JAMA | Review

Obesity Management in Adults
A Review

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IMPORTANCE Obesity affects approximately 42% of US adults and is associated with increased rates of type 2 diabetes, hypertension, cardiovascular disease, sleep disorders, osteoarthritis, and premature death.

OBSERVATIONS A body mass index (BMI) of 25 or greater is commonly used to define overweight, and a BMI of 30 or greater to define obesity, with lower thresholds for Asian populations (BMI ≥25-27.5), although use of BMI alone is not recommended to determine individual risk. Individuals with obesity have higher rates of incident cardiovascular disease. In men with a BMI of 30 to 39, cardiovascular event rates are 20.21 per 1000 person-years compared with 13.72 per 1000 person-years in men with a normal BMI. In women with a BMI of 30 to 39.9, cardiovascular event rates are 9.97 per 1000 person-years compared with 6.37 per 1000 person-years in women with a normal BMI. Among people with obesity, 5% to 10% weight loss improves systolic blood pressure by about 3 mm Hg for those with hypertension, and may decrease hemoglobin A_{1c} by 0.6% to 1% for those with type 2 diabetes. Evidence-based obesity treatment includes interventions addressing 5 major categories: behavioral interventions, nutrition, physical activity, pharmacotherapy, and metabolic/bariatric procedures. Comprehensive obesity care plans combine appropriate interventions for individual patients. Multicomponent behavioral interventions, ideally consisting of at least 14 sessions in 6 months to promote lifestyle changes, including components such as weight self-monitoring, dietary and physical activity counseling, and problem solving, often produce 5% to 10% weight loss, although weight regain occurs in 25% or more of participants at 2-year follow-up. Effective nutritional approaches focus on reducing total caloric intake and dietary strategies based on patient preferences. Physical activity without calorie reduction typically causes less weight loss (2-3 kg) but is important for weight-loss maintenance. Commonly prescribed medications such as antidepressants (eg, mirtazapine, amitriptyline) and antihyperglycemics such as glyburide or insulin cause weight gain, and clinicians should review and consider alternatives. Antiobesity medications are recommended for nonpregnant patients with obesity or overweight and weight-related comorbidities in conjunction with lifestyle modifications. Six medications are currently approved by the US Food and Drug Administration for long-term use: glucagon-like peptide receptor 1 (GLP-1) agonists (semaglutide and liraglutide only), tirzepatide (a glucose-dependent insulinotropic polypeptide/GLP-1 agonist), phentermine-topiramate, naltrexone-bupropion, and orlistat. Of these, tirzepatide has the greatest effect, with mean weight loss of 21% at 72 weeks. Endoscopic procedures (ie, intragastric balloon and endoscopic sleeve gastroplasty) can attain 10% to 13% weight loss at 6 months. Weight loss from metabolic and bariatric surgeries (ie, laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass) ranges from 25% to 30% at 12 months. Maintaining long-term weight loss is difficult, and clinical guidelines support the use of long-term antiobesity medications when weight maintenance is inadequate with lifestyle interventions alone.

CONCLUSION AND RELEVANCE Obesity affects approximately 42% of adults in the US. Behavioral interventions can attain approximately 5% to 10% weight loss, GLP-1 agonists and glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonists can attain approximately 8% to 21% weight loss, and bariatric surgery can attain approximately 25% to 30% weight loss. Comprehensive, evidence-based obesity treatment combines behavioral interventions, nutrition, physical activity, pharmacotherapy, and metabolic/bariatric procedures as appropriate for individual patients.

JAMA. 2023;330(20):2000-2015. doi:10.1001/jama.2023.19897

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Section Editor: Mary McGrae McDermott, MD, Deputy Editor.

Obesity, currently defined as a body mass index (BMI) of 30 or greater, affects 800 million people worldwide.[1] In the United States, approximately 42% of adults have obesity,[2] and obesity-related costs are estimated at $173 billion annually.[3] Obesity is a chronic disease defined by excess adiposity with structural and functional consequences resulting in increased risk of comorbidities and premature mortality.[4,5] Obesity is often associated with stigma, which impairs quality of life and increases morbidity.[6] Obesity bias contributes to decreased use of preventive cancer screenings among patients with obesity, particularly in women.[7] Weight loss improves glucose, lipids, blood pressure, and obesity-related comorbidities,[4,5,8] and clinicians can offer multiple effective obesity treatments.[9-11] This Review summarizes current evidence regarding the pathophysiology, diagnosis, and treatment of obesity.

Methods

We reviewed 9 clinical practice guidelines from relevant medical associations published in the last 10 years.[4-6,9-14] We then conducted a PubMed search on March 1, 2023, which identified 2418 obesity-related systematic reviews and meta-analyses published since 2018. We performed 3 additional PubMed searches on March 6, 2023, to identify systematic reviews of antiobesity medications published since 2018 (127 articles), clinical practice guidelines for obesity published since 2018 (135 articles), and randomized clinical trials (RCTs) published since 2021 on glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonists to identify studies of newer medications (210 articles). We reviewed high-quality studies referenced in these articles as well as policy guidelines released during the writing of this article. A total of 126 articles were selected for this Review, consisting of 26 RCTs, 29 meta-analyses/systematic reviews, 14 longitudinal/population-based studies, 15 clinical practice guidelines, 4 policy guidelines, 2 cross-sectional studies, 2 study/intervention descriptions, and 34 narrative reviews. Highest-quality articles and those most relevant to general medical practice were prioritized for inclusion.

Epidemiology

The prevalence of obesity worldwide increased between 1975 and 2014 from 3.2% to 10.8% in men and from 6.4% to 14.9% in women.[15] By 2025, it is anticipated that 18% of men and 21% of women worldwide will have obesity.[15] The prevalence of obesity in the US is higher: 17.4% of non-Hispanic Asian (22.4% using Asian-specific cutoffs[16]), 49.6% of non-Hispanic Black, 44.8% of Hispanic, and 42.2% of non-Hispanic White adults have obesity.[2] It is anticipated that by 2030, 48.9% of US adults will have obesity and that racial differences in rates of obesity will increase.[17] The World Health Organization Acceleration Plan to Stop Obesity, adopted in 2022, outlines multisectoral policies, including taxes on sugar-sweetened beverages and subsidies to promote healthy diets, school nutrition reforms, and reductions in physical inactivity, with the goal of attaining a major reduction in obesity by 2030.[1]

Risk Factors

Obesity reflects a chronic energy imbalance, with greater calorie consumption than energy expenditure,[18] and is influenced by multiple factors. Genetic variants are implicated in its development.[19] Most forms of obesity have polygenic risk factors with several variants strongly associated with BMI, while obesity due to a single gene variant is rare.[19] The environment influences the relationship between genetics and obesity risk.[19] Adverse workplace, school, social, and home environments, known as "obesogenic environments," affect physical and social structures.[20] For example, greater availability of fast-food restaurants, poor neighborhood walkability, and perceived safety risks can limit physical activity and healthy food options.[20] There is a bidirectional association between depression and obesity, wherein each diagnosis is associated with increased risk of developing the other.[21] Additional risks include insufficient sleep and low socioeconomic status, in part mediated by chronic stress and food insecurity, which are commonly experienced by racial and ethnic minority populations.[22]

Pathophysiology of Obesity

Influenced by genetic expression, energy homeostasis is determined by feedback between circulating neuropeptide hormones and the central nervous system.[19,23] The gut-brain axis responds to peripheral signals from the gastrointestinal tract, adipose tissue, and circulating hormones to stimulate or inhibit central neurons based on satiety or hunger.[24] Dysregulation of this system develops in obesity, often leading to increased hunger and decreased satiety.[18] Hormones involved in this process include leptin and ghrelin.[18] Additionally, hormone response and metabolic adaptation promote weight regain.[18]

Obesity increases rates of comorbid conditions through pathophysiologic and mechanical changes related to excess adiposity and increased weight.[23,24] Related conditions include asthma, type 2 diabetes, hypertension, obstructive sleep apnea, osteoarthritis, and cardiovascular disease (CVD).[4,5] Compared with normal BMI, obesity is associated with higher rates of incident CVD events, eg, in a pooled cohort of adults aged 40 to 59 years with 856 523 person-years of follow-up, cardiovascular event rates were 20.21 per 1000 person-years in men with a BMI of 30 to 39.9 compared with 13.72 per 1000 person-years in men with a normal BMI.[25] Cardiovascular event rates were 9.97 per 1000 person-years in women with a BMI of 30 to 39.9 compared with 6.37 per 1000 person-years in women with a normal BMI.[25] Even among patients with obesity without other CVD risk factors, the long-term incidence of CVD is increased compared with people without obesity.[26] Weight-related cardiometabolic abnormalities occur due to excess visceral adipose tissue (and possibly an impaired ability to deposit fat into the peripheral adipose tissue such as the gluteofemoral fat compartment), which secretes hormones and proinflammatory cytokines, leading to low-grade systemic inflammation.[23,24,27] Lipid deposition into adipose tissue and occurrence of adiposity leads to anatomical changes such as increased pharyngeal soft tissue, contributing to obstructive sleep apnea or mechanical joint load that results in osteoarthritis.[23]

Table 1. Evidence-Based Screening Recommendations for Weight-Related Comorbidities[4,6,14]

Comorbidities[a]	Screening method/diagnostic criteria
Asthma/respiratory disease	History, physical examination; spirometry as indicated
Diabetes	Fasting plasma glucose ≥126 mg/dL; hemoglobin A_{1c} ≥6.5%; 2-h oral glucose tolerance test
Dyslipidemia	Lipid panel that includes triglycerides, HDL-C, LDL-C, total cholesterol, and non-HDL-C
Gastroesophageal reflux disease	History; endoscopy as indicated
Hypertension	Sitting blood pressure ≥130/80 mm Hg
Metabolic syndrome	Three or more of the following: waist circumference ≥88 cm for women, ≥102 cm for men; triglycerides ≥150 mg/dL; fasting plasma glucose ≥100 mg/dL; blood pressure ≥130/85 mm Hg; HDL-C <40 mg/dL in men, <50 mg/dL in women
Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis	Liver function tests; consider calculation of Fibrosis-4 Index; imaging as indicated
Obstructive sleep apnea	Neck circumference, clinical screening questionnaires (eg, STOP-BANG score); polysomnography as indicated
Osteoarthritis	History, physical examination (eg, weight-bearing joints); radiography as indicated
Prediabetes	Fasting plasma glucose 100-125 mg/dL, hemoglobin A_{1c} 5.7%-6.4%, 2-h oral glucose tolerance test

Abbreviations: HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

SI conversions: To convert total, HDL-, LDL-, and non-HDL cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.

[a] The Association of Clinical Endocrinologists and the American College of Endocrinology guidelines also recommend screening for cardiovascular disease, polycystic ovary syndrome, female infertility, male hypogonadism, urinary stress incontinence, depression, anxiety, binge eating disorder, and stigmatization.[4] These should be evaluated as indicated or consider referral to a specialist.

Diagnosis and Classification of Obesity

Body mass index, calculated as weight in kilograms divided by height in meters squared, is most commonly used to classify obesity on a population level.[28] The World Health Organization uses BMI to define overweight (25-29.99), class I obesity (30-34.99), class II obesity (35-39.99), and class III obesity (≥40).[28] Among Asian populations, cardiometabolic diseases occur at lower BMI levels; therefore, some expert guidelines recommend lower BMI thresholds (guidelines differ in thresholds of BMI ≥25 and ≥27.5 for obesity).[4,9,11] Clinical use of BMI is controversial, as it does not directly measure adiposity or account for individual differences in risk; therefore, additional measures can be used.[29] For example, waist circumference is a marker of visceral adiposity associated with increased cardiometabolic risk,[4,5] and guidelines recommend risk stratification based on waist circumference (≥102 cm for men and ≥88 cm for women) in patients with a BMI of 25 to 34.9.[4-6] The Edmonton Obesity Staging System classifies risk based on several factors independent of BMI[6]; higher severity scores are associated with increased all-cause mortality (hazard ratio, 2.69; 95% CI, 1.98-3.67).[30]

Screening for secondary causes of obesity may be considered based on history and physical examination, including hormonal abnormalities (eg, hypothyroidism, hypercortisolism), psychiatric diagnoses (eg, binge eating disorder), iatrogenic obesity (eg, medications), and genetic syndromes (eg, proopiomelanocortin deficiency).[4] Assessment for weight-related comorbidities such as nonalcoholic fatty liver disease or obstructive sleep apnea (**Table 1**) is important to guide referrals and treatment.[4,14]

Patient-Centered Approach to Obesity Care

Evidence-based counseling strategies can help initiate treatment discussions with patients. For example, the 5As[6] (Assess, Advise, Agree, Assist, Arrange) can guide shared decision-making (**Figure**), and visits that use this approach are covered by Medicare for obesity. The clinician should begin by asking permission to talk to the patient about their weight and which terms the patient would prefer (ie, *unhealthy weight*, *elevated BMI*, *overweight*).[34] Each "A" can occur when appropriate during the clinician-patient discussion and/or over several visits, and each additional counseling step is associated with increased patient motivation to lose weight (odds ratio, 1.31; 95% CI, 1.11-1.55).[35] Patients are also more likely to lose weight when clinicians communicate using a supportive, nonjudgmental approach.[36]

Establishing a supportive environment for patients with obesity can be facilitated with examination tables and chairs that accommodate all body sizes.[37] Staff training on obesity and bias may improve the patient experience, including asking patients' permission to be weighed and providing alternatives including weighing in a private room or self-report of weight.[37] Given disparities in obesity prevalence by race, ethnicity, and income,[17] equitable access to obesity treatment must be considered.[38] Clinicians should be aware of health insurance coverage, governmental nutrition programs, social determinants of health, psychosocial stressors, and weight and racial discrimination when treating obesity.[38]

Weight-Loss Goals

Setting personal weight-loss targets can increase the rate of achieving at least 10% weight loss at 12 months compared with not setting goals (68.2% vs 31.8% in a study of 24 447 patients with obesity).[39] Weight-loss goals should be individualized to patient preference, body composition, and comorbidities.[5,8] A 5% weight loss may reduce systolic and diastolic blood pressure by 3 mm Hg and 2 mm Hg among those with hypertension, respectively; 5% to 10% loss may decrease hemoglobin A_{1c} by 0.6% to 1.0% among those with type 2 diabetes and can increase high-density lipoprotein cholesterol level by 2 mg/dL [0.052 mmol/L].[5,8] A 10% to 15% loss may be required to improve other conditions (eg, hepatic steatosis, obstructive sleep apnea).[8] Weight loss beyond 15% is associated with lower rates of all-cause mortality among those who undergo bariatric surgery and greater weight loss is associated with improved quality of life.[8]

Selecting Treatment Options

Evidence-based obesity treatment combines interventions that can be organized into 5 major categories: behavioral interventions, nutrition, physical activity, pharmacotherapy, and bariatric procedures.[4-6,9-13] Comprehensive obesity care plans should include interventions from all appropriate categories, individualized at the patient level (**Table 2**).

Behavioral Interventions

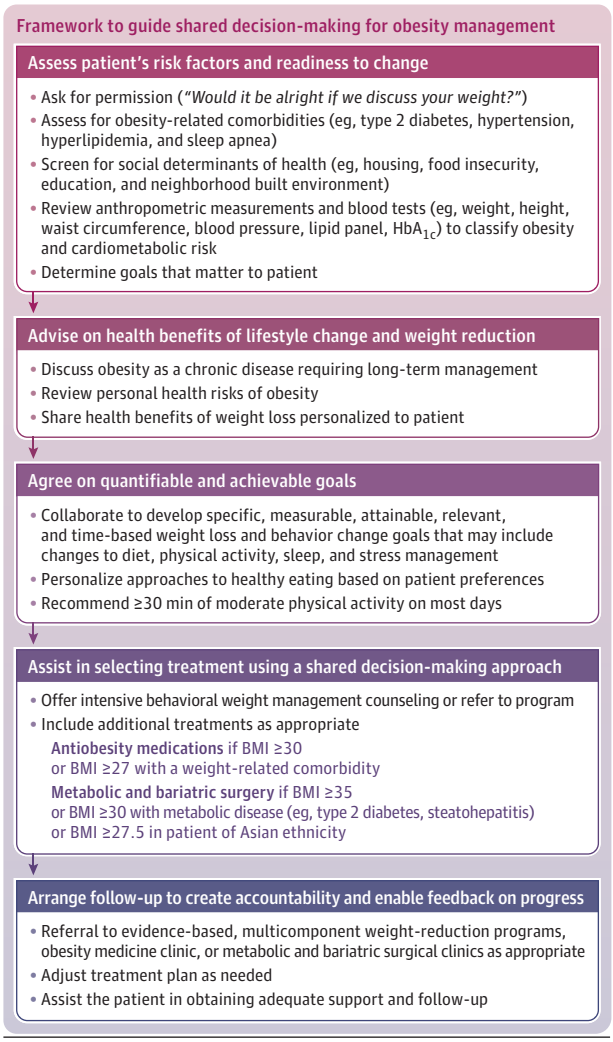
All patients with obesity (or overweight with a cardiometabolic abnormality) should be offered or referred to intensive, multicomponent behavioral interventions within primary care, community settings or to evidence-based commercial programs (**Table 3**).[4,6,13] Moderate- to high-intensity programs include 12 or more sessions in the first year (ideally ≥14 sessions in 6 months), followed by a maintenance phase for up to 24 months.[5,11,13] The Diabetes Prevention Program is covered by Medicare for eligible beneficiaries with prediabetes,[63] while coverage by Medicaid varies by state; commercial health insurance plans may provide coverage for some weight-loss programs. Interventions include group, individual, or technology-based delivery for lifestyle changes, education, peer support, coaching, self-monitoring, cognitive restructuring, and goal setting.[4,64] Interventions may also address insufficient sleep and chronic stress, which can negatively affect appetite and metabolism.[65] Moderate- to high-intensity interventions often produce 5% to 10% weight loss (mean, −2.39 kg; 95% CI, −2.86 kg to −1.93 kg),[64] with maximal loss achieved between 6 and 12 months.[5,13,64,66] Frequent self-weighing improves weight loss and weight loss maintenance.[5,67,68]

Weight regain is common after program cessation; in a study of 3739 participants, more than 25% of participants regained 2% or more of weight at 2-year follow-up.[46] Weight loss typically plateaus after 6 months due to metabolic adaption and hormonal changes contributing to decreased adherence, but metabolic adaptation usually slows after 12 months.[18,67]

Nutritional Approaches

Reduced caloric intake (500- to 750-kcal/d deficit, adjusted for individual body weight and activity) is advised for weight reduction.[5] Specific strategies that can reduce energy intake and promote weight-loss maintenance include portion control, reduction or elimination of ultraprocessed foods (eg, sugar-sweetened beverages), and increased fruit and vegetable intake.[67] Evidence-based healthy eating approaches can be selected based on individual preference, metabolic risk, and likelihood of long-term adherence.[4,5,11] Table 3 provides examples of evidence-based dietary strategies associated with weight loss; additional plans such as DASH (Dietary Approaches to Stop Hypertension), when combined with caloric reduction, can also be considered.[4] High-protein shakes or bars to replace 1 or 2 meals a day improves weight loss compared with diet alone (mean difference, −1.44 kg; 95% CI, −2.48 kg to −0.39 kg).[5,69] However, very low-calorie diets (≤800 kcal/d) should be offered only under close medical supervision.[5] While some evidence demonstrates weight loss and improved CVD risk factors with other popular weight-loss approaches (eg, time-restricted eating, intermittent fasting, ketogenic diet),[70-72] clinical practice guidelines have not endorsed these strategies, and they may require dietitian support.

Figure. 5A Framework (Assess, Advise, Agree, Assist, Arrange) for Obesity Counseling in the Outpatient Setting[6,31-33]



BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); HbA_{1c}, hemoglobin A_{1c}.

Physical Activity

Given its modest effect on weight, physical activity is not used as a stand-alone obesity treatment but helps with weight maintenance and cardiometabolic health.[73] Moderate-intensity aerobic exercise (defined as 50% to 70% of maximal heart rate) is associated with decreased visceral adiposity and modest weight loss (mean effect of −2 kg to −3 kg).[73,74] Resistance training (muscle strengthening) preserves lean/fat-free mass during weight loss.[73,74] Clinical guidelines recommend that all patients participate in 150 to 300 min/wk of moderate or 75 to 150 min/wk of vigorous physical activity, as well as resistance training 2 to 3 times a week.[4,5,40] Clinicians can encourage nonsedentary behaviors throughout the day, such as walking for 2 minutes each hour or use of stairs.[75] Additional tools such as wearable activity trackers can encourage increased physical activity of an additional 1800 steps per day on average, or 0.5 to 1.5 kg of weight loss.[76]

Table 2. Components of Comprehensive, Evidence-Based Weight Management for Adults With Obesity[4,5,9,13,14,40-47a]

Approach	Eligible patients[b]	Description or examples	Mean weight loss at 12-24 mo[c]	Other considerations
Multicomponent intensive behavioral lifestyle interventions[13]	• BMI ≥30 • BMI ≥25 with obesity-associated comorbidity[d]	• Evidence-based approaches include goal setting, self-monitoring (eg, food intake, physical activity, daily body weight), dietary change, stimulus control, stress management, cognitive therapy[13,14] • Multicomponent interventions combine these approaches and are delivered by trained facilitators, often referred from a primary care setting[13] • Intensive programs are administered over 1-2 y with ≥12-14 sessions in 6 mo[5] (see Table 3 for examples of programs)	1%-9%[4,5,13]	Higher intensity of weight loss instruction is associated with greater weight loss vs low- and moderate-intensity interventions[4]
Nutritional intervention	• BMI ≥30 • BMI ≥25 with obesity-associated comorbidity[d]	• Restricting/eliminating certain types of foods to create calorie deficit[5] • Generally 1200-1500 kcal/d for women and 1500-1800 kcal/d for men[5]; very low-calorie diets (<800 kcal/d) require specialized medical supervision[5] • Clinicians can provide counseling or refer to dietician • See more details on 3 evidence-based diet patterns in Table 3	3%-8%; 10% with very low-calorie diets[47]	Specific dietary recommendations need to account for patient preference and potential for long-term adherence
Physical activity	All adults regardless of BMI[40]	• ≥150 min/wk moderate-intensity physical activity (30 min 5 times per wk), or 75-150 min/wk vigorous-intensity physical activity[40] • Resistance exercise 2-3 times per wk[4] • >200 min/wk is associated with better maintenance of weight loss[5]	1%-3%[4]	Exercise should be individualized to patients' health and physical limitations and increased as patient is able to tolerate intensity to reach goals[4]

Pharmacotherapy[e]	• BMI ≥30
	• BMI ≥27 with obesity-associated comorbidity[5]
	• Consider with inadequate response to lifestyle therapy and/or presence of mild to moderate obesity complications[4]
		Medications vary in terms of administration and dosage (minimum-maximum dose):
		• FDA approved for long-term use
		  • Semaglutide (0.25-2.4 mg/wk subcutaneously)
		  • Phentermine-topiramate ER (3.75/23 mg/d to 15/92 mg/d orally)
		  • Liraglutide (0.6-3 mg/d subcutaneously)
		  • Naltrexone-bupropion ER (8 mg/90 mg daily to 16 mg/180 mg twice daily orally)
		  • Orlistat (60-120 mg 3 times daily orally)
		• FDA approved for short-term use
		  • Diethylpropion (IR: 25 mg 3 times daily; ER: 75 mg/d orally)
		  • Phentermine (8 mg/d to 8 mg 3 times daily or 15-37.5 mg/d orally)
		• Commonly used off label
		  • Tirzepatide (2.5-15 mg/wk subcutaneously)
		  • Semaglutide (3-50 mg/d orally) (50-mg/d oral dose not yet available)
		  • Topiramate (12.5-200 mg/d in 1 to 2 divided doses)
		  • Semaglutide (0.25-2.0 mg/wk subcutaneously)
		  • Liraglutide (0.6-1.8 mg/d subcutaneously)
		  • Bupropion (SR: 100-200 mg twice daily orally; ER: 150-450 mg/d orally)
		  • Metformin (500-2500 mg/d orally)
			5% (naltrexone-bupropion, 32 mg/360 mg daily)[41] to 21% (tirzepatide, 15 mg once weekly)[42f]	• See Table 4; adverse effects can often be avoided with slow dose titration or reducing dose to last tolerated dose
				• Administer concurrent with lifestyle interventions

Metabolic and bariatric surgery	• BMI ≥35 • BMI ≥30 with obesity-associated comorbidity[9] • Consider with inadequate response to lifestyle therapy and/or presence of severe obesity complications[4]	• Laparoscopic sleeve gastrectomy: approximately 85% of stomach removed by separation along greater curvature[43] • Roux-en-Y gastric bypass: small gastric pouch connected directly to jejunum[43]	25%-35%[5,44]	• Major complications <5%[44,45] • Long-term monitoring necessary for risks related to nutritional deficiency and bone health[45] • Administer concurrent with lifestyle interventions

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ER, extended release; FDA, US Food and Drug Administration; IR, immediate release; SR, sustained release.

[a] Interventions should be used simultaneously or serially with long-term follow-up. Randomized trials cannot fully replicate clinical care, in which clinicians see patients over long periods and add or adjust weight-loss approaches for individual patients. All patients undergoing weight-loss interventions should engage in nutrition, physical activity, and/or behavioral interventions.

[b] Lower thresholds in Asian populations.

[c] Expected ranges are approximate based on meta-analysis and clinical guidelines, generally in a 12- to 24-month time frame.

[d] Obesity-related comorbidity is defined based on the presence of at least 1 risk factor, including abnormal blood glucose levels, hypertension, and dyslipidemia.

[e] See Table 4 for detailed information.

[f] Range is listed for antiobesity medications FDA approved for long-term use.

Table 3. Examples of Intensive Multicomponent Programs and Nutritional Approaches for Weight Reduction

Approach	Mean 12-mo weight loss (95% CI) vs control, kg	Overview	Other benefits and considerations	Dietary Guidelines for Americans recommended[48]
Intensive multicomponent programs				
Weight Watchers[49]	5.9 (3.9-8.1)[50]	• Food tracking with points to reduce calorie intake • Activity tracking • Self-monitoring • Group sessions • Optional online coaching	• Decrease in hemoglobin A_{1c}; appropriate for patients with prediabetes[6] • Low cost, cost-effective[51]	No
Diabetes Prevention Program[52]	2.3 (1.1-3.4)[53]	• 16-Session curriculum delivered by a lifestyle coach over 6 mo in groups • Self-monitoring of weight at least weekly • Food tracking, setting calorie goals • ≥150 min/wk of moderate physical activity	• Decrease in incidence of type 2 diabetes at 2.8 y vs placebo; appropriate for patients with impaired fasting glucose or prediabetes[54] • Decrease in blood pressure, lipids, markers of inflammation[4] • Covered for eligible Medicare beneficiaries; may be covered by other insurers[51] • Low cost, cost-effective[55]	No
Veterans Affairs MOVE! program[56]	Not reported[a]	• Workbook with 16 lifestyle behavioral modules can be delivered remotely or in person via group sessions or by one-on-one counseling by various clinicians, depending on resources at local Veterans Affairs site • Curriculum includes goal setting, nutrition education, and self-monitoring, among other topics	• Program designed for veterans and available at all Veterans Affairs hospitals • Delivered by Veterans Health Administration for patients with body mass index ≥25 • Workbook and other materials (eg, food diaries and mobile application) are publicly available; written materials in English and Spanish	No
Nutritional approaches				
Low-fat vegan- or vegetarian-style diet[57]	6.6 (3.4-9.8)[50]	• 10%-25% of calories from fat • Eliminate meat and fish; may include eggs/dairy • Often low in saturated fats, high in fiber	• Increase in insulin sensitivity[57] • Potential reduced environmental impact[58]	Yes
Low-carbohydrate diet[59]	6.4 (3.9-8.9)[50]	<40% of calories from carbohydrates	• Decrease in SBP, DBP, glucose, insulin resistance, and triglycerides[59,60] • Increase in HDL-C[59,60]	No
Mediterranean diet[4]	2.5 (1.9-3.1)[61]	• Focus on dark green vegetables, fruits, nuts, and legumes • Moderate to high intake of fish and seafood • Low intake of red meat and dairy fat • Use of extra virgin olive oil as main source of dietary fat	• Decrease in SBP, DBP, LDL-C,[59] hemoglobin A_{1c}, and triglycerides[61] • Increase in HDL-C[61] • Potential reduced environmental impact[58]	Yes

Abbreviations: DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

[a] Since this program was implemented at all Veterans Affairs sites, randomized clinical trials with 12-month outcomes compared with usual care have not been completed. Data from a systematic review of comparative effectiveness of prospective and retrospective studies found a mean weight loss of 0.13-3.3 kg.[62]

Weight-Gain Effect of Common Medications

Many commonly used medications are associated with weight gain.[12] Medication classes promoting weight gain include antihyperglycemics (eg, glyburide, insulin), antidepressants (eg, amitriptyline, mirtazapine), antipsychotics (eg, olanzapine, quetiapine), antiepileptics (eg, gabapentin, carbamazepine), β-blockers, progesterone-based contraceptives, corticosteroids, and antiretroviral therapy (eg, protease inhibitors).[12,77] Many weight gain–promoting medications increase the risk of weight-related complications, including CVD, diabetes, and hepatic steatosis.[78]

When initiating medications, clinicians should select therapies least likely to cause weight gain among options with similar efficacy.[12] When prescribing medications that promote weight gain, clinicians should counsel patients on the risk of weight gain, discuss lifestyle modifications, and monitor weight trajectory (eg, unintentional weight gain >2 kg in a month, ≥7% increase from baseline body weight).[77] Metformin (1000 mg total daily dose) and topiramate (100 mg/d) counteract the effects of some weight gain–promoting agents, particularly antipsychotics and can be considered as adjunctive therapy (topiramate: mean difference, −3.76 kg; 95% CI, −4.92 kg to −2.69 kg; metformin: mean difference, −3.27 kg; 95% CI, −4.66 kg to −1.89 kg).[79,80]

Antiobesity Medications

Significant advances in pharmacotherapy for obesity treatment have occurred with increasing numbers of medications approved by the US Food and Drug Administration (FDA). Among individuals with inadequate response to lifestyle modifications, guidelines recommend initiating an antiobesity medication in nonpregnant patients with obesity or with overweight (BMI ≥27) and weight-related complications (**Table 4**).[4,10,11] When initiating therapy, clinicians should consider dual health benefits of antiobesity medications. For example, in patients with diabetes, a GLP-1 receptor agonist can improve glycemic control and promote weight loss. Patients should be counseled that antiobesity medications must be used in conjunction with lifestyle changes and may need to be used lifelong since weight regain is common on discontinuation.[10,96] Use of weight-loss supplements, such as green tea extract or herbs, is not recommended.[6,97]

GLP-1 Receptor Agonists (Semaglutide and Liraglutide)

GLP-1 receptor agonists mimic the effects of GLP-1. After eating, GLP-1 acts on the hypothalamus to suppress appetite, delay gastric emptying, increase glucose-dependent insulin release, decrease glucagon secretion, and increase pancreatic β-cell growth.[98]

Subcutaneous semaglutide was FDA approved to treat obesity in 2021 and is dosed once weekly.[10] The STEP trials examined the efficacy of semaglutide. The STEP 1 and STEP 3 trials included individuals with obesity without diabetes (mean BMI, 38).[81,99] In these clinical trials, mean weight loss at 68 weeks was 14.9% (placebo, 2.4%; difference, 12.4%; 95% CI, 11.5%-13.4%) and 16.0% (placebo, 5.7%; difference, 10.3%; 95% CI, 8.6%-12.0%), respectively.[81,99] In STEP 1, participants were encouraged to follow a reduced-calorie diet and participate in 150 min/wk of physical activity.[81] In STEP 3, participants started with low-calorie meal replacements for 8 weeks followed by a reduced-calorie diet, a goal of 200 min/wk of physical activity, and 30 individual visits with a dietitian.[99] After cessation of semaglutide, participants regained significant amounts of weight.[96,100] Among participants followed up for an additional 52 weeks after completing 68 weeks of semaglutide treatment, mean weight regain was 11.6% of lost weight.[100] In the STEP 4 trial, participants completed 20 weeks of semaglutide treatment and were transitioned to placebo for an additional 48 weeks.[96] Mean weight regain was 6.9% of lost weight during the placebo administration.[96] These results suggest that long-term use is necessary.[96,100] In a clinical trial that randomized 667 adults with obesity without diabetes to either semaglutide or placebo for 68 weeks, mean weight loss with 50 mg/d oral semaglutide was 15.1% vs 2.4% for placebo.[89] Oral semaglutide is not yet FDA approved for obesity alone.[89]

Subcutaneous liraglutide was FDA approved to treat obesity in 2014.[10] In an RCT of 3731 individuals with obesity, compared with placebo, liraglutide achieved a mean weight loss of 8.0% at 56 weeks (difference, 5.4%; 95% CI, 5.8%-5.0%).[85] Although it is dosed daily, it is widely used and preferred for some patients due to cost and availability. Systematic reviews and meta-analyses of GLP-1 receptor agonists reported that subcutaneous semaglutide reduced weight and improved weight-related comorbidities significantly more than liraglutide and was associated with lower rates of gastrointestinal adverse events.[101,102]

Both GLP-1 receptor agonists have been shown in a meta-analysis to decrease risk of CVD events in adults with overweight or obesity without diabetes (at follow-up of 32-160 weeks, 8.7% of participants receiving GLP-1 receptor agonists and 11.2% receiving placebo had an event).[82] The SELECT study showed that in 17 604 participants with CVD, with a BMI of 27 or greater, and without diabetes, those randomized to semaglutide, 2.4 mg, vs placebo had a lower composite incidence of death due to cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke at 39.8 months (hazard ratio, 0.80; 95% CI, 0.72-0.90).[103] Among 529 patients with heart failure and preserved ejection fraction, compared with placebo, semaglutide reduced heart failure–related symptoms and improved physical limitations.[104]

Tirzepatide

Tirzepatide is a synthetic peptide with dual-hormone agonistic activity at the GLP-1 receptor, like semaglutide, and additionally at the glucose-dependent insulinotropic polypeptide receptor. Tirzepatide is dosed subcutaneously once weekly.[42] An RCT of 2539 adults with obesity and without diabetes randomized participants to 1 of 4 groups: 15 mg, 10 mg, or 5 mg of tirzepatide or placebo; all participants received lifestyle counseling sessions, a reduced-calorie diet, and physical activity for 72 weeks.[42] At 72-week follow-up, mean weight loss for tirzepatide was 20.9% for 15 mg of tirzepatide, 19.5% for 10 mg of tirzepatide, 15.0% for 5 mg of tirzepatide, and 3.1% for placebo.[42] Tirzepatide was FDA approved for treatment of obesity in November 2023. A recent meta-analysis of RCTs that included 12 371 adults with overweight or obesity without diabetes reported that 15 mg weekly of tirzepatide was associated with greater weight loss compared with 2.4 mg weekly of subcutaneous semaglutide (mean difference, 5.1%; 95% CI, 0.6%-9.8%) and 3 mg daily of subcutaneous liraglutide (mean difference, 13.0%; 95% CI, 8.8%-17.4%).[105]

Phentermine-Topiramate

Combined oral phentermine-topiramate was FDA approved in 2012 for obesity.[10] Phentermine, a noradrenergic drug, reduces appetite

Table 4. Antiobesity Medication Management, Ordered by Greatest Difference in Percentage Weight Loss

Medications (trial)	Mechanism of action	Mean weight loss from baseline[a]	Dosing[b]	Additional benefits	Most common adverse effects (placebo, treatment)[c,d]	Monitoring[d]	Contraindications[d]	Mean 30-d retail cost, $ (dose)[e]
FDA approved for long-term use[10]								
Tirzepatide (SURMOUNT-1[42])	Dual-hormone agonistic activity at GLP-1 and glucose-dependent insulinotropic polypeptide receptors, regulating energy balance by signals in CNS and adipose tissue[42]	Treatment: 20.9%; placebo: 3.1%; difference, 17.8% with 15 mg at 72 wk	• Starting dose: 2.5 mg/wk subcutaneously • Titration speed: not faster than every 4 wk • Titration: by 2.5 mg • Maximum dose: 15 mg/wk subcutaneously	• Improved: waist circumference, blood pressure, hemoglobin A_{1c}, lipid profile[42] • Consider use in patients with impaired glucose tolerance	Nausea (10%, 31%), diarrhea (7%, 23%), vomiting (2%, 12%), constipation (6%, 12%), alopecia (1%, 6%), abdominal pain (3%, 5%)	• Glucose if taking insulin or sulfonylurea • Hydration if gastrointestinal adverse effects • Signs/symptoms of pancreatitis or gallbladder disorders • Anticipatory guidance about symptoms of thyroid mass	• Personal or family history of medullary thyroid carcinoma • MEN type 2	1022-1221 (15 mg)
Semaglutide, subcutaneous (STEP 1[81])	Activates GLP-1 receptor, with metabolic effects on glucose-dependent stimulation of insulin secretion, delayed gastric emptying[10]	Treatment: 14.9%; placebo: 2.4%; difference, 12.5% with 2.4 mg at 68 wk	• Starting dose: 0.25 mg/wk subcutaneously • Titration speed: not faster than every 4 wk • Doses: 0.25, 0.5, 1.0, 1.7 mg/wk • Maximum dose: 2.4 mg/wk subcutaneously	• Improved: waist circumference, blood pressure, hemoglobin A_{1c}, CVD events, lipid profile[81,82] • Consider use in patients with impaired glucose tolerance	Nausea (17%, 44%), diarrhea (16%, 32%), constipation (10%, 23%), dyspepsia (4%, 10%), vomiting (7%, 25%)	• Glucose if taking insulin or sulfonylurea • Hydration if gastrointestinal adverse effects • Signs/symptoms of pancreatitis or gallbladder disorders • Diabetic retinopathy	• Personal or family history of medullary thyroid carcinoma • MEN type 2 • History of pancreatitis is a precaution but not a contraindication	1333-1648 (2.4 mg)
Phentermine-topiramate ER (EQUATE[83])	Phentermine increases norepinephrine in CNS, topiramate modulates GABA receptors in the CNS[10,12]	Treatment: 9.2%; placebo: 1.7%; difference, 7.5% with 15 mg/92 mg at 28 wk	• Starting dose: 3.75 mg/23 mg daily • Next dose: 7.5 mg/46 mg daily for 12 wk • Titration speed: not faster than every 2 wk • Titration amount: by 3.75 mg/23 mg • Maximum dose: 15 mg/92 mg daily	• Improved: waist circumference, systolic blood pressure, hemoglobin A_{1c}, lipid profile[83,84] • Consider use in patients with comorbid migraines[10]	Paresthesia (4%, 23%), dry mouth (0%, 19%), constipation (8%, 16%), headache (13%, 16%), insomnia (5%, 10%), dizziness (2%, 8%)	• Heart rate, blood pressure • Serum bicarbonate • Symptoms of acute metabolic acidosis, nephrolithiasis, suicidality, or angle-closure glaucoma • Potassium if taking potassium-sparing diuretic • Dermatologic reactions	• CVD • Uncontrolled hypertension • Untreated hyperthyroidism • History of glaucoma, calcium-phosphate nephrolithiasis • Within 14 d of MAOI use	98-214 (15 mg/92 mg)
Liraglutide (SCALE[85])	Activates GLP-1 receptor, with metabolic effects on glucose-dependent stimulation of insulin secretion, delayed gastric emptying[10]	Treatment: 8.0%; placebo: 2.6%; difference, 5.4% with 3 mg at 56 wk	• Starting dose: 0.6 mg/d subcutaneously • Titration speed: not faster than weekly • Titration: by 0.6 mg • Maximum dose: 3 mg/d subcutaneously	• Improved: waist circumference, blood pressure, hemoglobin A_{1c}, CVD events, lipid profile[82,85] • Consider use in patients with impaired glucose tolerance	Nausea (15%, 40%), diarrhea (9%, 21%), constipation (9%, 20%), dyspepsia (5, 10%), vomiting (4%, 16%)	• Glucose if taking insulin or sulfonylurea • Signs/symptoms of pancreatitis or gallbladder disorders • Worsening depression, suicidal thoughts, behavior change • Heart rate	• Personal or family history of medullary thyroid cancer • MEN type 2 • Pancreatitis is a precaution but not a contraindication	1333-1498 (3 mg)
Naltrexone-bupropion ER (COR-II[41])[f]	Bupropion activates proopiomelanocortin neurons in the hypothalamus, naltrexone blocks opioid-mediated proopiomelanocortin autoinhibition	Treatment: 5.6%; placebo: 1.2%; difference, 4.4% with 32 mg/360 mg at 56 wk	• Starting dose: 8 mg/90 mg daily • Titration speed: not faster than weekly • Titration amount: by 8 mg/90 mg • Maximum dose: 32 mg/360 mg daily (dosed as 16 mg/180 mg twice daily)	• Improved: waist circumference, hemoglobin A_{1c} in type 2 diabetes, lipid profile[41] • Consider use in patients interested in reducing tobacco or alcohol use[10,86]	Nausea (7%, 33%), constipation (7%, 19%), headache (10%, 18%), vomiting (3%, 11%), dizziness (3%, 10%), insomnia (6%, 9%), dry mouth (2%, 8%), diarrhea (5%, 7%)	• Heart rate, blood pressure • Kidney and liver function • Depression, suicidal ideation, anxiety, mania, panic attacks	• Uncontrolled hypertension • History of seizures • At risk of alcohol withdrawal • Bulimia or anorexia nervosa • Within 14 d of MAOI use • Long-term opioid use	99-698 (8 mg/90 mg; 4 tablets/d)

(continued)

Table 4. Antiobesity Medication Management, Ordered by Greatest Difference in Percentage Weight Loss (continued)

Medications (trial)	Mechanism of action	Mean weight loss from baseline[a]	Dosing[b]	Additional benefits	Most common adverse effects (placebo, treatment)[c,d]	Monitoring[d]	Contraindications[d]	Mean 30-d retail cost, $ (dose)[e]
Orlistat (European Multicenter Orlistat Study[87])	Gastric and pancreatic lipase inhibitor with decreased absorption of triglycerides[10]	Treatment: 10.2%; placebo: 6.1%; difference, 4.1% with 120 mg 3 times daily at 52 wk	• 60 mg 3 times daily • 120 mg 3 times daily	• Improved: blood pressure, glucose, lipid profile[87] • Consider if patient has chronic constipation[g]	Steatorrhea (5%, 31%), increased defecation (7%, 20%), oily spotting (1%, 18%), liquid stool (10%, 13%), fecal urgency (3%, 10%), flatus with discharge (0%, 7%), fecal incontinence (0%, 7%)	• Fat-soluble vitamin levels (A, D, E, K) • Liver function if symptoms of hepatic impairment • Administer multivitamin 2 h apart from orlistat	• Deficiency in fat-soluble vitamins • Calcium oxalate nephrolithiasis • Chronic malabsorption • Cholestasis	• 49-67 (Over the counter) • 280-597 (Prescription)
FDA approved for short-term use (12 wk)[10]								
Diethylpropion[88]	Increases norepinephrine release in CNS[10]	Treatment: 9.8%; placebo: 3.2%; difference, 6.6% with 50 mg twice daily at 24 wk	• IR: 25 mg 3 times daily before meals • ER: 75 mg/d	Waist circumference improved[88]	• Dry mouth (41%, 69%), insomnia (22%, 53%), constipation (14%, 39%), headache (25%, 33%), dizziness (9%, 14%) • Incidence of all adverse effects decreased at 3-6 mo	• Can cause direct cardiac myocyte toxicity • Heart rate, blood pressure • Mood	• Sedative use • Susceptibility to amphetamines • CVD • Avoid use with ethanol • Use within 1 y of another anorectic medication	19-60 (Generic; 75 mg ER)
Phentermine (EQUATE[83])	Increases norepinephrine release in CNS[10]	Treatment: 6.1%; placebo: 1.7%; difference, 4.4% with 15 mg at 28 wk	• Starting dose: 8 mg/d (tablet) or 15 mg/d (capsule) • Titration speed: not faster than every 2 wk • Titration: can combine 8 mg + 15 mg as 23 mg or increase from 15 mg to 30 mg • Maximum dose: 37.5 mg/d	Nonsignificant reduction in systolic and diastolic blood pressure and waistline vs placebo for 7.5 mg and 15 mg phentermine[83]	Paresthesia (4%, 5%), dry mouth (0%, 12%), headache (13%, 10%), constipation (8%, 8%), insomnia (6%, 11%), dizziness (2%, 3%)	Heart rate, blood pressure	• CVD • Uncontrolled hypertension • Untreated hyperthyroidism • Within 14 d of MAOI use	• 12-17 (Generic; 37.5 mg) • 15-27 (Brand name; 8 mg)
Commonly used off label								
Semaglutide, 50 mg oral (OASIS 1[89])	Activates GLP-1 receptor, with metabolic effects on glucose-dependent stimulation of insulin secretion, delayed gastric emptying[10]	Treatment: 15.1%; placebo: 2.4%; difference, 12.7% with 50 mg at 68 wk	• Starting dose: 3 mg/d • Titration speed: not faster than every 4 wk • Titration: 7 mg, 14 mg, 25 mg, 50 mg • Maximum dose: 50 mg/d	• Improved: waist circumference, blood pressure, hemoglobin A_{1c}, lipid profile[89] • Consider use in patients with impaired glucose tolerance	Nausea (15%, 52%), constipation (15%, 28%), diarrhea (17%, 27%), vomiting (4%, 24%)	Not reported	Not reported	926-1041 (7 mg)
Topiramate (EQUATE[83])	Topiramate modulates GABA receptors in CNS[10]	Treatment: 6.4%; placebo: 1.7%; difference, 4.7% with 92 mg at 28 wk	• Starting dose (IR): 12.5 mg/d to 25 mg/d • Titration speed: not faster than weekly • Titration amount: by 25 mg • Maximum dose (IR): 200 mg twice daily	Consider use in patients with migraines, antipsychotic-induced weight gain, binge eating disorder, alcohol use disorder[10,79,86]	Paresthesia (4%, 22%), dry mouth (0%, 7%), constipation (8%, 6%), insomnia (6%, 5%), dizziness (2%, 4%)	• Symptoms of acute angle-closure glaucoma • Acute metabolic acidosis • Nephrolithiasis • Depression, anxiety, suicidal ideation	Use with care if history of glaucoma, metabolic acidosis, calcium phosphate kidney stones	9-37 (Generic)
Semaglutide (SUSTAIN 1[67,90])[h]	Activates GLP-1 receptor, with metabolic effects on glucose-dependent stimulation of insulin secretion, delayed gastric emptying[10]	Treatment: 4.7%; placebo: 1.1%; difference, 3.6% with 1.0 mg at 30 wk in patients with type 2 diabetes	• Starting dose: 0.25 mg/wk subcutaneously • Titration speed: not faster than every 4 wk • Doses: 0.25, 0.5, 1.0, 2.0 mg/wk • Maximum dose: 2 mg/wk subcutaneously	• Improved: waist circumference, blood pressure, hemoglobin A_{1c}, CVD events, lipid profile[90] • Consider use in patients with impaired glucose tolerance	Nausea (8%, 24%), diarrhea (2%, 11%), constipation (1%, 4%), vomiting (2%, 7%)	• Glucose if taking insulin or sulfonylurea • Signs/symptoms of pancreatitis or gallbladder disorders • Diabetic retinopathy	• Personal or family history of medullary thyroid carcinoma • MEN type 2 • Pancreatitis is a precaution but not a contraindication	926-1041 (2 mg)

(continued)

Table 4. Antiobesity Medication Management, Ordered by Greatest Difference in Percentage Weight Loss (continued)

Medications (trial)	Mechanism of action	Mean weight loss from baseline[a]	Dosing[b]	Additional benefits	Most common adverse effects (placebo, treatment)[c,d]	Monitoring[d]	Contraindications[d]	Mean 30-d retail cost, $ (dose)[e]
Liraglutide (LEAD-3[91])[h]	Activates GLP-1 receptor, with metabolic effects on glucose-dependent stimulation of insulin secretion, delayed gastric emptying[10]	Treatment (1.8 mg): 2.6%; control (glimepiride, 8 mg): +1.2%; difference, 3.8% at 52 wk in patients with type 2 diabetes	• Starting dose: 0.6 mg/d subcutaneously • Titration speed: not faster than weekly • Titration: by 0.6 mg • Maximum dose: 1.8 mg/d subcutaneously	• Improved: waist circumference, blood pressure, hemoglobin A_{1c}[91] • Consider use in patients with impaired glucose tolerance	Nausea (8%, 29%), diarrhea (9%, 19%), constipation (5%, 11%), vomiting (4%, 9%) (glimepiride; no placebo in this study)	• Glucose if taking insulin or sulfonylurea • Signs/symptoms of pancreatitis or gallbladder disorders • Worsening depression, suicidal thoughts, behavior change • Heart rate	Pancreatitis is a precaution but not a contraindication	1104-1340 (3 mg)
Bupropion[92]	Bupropion activates proopiomelanocortin neurons in the hypothalamus[41]	Treatment: 4.9% (up to 12.9% with gradual increase to 200 mg twice daily at 24 wk); placebo: 1.3%; difference, 3.6% with 200 mg SR twice daily at 8 wk (n = 50)	• Starting dose (SR): 100 mg/d • Titration speed: not faster than every 2 wk • Maximum dose: 200 mg twice daily • Starting dose (ER): 150 mg/d • Titration speed: every 1 to 2 wk • Maximum dose: 450 mg/d	Consider use in patients with depression, seasonal affective disorder, anxiety, attention-deficit/ hyperactivity disorder, dysthymia if indicated	Insomnia (4%, 20%), dry mouth (20%, 52%), rash (0%, 8%), nervousness (4%, 16%)	• Blood pressure • Depression, suicidal ideation, anxiety, mania, panic attacks • Because bupropion lowers seizure threshold, it should be weaned slowly	• Uncontrolled hypertension • Seizure disorder • Bulimia or anorexia nervosa • Within 14 d of MAOI use	5-27 (Generic; 300 mg ER)

Metformin (Diabetes Prevention Program Outcomes Study[93])	Increased insulin and leptin sensitivity, decreased hunger and ghrelin levels[94]	Treatment: 6.2%; placebo, 2.8%; difference, 3.5% with 1500 mg at 15 y	• Both IR and ER can be taken once or twice daily
			• For IR and ER:
			  • Starting dose: 500 mg/d
			  • Titration speed: not faster than weekly
			  • Titration amount: by 500 mg
			  • Dose: 2500 mg/d
				• Hemoglobin A_{1c} improved[94]
				• Consider use in patients with polycystic ovary syndrome, antipsychotic-induced weight gain, impaired glucose tolerance, or chronic constipation[94g]
					• Gastrointestinal adverse effects in 10%-20% (treatment group)
					• Some patients tolerate one formulation but not the other
					• Taking at the end of a meal can reduce risk of adverse effects
						• Glucose if taking insulin or sulfonylurea
						• Vitamin B_{12} after long-term use
						• Reassess dose if glomerular filtration rate decreases to <45 mL/min
							• Advanced cirrhosis (class C)
							• Glomerular filtration rate <30 mL/min
							• Heart failure with poor perfusion
								• 3-13 (Generic)
								• IR is less expensive than ER

Abbreviations: ER, extended release; CNS, central nervous system; CVD, cardiovascular disease; GABA, γ-aminobutyric acid; GLP-1, glucagon-like peptide 1; IR, immediate release; MAOI, monoamine oxidase inhibitor; MEN, multiple endocrine neoplasia; SR, sustained release.

[a] Rounded to the first decimal place, presented for maximum dose or as indicated.

[b] Weight loss may vary by dose. Suggested titration by manufacturer is presented; titration should be personalized to patients and based on weight loss. If a patient is losing ≥1 lb per week while taking a given dose, dose titration may not be needed unless that weight loss has slowed.

[c] Most common adverse effects are presented with frequencies in the placebo and treatment groups from the primary clinical trial for the maximum dose reported. Most adverse effects are less frequent with lower doses. For all medications, slow dose titration may mitigate adverse effects. For GLP-1 receptor agonists and glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonists, consider behavior modification, including reduced portion size and increased fiber intake. For metformin, taking with meals can mitigate adverse effects.

[d] For comprehensive information on adverse effects, monitoring, and contraindications, please refer to prescribing information for each medication. Reproductive considerations and use during pregnancy and lactation: metformin is used to improve fertility and recommended by the American College of Obstetricians and Gynecologists as a second-line medication for diabetes during pregnancy; it is safe during lactation.[95] All other antiobesity medications should not be used during pregnancy or lactation. Women of reproductive age should be counseled on the use of effective contraception. GLP-1 receptor agonists: safety during pregnancy and lactation is not fully known. These medications can decrease the effectiveness of oral contraceptives because of delayed gastric emptying; addition of barrier method is recommended for 4 weeks after initiation of a GLP-1 receptor agonist and after each dose increase. Phentermine-topiramate: topiramate can cause fetal malformations. The US Food and Drug Administration label for phentermine-topiramate recommends testing for pregnancy at initiation and monthly thereafter; however, neither phentermine nor topiramate individually has a recommendation for monthly pregnancy testing.

[e] Prices are average retail price (without insurance) accessed at GoodRx.com on April 11, 2023, and July 15, 2023; lower prices are often available with coupons or by mail order.

[f] Naltrexone is sometimes prescribed off label as a single agent without bupropion, but not as often as bupropion is prescribed off label.

[g] Expert opinion based on clinical experience.

[h] Percentage weight loss manually calculated from mean weight loss in kilograms and mean kilograms at baseline.

and affects food intake via the enhancement of norepinephrine release and blockade of norepinephrine reuptake.[106] Topiramate's exact weight-loss mechanism is unknown but is thought to alter appetite and decrease energy intake.[106] A clinical trial randomized 1267 individuals with a BMI of 35 or greater to phentermine-topiramate, 3.75/23 mg/d; phentermine-topiramate, 15/92 mg/d; or placebo.[107] At 56-week follow-up, weight loss was 5.1% with the lower dose of phentermine-topiramate, 10.9% with the higher dose of phentermine-topiramate, and 1.6% in the placebo group.[107] In systematic reviews, phentermine-topiramate was associated with greater weight loss compared with orlistat and naltrexone-bupropion.[108,109] Since topiramate is also used to prevent migraines, phentermine-topiramate may be considered in patients with obesity and migraine headaches.[10]

Naltrexone-Bupropion

The combination of oral naltrexone-bupropion was FDA approved for obesity in 2014.[10] Bupropion stimulates hypothalamic proopiomelanocortin neurons while naltrexone simultaneously blocks opioid-mediated proopiomelanocortin autoinhibition, which reduces reactivity to food cues and improves dysregulation of eating control in mesolimbic pathways.[41] Both the Contrave Obesity Research I and II trials were conducted among individuals with a BMI of 30 to 45 or a BMI of 27 to 45 with dyslipidemia or hypertension (1742 and 1496 participants, respectively).[110,111] Groups receiving naltrexone-bupropion, 32/360 mg/d, achieved significant 56-week weight loss compared with placebo (approximately 6% and 1%, respectively).[110,111] Naltrexone-bupropion may be considered in patients with obesity and comorbid depression or desire for smoking cessation or alcohol use reduction.[10]

Orlistat

Orlistat is a pancreatic lipase inhibitor oral medication that prevents triglycerides from being hydrolyzed, thus deceasing the absorption of free fatty acids. Orlistat was FDA approved for obesity in 1999.[10] Mean weight loss with orlistat is 2.8% to 4.8%, and gastrointestinal adverse effects are frequent, including flatulence, steatorrhea, and diarrhea.[10,109] Orlistat may cause malabsorption of fat-soluble vitamins; thus, patients should take a multivitamin containing vitamins A, D, E, and K 2 hours apart from orlistat daily.[10] Recent American Gastroenterological Association guidelines conditionally recommended against orlistat use given its modest weight loss and gastrointestinal adverse effects.[10] It is available over the counter and may be appropriate for certain patients (eg, when other antiobesity medications are contraindicated, unavailable, or unaffordable).

Gelesis100

Gelesis100 is a nonsurgical device that was FDA approved in 2019 to treat obesity. It is a superabsorbent orally administered hydrogel capsule that releases cellulose and citric acid particles, thereby increasing bulk in the stomach and creating a sensation of satiety.[10] An RCT of 436 participants showed a mean weight loss of 2.1% more with Gelesis100 compared with placebo ($P < .001$), and 59% of those receiving Gelesis100 attained 5% or greater weight loss compared with 42% of those receiving placebo ($P < .001$).[112] It is indicated for those with a BMI of 25 to 40; given limited knowledge due to its recency, guidelines do not currently recommend its use.[10] Gastrointestinal adverse effects occurred in 38% of Gelesis100 participants and 28% of placebo participants.[112]

Antiobesity Medications Approved by the FDA for Short-Term Use

Four sympathomimetic oral amines, phentermine, diethylpropion, benzphetamine, and phendimetrazine are currently FDA approved for short-term use (12 weeks).[10,113,114] These agents increase norepinephrine, leading to appetite suppression.[113] While use beyond 12 weeks is common, local laws and state medical boards should be consulted.[12] Phentermine is the most commonly prescribed antiobesity medication[115] and is an affordable alternative to other therapies, but it has sympathomimetic effects.[116] Therefore, clinicians should avoid these medications in patients with a history of coronary artery disease, uncontrolled hypertension, glaucoma, and history of substance use disorder.[12,116] Phentermine and diethylpropion are Schedule IV controlled substances but are associated with low risk of dependency or abuse.[113,114,116] A recent review found that phentermine was not associated with increased risk of major adverse cardiac events compared with usual care.[108]

Medications Commonly Used Off Label for Long-Term Treatment

Table 4 lists several medications that are commonly used off label to treat obesity. Medications commonly used off label for obesity include Mounjaro (tirzepatide injection), Ozempic (semaglutide injection), Rybelsus (oral semaglutide), and Victoza (liraglutide injection). These brand names are approved by the FDA for diabetes only, and health insurance coverage may be restricted to their FDA-approved indication.

Metformin

In RCTs and prospective studies, oral metformin was associated with approximately 3% weight loss, and approximately 25% to 50% of participants achieve at least 5% weight loss.[94] The Diabetes Prevention Program randomized 3234 adults without diabetes to metformin, placebo, or intensive lifestyle intervention for the primary outcome of preventing diabetes.[93] The mean weight loss at 15-year follow-up was 6.2% (95% CI, 5.2%-7.2%) for metformin, 3.7% (95% CI, 3.1%-4.4%) for intensive lifestyle intervention, and 2.8% for placebo (95% CI, 1.3%-4.4%).[93] Doses of metformin greater than 1500 mg are associated with the greatest weight loss.[93,94] Metformin's pleiotropic effects include decreased inflammation, increased insulin and leptin sensitivity, and decreased hunger and ghrelin levels, especially with twice-daily dosing.[94] Metformin is widely available and inexpensive. Metformin is frequently offered to patients with prediabetes, polycystic ovary syndrome, and overweight/obesity and to mitigate weight gain due to antipsychotic medication, although it is not FDA approved for these diagnoses.[94]

Challenges to Prescribing Antiobesity Medications in Clinical Practice

Medicare currently excludes coverage of FDA-approved antiobesity medications for a diagnosis of obesity alone. Often these medications are costly. Global shortages of some medications currently exist, especially GLP-1 receptor agonists. More studies are needed to determine dosing for weight loss vs weight maintenance and long-term use beyond studied time periods.

Bariatric Endoscopic Procedures

Currently, 2 bariatric endoscopic procedures are FDA approved: intragastric balloons and endoscopic sleeve gastroplasty.

Intragastric balloons occupy space in the stomach, delay gastric emptying, and increasing satiety.[117] Patients with a BMI of 30 to 40 are eligible and typically require an upper endoscopy to place the balloon and fill it with saline. The devices are removed via endoscopy after 6 to 8 months. In a clinical trial of 255 patients with a BMI of 30 to 40 randomized to lifestyle intervention plus balloon (placed for 6 months) vs lifestyle intervention alone, lifestyle intervention plus balloon reduced weight by 10.2% (range, 9.6%-29.2%) compared with 3.3% (range, 5.4%-19%) for lifestyle intervention alone at 6 months.[117] Six months after balloon removal, patients regained some weight, with 7.6% vs 3.1% total weight loss.[117] Adverse effects include nausea/vomiting (20%) and abdominal pain (7%).[118]

Endoscopic sleeve gastroplasty is an organ-sparing, transoral endoscopic procedure designed to reduce stomach volume. In an RCT of 209 patients with obesity randomized to endoscopic sleeve gastroplasty plus lifestyle modifications (reduced-calorie diet and physical activity counseling) vs lifestyle modifications alone for 52 weeks,[119] endoscopic sleeve gastroplasty achieved 13.6% weight loss compared with 0.8% with lifestyle modifications alone.[119]

Both procedures should be considered based on patient preference, eligibility, benefits, risks, procedural contraindications (eg, hiatal hernia, gastric ulcers), and specialist availability.[118]

Metabolic and Bariatric Surgery

While previously limited to persons with a BMI of 40 or greater or patients with a BMI of 35 or greater with weight-related comorbidity, recent guidelines recommend that metabolic and bariatric surgery should be considered for patients with a BMI of 35 or greater and patients with a BMI of 30 to 34.9 who have concurrent metabolic disease. Lower weight thresholds should be applied to Asian populations.[9] For those with a BMI of less than 35, a trial of nonsurgical therapy is recommended prior to referral for metabolic and bariatric surgery.[9] After referral to metabolic and bariatric surgery, patients are often evaluated by the surgical clinic, and time to surgery is determined by their preoperative evaluations and health insurance requirements for evaluations. Presurgical nutrition and mental health evaluations are recommended, with additional evaluations determined by the surgeon.[9]

Two metabolic and bariatric procedures comprise more than 90% of all surgeries: (1) laparoscopic sleeve gastrectomy (LSG), in which approximately 85% of the stomach is removed by separation along the greater curvature, and (2) Roux-en-Y gastric bypass (RYGB) surgery, in which a small gastric pouch is connected directly to the jejunum.[43] Both are typically performed laparoscopically. Expected 12-month weight loss is approximately 25% after LSG and approximately 30% after RYGB, with sustained weight loss at 5 years.[44,120] Early complications include anastomotic leaks (LSG: 1%-7%; RYGB: 0.6%-4.4%), stenosis (LSG: 1%-9%; RYGB: 8%-19%), postoperative bleeding (11%), and venous thromboembolic events (incidence not reported); late complications include internal hernia and marginal ulceration (RYGB: 2.5%-5%).[121] Pre- and post-metabolic and bariatric surgery screening and supplementation for micronutrients (thiamin, vitamin B_{12}, folate, iron, vitamin D, calcium, vitamin A, vitamin E, vitamin K, zinc, and copper) is recommended; typical doses vary based on surgical procedure.[45]

Follow-Up

Arranging follow-up visits for patients can promote weight loss, potentially by influencing behavior change and accountability.[122] In the outpatient setting, close follow-up, ideally every 4 to 6 weeks, enables clinicians and care teams to support lifestyle changes and address adverse effects or complications of antiobesity medications. Procedural and surgical follow-up is determined by bariatric teams.

Weight-Loss Maintenance and Long-Term Obesity Management

Maintaining weight loss is difficult and may be supported by continued clinical intervention.[123] In longitudinal observational studies, people who successfully maintain weight often use behavioral strategies, such as physical activity, regular self-weighing,[67] a reduced-calorie diet, and a consistent eating pattern.[124,125] Patients may need to increase their physical activity (>200 min/wk is often required).[5] As pharmacotherapy produces greater weight-loss maintenance than lifestyle alone (eg, STEP 3 Trial: difference, 10.3%; 95% CI, 8.6%-12.0%),[12,99] clinical guidelines support long-term antiobesity medication use.[4,10] Similar to other chronic diseases, lifelong monitoring and treatment escalation may be required over time. For example, rapid weight regain after bariatric surgery may signal a need for additional intervention, such as antiobesity medications.[9,126]

Limitations

This Review has several limitations. First, some relevant studies may have been missed. Second, a formal quality assessment of the literature was not performed. Third, many RCTs included relatively few people from racial and ethnic minority groups and relatively small proportions of men.[81,99] Fourth, some RCTs had relatively poor follow-up rates or short durations.[13,64] Fifth, some medications used for obesity, such as lisdexamfetamine for binge eating disorder or setmelanotide for rare forms of obesity, were beyond the scope of this Review.

Conclusions

Obesity affects approximately 42% of adults in the US. Behavioral interventions can attain approximately 5% to 10% weight loss, GLP-1 and glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonists attain approximately 8% to 21% weight loss, and bariatric surgery attains approximately 25% to 30% weight loss. Comprehensive, evidence-based obesity treatment combines behavioral interventions, nutrition, physical activity, pharmacotherapy, and metabolic/bariatric procedures as appropriate for individual patients.

ARTICLE INFORMATION

Accepted for Publication: September 15, 2023.

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Conflict of Interest Disclosures: Dr Schwartz reported receipt of research support from the Ardmore Institute of Health. Drs Schwartz and Gudzune reported receipt of a grant from Novo Nordisk (to develop and test a clinical decision support tool for obesity treatment in primary care settings). Dr Nicklas reported receiving research funding through her institution from the McGowan Charitable Fund, Eli Lilly, and Cleerly Inc. Dr Gudzune reported receipt of personal fees from Eli Lilly, Novo Nordisk, the American Board of Obesity Medicine, and Johns Hopkins ACG System. No other disclosures were reported.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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