and have one or more mild-moderate complications (stage 1) or at least one severe complication (stage 2). A different func tional staging system for obesity, called the Edmonton Obesity Staging System (EOSS), classifies individuals with obesity into five graded categories (0–4), based on their morbidity and health-risk profile along

three domains—medical, functional, and psychological. In this system, staging occurs independent of BMI. Evaluation and Management of Obesity CHAPTER 414 Assessing the Patent's Readiness to Change An attempt to initiate lifestyle changes when the patient is not ready usually leads to frustration and may hamper future weight-loss efforts. Assessment includes patient motivation and support, stressful life events, psychi atric status, time availability and constraints, and appropriateness of goals and expectations. Readiness can be viewed as the balance of two opposing forces: (1) motivation, or the patient's desire to change; and (2) resistance, or the patient's barriers to change. A helpful method to begin a readiness assessment is to use the motivational interviewing technique of "anchoring" the patient's interest and confidence to change on a numerical scale. With this technique, the patient is asked to rate—on a scale from 0 to 10, with 0 being not so important (or confident) and 10 being very important (or confident)—their level of interest in and confidence about engaging in Stage 1 Stage 2 Mild-moderate complications Severe complications • Pre-hypertension • Hepatic steatosis • OSA with AHI 5–30 and mild symptoms • Osteoarthritis with WOMAC score 1–5 • Prediabetes • Metabolic syndrome • Type 2 diabetes • NASH • Hypertension • OSA with symptoms or AHI >30 • Osteoarthritis with WOMAC score 5–10 or knee replacement surgery

weight management at this time. This exercise helps establish readiness to change and also serves as a basis for further dialogue.

TREATMENT Obesity THE GOAL OF THERAPY The primary goals of treatment are to improve obesity-related com plications and comorbid conditions and quality of life and reduce the risk of developing future obesity-related complications. Infor mation obtained from the history, physical examination, and diag nostic tests is used to determine risk and develop a treatment plan. The decision of how aggressively to treat the patient and which modalities to employ is determined by using shared decision-mak ing that includes the patient's risk status, expectations and personal values, and available resources. Not all patients who are deemed to have obesity by BMI screening need to be treated, since BMI alone is an imperfect measurement of the disease of obesity. How ever, patients who present with obesity-related complications and comorbidities and who would benefit from weight-loss intervention should be managed proactively. Therapy for obesity always begins with lifestyle management and may include pharmacotherapy or bariatric surgery, depending on BMI risk category (Table 414-4). Setting an initial weight-loss goal of 8–10% over 6 months is a realistic and practical target. PART 12 Endocrinology and Metabolism LIFESTYLE MANAGEMENT Obesity care involves attention to three essential elements of life style: dietary habits, physical activity, and behavior modification. Because obesity is fundamentally a disease of energy imbalance, all patients must learn how and when energy is consumed (diet), how and when energy is expended (physical activity), and how to incor porate this information into their daily lives (behavioral therapy). Lifestyle management has been shown to result in a modest (typically 3–5 kg) weight loss when compared with no treatment or usual care. Diet Therapy The primary focus of diet therapy is to reduce overall calorie consumption. Guidelines from the American Heart Association/American College of Cardiology/The Obesity Society (AHA/ACC/TOS) recommend initiating treatment with a calorie deficit of 500–750 kcal/d compared with the patient's habitual diet. Alternatively, a diet of 1200–1500 kcal/d for women and 1500–1800 kcal/d for men (adjusted for the individual's body weight) can be prescribed. This reduction is consistent with a goal of losing ~1–2 lb/week. The calorie deficit can be instituted through dietary substitutions or alternatives. Examples include choosing smaller portion sizes, eating more fruits and vegetables,

consuming more whole-grain cereals, selecting leaner cuts of meat and skimmed dairy products, reducing consumption of fried foods and other foods with added fats and oils, and drinking water instead of sugar-sweetened beverages. It is important that dietary counseling remains patient centered and that the selected goals are SMART (specific, measurable, agreed upon, realistic, timely). The macronutrient composition of the diet will vary with the patient's preference and medical condition. The 2020 U.S. Depart ment of Agriculture Dietary Guidelines for Americans (Chap. 343), which focus on health promotion and risk reduction, can be applied to treatment of patients who are overweight or have obesity. The TABLE 414-4 A Guide to Opting for Treatment for Obesity TREATMENT 25–26.9 27–29.9 30–34.9 35–39.9 ≥40 Diet, exercise, behavioral therapy With comorbidities With comorbidities + + + Pharmacotherapy — With comorbidities + + + Surgery — — — With comorbidities + Source: Reproduced from U.S. Department of Health and Human Services Public Health Service. National Institute of Health National Heart, Lung and Blood Institute. The Practical Guide Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. NIH Publication Number 00-4084. October 2000.

recommendations include maintaining a diet rich in whole grains, fruits, vegetables, and dietary fiber; decreasing sodium intake to <2300 mg/d; consuming fat-free or low-fat dairy products; and keeping added sugars and saturated fat intake to <10% of daily calo ries. Application of these guidelines to specific calorie goals can be found on the website www.choosemyplate.gov. Since portion control is one of the most difficult strategies for patients to manage, the use of preprepared products such as meal replacements is a simple and convenient suggestion. Examples include frozen entrees, protein shakes, and bars. Use of meal replacements in the diet has been shown to result in a 7–8% weight loss. Numerous randomized trials comparing diets of different mac ronutrient composition (e.g., low-carbohydrate, low-fat, Mediterra nean) have shown that weight loss depends primarily on reduction of total caloric intake and adherence to the prescribed diet, not the specific proportions of carbohydrate, fat, and protein in the diet. The macronutrient composition will ultimately be determined by the patient's taste preferences, cooking style, and culture. However, the patient's underlying medical problems are also important in guiding the recommended dietary composition. The dietary pre scription will vary according to the patient's metabolic profile and risk factors. A consultation with a registered nutritionist for medical nutrition therapy is particularly useful in considering patient pref erence and treatment of comorbid diseases. Another dietary approach to consider is based on the concept of energy density, which refers to the number of calories (i.e., amount of energy) a food contains per unit of weight. People tend to ingest a constant volume of food regardless of caloric or macronutrient content. Adding water or fiber to a food decreases its energy density by increasing weight without affecting caloric content. Examples of foods with low energy density include soups, fruits, vegetables, oat meal, and lean meats. Dry foods and high-fat foods such as pretzels, cheese, egg yolks, potato chips, and red meat have a high energy density. Diets containing low-energy-dense foods have been shown to control hunger and thus to result in decreased caloric intake and weight loss. Occasionally, very-low-calorie diets (VLCDs) are prescribed as a form of aggressive dietary therapy. The primary purpose of a VLCD is to promote a rapid and significant (13- to 23-kg) short-term weight loss over a 3- to 6-month period. The proprietary formulas designed for this purpose typically supply ≤800 kcal, 50–80 g of pro tein, and 100% of the recommended daily intake for vitamins and minerals. Indications for initiating a VLCD include the involvement of well-motivated individuals who have moderate to severe obesity, have failed at more conservative approaches to weight loss, and have a medical condition that would be immediately improved with rapid weight loss. These conditions

include poorly controlled type 2 diabetes, hypertriglyceridemia, obstructive sleep apnea, and symp tomatic peripheral edema. In the DiRECT trial of patients with type 2 diabetes and obesity, a low-energy formula diet (825–853 kcal/d) was administered for 3 months following by a structured monthly program. At 12 months, almost half of the participants achieved remission to a nondiabetic state off of all antidiabetic drugs. Use of formula diets should be prescribed by trained practitioners in a medical care setting where medical monitoring and high-intensity lifestyle intervention can be provided. Physical Activity Therapy Although exercise alone is only moderately effective for weight loss, the combination of dietary BMI CATEGORY (kg/m2)

modification and exercise is the most effective behavioral approach for the treatment of obesity. The most important role of exercise appears to be in the maintenance of weight loss. The 2018 Physical Activity Guidelines for Americans (www.health.gov/paguidelines) recommend that adults should engage in 150 min of moderateintensity or 75 min a week of vigorous-intensity aerobic physical activity per week, preferably spread throughout the week. Focusing on simple ways to add physical activity into the normal daily rou tine through leisure activities, travel, and domestic work should be suggested. Examples include brisk walking, using the stairs, doing housework and yard work, and engaging in sports. Additionally, it is important to reduce sedentary behavior, which is associated with all-cause and cardiovascular disease mortality in adults. Asking the patient to use a wearable activity tracker to monitor total accumula tion of steps or kcal expended as part of the activities of daily living is a useful strategy. Step counts are highly correlated with activity level. Studies have demonstrated that lifestyle activities are as effec tive as structured exercise programs for improving cardiorespira tory fitness and weight loss. A high level of physical activity (>300 min of moderate-intensity activity per week) is often needed to lose weight and sustain weight loss. These exercise recommendations are daunting to most patients and need to be implemented gradu ally. Consultation with an exercise physiologist or personal trainer may be helpful. Behavioral Therapy Cognitive behavioral therapy is used to help change and reinforce new dietary and physical activity behaviors. Strategies include self-monitoring techniques (e.g., journaling, weighing, and measuring food and activity); stress management; stimulus control (e.g., using smaller plates, not eating in front of the television or in the car); social support; problem solving; and cognitive restructuring to help patients develop more positive and realistic thoughts about themselves. When recommending any behavioral lifestyle change, the patient should be asked to identify what, when, where, and how the behavioral change will be per formed. The patient should keep a record of the anticipated behav ioral change so that progress can be reviewed at the next office visit. Because these techniques are time consuming to implement, their supervision is often undertaken by ancillary office staff, such as an advanced practice provider or registered nutritionist. PHARMACOTHERAPY Adjuvant pharmacologic treatments should be considered for patients with a BMI ≥30 kg/m2 or a BMI ≥27 kg/m2 who have con comitant obesity-related diseases and for whom dietary and physi cal activity therapy has not been successful. When an antiobesity medication is prescribed, patients should be actively engaged in a lifestyle program that provides the strategies and skills needed to use the drug effectively since such support increases total weight loss. Medications for obesity have traditionally fallen into two major categories: those that affect appetite and those that inhibit gastro intestinal fat absorption. However, since the introduction of more effective nutrient-stimulated hormone-based therapeutics in 2021, an additional designation of first- and second-generation medica tions has been adopted. Antiobesity medications are approved by the U.S. Food and Drug Administration (FDA) with an indication for chronic weight management, with the exception of phentermine and other

sympathomimetics, which are only approved for shortterm use. The centrally active medications work biologically to suppress appetite, affecting hunger, satiety, and response to highly rewarding foods, and thus making it easier for patients to follow their dietary intentions to reduce caloric intake. In addition, one capsule that is considered a medical device was marketed in 2020. Characteristics of the currently approved antiobesity medications are shown in Table 414-5. First-Generation Centrally Acting Medications This class of medications directly targets neurotransmitters in the hypothalamus and reward centers in the central nervous system (Chap. 413) to affect satiety (feeling of fullness after a meal), hunger (the biologic

sensation that prompts eating), and craving (intense desire for a specific food). By controlling appetite, these agents help patients reduce caloric intake without a sense of deprivation. The classic sympathomimetic adrenergic agents (benzphetamine, phendimet razine, diethylpropion, and phentermine) function by stimulating norepinephrine release or by blocking its reuptake. Among these agents, phentermine is the most commonly prescribed; however, there is limited long-term data on its effectiveness. A 2002 review of six randomized, placebo-controlled trials of phentermine for weight control found that patients lost 0.6–6.0 additional kg of weight over 2–24 weeks of treatment. The most common side effects of the amphetamine-derived agents are restlessness, insomnia, dry mouth, constipation, and increased blood pressure and heart rate.

Evaluation and Management of Obesity CHAPTER 414 Phentermine/topiramate (PHEN/TPM) is a combination drug that contains a catecholamine releaser (phentermine) and an anti convulsant (topiramate). Topiramate is approved by the FDA as an anticonvulsant for the treatment of epilepsy and for the prophylaxis of migraine headaches. Weight loss was identified as an unintended side effect of topiramate during clinical trials for epilepsy. The mechanism responsible for weight loss is uncertain but is thought to be mediated through the drug’s modulation of γ-aminobutyric acid receptors, inhibition of carbonic anhydrase, and antagonism of glutamate. PHEN/TPM has undergone two 1-year pivotal ran domized, placebo-controlled, double-blind trials of efficacy and safety: EQUIP and CONQUER. In a third study, SEQUEL, 78% of CONQUER participants continued to receive their blinded treatment for an additional year. All participants received diet and exercise counseling. Mean percent weight loss for participants randomized to medication and placebo are displayed in Fig. 414-2. Intention-to-treat 1-year placebo-subtracted weight loss for PHEN/ TPM was 9.3% (15-mg/92-mg dose) and 6.6% (7.5-mg/46-mg dose), respectively, in the EQUIP and CONQUER trials. Clinical and statistical dose-dependent improvements were seen in selected cardiovascular and metabolic outcome measurements that were related to the weight loss. The most common adverse events experi enced by the drug-randomized group were paresthesias, dry mouth, constipation, dysgeusia, and insomnia. Because of an increased risk of congenital fetal oral-cleft formation from topiramate, women of childbearing age should have a negative pregnancy test before treatment and monthly thereafter and use effective contraception consistently during medication therapy. Naltrexone SR/bupropion SR (NB) is a combination of an opioid antagonist and a dopamine and norepinephrine reuptake inhibitor, respectively. Individually, naltrexone is approved by the FDA for the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids, whereas bupropion is approved as an antidepressant and smoking cessation aid. As a combination drug, each component works in consort: bupropion stimulates secretion of α-melanocyte-stimulating hormone (MSH) from proopiomelanocortin (POMC), whereas naltrexone blocks the feedback inhibitory effects of opioid receptors activated by the β-endorphin released in the hypothalamus, thus allowing the inhibitory

effects of MSH to reduce food intake. The medication has undergone three randomized, placebocontrolled, double-blind trials for efficacy and safety. Participants were randomized to receive NB (8 mg/90 mg two tablets bid) or placebo in the three COR studies. Whereas participants received standardized nutritional and exercise counseling in COR-I and COR-II, a more intensive behavior modification program was provided in COR-BMOD (Table 414-5). Intention-to-treat 1-year placebo-subtracted weight loss was 4.8%, 5.1%, and 4.2%, respec tively, in the COR-I, COR-II, and COR-BMOD trials. Clinical and statistical dose-dependent improvements were seen in selected car diovascular and metabolic outcome measurements that were related to the weight loss. However, the medication led to slight increases or smaller decreases in blood pressure and pulse than placebo. The most common adverse events experienced by the drug-randomized groups were nausea, constipation, headache, vomiting, dizziness, diarrhea, insomnia, and dry mouth.

TABLE 414-5 Antiobesity Medications DRUG CHARACTERISTIC PHENTERMINE ORLISTAT PHEN/TPM NAL/BUP LIRAGLUTIDE SEMAGLUTIDE TIRZEPATIDE Mechanism of action Sympathomimetic, increases norepinephrine release in CNS Gastrointestinal lipase enzyme inhibitor Phen: sympathomimetic in CNS; TPM: modulates GABA receptors in the CNS Route of administration, frequency, and dose Oral, once to 3 times daily, doses of 8, 15, 30, and 37.5 mg Oral, 3 times daily, within 1 h of fatcontaining meals Oral, once daily. Start 3.75/23 mg/d × 2 weeks, then 6.5/46 mg/d; can escalate to max dose of 15/2 mg/d PART 12 Endocrinology and Metabolism Percent weight loss (placebo subtracted)a 4.4% 4.1% 8.0% 5.1% 5.4% 12.5% 17.8% Most common adverse effects Dry mouth Insomnia Constipation Headache Dizziness Steatorrhea Increased defecation Oily spotting Liquid stool Fecal urgency Paresthesia Dry mouth Constipation Headache Insomnia Dizziness Contraindications Uncontrolled hypertension, untreated hyperthyroidism, within 14 d of MAOI use Chronic malabsorption Uncontrolled hypertension, untreated hyperthyroidism, history of glaucoma, calcium oxalate nephrolithiasis, within 14 d of MAOI use aBased on maximal dose. Abbreviations: CNS, central nervous system; GABA, γ-aminobutyric acid; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; MAOI, monoamine oxidase inhibitor; MEN, multiple endocrine neoplasia; Nal/Bup, naltrexone/bupropion; Phen/TPM, phentermine/topiramate; POMC, proopiomelanocortin; qW, every week. Liraglutide was the first glucagon-like peptide 1 receptor agonist (GLP-1 RA) with 97% homology to human GLP-1 that introduces nutrient-stimulated, hormone-based therapy for the treatment of obesity. In addition to its effect as an incretin hormone (glucoseinduced insulin secretion), liraglutide inhibits both gastric empty ing and glucagon secretion and stimulates GLP-1 receptors in the arcuate nucleus of the hypothalamus, the nucleus tractus solitarius of the brainstem, and projections to other appetite-modulating relay nuclei to reduce appetite. As a result of molecular modifications of the structure, liraglutide has reduced susceptibility to DPP-4 and can be dosed once daily by subcutaneous (SC) administration with a half-life of ~11–15 h. Liraglutide was initially approved for the treatment of type 2 diabetes in the United States in 2010 at doses up to 1.8 mg once daily. It was subsequently approved for obesity treatment at doses up to 3.0 mg once daily in 2014 for adults and, in 2020, for adolescents (aged ≥12 years). Specifically targeting obesity, liraglutide has undergone five ran domized, double-blind, placebo-controlled trials in adults called SCALE (Satiety and Clinical Adiposity–Liraglutide Evidence) involving >5000 adult participants to evaluate its efficacy and safety for weight management. All participants received diet and physi cal activity counseling and were randomized to receive liraglutide (3.0 mg SC daily) or placebo with the primary outcome of change in body weight. Intention-to-treat 1-year placebo-subtracted weight loss for these trials ranged from 3.4 to 6.1%. Clinical and statistical dose-dependent improvements were seen in selected cardiovascular

Nal: blocks opioidmediated POMC autoinhibition; bup: activates POMC in the hypothalamus GLP-1 receptor agonist GLP-1 receptor agonist GLP-1/GIP dual receptor agonist Oral, 1 tablet (8 mg/90 mg) qAM × 1 week; 1 tablet in morning and evening × 1 week; 2 tablets in morning and 1 tablet in evening × 1 week; then 2 tablets in morning and 2 tablets in evening Subcutaneous, once daily; initiate at 0.6 mg/d × 1 week; increase by 0.6 mg weekly to 3 mg/d Subcutaneous, once weekly; 0.25 mg qW × 4 weeks, then 0.5 mg qW × 4 weeks, then 1 mg qW × 4 weeks, then 1.7 mg qW × 4 weeks, then 2.4 mg qW Subcutaneous, once weekly; 2.5 mg qW × 4 weeks, then 5 mg qW × 4 weeks, then 7.5 mg qW × 4 weeks, then 10 mg qW × 4 weeks, then 12.5 mg qW, then 15 mg qW Nausea Constipation Headache Vomiting Dizziness Insomnia Nausea Diarrhea Constipation Dyspepsia Vomiting Nausea Diarrhea Constipation Dyspepsia Vomiting Nausea Diarrhea Constipation Abdominal pain Uncontrolled hypertension, history of seizures, bulimia or anorexia nervosa, within 14 d of MAOI use, long-term opioid use Personal or family history of medullary thyroid cancer, MEN type 2; pancreatitis is a caution Personal or family history of medullary thyroid cancer; MEN type 2; pancreatitis is a caution Personal or family history of medullary thyroid cancer, MEN type 2; pancreatitis is a caution and metabolic outcome measurements. In SCALE TEENS, which involved adolescents with obesity (average age 14.6 years), the liraglutide-treated group demonstrated a placebo-subtracted weight loss of 5%. The most common adverse events from the SCALE tri als were nausea, diarrhea, constipation, and vomiting, which were reported as mild and transient. GLP-1 agonists should not be pre scribed in patients with a family or personal history of medullary thyroid cancer or multiple endocrine neoplasia. Setmelanotide is a melancortin-4 (MC4) receptor agonist that was FDA approved in 2020 for daily SC administration for chronic weight management in adults and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to BardetBiedl syndrome (BBS) or POMC, proprotein convertase subtilisin/ kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency. The medication addresses the underlying hyperphagia and specific molecular mechanism of these rare genetic diseases. The most common side effects include injection site reactions, skin hyperpig mentation, nausea, and spontaneous penile erections. First-Generation Peripherally Acting Medication Orlistat is cur rently the only medication in this class. It is a synthetic hydroge nated derivative of a naturally occurring lipase inhibitor, lipostatin, that is produced by the mold Streptomyces toxytricini. This drug is a potent, slowly reversible inhibitor of pancreatic, gastric, and carboxylester lipases and phospholipase A2, which are required for the hydrolysis of dietary fat into fatty acids and monoacylglycerols.

Orlistat Phen/TPM NB Lira Sema TZP 24.3

Percent weight loss

10.4 10.9 10.2

8.8 6.1 5.8 6.5 6.1

1.9 1.3 1.2 1.6

Davidson CONQUER COR-I COR-II COR-BMOD Sjostrom EQUIP FIGURE 414-2 One-year mean weight loss for antiobesity medications compared to placebo. Lira, liraglutide; NB, naltrexone/bupropion; Phen/TPM, phentermine/ topiramate; Sema, semaglutide; TZP, tirzepatide. Orlistat acts in the

lumen of the stomach and small intestine by forming a covalent bond with the active site of these lipases. Taken at a therapeutic dose of 120 mg tid, orlistat blocks the digestion and absorption of ~30% of dietary fat. After discontinuation of the drug, fecal fat content usually returns to normal within 48–72 h. Multiple randomized, double-blind, placebo-controlled studies have shown an intention-to-treat 1-year placebo-subtracted weight loss of 2.7–4.1%. Because orlistat is minimally (<1%) absorbed from the gastrointestinal tract, it has no systemic side effects. Tolerability is related to the malabsorption of dietary fat, and this is generally diminished as patients control their dietary fat intake. Because serum concentrations of the fat-soluble vitamins D and E and β-carotene may be reduced by orlistat treatment, vitamin supple ments are recommended to prevent potential deficiencies. Orlistat was approved for over-the-counter use in 2007. Second-Generation Medications Semaglutide is generally recog nized as the first drug in this category based on its greater weight loss efficacy and further chemical modification that allows for once-weekly SC administration with a longer half-life. Semaglutide was initially approved for the treatment of type 2 diabetes in the United States at doses up to 1.0 mg once weekly in 2017 and at 2.0 mg once weekly in 2022. It was subsequently approved at doses up to 2.4 mg once weekly for chronic weight management for adults in 2021 and for adolescents in 2022. Semaglutide has undergone multiple prospective, randomized, placebo-controlled trials in the STEP (Semaglutide Treatment Effect in People with Obesity) program that was designed to inves tigate the effect of semaglutide 2.4 mg SC weekly versus placebo on weight loss, safety, and tolerability in adults with obesity or over weight. Intention-to-treat placebo-subtracted weight loss for the STEP 1 to 4 trials ranged from 6.2 to 14.8% at 68 weeks depending on the population and study design, and loss of 12.6% occurred after 104 weeks for STEP 5. Clinical and statistical dose-dependent improvements were seen in selected cardiovascular and metabolic outcome measurements. The most common adverse effects include nausea, diarrhea, constipation, and vomiting. GLP-1 RAs should

Drug Placebo 20.9 17.4 Evaluation and Management of Obesity CHAPTER 414

11.3 9.3

5.7 5.1 4.5 3.1 2.6 2.4 SCALE MAIN SCALE STEP 1 STEP 3 STEP 4 SURMOUNT-1 SURMOUNT-3 not be prescribed in patients with a family or personal history of medullary thyroid cancer or multiple endocrine neoplasia. In the STEP TEENS trial, adolescents with overweight or obesity randomized to semaglutide 2.4 mg achieved a 16.1% reduction in BMI versus a 0.6% increase for placebo. The recent SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial demonstrated a 20% reduction in major adverse cardiovascular events in patients with preexisting cardiovascular disease and overweight or obesity but without dia betes who were randomized to semaglutide 2.4 mg versus placebo, and the STEP-HFpEF trial observed improved heart failure–related symptoms, physical limitations, and exercise function and reduced body weight and inflammation in patients randomized to semaglu tide versus placebo. Tirzepatide is the first long-acting, weekly, injectable, dual GLP-1/ gastric inhibitory polypeptide (GIP) peptide analogue, engineered from the native GIP sequence with agonist activity at both the GLP-1 and GIP receptors with a half-life of ~117 h. Whereas GIP receptor agonism is equal to native GIP, the molecule’s GLP-1 recep tor affinity is approximately five times weaker than native GLP-1. GIP in the brain appears to act synergistically with GLP-1 recep tor activation to allow greater weight loss. Tirzepatide was FDA approved for type 2 diabetes in 2022 and subsequently approved for chronic weight management in adults in 2023, at 5-, 10-, and 15-mg doses. Tirzepatide has undergone

multiple prospective, randomized, placebo-controlled trials in the SURMOUNT clinical development program that was designed to investigate the effect of tirzepatide 5-, 10-, and 15-mg SC weekly doses versus placebo on weight loss, safety, and tolerability in adults with obesity or overweight. Intention-to-treat placebo-subtracted weight loss for SURMOUNT 1 to 4 trials at the 15-mg dose ranged from 11.6 to 21.4% depend ing on the study population and design. Clinical and statistical dose-dependent improvements were seen in selected cardiovascular and metabolic outcome measurements. Similar to GLP-1 RAs, the most common adverse events are gastrointestinal (nausea, diarrhea,

constipation, and vomiting) and reported as mild and transient; tirzepatide should not be prescribed in patients with a family or personal history of medullary thyroid cancer or multiple endocrine neoplasia.

Oral Device Gelesis100 is a nonsystemic, water-soluble gel that was approved by the FDA in 2019. In the stomach, the capsule releases the cellulose microgel, which absorbs water and forms a matrix with the consistency of food, occupying ~25% of the stomach. In the large intestine, it is broken down by enzymes and the cellulose is excreted. Gelesis100 and placebo were evaluated over 24 weeks in patients with BMI of 27 to ≤40 kg/m2 and fast ing plasma glucose of 90–145 mg/dL. Intention-to-treat, 24-week, placebo-subtracted weight loss was 2.1% (6.4 vs 4.4%). Gelesis100 treatment had no apparent increased safety risks. The capsules are approved for patients with a BMI of ≥25 kg/m2, with or without comorbidities. SURGERY Bariatric surgery (Fig. 414-3) can be considered for patients with severe obesity (BMI ≥40 kg/m2) or for those with moderate obesity (BMI ≥35 kg/m2) associated with a number of comorbid conditions. The clinical benefits of bariatric surgery in achieving weight loss and alleviating metabolic complications and comorbidities have been attributed largely to changes in the physiologic responses of gut hormones, bile acid metabolism, the microbiota, and adipose tissue metabolism. Metabolic effects resulting from bypassing the foregut include altered responses of ghrelin, GLP-1, peptide YY3-36, and oxyntomodulin. Additional effects on food intake and body weight control may be attributed to changes in vagal signaling. The loss of fat mass, particularly visceral fat, is associated with multiple meta bolic, adipokine, and inflammatory changes that include improved insulin sensitivity and glucose disposal; reduced free fatty acid flux; increased adiponectin levels; and decreased interleukin 6, tumor necrosis factor α, and high-sensitivity C-reactive protein levels. PART 12 Endocrinology and Metabolism A B x x D E C FIGURE 414-3 Bariatric surgical procedures. Examples of operative interventions used for surgical manipulation of the gastrointestinal tract. A. Laparoscopic adjustable gastric banding. B. Laparoscopic sleeve gastrectomy. C. The Roux-en-Y gastric bypass. D. Biliopancreatic diversion with duodenal switch. E. Biliopancreatic diversion.

Restrictive surgeries limit the amount of food the stomach can hold and slow the rate of gastric emptying. Laparoscopic adjustable gastric banding is the prototype of this category. The first banding device was approved for use in the United States in 2001. In con trast to previous devices, this band has a diameter that is adjustable by way of its connection to a reservoir that is implanted under the skin. Injection of saline into the reservoir and removal of saline from the reservoir tighten and loosen the band’s internal diameter, respectively, thus changing the size of the gastric opening. Although the mean percentage of total body weight lost at 5 years is estimated at 20–25%, longer-term follow-up has been more disappointing, leading to near abandonment of the procedure. In the laparoscopic sleeve gastrectomy, the stomach is restricted by stapling and dividing it vertically, removing ~80% of the greater curvature and leaving a slim banana-shaped

remnant stomach along the lesser curvature. Weight loss after this procedure is superior to that after laparo scopic adjustable gastric banding. The three restrictive-malabsorptive bypass procedures combine the elements of gastric restriction and selective malabsorption: Roux-en-Y gastric bypass, biliopancreatic diversion, and biliopan creatic diversion with duodenal switch (Fig. 414-3). These proce dures are routinely performed by laparoscopy. These procedures generally produce a 28–33% average total body weight loss at 12–18 months followed by variable weight recurrence. Significant improvement in multiple obesity-related comorbid conditions, including type 2 diabetes, hypertension, dys lipidemia, obstructive sleep apnea, quality of life, and long-term cardiovascular events, has been reported. A meta-analysis of con trolled clinical trials comparing bariatric surgery versus no surgery showed that surgery was associated with a reduced odds ratio (OR) risk of global mortality (OR = 0.55), cardiovascular death (OR = 0.58), and all-cause mortality (OR = 0.70). Among the observed improvements in comorbidities, the pre vention and treatment of type 2 diabetes resulting from bariatric z y z 150 cm y 100 cm

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