

# Obesity and Its Medical Management

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**O**besity is well recognized as a serious and growing public health problem. In the United States, nearly one third of adults over age 20 years are obese (defined as a body mass index [BMI] of  $\geq 30$  kg/m<sup>2</sup>) and another one third are overweight (BMI of 25–29.9 kg/m<sup>2</sup>), according to national survey data.<sup>1</sup> Furthermore, studies suggest that the prevalence of obesity is on the rise in adults as well as in children and adolescents.<sup>2–5</sup> These trends are concerning as obesity and being overweight are associated with increased morbidity and all-cause mortality, with the risk related to the amount of extra body fat, the distribution of fat, and the age of patients.<sup>6–9</sup> Overweight and obese persons are at increased risk for developing serious medical conditions such as diabetes mellitus, hypertension, and cardiovascular disease, and obese persons are at increased risk of death from cardiovascular disease, diabetes, kidney disease, and cancer.<sup>7,10,11</sup> Modest weight loss (ie, 5%–10% of current weight) is sufficient to modify the clinical complications and mortality risk associated with being overweight and obesity.<sup>12–14</sup> However, achieving and maintaining even small weight reductions can be difficult for most people because it requires significant lifestyle changes with respect to eating habits and physical activity level. This article reviews the assessment and diagnosis of obesity and discusses options for promoting weight loss with a focus on nonsurgical therapies.

## MECHANISMS OF OBESITY

Most cases of obesity result from a sedentary lifestyle and food consumption that is excessive, inappropriate, or both. A survey by the Centers for Disease Control and Prevention concluded that more than 50% of the US population does not engage in the recommended minimum amount of exercise,<sup>15</sup> which is 30 minutes of moderate physical activity 3 times a week. An imbalance between energy intake and expenditure results in storage of energy as body fat. Intake of energy in the form of food and nutrients and its subsequent utilization and/or storage are regulated by a feedback control system that consists of hormones, neurotransmitters, and the central

**TAKE HOME POINTS**

- Loss of 5% to 15% of initial weight has been shown to be sufficient to reduce morbidity associated with obesity (body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>).
- For weight loss to occur, caloric expenditure from the resting metabolic rate and daily activities must exceed caloric intake; thus, diet and exercise are the cornerstones to achieving and maintaining weight loss.
- In counseling patients on lifestyle changes, it is important to set realistic goals in all aspects of weight management.
- Behavioral treatment can help patients achieve short-term loss of 7% to 10% of initial weight and maintain losses for up to 18 months.
- Weight-loss medications can be useful adjuncts to diet and exercise for obese patients with a BMI greater than 30 kg/m<sup>2</sup> and in overweight patients with a BMI greater than 27 kg/m<sup>2</sup> and comorbid conditions.
- It is important to explain to patients that lifestyle modification efforts must be continued while they try weight loss medications.

nervous system.<sup>16</sup> Ghrelin, growth hormone–releasing hormone, neuropeptide Y, melanocyte-concentrating hormone, peptide YY, and insulin increase appetite and decrease energy expenditure, while cholecystokinin, enterostatin, glucagon, leptin, and brain-derived neurotrophic factor suppress food intake and increase energy

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**Table 1.** Causes of Obesity

Excessive/inappropriate food intake
Sedentary lifestyle
Genetic disorders with obesity
Prader-Willi syndrome
Bardet-Biedl syndrome
Carpenter's syndrome (acrocephalopolysyndactyly type II)
Cohen syndrome
Endocrine disorders
Cushing's syndrome
Hypothalamic tumors/inflammation/trauma
Hypothyroidism
Polycystic ovary syndrome
Insulinoma
Drugs
Antipsychotics, especially atypical agents
Tricyclic antidepressants
Sulfonylureas
Insulin
β Blockers
Corticosteroids
Estrogen
Progestins

expenditure. Although the function of this system is to match energy intake to meet energy demand, when energy intake exceeds demand, weight gain is the result. Once weight gain occurs, the actions of this system to regulate energy storage make weight loss difficult.<sup>16</sup>

Although lifestyle factors are the predominant cause of obesity, other factors may underlie the development of excessive weight gain, including disturbances of hormones, use of new medications, and genetic factors (**Table 1**). Obesity is a feature of some single-gene disorders (eg, Prader-Willi syndrome), but these disorders are an uncommon cause of obesity in the general population. Furthermore, although studies suggest the existence of genetic factors in obesity,<sup>17,18</sup> genes contributing to obesity have not been clearly identified. Candidate genes for the genetic basis of obesity include the beta-3-adrenergic receptor gene,<sup>19</sup> peroxisome proliferator-activated receptor gamma 2 gene,<sup>20</sup> and the genes encoding the melanocortin-4 receptor as well as leptin and its receptors. An analysis of a contemporary cohort of 5092 pairs of twins aged 8 to 11 years quantified the relative contributions of genetic and environmental influences on BMI and abdominal adiposity.<sup>21</sup> Genetics contributed 40% to BMI and abdominal

adiposity, while environment contributed only 10%, suggesting that humans may be programmed to be obese, the environment permitting.

Studies of leptin illustrate the link between genetics, biochemical factors, and obesity. Leptin is a hormone secreted by adipocytes that provides a negative feedback signal to the brain to decrease energy intake. Deficiency in leptin as well as genetic defects in the leptin receptor are known to cause obesity in mice and have been proposed to play a role in obesity in humans.<sup>22</sup> Obesity due to leptin deficiency has been described in 2 consanguineous families in whom administration of leptin led to a marked decrease in weight similar to that seen in leptin-deficient mice.<sup>23</sup> However, most obese people do not have abnormalities of the leptin gene but rather have high serum leptin levels. Leptin resistance may be a consequence of obesity as chronic sustained leptin secretion from adipocytes is thought to lead to down-regulation of leptin receptor sensitivity.

#### EVALUATION OF OBESITY

The evaluation of the obese patient includes calculation of BMI and measurement of waist circumference, exploration of causes of weight gain, and investigation of comorbid conditions associated with obesity. BMI relates weight to height ( $\text{BMI} = \text{weight [kg]} / \text{height [m}^2\text{]})$  and is an easy method for assessing body fat. Both the National Heart, Lung, and Blood Institute and the World Health Organization (WHO) use BMI to define overweight and obesity. Overweight is defined as a BMI of 25 to 29.9 kg/m<sup>2</sup>, obesity as a BMI of 30 kg/m<sup>2</sup> or greater, moderate obesity as a BMI of 35 to 39.9 kg/m<sup>2</sup>, and severe obesity as a BMI of 40 kg/m<sup>2</sup> or greater. Currently, these classifications are applied to whites, Hispanics, and African Americans, although there is ongoing debate regarding the need for adjusted BMI cut-offs for different populations and ethnic groups. For Asians, overweight is defined as a BMI of 23 to 29.9 kg/m<sup>2</sup>. A recent WHO consultation reported that a substantial proportion of Asians are at high risk for type 2 diabetes mellitus and cardiovascular disease at a BMI lower than the traditional cut-off of 23 kg/m<sup>2</sup> for overweight.<sup>24</sup> However, since the cut-off for the risk varied among various Asian populations, the WHO has retained the current classification but included lower BMI as points of public health action. It is also important to note that BMI may overestimate body fat in patients who have a higher weight due to increased muscle mass (eg, athletes).

Waist circumference measured at the natural waistline or the narrowest aspect of the torso is easy to obtain and serves as an estimate of abdominal fat.

Assessing waist circumference is important because even when weight is nearly normal the presence of central adiposity and abdominal obesity confers a higher risk for morbidity and mortality.<sup>25,26</sup> Waist circumference of greater than 102 cm in men and greater than 88 cm in women is associated with higher risk of developing hypertension, diabetes, and dyslipidemia in those with a BMI of 25 to 34.9 kg/m<sup>2</sup>.<sup>27</sup> Values for waist circumference also vary with race and are lower for Asians, with values greater than 80 cm in women and greater than 90 cm in men being abnormal. Calculation of the waist-to-hips ratio (circumference of waist divided by circumference of the hips) as a method to assess central obesity has fallen out of favor since waist circumference is easier to measure and epidemiologic studies have shown that waist circumference is a better marker for abdominal obesity and more predictive of cardiovascular risk factors.<sup>28,29</sup>

History taking is directed at determining details regarding the onset and course of weight gain, previous attempts to manage weight gain, and the patient's diet and level of physical activity as well as motivation to change lifestyle. It also assesses whether any underlying conditions that cause obesity or any comorbidities associated with obesity are present (**Table 2**). A review of all medications is important in identifying underlying illnesses, comorbidities, and agents that may contribute to weight gain. In addition to assessing BMI, physical examination should include a search for evidence of treatable causes of obesity and documentation of comorbidities (eg, the presence of hypertension or arthritis that could limit a patient's exercise program). Evaluation for hypertension, coronary artery disease, sleep apnea, diabetes, and arthritis can be accomplished by measuring blood pressure, inquiring about a history of angina or snoring and daytime fatigue, measuring blood glucose, and noting painful or swollen joints on examination.

Laboratory evaluation is based on the findings of the history and physical examination and the concern for delineating treatable causes of obesity (eg, hypothyroidism or Cushing's disease) and identifying comorbidities. A complete blood count, comprehensive metabolic profile, lipid profile, and measurement of thyroid-stimulating hormone represent a reasonable starting point. However, an individualized approach to laboratory evaluation is required, with some patients needing a more comprehensive evaluation.

## MANAGEMENT

Several groups have issued guidelines to assist physicians in making risk-benefit evaluations and deciding

**Table 2.** Complications Associated with Obesity

Cardiovascular	Coronary artery disease, stroke, congestive heart failure, hypertension, dysrhythmias, pulmonary embolism
Pulmonary	Obstructive sleep apnea and obesity hypoventilation syndrome
Endocrine	Metabolic syndrome, insulin resistance, dyslipidemia, diabetes mellitus type 2, polycystic ovary syndrome
Gastrointestinal	Gallstones, abdominal hernia, nonalcoholic fatty liver disease, gastroesophageal reflux disease
Bone, joint, and skin	Osteoarthritis, low back pain, gout, acanthosis nigricans
Vascular	Venous stasis
Neurologic	Pseudotumor cerebri
Gynecologic/genitourinary	Stress incontinence, sexual dysfunction, abnormal menses

NOTE: Obesity is also associated with cancer of the esophagus, colon, pancreas, liver, prostate, breast, endometrium, cervix, and ovaries.

on therapy in the management of overweight and obese adults.<sup>30-32</sup> These guidelines recommend counseling all patients who are overweight (BMI > 25 kg/m<sup>2</sup>) or obese (BMI ≥ 30 kg/m<sup>2</sup>) with regard to diet and exercise; considering pharmacologic therapy for patients who fail to achieve weight loss with diet and exercise alone; and considering bariatric surgery for patients with severe obesity (BMI ≥ 40 kg/m<sup>2</sup>) who have failed diet and exercise (with or without drug therapy) as well as for patients with moderate obesity (BMI of 35-39.9 kg/m<sup>2</sup>) who have obesity-related comorbidities (eg, hypertension, impaired glucose tolerance, diabetes mellitus, dyslipidemia, sleep apnea). Successful weight loss involves a combination of modalities, including diet, exercise, behavior modification, and, in certain subsets of patients, drug therapy and/or bariatric surgery. The following sections review each of these weight loss modalities.

## Diet

To achieve weight loss, caloric expenditure from the resting metabolic rate and daily activities must exceed caloric intake. Discussing this physiologic requirement makes it easier for both the physician and the patient to have realistic expectations about the degree of weight loss that may be achieved with diet. A person weighing 100 kg requires 2200 kcal daily to remain in caloric balance as approximately 22 kcal are required to maintain 1 kg of body weight. A daily diet consisting of 1600 calories would produce a caloric deficit of 600 kcal/day and should result in a weight loss of nearly 0.5 kg per week. Thus, loss of more than 0.5 to 1 kg per week is

unrealistic for most diets. In terms of overall goals, loss of 5% of the initial body weight can be considered satisfactory since weight loss of 5% to 15% is associated with a significant reduction in comorbidities.<sup>33,34</sup> If for the first 3 months the loss of weight is less than 0.5 to 1 kg per week in spite of following a good dietary regimen, other options can be tried, including intensifying the diet restriction.

The most common diets are low-carbohydrate diets and low-fat diets. Low-carbohydrate diets without restriction of energy intake have been shown to be more efficacious than low-fat diets with energy restriction for short-term weight loss, but this difference was not maintained at 1 year.<sup>35</sup> Although low-fat diets have been shown to help in weight loss,<sup>36,37</sup> restriction of fat without a change in overall energy intake does not lead to weight loss.<sup>38</sup> Most dietary guidelines recommend that daily fat intake should be approximately 30% or less of total energy intake. A randomized trial comparing 4 commercial diets of various compositions (Atkins [low carbohydrate], Ornish [low fat], Weight Watchers [low calorie], and Zone [macronutrient balance] diets) found a similar modest mean weight loss at 1 year for all 4 diets (2.1–3.3 kg).<sup>39</sup> A study that compared a low-carbohydrate with a low-fat and a Mediterranean diet showed similar effects on weight loss, but the low-carbohydrate diet had more favorable effects on lipid levels and the Mediterranean diet had more favorable effects on glycemic control.<sup>40</sup> Weight loss was associated with adherence to diet but not to diet type. Another recent study that compared weight-loss diets with different compositions of fat, protein, and carbohydrates showed that any reduced-calorie diet can be effective, regardless of its consistency and content.<sup>41</sup> However, the composition of the diet may impact compliance in an individual patient.

Whichever diet is selected, it is important to recognize that diets that drastically alter nutrient patterns may be dangerous. Very low-calorie diets provide 800 kcal/day or less and are generally liquid meals formulated to be nutritionally complete. Sudden death and cardiac arrhythmias have been reported with such diets.<sup>42,43</sup> Although these diets are associated with significant short-term weight loss, long-term weight loss depends on the patient's subsequent dietary as well as physical activity habits. Very low-calorie diets are associated with hair loss, thinning of skin, and increased risk of gallstones. They are contraindicated in pregnant and lactating women and also in children. Patients must be under close medical supervision while participating in such diets, and their use should be limited to very obese, well-motivated patients.

## **Exercise**

Exercise is known to help with weight loss and is an important factor in maintaining weight loss. Physical activity alone results in less weight loss than the combination of exercise and calorie restriction. In a meta-analysis comparing weight loss using diet, exercise, or diet plus exercise, the combination of diet and exercise was shown to be superior.<sup>44</sup> In addition, regular physical activity and exercise have been shown to have a positive impact on overall health, with the most beneficial effects seen on cardiovascular risk factors such as hypertension and insulin resistance. Fitness level is an independent predictor of mortality as demonstrated in the Aerobics Center Longitudinal Study, which included 25,714 men. In this study, low cardiorespiratory fitness by itself was a predictor of mortality across the 3 BMI groups (normal weight, overweight, and obese). Thus, it is important for physicians to evaluate the physical activity and fitness level of all their patients, not only of those who are obese.<sup>45</sup>

Physicians and patients should be realistic in setting goals for exercise and recognize that obese patients may have conditions that limit exercise, such as joint abnormalities. It is also important to explain to patients that the aim is to increase the level of physical activity, which does not necessarily require joining a programmed exercise regimen or gym. Regular day-to-day lifestyle modifications to increase physical activity (eg, taking stairs instead of elevators, parking farther away) are comparable to structured exercise programs in terms of their effects on various health measures.<sup>46–48</sup> Progressive, incremental exercise is a realistic approach to achieve exercise goals. Some studies have shown that intermittent exercise (high intensity followed by low intensity) is more effective in weight loss than continuous low to medium intensity exercises.<sup>49</sup>

## **Behavior Modification**

The goal of behavioral treatment of obesity is to help patients make long-term lifestyle changes (eating habits and physical activity) by modifying the environment and patients' perception and response to various stimuli that trigger inappropriate eating and by reinforcing positive behaviors. Studies have shown that behavioral treatment results in a short-term loss of approximately 7% to 10% of initial weight.<sup>50–52</sup> It also has been shown to facilitate weight loss when compared with placebo and when added to diet and exercise.<sup>53</sup> Finally, behavioral modification programs are helpful in maintaining weight loss. A review of randomized controlled trials of weight loss interventions showed that adding behavioral therapy to diet or to diet and drug therapy was associated with improved weight loss for up to 18 months.<sup>54</sup>

Key elements of behavioral modification programs are self-monitoring, stimulus control, social support, and cognitive restructuring. Self-monitoring entails keeping daily records of food intake, physical activity, and weight, and is associated with short-term weight loss.<sup>52,55</sup> In addition, Wing and Phelan<sup>56</sup> found that regular self-monitoring of weight was 1 of several strategies used by patients who successfully maintained weight loss over the long term (ie, those who lost  $\geq 10\%$  of their body weight and kept it off  $\geq 1$  year). Stimulus control involves modifying the surrounding environment to control stimuli that promote eating or facilitate overeating, such as not keeping high-calorie foods on hand. Family and social support also have a positive influence on weight loss, with a meta-analysis of 7 small randomized controlled trials of family versus individual therapy showing that family therapy resulted in greater weight loss at 12 months (3 kg).<sup>57</sup> Similarly, it has been shown that behavioral programs are effective whether in an individual or group setting,<sup>58</sup> depending on patient preference, although the group setting is more cost-effective. Cognitive restructuring is frequently a part of behavioral treatment of obesity.<sup>52</sup> This component teaches patients to be aware of how thoughts affect feelings and behaviors and includes strategies such as setting realistic goals for weight loss, dealing effectively with setbacks, and controlling negative thoughts and reactions.

### Pharmacologic Therapy

Weight-loss medications can be useful adjuncts to diet and exercise for obese patients with a BMI greater than 30 kg/m<sup>2</sup> and in patients with a BMI greater than 27 kg/m<sup>2</sup> and comorbid conditions.<sup>59,60</sup> When prescribing weight-loss medications, it is important to explain to patients that drug therapy is only an adjunct to lifestyle modification efforts and that these efforts must be continued while they try medications. As with diet and exercise, expectations for weight loss with the drug therapy must be realistic, keeping in mind that loss of 5% to 10% of initial weight may be sufficient to obtain significant health benefits.<sup>61</sup> To be considered effective, drug therapy should lead to a loss of about 1 lb per week for the first month and an overall loss of approximately 5% from the baseline weight by 6 months.

Drugs approved by the US Food and Drug Administration (FDA) for treatment of obesity are sibutramine, phentermine, diethylpropion, and orlistat. Physicians should be familiar with the side effects of each agent and should exercise prudence in selecting patients for drug therapy. The safety of long-term use of weight-loss medications has not been established, and none of

these drugs has been approved for use for more than 2 years. The longest duration for which safety and efficacy data are available is 4 years for orlistat and 2 years for sibutramine.

Agents currently being studied for obesity treatment include melanocortin-4 receptor agonists and peptides such as leptin,<sup>62</sup> peptide YY,<sup>63</sup> and oxyntomodulin. Preliminary data with these agents show modest weight loss ranging from 1.5 to 7 kg.<sup>62</sup> **Table 3** provides a summary of pharmacologic agents that have been studied for weight loss.

**Appetite suppressants.** Sibutramine is a norepinephrine serotonin reuptake inhibitor that acts by inhibiting food intake. A meta-analysis of 29 trials<sup>64</sup> showed that patients receiving sibutramine plus lifestyle modification lost an average of 4.5 kg more at 1 year compared with patients receiving placebo and lifestyle modification. A more recent randomized trial showed that sibutramine plus lifestyle modification resulted in a 12 kg weight loss at 1 year.<sup>55</sup> In patients with diabetes, sibutramine resulted in weight loss as well as a modest improvement in hemoglobin A<sub>1c</sub>, a decrease in triglycerides and low-density lipoprotein cholesterol, and an increase in high-density lipoprotein cholesterol.<sup>65,66</sup> The main side effects of sibutramine include increased blood pressure and heart rate. Thus, this agent should be avoided in patients with poorly controlled hypertension, history of coronary heart disease, congestive heart failure, cardiac arrhythmia, or stroke. Precaution is also needed in patients receiving monoamine oxidase inhibitors or selective serotonin reuptake inhibitors because of the risk of acute serotonin syndrome.<sup>67</sup> Although rare, serotonin syndrome is a potentially life-threatening condition resulting from increased serotonin activity in the central nervous system and peripheral serotonin receptors. It causes a wide range of clinical manifestations, such as tachycardia, shivering, hyperthermia, hypertension, muscle rigidity, and mental status changes, including delirium. Sibutramine is available as 5, 10, or 15 mg tablets with the recommendation to start at 10 mg daily and titrate according to the response. The maximum approved dose is 15 mg daily.

Phentermine and diethylpropion are adrenergic stimulants that inhibit norepinephrine uptake. These agents are approved only for short-term use because of the potential for abuse. They have been shown to have a moderate effect on weight loss (3–3.5 kg).<sup>59</sup> Side effects include insomnia, euphoria, palpitations, and hypertension.

**Inhibitors of nutrient absorption.** Orlistat inhibits pancreatic lipase, preventing hydrolysis of ingested fat into fatty acids and glycerol and resulting in excretion

**Table 3.** Drugs Studied for Weight-Loss Effects

Class/Drug	Average Weight Loss	Side Effects	FDA Approval
<b>Sympathomimetics</b>			
Sibutramine	4.45 kg	Caution with cardiovascular issues and MAOIs	Yes
Phentermine	3.6 kg	Abuse potential	Yes
Diethylpropion	3 kg	Abuse potential	Yes
<b>Lipase inhibitor</b>			
Orlistat	Up to 11% below baseline	GI side effects	Yes
<b>Antidepressants</b>			
Fluoxetine	14.5 kg lost to 0.4 kg gained	Nausea, insomnia	No
Sertraline	0.45–0.9 kg	Nausea, diarrhea, insomnia	No
Bupropion	2.7 kg	Dry mouth, nausea	No
<b>Antidiabetic drugs</b>			
Metformin	1–2 kg	GI side effects	No
Pramlintide	0.5–1.5 kg	Nausea	No
Exenatide	1–2 kg	Nausea	No
<b>Experimental</b>			
Leptin	1.4–7 kg		No
Oxyntomodulin	2 kg		No
Melanocortin-4 receptor agonists	0–1.7 kg		No

Data from Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med* 2005;142:532–46.

FDA = US Food and Drug Administration; GI = gastrointestinal; MAOIs = monoamine oxidase inhibitors.

of approximately 30% of dietary fat. Many clinical trials have proven that orlistat leads to significant weight loss, up to 11% from baseline.<sup>68</sup> In a 2-year randomized trial in which patients received dietary modification plus orlistat (60 or 120 mg 3 times daily) or placebo, a greater percentage of the orlistat groups lost at least 5% of their initial weight by 1 year (48.8% and 50.5%) as compared with the placebo group (30.7%).<sup>69</sup> In addition, a larger proportion of orlistat patients maintained this loss over 2 years (34% versus 24%). A meta-analysis reported that in 22 studies of orlistat that reported 1 year outcomes, orlistat patients lost an average of 2.89 kg after 1 year.<sup>59</sup> Similar to sibutramine, orlistat decreases the hemoglobin A<sub>1c</sub> value, improves the serum lipid profile, and reduces both total and low-density lipoprotein cholesterol in patients with diabetes.<sup>70</sup> Interestingly, a trial that evaluated combination therapy with orlistat and sibutramine failed to show an additive weight loss.<sup>71</sup> Accordingly, combination therapy is not recommended.

Orlistat is relatively well tolerated, and its major side effects are gastrointestinal, most commonly cramps, flatus, large bowel movements, fecal urgency, and incontinence. Because reduced absorption of fat-soluble vitamins has been reported with orlistat therapy,<sup>72</sup> patients treated with this medication should receive supplements of fat-soluble vitamins, especially vitamin D.

Orlistat is available as 120 mg capsules, and the recommended dose is 120 mg 3 times daily with a diet containing less than 30% of fat. It is also available over the counter at a 60-mg dose.<sup>61</sup>

**Antidepressants and antiepileptics.** Other drugs that have been shown to facilitate weight loss include several antidepressant medications (eg, fluoxetine, sertraline, bupropion)<sup>59</sup> and antiepileptics (topiramate and zonisamide).<sup>27</sup> However, these agents are not FDA approved for obesity treatment and are not recommended for that purpose. The selective serotonin reuptake inhibitor fluoxetine has been shown to have a wide range of weight effect ranging from 14.5 kg lost to 0.4 kg gained at 1 year.<sup>59</sup> Doses that were used to achieve weight loss were higher than the doses used for treating depression (60 versus 20 mg). Its side effects include sweating, tremors, nausea, and somnolence. Bupropion, which is structurally similar to diethylpropion, is used in the treatment of depression and for smoking cessation. It has been associated with a modest weight loss of about 2.7 kg at 6 to 12 months.<sup>59</sup> Both of these drugs might provide the added benefit of weight loss when used in patients for their approved indications. Topiramate is the better studied of the 2 antiepileptics associated with weight loss, although the mechanism by which it results in weight loss is unclear. It has been

shown to result in a 6% weight loss compared with placebo at 6 months.<sup>59</sup> Reported side effects include paresthesias, changes in taste, metabolic acidosis, and memory effects.

**Antidiabetic agents.** Some drugs used in the treatment of diabetes have been associated with weight loss, including metformin, exenatide, and pramlintide. Although not approved for this purpose, these agents might be a good choice in obese diabetic patients. Patients who received metformin in the Diabetes Prevention Program trial had an average weight loss of 2.1 kg over 2.8 years.<sup>33</sup> Exenatide is a synthetic glucagon-like peptide receptor agonist that stimulates glucose-dependent insulin secretion and inhibits release of glucagon. It also slows down gastric emptying and acts on the hypothalamic satiety center. Trials of exenatide have shown dose-dependent weight loss of 1 to 2 kg in studies lasting up to 30 weeks.<sup>73,74</sup> The major side effect of exenatide is nausea. Pramlintide is a synthetic analog of human amylin that slows down gastric emptying, reduces postprandial blood glucose concentration, and has effects on the hypothalamic satiety center. In studies lasting up to 1 year, it produced modest weight loss of 0.5 to 1.5 kg.<sup>75</sup> The major side effects are nausea, vomiting, and hypoglycemia, especially when used in conjunction with insulin.

### Bariatric Surgery

Surgical options for obesity management are based on restriction of intake or malabsorption of nutrients to produce weight loss. The details of the various surgical procedures are beyond the scope of this article but have been reviewed previously.<sup>76</sup> Restriction of intake is achieved by creating a small stomach reservoir, which is a relatively simpler procedure but achieves less weight loss than malabsorptive techniques. Malabsorption of nutrients through a shortened small bowel length is a more effective weight loss procedure that can have significant although preventable metabolic complications. Bariatric surgery is associated with significant improvements in hypertension, hyperlipidemia, diabetes, and obstructive sleep apnea and, in several instances, resolution of these conditions.<sup>77-79</sup> A meta-analysis that determined the impact of bariatric surgery on weight loss showed a mean percentage weight loss of 61%.<sup>79</sup>

It is important that these procedures be performed at experienced centers and that patients undergoing them have good follow-up pre- and postoperatively with a multidisciplinary team that includes behavioral health, nutrition, endocrinology, and surgery. In addition, patients must be informed about the risks of bariatric surgery related to the procedure itself and the side effects of the

altered anatomy. Deficiencies of various vitamins and minerals such as iron, calcium, vitamin B<sub>12</sub>, thiamine, and folate have been observed, and supplementation of these nutrients is required following the procedure.<sup>80</sup> Contraindications for bariatric surgery are psychiatric disorders, eating disorders, severe cardiac disease, and the inability to comply with life-long follow-up, including taking long-term vitamin replacement.

### CONCLUSION

Obesity is a chronic medical condition that physicians must be prepared to manage using current best evidence. The focus of obesity management remains on lifestyle modifications with optimization of nutrition and physical fitness. Judicious use of the available pharmaceutical and surgical options can be effective for selected patients. Wide-ranging research into the genetic and molecular pathways that regulate energy balance, appetite, and satiety is promising, as improved understanding of the mechanisms of obesity will facilitate the development of new options to help patients treat and/or avoid obesity. The major obstacle in obesity management is the limited understanding among patients that lifestyle changes, including healthy eating habits and physical activity, are the cornerstones to losing weight. Further efforts are needed to increase patient awareness around this issue and to encourage selection and/or provision of healthier foods and controlled portions starting at very young ages. **HP**

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