Best Practices in the Management of Overweight and Obesity

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KEYWORDS

• Weight • Overweight • Obesity • Antiobesity medication • Bariatric surgery • Diet • Nutrition • Exercise

KEY POINTS

- Obesity is caused by dysregulated energy homeostasis pathways that encourage the accumulation of adiposity, which in turn results in the development or exacerbation of weight-related comorbidities.
- Obesity is a chronic disease that requires lifelong management.
- Weight reduction provides additional benefits for multiple comorbidities.
- Optimizing nutrition and physical activity is crucial to weight loss success.
- Pharmacotherapy or bariatric interventions can help patients achieve clinically significant weight loss when added to lifestyle modification.

INTRODUCTION

In 1998, the National Institutes of Health (NIH) recognized obesity as a disease, acknowledging its profound effects on individual health outcomes and socioeconomic costs.[1] The prevalence of obesity in the United States was 39.8% in 2015 to 2016[2] and is projected to be 48.9% by 2030.[3] It is linked to increased mortality and risks of cardiovascular disease (CVD), stroke, type 2 diabetes (T2D), and cancer.[4,5]

CAUSES AND PATHOPHYSIOLOGY

Obesity is caused by a state of neurohormonal imbalances in energy homeostasis that results in the development and defense of excess adiposity.[6] The hypothalamus is the

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primary center of energy regulation that communicates with the periphery to assess short-term and long-term energy status. It contains 2 populations of neurons that exert opposing effects on eating behavior (Fig. 1):

1. Orexigenic (increase appetite): agouti-related peptide (AgRP) and neuropeptide Y (NPY)
2. Anorexigenic (decrease appetite): proopiomelanocortin (POMC) and cocaine and amphetamine–regulated transcript (CART)

Rodent studies have shown that high-calorie diets cause inflammation in the hypothalamus and a reduction in POMC neurons.[7] In the periphery, adipocytes produce the anorexigenic hormone leptin to indicate the status of long-term energy reserves (ie, fat storage). Gastrointestinal (GI) peptides such as glucagonlike peptide-1 (GLP-1) signal the fed state by activating POMC/CART or suppressing AgRP/NPY. Ghrelin, the only known peripheral orexigenic hormone, stimulates AgRP.

The onset and severity of obesity caused by these pathophysiologic mechanisms are determined by genetics and the environment. The heritability of obesity, represented by body mass index (BMI), ranges from 40% to 70%.[6] Evolutions in food marketing and production, portion sizes, and occupation-related decreases in physical activity have also been identified as factors contributing to obesity.

Obesity is associated with several chronic diseases, with 2 predominant mechanisms to explain these effects: (1) mass effect and (2) adiposopathy.[8] In the former, the severity of diseases such as knee osteoarthritis and obesity hypoventilation syndrome are a direct response of the body to the weight of fat mass. In the latter,

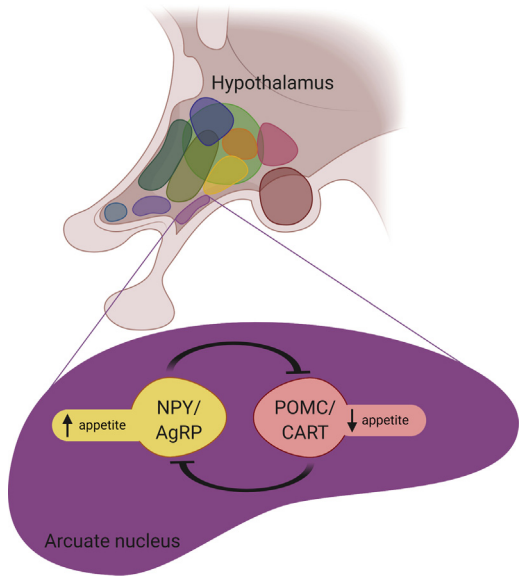

Fig. 1. Arcuate nucleus. The arcuate nucleus of the hypothalamus contains orexigenic (*yellow*) and anorexigenic (*red*) neurons that increase or decrease appetite. By communicating with the periphery, this nucleus is the primary energy homeostatic center of the brain. (*Courtesy of* Biorender, Toronto, Canada; with permission.) AgRP, Agouti-related peptide; CART, cocaine and amphetamine–regulated transcript; NPY, neuropeptide Y; POMC, proopiomelanocortin.

proinflammatory and prothrombotic cytokines, produced in the ischemic microenvironment of hypertrophic visceral adipocytes, lead to diseases such as T2D and CVD.

Clinical Evaluation

History

The clinical evaluation of a patient presenting for obesity management uses the standard interview process of the history of present illness (HPI), past medical history (PMH), past surgical history (PSH), social history, family history, medications, physical examination, and laboratory data.

The HPI should include a chronologic story of the patient's weight history that includes onset, duration, and precipitating and mitigating factors (**Table 1**). These open-ended questions allow the clinician to learn about the patient's behaviors while also providing an opportunity to explore the patient's nutrition knowledge, relationship with food, physical activity level, and life stressors.[9] PMH should focus on the identification of comorbidities associated with obesity, secondary causes of obesity, and potential contributors to obesity,[10] with the recognition that many of these relationships may be bidirectional[4] (**Box 1**).

PSH should include bariatric interventions (discussed later). Social history should include evaluation of nightshift work, pregnancy plans, smoking cessation, alcohol consumption, marijuana-induced hyperphagia, and stimulant use. Family history can assess the relative contribution of genetics versus environment to an individual's obesity and overall health status. Medication reconciliation must include both prescribed and over-the-counter medications because drug-induced weight gain is common and often missed (**Table 2**).[11]

Physical examination

Examination of patients with obesity includes standard blood pressure, heart rate, height, and weight measurements. Blood pressure cuffs of varied sizes and lengths should be available. Scales and examination room furniture with adequate weight capacities are also essential. Obesity severity is categorized by BMI class (**Table 3**), which may be adjusted for specific ethnic groups.[12] Because BMI does not distinguish between fat and muscle mass and does not account for distribution of adiposity, other measures of obesity that correlate to morbidity[5] have been entering clinical use, including waist circumference (WC), waist/hip ratio, and body fat percentage. WC is used to diagnose abdominal obesity, one of the components of the metabolic syndrome (see **Table 1**), and is commonly measured at the level of the anterior superior iliac spine.[1] The physical examination may require modification because standard techniques of inspection, palpation, and auscultation may be restricted by reduced mobility and increased subcutaneous adipose tissue. Practical suggestions for performing the examination include low-set examination tables, armless chairs, and enlisting the help of medical assistants for proper positioning. The clinician should look for signs of obesity-related complications (**Table 4**).

Laboratory data

Objective data to assess a patient's metabolic risk are a necessary component of the clinical evaluation (**Table 5**). Complete blood count and a comprehensive metabolic panel are essential. Patients should be screened for dyslipidemia and T2D.[4] Because thyroid-stimulating hormone (TSH) level is easily obtained and a higher prevalence of hypothyroidism exists in patients with obesity, TSH can be checked.[10] Assessment for other secondary causes of obesity and obesity-related comorbidities should be performed only if clinical suspicion exists.

Table 1
Initial evaluation of patients with obesity

HPI	General Questions
—	How did weight come to be a problem for you?
—	How long have you struggled with your weight?
—	Did any life events contribute to the weight issue? Onset after a diagnosis or initiation of a medication? Weights during or after high school, college, marriage, or pregnancy? Changes in employment or where you live? Weight gain around menopause?
—	What are the biggest challenges you face in losing weight or maintaining weight loss?
—	What has worked in the past to help you lose weight? Have you ever used medications for weight loss? Have you ever had weight loss surgery?
—	What is your lifetime weight range (nonpregnant)?
	Nutrition
—	Do you follow any special diet or have diet limitations for any reason?
—	How many meals per week do you eat in restaurants/order takeout?
—	What is your largest meal of the day?
—	Do you currently or have you ever had an eating disorder? Do you feel out of control when eating? Do you eat large volumes in a short period of time (binge)? Do you ever wake up in the middle of the night and eat?
	Physical Activity
—	What is your general activity level? How do you get to work?
—	Do you have an exercise routine?
—	Do you have any physical issues limiting your ability to be more active, other than weight?
PMH	**Secondary Causes or Contributors**
—	Single-gene mutations: leptin deficiency, MC4R deficiency Genetic syndromes: Prader-Willi Medications (see Table 2)
—	Cushing syndrome
—	Hypothyroidism
—	Male hypogonadism
—	Estrogen deficiency (menopause or premature ovarian failure)
—	PCOS
—	Growth hormone deficiency
	Physical Comorbidities
—	Metabolic syndrome

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Table 1
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HPI	General Questions
	• Waist circumference ○ >102 cm (40″) (non-Asian male), >89 cm (35″) (non-Asian female) ○ >89 cm (35″) (Asian male), >79 cm (31″) (Asian female) • Triglyceride levels ≥150 mg/dL or on triglyceride level–lowering medication • HDL level <40 mg/dL (male), <50 mg/dL (female), or on HDL level–increasing medication • Blood pressure ≥130/85 mm Hg or on antihypertensive agent • Fasting plasma glucose ≥100 mg/dL or on glucose level–lowering medication
—	Type 2 diabetes
—	Cardiovascular disease Hypertension Hyperlipidemia
—	Nonalcoholic fatty liver disease
—	Obstructive sleep apnea
—	Osteoarthritis
—	Cancer
	Psychological Comorbidities
—	Major depressive disorder
—	General anxiety disorder
—	Bipolar disorder, schizoaffective disorder, schizophrenia
—	Binge eating disorder
—	Anorexia nervosa, bulimia nervosa
PSH	Bariatric interventions Laparoscopic adjustable gastric band Laparoscopic sleeve gastrectomy Roux-en-Y gastric bypass Endoscopic sleeve gastroplasty Gastric balloon
Social history	Employment, shift work Sexual activity status, contraceptive use/method, and family planning Illicit substance use (eg, alcohol, smoking, marijuana, cocaine)
Family history	Obesity Type 2 diabetes, hyperlipidemia, hypertension, cardiovascular disease Cancer (especially medullary thyroid carcinoma)

Abbreviations: HDL, high-density lipoprotein; MC4R, melanocortin-4-receptor deficiency; PCOS, polycystic ovarian syndrome.
Data from Refs.[4,10,62]

Management

Guidelines recommend the following goals for weight management:[4,5]

• BMI ≤ 30 kg/m^2 without comorbidities	Avoid weight gain
• BMI 25–29.9 kg/m^2 with comorbidities	5%–10% weight loss over 6 mo
• BMI ≥ 30 kg/m^2	5%–10% weight loss over 6 mo

Box 1
Congestive heart failure and the obesity paradox

Some epidemiologic studies have suggested the existence of a so-called obesity paradox, in which higher BMIs are correlated to better outcomes in specific diseases, particularly congestive heart failure (CHF). Although experts unanimously agree that obesity increases the risk of incident CHF, once CHF is diagnosed mortalities seem to be lowest in the overweight and class I obesity ranges. However, subsequent investigations found that higher weights correlated with greater lean mass and better cardiorespiratory fitness, lending a potential explanation for the observed obesity paradox.

Data from Carbone S, Canada JM, Billingsley HE, Siddiqui MS, Elagizi A, Lavie CJ. Obesity paradox in cardiovascular disease: where do we stand? Vasc Health Risk Manag. 2019;15:89-100.

Depending on results from the diagnostic work-up, the clinician may be required to address secondary causes such as drug-induced weight gain (see **Table 2**) or refer to a specialist for endocrinologic disorders[10] and treatable genetic conditions.

Lifestyle modification

The foundation of obesity management is lifestyle modification. Intensive lifestyle interventions (ILIs) are classically structured as 14 sessions over 6 months that provide patients with education in nutrition, exercise, and behavior change.[5] The frequency of contact directly correlates to the magnitude of weight loss and durability of weight loss maintenance.

Nutrition

A caloric deficit is required for weight loss. Guidelines have recommended a daily caloric deficit of about 500 kcal,[4,5] which typically amounts to 1200 to 1500 kcal/d for women and 1500 to 1800 kcal/d for men. Very-low-calorie diets, defined as a caloric intake of 500 to 800 kcal/d, often use meal replacement shakes or bars and are effective short-term options that should be performed only under medical supervision.[5] More recently, a third strategy to achieve a hypocaloric diet has emerged, called intermittent fasting (IF). IF encompasses a variety of modalities in which individuals restrict their caloric intake based on time (eg, day of the week or time of day) (**Table 6**). Alternate-day fasting, in which "fasting" days of 500 to 800 kcal intake are alternated with usual intake, is comparable with continuous caloric restriction over 1 year.[13] Another option, called time-restricted feeding, reduces caloric intake by an average of 300 kcal/d when the window of consumption is condensed from 12 hours to 8 hours.[14]

The macronutrient composition of the ideal weight loss diet has been debated for decades. Robust data from randomized controlled trials (RCTs) of long duration[15,16] support the weight and health benefits of a low-fat diet, defined as less than or equal to 20% to 30% of total daily calories (**Table 7**).[5] For example, the Look Action for Health in Diabetes (Look AHEAD) trial showed that 50.3% of individuals randomized to ILI lost greater than or equal to 5% of baseline weight at 8 years, compared with 35.7% in the control group.[16] However, emerging evidence suggests that low-carbohydrate diets ($\leq$150 g/d) may have a metabolic advantage over low-fat diets because of reduction in insulin secretion[17] because insulin is anabolic and stimulates lipogenesis while suppressing lipolysis. Meta-analyses comparing low-carbohydrate with low-fat diets differ in their conclusions depending on the protocols of RCTs included.[18,19] Proponents of low-carbohydrate diets argue that their superiority is best demonstrated by the ketogenic diet, which establishes a nutritional ketosis via

Table 2
Drugs associated with weight gain and suggested alternatives

Category	Drug Class	Weight Gain	Alternatives
Psychiatry	Antipsychotics	Clozapine	Ziprasidone
		Risperidone	Lurasidone
		Olanzapine	
		Quetiapine	
		Haloperidol	
		Perphenazine	
		Quetiapine	
	Antidepressants/anxiolytics	TCAs	Bupropion[a]
		Amitriptyline	Fluoxetine
		Doxepin	Sertraline
		Imipramine	
		Nortriptyline	
		Trimipramine	
		Mirtazapine	
		SSRIs	
		Fluoxetine[b]	
		Sertraline[b]	
		Paroxetine	
		Fluvoxamine	
		MAOi	
		Phenelzine	
		Tranylcypromine	
	Mood stabilizer	Lithium	Topiramate[a]
Neurology	Anticonvulsants	Carbamazepine	Lamotrigine[b]
		Gabapentin	Topiramate[a]
		Valproate	Zonisamide
—	Sleep aids	Diphenhydramine-containing OTC agents	Melatonin
		Mirtazapine	Benzodiazepines
		Trazodone[b]	

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Table 2
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Category	Drug Class	Weight Gain	Alternatives
Endocrinology	Diabetes medications	Insulin Sulfonylureas Thiazolidinediones Sitagliptin[b] Meglitinides	Metformin[a] Acarbose Miglitol Pramlintide[a] Exenatide[a] Dulaglutide[a] Liraglutide[a] Semaglutide[a] Canagliflozin[a] Dapagliflozin[a] Empagliflozin[a] Ertugliflozin[a]
Obstetrics and gynecology	Contraceptives	Progestational steroids Medroxyprogesterone Injection Etonogestrel implant Levonorgestrel IUD	Barrier methods Nonhormonal IUD
Cardiology	Antihypertensives	α-Blockers[b] β-Blockers[b]	Carvedilol[b] ACEis[b] CCBs[b] ARBs

Allergy and immunology	Antihistamines	Diphenhydramine	Loratadine
		Cetirizine[b]	Decongestants
		Levocetirizine[b]	
		Fexofenadine[b]	
		Doxepin[b]	
		Cyproheptadine[b]	
	Immunosuppressants	Corticosteroids	NSAIDs
			Steroid inhalers[b]
Infectious disease	Antiretroviral therapy	Protease inhibitors	None

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-2 receptor blocker; CCBs, calcium channel blockers; IUD, intrauterine device; MAOi, monoamine oxidase inhibitor; NSAIDs, nonsteroidal antiinflammatory drugs; OTC, over the counter; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants.

[a] Medications known to reduce weight.

[b] Medications with poor-quality or mixed evidence for weight gain.

Adapted from Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline. The Journal of clinical endocrinology and metabolism. 2015;100(2):342-362; with permission.

Table 3
Classes of body mass index

	BMI (kg/m^2)
Overweight	25.0–29.9
Obesity, class I	30.0–34.9
Obesity, class II	35.0–39.9
Obesity, class III	≥40.0

Data from National Heart Lung and Blood Institute. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. Obesity Education Initiative. 1998;98-4083 and Garvey WT, Mechanick JI, Brett EM, et al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR MEDICAL CARE OF PATIENTS WITH OBESITY. Endocrine practice: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2016;22 Suppl 3:1-203.

Table 4
Potential physical examination findings in patients with obesity

Domain	Possible Findings	Associated Comorbidity
Head and neck	Supracervical or supraclavicular fullness	Hypercortisolism
	Moon facies	Hypercortisolism
	Poor visualization of soft palate or uvula	OSA
Cardiovascular	Tachycardia or irregular heart beat	Atrial fibrillation
	Valvular murmur	CHF
Lung	Wheezing	Reactive airway disease
Abdomen	Hepatomegaly	NAFLD
	Predominant truncal adiposity	Insulin resistance
Gonadal	Vaginal atrophy	Menopause
	Small testicular size	Hypogonadism
Neurologic	Reduced distal sensation to light touch, temperature, or vibration	T2D
Musculoskeletal	Enlarged joints	OA
	Reduced range of motion	OA
	Proximal muscle weakness	Hypercortisolism
Skin and hair	Erythematous rash within skin folds	Cutaneous candidiasis
	Skin tags	Insulin resistance
	Velvety hyperpigmentation in skin folds	Acanthosis nigricans
	Hirsutism	PCOS
	Excess acne	PCOS
	Wide hyperpigmented striae	Hypercortisolism
	Edema	CHF

Abbreviations: CHF, congestive heart failure; NAFLD, nonalcoholic fatty liver disease; OA, osteoarthritis; OSA, obstructive sleep apnea.

Table 5
Laboratory screening evaluation in obesity

Recommended	Reason for Screening
CBC	Standard of care Platelet count is used in calculated risk scores for hepatic fibrosis
CMP	Standard of care Increased liver function tests may be the first sign of NAFLD
Lipid profile	Dyslipidemia, hyperlipidemia, and hypertriglyceridemia are components of the metabolic syndrome and have high correlation with obesity/overweight Screening recommendations: USPSTF: age $\geq$ 20 y with obesity NCEP ATP III: age $\geq$ 20 y
Hemoglobin A1c	Prediabetes and T2D are components of the metabolic syndrome and have high correlation with obesity/overweight Screening recommendations: USPSTF: age $\geq$ 40 y with overweight or obesity ADA: overweight or obesity and at least 1 additional risk factor
TSH	Low-cost test for potential secondary cause or contributor to weight gain
Not Recommended	**Reason for not Screening**
Total testosterone	High prevalence of false-positive caused by low sex hormone binding globulin level in obesity
Free testosterone	Low free testosterone level commonly improves with weight loss and is not evidence of an independent disease
Estradiol, luteinizing hormone, follicle-stimulating hormone	Perimenopause and menopause have not been definitively established as causative factors
Insulin	Both fasting and postprandial insulin levels are highly dependent on macronutrient composition of recent dietary intake
Cortisol	Diurnal variations, circadian rhythm disruptions, and environmental stressors cause physiologic changes to cortisol levels and do not necessarily represent meaningful disorder
Leptin	Congenital leptin deficiency is an extremely rare monogenic obesity disorder

Abbreviations: ADA, American Diabetes Association; CBC, complete blood count; CMP, comprehensive metabolic panel; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; TSH, thyroid-stimulating hormone; USPSTF, United States Preventive Services Task Force.
Data from Refs.[63–66]

Table 6
Types of intermittent fasting

	Pattern of Eating
Alternate-day fast	Alternating days of hypocaloric intake with normal caloric intake
5:2	2 d/wk of hypocaloric intake (500–800 kcal/d), which can be consecutive or nonconsecutive
Fast mimicking	Hypocaloric intake (classically 600 kcal/d) for 5–14 d at a time, repeated monthly or as needed
Time-restricting feeding	Limiting daily caloric intake to designated hours of the day; caloric intake is not specified

Data from Refs.[13,14,67,68]

Table 7
Characteristics of common diets

	Carbohydrate	Fat	Protein
Macronutrient Restricted			
Low carbohydrate	≤150 g/d	Not standardized	Not standardized
Atkins	<20 g/d for 2 wk; can +5 g/d weekly for maintenance	Not standardized	High
Ketogenic	<20–50 g/d	High	Not standardized
Low fat	Not standardized	<20%–30%	Not standardized
Ornish	Not standardized	<10%	Not standardized
Diabetes Prevention Program	Not standardized	<30%	Not standardized
Zone	40%	30%	30%
Non–macronutrient Restricted			
DASH	Vegetables, fruits, whole grains, fat-free or low-fat dairy products, fish, poultry, beans, nuts, and vegetable oils		
Paleo	Vegetables, fruits, grass-produced meat, fish/seafood, eggs, nuts and seeds, nut/seed/fruit oils		
Vegan	No meat or animal products		
Vegetarian	No meat. Secondary animal products such as eggs, dairy, and cheese are allowed		
Pescatarian	Vegetarian with the allowance for fish		
Flexitarian	Mostly plant-based foods with occasional meat and animal products		

Abbreviation: DASH, Dietary Approaches to Stop Hypertension.
Data from U.S. News & World Report, Best Diets 2020. Available at: https://health.usnews.com/best-diet. Accessed on February 25, 2020.

high fat and very low carbohydrate consumption,[20] but long-term studies show poor adherence.[21] Diets that avoid specific macronutrient restriction, such as the Mediterranean diet[22] and MyPlate,[23] also have health benefits. Given the variety of dietary options, researchers have found weight loss efficacy is best predicted by adherence, not macronutrient composition.[24]

General consensus on the optimal timing of food intake seems to be that earlier is better.[25] A larger breakfast instead of a larger dinner results in more weight loss,[26] and earlier lunches or dinners result in better insulin-glucose profiles.[27,28] However, the addition of breakfast in individuals already skipping breakfast does not reduce evening caloric intake and may cause weight gain.[29]

Physical activity

The role of physical activity in weight management is 2-fold: to support an energy deficit and to preserve lean muscle mass. Total energy expenditure (TEE) is partitioned into basal metabolic rate (BMR), diet-induced thermogenesis (DIT), nonexercise activity thermogenesis (NEAT), and exercise (**Fig. 2**). Exercise, both cardiovascular and resistance training (RT), is the only component of TEE that is significantly modifiable. The combination of diet and exercise always results in greater weight loss than either modality alone.

The American College of Sports Medicine (ACSM) provides evidence-based recommendations for cardiovascular exercise to prevent weight gain, achieve weight loss, and maintain weight loss:[30]

• Weight maintenance	150–250 min/wk
• Weight loss	>150–420 min/wk
• Weight loss maintenance	200–300 min/wk

The individual's response to exercise is dose responsive and heterogeneous. For example, the landmark Midwest Exercise Trial-1 showed that a prescription of 225 min/wk of moderate-intensity cardiovascular exercise allowed most men to lose weight, but roughly 50% of women gained weight.[31]

RT plays an important role in weight loss maintenance because it preserves lean muscle mass, which determines BMR, and weight loss is accompanied by a reduction in BMR.[32] RT mitigates lean muscle loss in weight loss[30] and increases BMR and lean muscle mass when applied without a hypocaloric diet.[33,34]

Behavior

In addition to nutrition and physical activity modifications, behavioral changes also assist in weight loss success. Behavioral interventions are often delivered on a scheduled basis (eg, weekly or monthly education sessions) in person or electronically,[35] and can be in an individual or group setting. The tenets of behavioral treatment of obesity are goal setting, self-monitoring, and stimulus control (**Table 8**),[36] which have been shown to be beneficial in weight loss and weight loss maintenance.[37,38]

Fig. 2. Components of TEE. BMR is the largest contributor to TEE and cannot be directly modulated by daily activities. The types of physical activity, NEAT and exercise, are targets of many interventions to increase TEE.

Table 8
Behavioral treatment of obesity

Goal Setting	Self-monitoring	Stimulus Control
• Goals should be specific and feasible	• Food logging increases awareness of caloric and macronutrient intake	• Patients learn to modify external cues to create an environment more conducive to behavior change
• Individuals should report their successes or challenges at every session	• Electronic activity monitoring devices provide information about energy expenditure	• Uses problem-solving strategies, cognitive restructuring, stress management
• Promotes accountability	• Frequent weighing is associated with better weight loss maintenance	• Stress-related eating behaviors (binge eating, comfort eating, emotional eating) may require collaboration with psychologist or psychiatrist

Data from Butryn ML, Webb V, Wadden TA. Behavioral treatment of obesity. Psychiatr Clin North Am. 2011;34(4):841-859 and Burke LE, Wang J, Sevick MA. Self-Monitoring in Weight Loss: A Systematic Review of the Literature. J Am Diet Assoc. 2011;111(1):92-102.

Pharmacotherapy

Pharmacotherapy for weight loss (**Table 9**) should be considered to help patients achieve targeted weight loss and health goals as an adjunct to comprehensive lifestyle intervention for individuals who are motivated to lose weight and have a BMI greater than or equal to 30 kg/m^2 or a BMI greater than or equal to 27 kg/m^2 with at least 1 obesity-associated comorbidity (eg, T2D, hypertension, hyperlipidemia, and obstructive sleep apnea).[39] The rationale for adding antiobesity medication (AOM) to lifestyle modifications is 2-fold:

1. To help patients adhere to a lower-calorie diet more consistently to achieve weight loss and improve health[5]
2. To directly address the pathophysiologic mechanisms that cause weight gain and the metabolic adaptations that drive weight regain[32,40]

Before starting a medication for weight loss, it is important to discuss with patients that obesity is a chronic disease that may require long-term treatment.

Phentermine

Phentermine is an adrenergic agonist that leads to weight loss by activation of the sympathetic nervous system with a subsequent decrease in appetite and increase in BMR.[41,42] It remains the most frequently prescribed AOM. Phentermine as a monotherapy is only US Food and Drug Administration (FDA)–approved for short-term use (3 months), but, in clinical practice, many practitioners prescribe it for a longer duration. The recommended dosage of phentermine is 15 to 37.5 mg orally once daily in the morning.[43] Low-dose phentermine is available as a scored 8-mg tablet that can be prescribed up to 3 times per day.

Optimal candidates for phentermine include patients with obesity who need assistance with appetite suppression. Because of the mild increase in heart rate and/or

Table 9
Summary of antiobesity medications

Medication (Year Approved)	Mechanism of Action and Typical Dosage	Trial	Trial Arms	Average Weight Loss (%)	≥5% TBW (%)	≥10% TBW (%)	Most Common Side Effects
Phentermine (1959, schedule IV controlled substance)	Adrenergic agonist Typical dosing: 8–37.5 mg QAM	Aronne et al[43] 28 wk	15 mg daily 7.5 mg daily Placebo [a]Topiramate ER and phentermine/topiramate ER arms excluded	6.1[a] 5.5[a] 1.7	46.2 43.3 15.5	20.8 12.5 6.8	Dry mouth, difficulty sleeping, irritability
Orlistat (1999)	Lipase inhibitor Typical dosing: 60–120 mg TID with meals	XENDOS 208 wk	120 mg TID (week 52) 120 mg TID (week 208) Placebo (week 52) Placebo (week 208)	9.6[a] 5.3[a] 5.6 2.7	72.8 52.8 45.1 37.3	41.0 26.2 20.8 15.6	Fecal urgency, oily stool, flatus with discharge, fecal incontinence
Phentermine/topiramate ER (2012, schedule IV controlled substance)	Adrenergic agonist/neurostabilizer Typical dose titration: 3.75/23 mg daily for 2 wk, increasing to 7.5/46 mg daily, with further dose escalation as needed/tolerated thereafter	EQUIP 56 wk CONQUER 56 wk SEQUEL 108 wk (52-wk extension of CONQUER trial)	15/92 mg daily 3.75/23 mg daily Placebo 15/92 mg daily 7.5/46 mg daily Placebo 15/92 mg daily 7.5/46 mg daily Placebo	10.9[a] 5.1[a] 1.6 9.8[a] 7.8[a] 1.2 10.5[a] 9.3[a] 1.8	66.7 44.9 17.3 70.0 62.1 20.8 79.3 75.2 30.0	47.2 18.8 7.4 47.6 37.3 7.4 53.9 50.3 11.5	Paresthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth

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Table 9
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Medication (Year Approved)	Mechanism of Action and Typical Dosage	Trial	Trial Arms	Average Weight Loss (%)	≥5% TBW (%)	≥10% TBW (%)	Most Common Side Effects
	(11.25/69 mg, then 15/92 mg)			Data from weeks 0–108			
Naltrexone/bupropion ER (2014)	Opioid receptor antagonist/dopamine and norepinephrine reuptake inhibitor Typical dose titration: Week 1: 8/90 mg QAM Week 2: 8/90 mg BID Week 3:16/180 mg QAM, 8/90 mg QPM Week 4 (and beyond): 16/180 mg BID	COR-I 56 wk COR-II 56 wk COR-BMOD 56 wk COR-DIABETES 56 wk	16/180 mg BID 8/180 mg BID Placebo 16/180 mg BID Placebo 16/180 mg BID Placebo 16/180 mg BID Placebo	6.1[a] 5.0[a] 1.3 6.4[a] 1.2 9.3[a] 5.1 5.0[a] 1.8	48.0 39.5 16.4 50.2 17.1 66.4 42.5 44.5 18.9	24.6 20.2 7.4 28.3 5.7 41.5 20.2 18.5 5.7	Nausea, constipation, headache, dizziness, insomnia, dry mouth
Liraglutide 3.0 mg (2014)	GLP-1 receptor agonist Typical dose titration: Week 1: 0.6 mg daily Week 2: 1.2 mg daily Week 3: 1.8 mg daily Week 4: 2.4 mg daily Week 5 (and beyond): 3.0 mg daily	SCALE Obesity and Prediabetes 56 wk SCALE Diabetes 56 wk SCALE Maintenance 56 wk (after initial ≥5% weight loss with LCD)	3.0 mg daily Placebo 3.0 mg daily 1.8 mg daily Placebo 3.0 mg daily Placebo	8.0[a] 2.6 6[a] 4.7[a] 2.0 6.2[a] 0.2	63.2 27.1 54.3 40.4 21.4 50.5 21.8	33.1 10.6 25.2 15.9 6.7 26.1 6.3	Nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain

Abbreviations: BID, twice daily; ER, extended release; LCD, low-calorie diet; QAM, every morning; QPM, every evening; TBW, total body weight; TID, thrice daily; XENDOS, Xenical in the Prevention of Diabetes in Obese Subjects.

[a] *P*<.001 versus placebo.

Adapted from Igel LI, Kumar RB, Saunders KH, Aronne LJ. Practical Use of Pharmacotherapy for Obesity. Gastroenterology. 2017 Feb 9. pii: S0016-5085(17)30142-7; with permission.

blood pressure that can accompany phentermine use, this medication is generally used in younger patients without evidence of unstable coronary disease or uncontrolled hypertension. Patients who have anxiety or insomnia may find these conditions exacerbated by phentermine and would not be ideal candidates.

Orlistat

Orlistat promotes weight loss by inhibiting gastrointestinal lipases, thereby decreasing the absorption of fat from the gastrointestinal tract. Orlistat 120 mg ingested 3 times per day with meals decreases fat absorption by approximately 30%.[44] Half-strength orlistat (60 mg) ingested 3 times daily is approved for over-the-counter use.

Orlistat can lead to gastrointestinal side effects, which can often be ameliorated by following a balanced, reduced-calorie diet with no more than ~30% of calories from fat at any meal.[45] The addition of a fiber supplement can also be helpful. Orlistat decreases the absorption of fat-soluble vitamins (A, D, E, and K), and patients should be instructed to take a multivitamin (separately from the medication) to ensure adequate nutrition.

Optimal candidates for orlistat use include patients with obesity and constipation and/or concomitant hypercholesterolemia. Orlistat is contraindicated in patients with malabsorptive syndromes or cholestasis.

Phentermine/topiramate extended release

Phentermine/topiramate extended release (ER) combines the sympathomimetic amine phentermine (discussed earlier) with topiramate ER. Topiramate monotherapy is FDA approved for epilepsy as well as migraine prophylaxis and has been found to decrease caloric intake and reduce cravings via GABA (gamma-aminobutyric acid) and glutamate modulation as well as carbonic anhydrase inhibition. The combination of phentermine plus topiramate ER leads to additive weight loss by targeting different appetite pathways simultaneously. Phentermine/topiramate is available in 4 doses: 3.75/23 mg, 7.5/46 mg, 11.25/69 mg, and 15/92 mg.

Ideal candidates for phentermine/topiramate ER include younger patients with obesity (because older patients may have undiagnosed heart disease that could potentially be worsened by sympathomimetics) and patients with concomitant migraines who could benefit from the appetite suppressant effects of the agent. Because of the phentermine component, this medication should not be prescribed to patients with a history of CVD or other conditions that could be exacerbated by a stimulant. In addition, because of teratogenicity associated with topiramate, the FDA requires a risk evaluation and mitigation strategy to inform prescribers and female patients of reproductive potential about the possible increased risk of orofacial clefts in infants exposed to topiramate during the first trimester of pregnancy.[46–48]

Naltrexone/bupropion extended release

Naltrexone/bupropion combines the dopamine/norepinephrine reuptake inhibitor bupropion with the opioid antagonist naltrexone. Bupropion monotherapy is FDA approved as an antidepressant and to assist with smoking cessation. Inhibiting reuptake of dopamine and norepinephrine modulates the central reward pathways triggered by food. Naltrexone monotherapy is FDA approved for the treatment of alcohol and opioid dependence. Naltrexone antagonizes an inhibitory feedback loop that would otherwise limit bupropion's anorectic properties, and the combination of naltrexone/bupropion has been shown to activate POMC neurons in the arcuate nucleus of the hypothalamus.[49]

Naltrexone/bupropion should be avoided in patients with uncontrolled hypertension, uncontrolled pain, history of seizures, or any condition that predisposes to

seizure, such as anorexia or bulimia nervosa, or abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs. Bupropion carries a black box warning related to a potential increase in suicidal thoughts in young adults (< 24 years old) within the first few months of treatment initiation, and patients should be monitored closely for any mood changes (although no evidence of suicidality was reported in phase III studies).[50–53]

Ideal candidates for naltrexone/bupropion include patients who describe strong cravings for food and/or addictive behaviors related to food. Patients who have concomitant depression, are trying to quit smoking or decrease alcohol consumption are also good candidates.

Liraglutide 3.0

Liraglutide is a GLP-1 receptor agonist that is also FDA approved for the treatment of T2D in doses up to 1.8 mg daily. Liraglutide works both centrally (eg, the hypothalamus) and in the gastrointestinal tract to delay gastric emptying and decrease food intake as well as subjective hunger.[54,55]

Liraglutide carries a black box warning related to an association with medullary thyroid cancer (MTC) in rodents, although the relevance to humans has not been determined. Nonetheless, liraglutide is contraindicated in patients who have had MTC or who have a family history of multiple endocrine neoplasia type 2.[55] Concomitant use of liraglutide with insulin or insulin secretagogues increases the risk of hypoglycemia.

Ideal patients for liraglutide include those with overweight or obesity who report inadequate meal satiety, and/or have T2D, prediabetes, or impaired glucose tolerance. Liraglutide is not appropriate for patients with an aversion to needles, because it requires a daily subcutaneous injection.

Bariatric surgery and devices

Bariatric surgery results in greater improvement in weight loss outcomes and weight-associated comorbidities compared with nonsurgical interventions.[56] The 3 most commonly performed procedures in the United States are the laparoscopic sleeve gastrectomy (LSG), the Roux-en-Y gastric bypass (RYGB), and the laparoscopic adjustable gastric band (LAGB) (**Table 10**).[57] Bariatric surgery should be considered in patients who are motivated to lose weight but have not achieved sufficient weight loss for target health goals following behavioral treatment, with or without pharmacotherapy.[57] Patients should have a BMI greater than or equal to 40 kg/m^2 or a BMI greater than or equal to 35 kg/m^2 with at least 1 significant obesity-related comorbid condition, such as obstructive sleep apnea.[58]

The LSG and RYGB are performed more frequently than the LAGB because they are associated with greater weight reduction, better management of obesity-associated comorbidities, and fewer adverse events.[5] Contraindications include poor adherence to medical treatment, severe psychological disorders, and illnesses that significantly reduce life expectancy and are unlikely to improve with weight loss. Better outcomes are achieved when patients commit to long-term lifestyle changes and medical follow-up; however, most patients regain some weight.

Laparoscopic sleeve gastrectomy

LSG removes ~70% of the stomach along the greater curvature. The fundus, which secretes the hunger hormone ghrelin, is removed. The remaining stomach is shaped like a sleeve and the pyloric sphincter remains intact. There is a lower risk of nutritional deficiencies with LSG compared with RYGB, and LSG is associated with fewer

Table 10
Most commonly performed bariatric surgeries

Procedure	Description	Total Body Weight Loss at One Year (%)	Reversibility	Procedures Performed in 2018 (%)
LSG	~70% of stomach removed along greater curvature	25	No	61.4
RYGB	Small pouch (~<50 mL) created from proximal stomach and attached to jejunum, bypasses most of stomach, duodenum, and most of jejunum	30	Yes (rarely done)	17.0
LAGB	Inflatable silicone band placed around fundus of stomach to create small pouch (~30 mL); pouch capacity adjusted by increasing or decreasing quantity of saline in band via subcutaneous port	15–20	Yes	1.1

Data from Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. N Engl J Med. 2017;376:254-266 and American Society for Metabolic and Bariatric Surgery. Estimate of Bariatric Surgery Numbers, 2011-2018. Available at: https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers. Accessed February 24, 2020.

complications than RYGB and LAGB. Early adverse events include bleeding, stenosis, leakage at the staple line, reflux, and vomiting; late complications include stomach expansion, which can lead to decreased restriction.[56] Unlike RYGB and LAGB, LSG is not reversible.

Roux-en-Y gastric bypass

In the RYGB, a small pouch is created from the proximal stomach and attached to the jejunum, thereby bypassing the rest of the stomach, the duodenum, and most of the jejunum. There is a lower rate of gastroesophageal reflux following RYGB compared with LSG; RYGB can often improve symptoms of reflux. Early adverse events include obstruction, stricture, leakage, and failure of the staple line; late adverse events include anastomosis ulceration and nutritional deficiencies.[56] Dumping syndrome can develop at any time. The RYGB is technically reversible; however, it is generally only reversed in extreme situations.

Laparoscopic adjustable gastric band

The LAGB is an inflatable band that is placed around the fundus of the stomach in order to produce a small, proximal pouch. The capacity of the pouch is adjusted by adding or removing saline to the band through a subcutaneous port. Although the procedure is reversible and less invasive than LSG and RYGB, many bands are eventually removed because of insufficient weight loss and/or complications.[59] The most common adverse events include nausea, vomiting, reflux, obstruction, band erosion, and band migration.[60]

Antiobesity devices

Devices are emerging as options for the treatment of obesity (**Table 11**). Not only are they minimally invasive and reversible but they are potentially more effective than AOMs, generally safer for poor surgical candidates, and possibly less expensive than bariatric surgery.[61] The 5 FDA-approved devices are 2 intragastric balloons, an aspiration device, superabsorbent hydrogel capsules, and the TransPyloric Shuttle. Although the devices are not widely used currently, they may become more widespread in the future as more health care providers are trained to use them and insurance coverage improves.

Table 11
Devices approved for overweight and obesity by the Food and Drug Administration

Device (Year Approved)	BMI Indication (kg/m^2)	Description	Total Body Weight Loss (%)	Duration of Intervention (mo)
Orbera Intragastric Balloon (2015)	30–40	Endoscopically placed intragastric balloon filled with 400–700 mL of saline, removed endoscopically after 6 mo	Device: 10.2 Sham: 3.3	6
Obalon Balloon System (2016)	30–40	3 sequentially swallowed balloons filled with 250 mL of gas each, removed endoscopically 6 mo after first balloon placed	Device: 6.6 Sham: 3.4	6
AspireAssist (2016)	35–55	Endoscopically placed percutaneous gastrostomy aspiration tube; 30% of each meal removed from the stomach	Device: 12.1 Lifestyle alone[a]:3.5	12
Plenity (2019)	25–40	Capsules containing superabsorbent hydrogel, occupy one-quarter of stomach volume when hydrated, 3 capsules (2.25 g/dose) administered with water before lunch and dinner	Device: 6.4 Placebo: 4.4	6
TransPyloric Shuttle (2019)	30–40	Endoscopically placed device comprising a large spherical bulb (above pylorus) attached to small cylindrical weight (moves freely in duodenum); removed endoscopically after 12 mo	Device: 9.5 Sham: 2.8	12

[a] Lifestyle comprises diet and exercise counseling.
Data from Refs.[69–80]

Intragastric balloons

Intragastric balloons are space-occupying devices that are placed in the stomach to reduce functional gastric volume. The Orbera balloon is placed endoscopically and filled with 400 to 700 mL of saline. After 6 months, it is removed endoscopically. The Obalon balloon system comprises 3 balloons, which are swallowed as capsules sequentially over 3 months. Each balloon is filled with 250 mL of gas. Six months after the first balloon is placed, the 3 balloons are removed endoscopically.

Aspiration therapy

The AspireAssist device consists of a percutaneous gastrostomy tube that is placed endoscopically and attached to an external aspiration port positioned at the abdominal surface. Patients must chew thoroughly and drink sufficient liquid with each meal so that food particles are 5 mm or less in diameter to flow through the gastrostomy tube in a slurry. After each meal, patients aspirate 30% of ingested food.

Hydrogel capsules

Plenity is a capsule composed of superabsorbent hydrogel particles. When capsules are taken with water before a meal, they can absorb up to 100 times their weight in water to occupy a quarter of average stomach volume. The recommended dose is 3 capsules (2.25 g/dose) before lunch and dinner.

TransPyloric Shuttle

The TransPyloric Shuttle is a device composed of a large spherical bulb connected to a small cylindrical weight. Following endoscopic placement, an overtube facilitates coiling of a silicone cord into the bulb. Although the weight moves freely in the duodenum, the bulb remains above the pylorus to prevent migration. Peristaltic contractions result in intermittent gastric outlet obstruction and delayed gastric emptying.

Future directions

Although the primary tools of obesity management remain lifestyle modification, pharmacotherapy, and bariatric interventions, the future of obesity medicine is rapidly evolving to accommodate the variety of patients who present for weight management. Nutrition science is investigating genome-based diets to provide precision medicine and is finding nutrient sequencing (ie, the order in which macronutrients are ingested) can also affect hormonal responses and weight management. The microbiome is playing a growing role in how energy regulation is understood. AOMs are expanding to include triple agonists/antagonists to address the multiple pathophysiologic mechanisms that drive weight gain. New nonsurgical bariatric interventions, such as the endoscopic sleeve gastroplasty, are also emerging tools. The future of obesity management is progressing toward multimodal approaches that optimize the complimentary effects of lifestyle changes, medications, and procedures.

SUMMARY

Obesity is a chronic disease caused by dysregulated energy homeostasis pathways that encourage the accumulation of adiposity, which, in turn, results in the development or exacerbation of weight-related comorbidities. Treatment of obesity relies on a foundation of lifestyle modification. Weight loss pharmacotherapy, bariatric surgeries, and novel devices are additional tools to help patients achieve their health and weight goals. Appropriate management of patients with obesity provides multiple metabolic benefits beyond weight loss.

CLINICS CARE POINTS

- Obesity is a chronic disease caused by dysfunctional communication pathways between hypothalamic and peripheral orexigenic and anorexigenic signals, which is propagated by both genetics and environmental stressors.
- Treatment of obesity requires lifelong management, but the metabolic benefits of weight reduction extend beyond weight loss alone.
- Because many diets have been shown to be effective for weight loss, nutrition advice should be individualized to each patient to optimize adherence.
- Aerobic exercise and RT are tools to support weight loss, weight maintenance, and general health.
- AOMs help patients achieve clinically significant weight loss when added to lifestyle modification; the choice of AOM depends on the potential benefits and side effects in each individual.
- Bariatric surgery is an option for eligible patients with proven efficacy and durability in improving morbidity and mortality.
- Bariatric devices are a growing field of intervention that can further support patients in achieving their weight loss goals.

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