

# Treatment of Overweight and Obesity: Lifestyle, Pharmacologic, and Surgical Options

**CHRISTOPHER P. CANNON, MD**

Senior Investigator, TIMI Study Group  
Associate Professor of Medicine  
Harvard Medical School  
Cardiovascular Division  
Brigham and Women's Hospital  
Boston, Massachusetts

**AMIT KUMAR, MD**

Assistant Professor  
Department of Hospital Medicine  
University of Massachusetts Medical School  
Worcester, Massachusetts

Recent statistics indicate that overweight and obesity have become an increasingly serious clinical and socioeconomic problem worldwide, and one of the greatest public health challenges of our time. In the United States, 133.6 million (66%) adults are overweight or obese (body mass index [BMI]  $\geq 25$  kg/m<sup>2</sup>), with 63.3 million (31.4%) considered to be obese (BMI  $\geq 30$  kg/m<sup>2</sup>). The International Obesity Task Force estimates that worldwide at least 1.1 billion adults are overweight, including 312 million who are obese. Overweight and obese patients are at an increased risk for developing numerous cardiometabolic complications, including hypertension, type 2 diabetes mellitus, dyslipidemia, and cardiovascular diseases, as well as conditions such as osteoarthritis, obstructive sleep apnea, hepatobiliary diseases, and certain types of cancers. Owing to the major health risks and complications associated with obesity, which negatively affect quality of life and reduce average life expectancy, in addition to placing an enormous burden on health care resources, the treatment of overweight and obesity is a public health imperative. Treatment must begin with long-term lifestyle changes, including increased physical activity and dietary modifications. For overweight and obese individuals for whom lifestyle changes alone are insufficient, pharmacotherapy may be added. However, patients who choose adjunctive pharmacotherapy should be advised of the risks and benefits of drug therapy, the lack of long-term safety data, and the temporary and modest nature of the weight loss that can be achieved with these agents. Bariatric surgery is an effective treatment option for morbidly obese patients or obese patients with multiple comorbidities who have not been successful in achieving sufficient weight loss with nonsurgical approaches. However, appropriate candidates for bariatric surgery must also be committed to long-term lifestyle changes. (*Clinical Cornerstone*. 2009;9[4]:55–71) © 2009 Elsevier. All rights reserved.

The prevalence of obesity, defined as body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>, has increased steadily worldwide and is considered a major public health issue in both developed and developing nations.<sup>1,2</sup> According to the National Health and Nutrition Examination Survey (2001–2004), 133.6 million (66%) US adults aged  $\geq 20$  years are overweight or obese (BMI  $\geq 25$  kg/m<sup>2</sup>), with 63.3 million (31.4%) considered to be obese (BMI  $\geq 30$  kg/m<sup>2</sup>).<sup>3</sup> Indeed, the prevalence of obesity among US adults has doubled in the last 30 years.<sup>1</sup> The International Obesity Task Force estimates that worldwide at least 1.1 billion adults are overweight, including 312 million who are obese.<sup>4,5</sup> The prevalence is rising at an even faster rate

among children and adolescents:  $\geq 155$  million children worldwide are overweight or obese,<sup>5</sup> which if left unchecked, will lead to major health consequences that will overwhelm our health care system. The increase in the prevalence of obesity worldwide has been attributed to several factors, including high dietary fat intake,<sup>6,7</sup> the availability and overconsumption of inexpensive, energy-dense foods,<sup>1,5,8,9</sup> low intake of fruits and vegetables, and an increasingly sedentary lifestyle.<sup>1,5,10</sup>

Obesity is associated with an increased mortality rate, with obese adults aged 50 to 71 years having a risk of death 2 to 3 times higher than do individuals of normal weight.<sup>11</sup> Furthermore, obesity is an independent risk

factor for coronary artery disease.<sup>12</sup> A large part of the increased coronary risk seen in obese persons may be related to the higher prevalence of cardiometabolic complications, such as hypertension, type 2 diabetes mellitus (DM), and dyslipidemia, in this population.<sup>13–16</sup>

### KEY POINT

**A large part of the increased coronary risk seen in obese persons may be related to the higher prevalence of cardiometabolic complications, such as hypertension, type 2 DM, and dyslipidemia, in this population.**

The risk of developing obesity-associated cardiometabolic complications appears to be a function of one's degree of insulin sensitivity.<sup>17</sup> In a recent analysis of 211 apparently healthy obese adults,<sup>17</sup> subjects with the highest degree of insulin resistance had higher blood pressure, fasting and postprandial glucose, and plasma triglyceride levels, and lower high-density lipoprotein cholesterol (HDL-C) levels than did obese subjects with the highest degree of insulin sensitivity. These findings suggest that antiobesity therapies that address the problem of insulin resistance may help to reduce the increased cardiovascular risk associated with obesity. Other cardiovascular diseases, such as stroke and peripheral arterial disease, and illnesses, such as osteoarthritis, obstructive sleep apnea, hepatobiliary diseases, polycystic ovary syndrome, and certain types of cancers, also occur more frequently in obese individuals than they do in normal-weight individuals.

Weight loss, particularly a reduction in waist circumference, has been shown to have positive effects on the risk for hypertension, insulin resistance, type 2 DM, and cardiovascular disease (CVD) (Table I).<sup>18</sup> In a study by Wadden et al,<sup>19</sup> moderate reductions in body weight in obese individuals, regardless of the method of weight loss, resulted in reductions in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and serum triglyceride levels. Furthermore, modest weight loss of 5% to 10% can not only improve glycemic control in patients with

type 2 DM<sup>20</sup> but also prevent the onset of diabetes in high-risk individuals.<sup>21,22</sup> In the Diabetes Prevention Program,<sup>21</sup> patients with a baseline BMI >24 kg/m<sup>2</sup> who had a modest weight loss of 5.6 kg had a 58% reduction in the risk of developing diabetes. More extensive weight loss, as achieved after bariatric surgery, can even lead to remission of type 2 DM and hypertension in obese patients.<sup>23</sup>

Obesity-induced inflammatory processes are thought to be important in the development of insulin resistance and cardiometabolic syndrome.<sup>24</sup> Weight loss has been shown to lead to a reduction in the level of C-reactive protein (CRP), a marker of inflammation, which continues even after weight stabilization.<sup>25</sup> Weight loss reduces blood pressure levels in hypertensive and nonhypertensive obese individuals.<sup>18</sup> It is the key therapeutic goal in the management of obesity and a strategy recommended to (1) lower elevated blood pressure levels in hypertensive obese persons, (2) lower total cholesterol, LDL-C, and triglyceride levels and increase HDL-C levels in obese persons with dyslipidemia, and (3) lower blood glucose levels in obese persons with type 2 DM.<sup>18</sup> Weight loss may be achieved by lifestyle (dietary/exercise/behavioral) interventions, pharmacotherapy, surgery, or a combination of these modalities. This paper discusses lifestyle, pharmacologic, and surgical therapies for the management of obesity and the effects of these therapies

**TABLE I. PROVEN BENEFITS OF WEIGHT LOSS.**

Reduces risk factors for diabetes and CVD
Reduces serum triglyceride levels
Increases HDL-C levels
Moderately reduces total serum cholesterol
Moderately reduces LDL-C levels
Reduces blood glucose concentrations in overweight/obese patients without diabetes
Improves glucose tolerance in overweight individuals with impaired glucose tolerance
Reduces blood glucose and HbA1c levels in some patients with type 2 diabetes mellitus

CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; HbA1c = glycosylated hemoglobin.

Source: National Heart, Lung, and Blood Institute in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report.* Bethesda, MD: National Institutes of Health; September 1998. NIH publication 98-4083.

on body weight and other obesity-associated cardiovascular risk factors.

## TREATMENT OF OVERWEIGHT AND OBESITY

### Treatment Goals

The goals for treatment of overweight and obesity are to reduce body weight, and to maintain lower body weight over the long term. An alternative goal is to prevent further weight gain as a minimum goal in patients who are unable to lose weight. Successful treatment of obesity should result in a preferential reduction of abdominal fat, an amelioration of obesity-related health risks, an improvement in quality of life, and a reduction in mortality rate.

#### KEY POINT

**Successful treatment of obesity should result in a preferential reduction of abdominal fat, an amelioration of obesity-related health risks, an improvement in quality of life, and a reduction in mortality rate.**

According to treatment guidelines issued by the National Heart, Lung, and Blood Institute (NHLBI),<sup>18</sup> the initial goal of weight loss therapy is to reduce body weight by ~10% from baseline, with further weight loss attempted only if the first goal is achieved. The NHLBI guidelines advocate a weight loss of 1 to 2 lb/wk, resulting from a calorie deficit of 500 to 1000 kcal/d, over a period of 6 months, after which the priority should be on weight maintenance. Further weight loss can be considered after a period of weight maintenance. More recent guidelines from the American College of Physicians (ACP) suggest that goals for weight loss should be based on each patient's individual risk factors and may include not only weight loss but also other parameters, such as reducing blood pressure or fasting glucose levels.<sup>26</sup>

The treatment of obesity should be tailored to the individual patient. Important factors to consider when designing a weight loss strategy include a patient's age, gender, degree of obesity, individual health risks, ability

to exercise, and psychobehavioral characteristics, as well as the outcomes of previous weight loss attempts. The goals and treatment plan should be discussed with the patient and recorded, and achievement of a significant milestone should be noted and acknowledged. Opportunity should be utilized at every visit to introduce additional small changes to optimize weight loss.

## LIFESTYLE INTERVENTIONS

Lifestyle interventions to achieve weight loss comprise dietary therapy and increased physical activity to induce weight loss (Table II)<sup>18</sup> and behavioral therapy to reinforce weight reduction behaviors.

### Diet

Dietary interventions include low-calorie diets, very-low-calorie diets (VLCDs), vegetarian diets, the American Heart Association diet, the National Cholesterol Education Program Step I diet with calorie restriction, and

**TABLE II. DIETARY THERAPY AND PHYSICAL ACTIVITY TO INDUCE WEIGHT LOSS IN OVERWEIGHT AND OBESE PATIENTS.**

Initial goal: 10% Reduction (from baseline) in body weight

Rate: ½ to 1 lb/wk\*  
1 to 2 lb/wk†

#### Dietary Therapy

Achieve calorie deficit  
300 to 500 kcal/d\*  
500 to 1000 kcal/d†

Reduce total caloric intake  
Women: 1000 to 1200 kcal/d  
Men: 1200 to 1500 kcal/d

Low-calorie diet: consistent with NCEP Step I or II diet

Reduce dietary carbohydrates

Decrease saturated fat intake

Total fat intake: ≤30% of total calories

#### Physical Activity

Begin slowly (eg, walking, swimming): 30 to 45 min, 3 to 5 days per week

Long-term goal: moderate-intensity physical activity ≥30 min, most or all days per week

NCEP = National Cholesterol Education Program.

\*Overweight patients with a body mass index (BMI) in the 27 to 35 mg/m<sup>2</sup> range.

†Obese patients with a BMI >35 kg/m<sup>2</sup>.

Source: National Heart, Lung, and Blood Institute in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report.* Bethesda, MD: National Institutes of Health; September 1998. NIH publication 98-4083.

others. Much has been written about diets and there is a large diet industry; however, the main principle is to eat less to induce a state of negative energy balance. In obese patients, the goal of dietary intervention is to create a deficit of 500 to 1000 kcal/d to achieve a weight loss of 1 to 2 lb/wk; in overweight patients, the goal is to create a deficit of 300 to 500 kcal/d to achieve a weight loss of ½ to 1 lb/wk. An expert panel review<sup>18</sup> of randomized controlled trials of various types of diets concluded that a weight loss of ~8% of initial body weight can be achieved by maintaining a low-calorie diet for 3 to 12 months. This degree of weight loss can lead to a reduction in abdominal fat. The panel also found that, generally, low-calorie diets with targeted calorie restriction result in greater weight loss than do diets without a targeted restriction component. VLCDs (<800 kcal/d) were found to induce greater weight loss initially than did low-calorie diets; but in the long term, overall weight loss was the same with both of these diets. VLCDs might be considered for patients in whom rapid weight loss is desired (eg, certain obese patients with type 2 DM); however, such diets should be followed only for short periods, and they should be avoided in patients with liver or kidney disease. Vitamins, minerals, and trace elements should be added as supplements to cover recommended daily allowances. The drug dosages of antidiabetic and antihypertensive agents should be adjusted to avoid hypoglycemia or an inappropriate blood pressure reduction. Meal replacement diets (ie, substitution of 1 or 2 daily meal portions with a liquid supplement or portion-controlled entrée) appear to be a useful long-term strategy to maintain weight loss while preserving nutritional balance.

#### KEY POINT

**A weight loss of ~8% of initial body weight can be achieved by maintaining a low-calorie diet for 3 to 12 months. However, reducing dietary fat alone may not be sufficient and, therefore, should be combined with a reduced intake of carbohydrates and an overall caloric restriction.**

Reducing dietary fat alone may not be sufficient to lose weight and should be combined with a reduced intake of carbohydrates and an overall caloric restriction. A recent study<sup>27</sup> examined the effects of 4 different diets that varied in their relative compositions of protein, fat, or carbohydrates on weight loss. The degree of weight loss achieved after 2 years was similar with each of these reduced-calorie diets (an average of 4 kg among participants who completed the trial) regardless of which macronutrients they emphasized. Another study<sup>28</sup> that compared the effects of low-carbohydrate, Mediterranean, or low-fat diets on weight loss found greater mean weight loss at 24 months and more favorable metabolic effects with the Mediterranean and low-carbohydrate diets than with the low-fat diet. A Mediterranean diet is characterized by a higher intake of vegetables, legumes, fruits, nuts, whole grains, cheese or yogurt, fish, and monounsaturated versus saturated fatty acids. The benefits of a Mediterranean diet were also demonstrated in a recent meta-analysis,<sup>29</sup> which found strong evidence for a protective effect of such a diet on the risk for coronary artery disease (CAD). This study also found strong evidence of increased CAD risk from consuming trans-fatty acids and foods with a high glycemic index, such as white potatoes, sugar, white rice, and white bread.

#### Physical Activity

Increased physical activity should be an integral part of any weight loss program.<sup>18</sup> A patient's baseline physical activity might be assessed by using a physical activity questionnaire or, perhaps, by using a pedometer. Initially, the goal is to have the patient engage in a physical activity (eg, walking or swimming) for 30 to 45 minutes, 3 to 5 days per week. However, the long-term goal is to have the patient engage in ≥30 minutes of moderate-intensity physical activity most days or every day of the week. Physical activity results in modest weight loss and increased cardiorespiratory fitness. It also protects against the loss of lean body mass, reduces obesity-related cardiometabolic health risks, and evokes sensations of well-being. Although increased physical activity might only have a modest effect on abdominal fat, it independently reduces the risk for CVD. One study<sup>30</sup> found that the engagement of physical activity in a weight management program was positively related to a patient's level of education and inversely associated with the occurrence of serious comorbidities, as well as the patient's age and

degree of obesity. Exercising in heated water is recommended for patients with arthritis and for those who have problems with mobility. Strength/resistance training should also be used, especially in less mobile, disabled individuals, for preservation of lean body mass and amelioration of obesity-related health risks.

### KEY POINT

**Physical activity results in modest weight loss, increases cardiorespiratory fitness, protects against the loss of lean body mass, reduces obesity-related cardiometabolic health risks, and evokes sensations of well-being. It also reduces the risk for CVD.**

The combination of a low-calorie diet and increased physical activity results in greater weight loss and produces modestly greater reductions in abdominal fat than does either intervention alone.<sup>18</sup> Combination therapy also improves cardiorespiratory fitness.<sup>18</sup>

### Behavioral Therapy

Behavioral therapy refers to strategies designed to reinforce weight reduction behaviors, and should be included in any comprehensive weight management program. Behavioral therapy originated from the belief that obesity was the result of maladaptive eating and exercise habits, which could be corrected by the application of learning principles. However, today we know that there are factors other than behavior, such as genetic, hormonal, and metabolic influences, that play an important role in the development of obesity. Although some individuals may never be thin despite heroic efforts to lose weight, behavioral therapy may help such individuals to develop a set of skills that leads to attainment of a healthier, though not ideal, body weight.

Behavioral therapy clearly specifies weight reduction goals, identifies strategies to overcome barriers to achieving those goals, and focuses on small incremental changes. Behavioral therapy comprises self-monitoring (ie, keeping food and activity logs), stimulus control (ie, control-

ling cues associated with eating), stress management, nutrition education, slower eating habits, physical activity, problem-solving, the rewarding of changes in behavior, cognitive restructuring, social support, and relapse prevention training.<sup>31–33</sup> Clinical studies of behavioral treatment strategies indicate that these strategies result in a mean short-term weight loss of 10.6% during the treatment phase and a mean weight loss of 8.6% during follow-up.<sup>31</sup> Behavioral therapy is particularly effective when combined with other interventions, such as food provision (eg, provision of prepackaged meals or written meal plans), meal replacement, or pharmacotherapy.<sup>31</sup>

### PHARMACOLOGIC OPTIONS

When lifestyle interventions do not induce sufficient weight loss, it may be necessary to add a pharmacologic agent to the treatment regimen; however, pharmacotherapy should never be initiated without concomitant lifestyle modifications. Antiobesity medications should be used as part of a comprehensive weight loss program that includes dietary therapy and physical activity for obese patients and for those with a BMI  $\geq 27$  kg/m<sup>2</sup> and concomitant obesity-related risk factors or diseases.<sup>18</sup> The ACP guidelines recommend that patients on drug therapy for obesity should be monitored periodically to assess safety and efficacy.<sup>26</sup> In addition, patients who desire adjunctive pharmacotherapy should be advised of the risks and benefits of therapy, the lack of long-term safety data, and the temporary and modest nature (~5 kg over 1 year) of the weight loss induced by these agents.<sup>26</sup>

Our current potential to treat obesity with drugs is limited to only a few options in comparison to the arsenal of drugs available to treat other chronic diseases such as hypertension, diabetes, and dyslipidemia. The pharmacologic agents available for weight loss can be broadly classified into 2 groups: the anorexiant (eg, sympathomimetic amines, sibutramine), which act centrally to suppress appetite, and the lipase inhibitors (eg, orlistat), which act peripherally to reduce absorption of dietary fat in the gut (**Table III**). Currently, only 2 drugs—sibutramine and orlistat—are approved for long-term use by the US Food and Drug Administration (FDA) for weight loss and weight maintenance. The sympathomimetic amines phentermine, diethylpropion, phendimetrazine, and benzphetamine are approved for short-term use (ie, 12 weeks in a 12-month period).<sup>34</sup> Rimonabant, a drug that was developed to treat obesity with mechanisms of action

**KEY POINT**

**Pharmacotherapy should never be initiated without concomitant lifestyle modifications. Furthermore, patients who desire adjunctive pharmacotherapy should be advised of the risks and benefits, the lack of long-term safety data, and the temporary and modest nature of the weight loss induced by these agents.**

involving cannabinoid receptors in the central nervous system and peripheral tissues (eg, adipocytes), failed to win FDA approval and was recently withdrawn from the market in Europe because of its serious psychiatric adverse effects. Other drugs that have been evaluated for use as weight loss agents include the antidepressants bupropion and fluoxetine, and the anticonvulsants topiramate and zonisamide. The efficacy and safety of anti-

obesity drugs have been evaluated in children and adolescents, and currently, the only drug approved by the FDA for use in these age groups is orlistat. Ongoing trials are also evaluating these drugs in the elderly; however, at present, drug treatment is limited to obese adults  $\leq 65$  years of age.

**Sibutramine**

Sibutramine is a combined norepinephrine and serotonin reuptake inhibitor that acts primarily as an appetite suppressant. Its efficacy in treating obesity is due to the activity of its pharmacologically active metabolites, which induce satiety and stimulate thermogenesis by increasing efferent sympathetic activity to thermogenically active brown adipose tissue.<sup>35</sup> Brown adipose tissue has long been known to be present in newborn humans, but a recent study<sup>36</sup> demonstrated the presence of functionally active brown adipose tissue in adult humans. Importantly, the amount of brown adipose tissue was inversely correlated with BMI, especially in older people, suggesting its potential role in adult human metabolism.

Sibutramine effectively achieves the goals of obesity treatment: it induces and maintains weight loss and ap-

**TABLE III. AGENTS APPROVED FOR WEIGHT LOSS IN OVERWEIGHT AND OBESE ADULTS IN THE UNITED STATES.**

Agent	Drug Class/Mechanism of Action	Approved for Long-Term Use*	Average Weight Loss <sup>†</sup>	Contraindications
Phentermine	Sympathomimetic amine/suppresses appetite	No	~3.6 kg	Advanced arteriosclerosis, CVD, moderate to severe hypertension, hyperthyroidism, glaucoma
Diethylpropion	Sympathomimetic amine/suppresses appetite	No	~3.0 kg	Pulmonary hypertension, severe hypertension, advanced arteriosclerosis, hyperthyroidism, glaucoma
Phendimetrazine	Sympathomimetic amine/suppresses appetite	No	—	Advanced arteriosclerosis, symptomatic CVD, moderate and severe hypertension, pulmonary hypertension, hyperthyroidism, glaucoma
Benzphetamine	Sympathomimetic amine/suppresses appetite	No	—	Advanced arteriosclerosis, symptomatic CVD, moderate to severe hypertension, hyperthyroidism, glaucoma, pregnancy, breastfeeding
Sibutramine	Norepinephrine and serotonin reuptake inhibitor/suppresses appetite	Yes	~4.5 kg at 1 yr	Uncontrolled or poorly controlled hypertension, pulmonary hypertension, hyperthyroidism, glaucoma
Orlistat	Lipase inhibitor/reduces absorption of dietary fat	Yes	~2.9 kg at 1 yr	Chronic malabsorption syndrome, pregnancy, breastfeeding

CVD = cardiovascular disease.

\*More than 12 weeks.

<sup>†</sup>Based on meta-analysis.<sup>26</sup>

pears to prevent weight gain. In the Sibutramine Trial of Obesity Reduction and Maintenance (STORM),<sup>37</sup> all patients received sibutramine and began dietary restriction to induce a weight loss of  $\geq 5\%$  over 6 months. At the end of the 6-month period, patients received a maintenance diet and were randomized to receive either placebo or sibutramine for an additional 18 months. At 2 years, 43% of participants in the sibutramine group maintained their weight loss versus only 16% of those in the placebo group. Patients who maintained their weight loss had improvements in their lipid profile, with significant increases in HDL-C levels and decreases in very-low-density lipoprotein cholesterol and triglyceride levels. In obese patients with type 2 DM, sibutramine was found to reduce glycosylated hemoglobin (HbA1c) and fasting plasma glucose (FPG) levels in addition to inducing weight loss.<sup>38,39</sup> Treatment with sibutramine improved insulin sensitivity in diabetic and nondiabetic obese individuals<sup>40–42</sup> and in obese hypertensive individuals.<sup>43</sup>

The most common side effects reported with the use of sibutramine in clinical trials were dry mouth, constipation, and insomnia. Sibutramine induces slight increases in blood pressure (1–3 mm Hg) and heart rate (4–5 beats/min) and, therefore, is contraindicated in patients with heart disease, uncontrolled hypertension, and cerebral vascular disease. Blood pressure should be monitored at weekly or biweekly intervals.<sup>34</sup>

The Sibutramine Cardiovascular Outcomes (SCOUT) trial<sup>44</sup> is investigating the effects of sibutramine on cardiovascular outcomes in an off-label population of obese patients at high risk for cardiovascular events (in whom sibutramine is often contraindicated). Tolerability of the drug during a 6-week treatment period has been confirmed in a preliminary analysis of the trial results, but efficacy results are still pending publication.

## Orlistat

Orlistat is an inhibitor of gastrointestinal (GI) lipase, an enzyme that catalyzes lipolysis.<sup>34</sup> Inhibition of lipase by orlistat results in a 30% reduction in dietary fat absorption, and the reduction in energy intake results in weight loss. Orlistat acts primarily on the GI tract; thus, its side effects mainly include loose stools with oily discharge and fecal incontinence. Eating a diet low in fat (10–15 g/meal) may help patients avoid these side effects. These side effects might be used as a “learning experience,” providing a hint to patients that the fat content of foods consumed was

higher than they realized. Because orlistat works by reducing the absorption of dietary fat, absorption of fat-soluble vitamins (eg, vitamin D) from the diet may also be affected. For this reason, it is recommended that patients take a multivitamin supplement during orlistat therapy.

Weight loss with orlistat ranges from 5% to 10% over a 1-year period.<sup>45,46</sup> Long-term therapy with orlistat was found to reduce overall cardiovascular risk in obese patients with comorbidities, with a reduction in BMI and waist circumference, early reductions in systolic and diastolic blood pressure levels, and improvements in glucose metabolism and the lipid profile.<sup>45,46</sup> Orlistat therapy has been shown to induce reductions in blood pressure in obese patients with hypertension,<sup>47,48</sup> improve glycemic control by lowering HbA1c and FPG levels in obese patients with type 2 DM and hypertension,<sup>49–52</sup> and improve the lipid profile by lowering total cholesterol and LDL-C levels in obese patients with hypercholesterolemia, hypertension, or type 2 DM.<sup>48–51,53</sup> In obese patients with hypercholesterolemia, orlistat appears to have a direct cholesterol-lowering effect that is independent of weight loss.<sup>53</sup> A retrospective analysis<sup>54</sup> of pooled data from 7 trials enrolling obese patients with type 2 DM suggested that the improvement in glycemic control with orlistat therapy may be independent of weight loss and may be related instead to reductions in abdominal fat.

Treatment with orlistat, when combined with lifestyle modifications, has been shown to reduce the risk of developing diabetes in obese patients by 37.3%.<sup>55</sup> In the XENDOS (XENical in the prevention of Diabetes in Obese Subjects) study,<sup>55</sup> patients treated with orlistat in addition to a low-calorie diet and increased physical activity had a diabetes incidence of 6.2% at 4 years compared with a 9.0% incidence among patients managed with lifestyle changes alone. Mean weight loss was significantly higher with orlistat (5.8 vs 3.0 kg;  $P < 0.001$ ) and was similar in orlistat-treated patients with or without impaired glucose tolerance.

Combination therapy with sibutramine and orlistat has been studied in some small trials; however, no additive effect on weight loss was found in these trials.<sup>56</sup> This lack of additive effect may be the result of the mechanisms of action of the 2 drugs cancelling each other out—a reduction in food intake with sibutramine results in reduced fecal fat loss, which is the primary mechanism wherein orlistat exerts its effect.

### Sympathomimetic Amines: Phentermine, Diethylpropion, Phendimetrazine, and Benzphetamine

The sympathomimetic amines are derivatives of amphetamine and work by stimulating neurons to maintain high concentrations of the catecholamines dopamine and norepinephrine, which helps suppress hunger signals and appetite. As might be expected from their mechanism of action, these drugs can increase heart rate and blood pressure levels and stimulate lipolysis.

Both phentermine and diethylpropion are classified as Drug Enforcement Administration (DEA) Schedule IV drugs, meaning they have a very low potential to cause physical tolerance. Phentermine has been approved for use for >45 years and is the most commonly used weight loss drug.<sup>34</sup> In a study from the 1960s,<sup>57</sup> obese women treated with phentermine who also maintained a 1000-calorie low-carbohydrate diet lost a mean of 27 lb over 36 weeks compared with the mean loss of 10 lb among women who maintained the low-calorie diet alone. Phentermine may be used during alternate months, as this regimen has been found to be as effective as continuous dosing. A recent meta-analysis<sup>58</sup> showed that phentermine, when combined with lifestyle changes, induces a mean weight loss of ~3.6 kg, while treatment with diethylpropion in combination with lifestyle changes is associated with a mean weight loss of 3.0 kg.

Phendimetrazine and benzphetamine are also approved for use as weight loss agents, but they are rarely prescribed today. These agents are classified as DEA Schedule III drugs because of the increased potential for developing physical tolerance.<sup>34</sup>

The amphetamines are contraindicated in various conditions, including CVD, moderate to severe hypertension, pulmonary hypertension, hyperthyroidism, glaucoma, pregnancy, and lactation (**Table III**). Their contraindication in patients with moderate to severe hypertension and CVD makes the use of these agents particularly difficult in obese patients who often have these comorbidities.

### Antidepressants in the Treatment of Obesity

The antidepressant drugs bupropion and fluoxetine have been evaluated for the treatment of obesity but are not approved as weight loss agents. Bupropion enhances norepinephrine and is a weak inhibitor of dopamine reuptake. In a double-blind, placebo-controlled trial of sustained-release (SR) bupropion,<sup>59</sup> patients were ran-

domized to placebo, bupropion SR 300 mg/d, or bupropion SR 400 mg/d. They received behavioral modification therapy, including instruction in energy-restricted diets and recommended exercise goals. Their menu plan required the use of liquid meal replacements twice a day. By 24 weeks, weight loss was 5%, 7.2%, and 10.1% of baseline, respectively. Weight losses in the 2 bupropion groups were sustained at 48 weeks.

Fluoxetine is a classic selective serotonin reuptake inhibitor indicated for the treatment of mood disorders such as bipolar disorder and depression-anxiety disorder. Pooled results of studies of obese patients treated with fluoxetine indicate a modest weight loss of 4.74 kg at 6 months and 3.15 kg at 12 months.<sup>26</sup> In one study of 84 obese patients referred for medical weight reduction and dietary counseling before undergoing bariatric surgery,<sup>60</sup> male patients treated with high doses of fluoxetine (60 mg daily) lost an average of 8.3 kg and female patients lost an average of 13.3 kg at 6 months.

### Anticonvulsants in the Treatment of Obesity

Topiramate and zonisamide are antiepileptic drugs that have been shown to induce weight loss both in patients with epilepsy and in obese patients without epilepsy. Although the mechanism of action of these agents in inducing weight loss has not been established, recent research points to inhibition of carbonic anhydrases as a possible mechanism.<sup>61</sup> Carbonic anhydrases are involved in lipogenesis in the mitochondria and cell cytosol; therefore, topiramate and zonisamide may work by inhibiting lipogenesis in adipocytes.<sup>61</sup>

In a study by Wilding et al,<sup>62</sup> 1289 obese patients were randomized to 1 of 3 doses of topiramate (96, 192, or 256 mg/d) or placebo. All patients also participated in a nonpharmacologic weight loss program. At 60 weeks, weight loss in the 3 topiramate groups (modified [m] intent-to-treat [ITT] population, n = 854) was 7.0%, 9.1%, and 9.7%, respectively, compared with 1.7% in the placebo group ( $P < 0.001$ ) and was accompanied by improvements in blood pressure, insulin sensitivity, and glucose. Adverse events were related to the central or peripheral nervous system and included paresthesia, difficulty with concentration/attention, depression, memory and language problems, nervousness, and psychomotor slowing. In a study<sup>63</sup> of obese patients with untreated type 2 DM who were also participating in a nonpharmacologic weight loss program, treatment with topiramate

192 mg/d resulted in a 9.1% weight loss (mITT population,  $n = 229$ ) from baseline, as well as positive effects on blood pressure and urinary albumin excretion. In a study<sup>64</sup> of 646 obese patients with diabetes who were being treated with metformin and a nonpharmacologic program of diet, exercise, and behavioral modification, topiramate significantly reduced body weight ( $P < 0.001$ ) and HbA1c levels ( $P < 0.001$ ) versus placebo in the mITT population ( $n = 307$ ).

Zonisamide at doses ranging from 100 to 600 mg/d, in combination with a hypocaloric diet, was shown in a randomized, placebo-controlled trial<sup>65</sup> to induce a weight loss of 9.2 kg (9.4%) from baseline to 32 weeks compared with 1.5 kg (1.8%) for placebo ( $P < 0.001$ ). Treatment with zonisamide was also associated with reductions in waist circumference and systolic blood pressure levels. Zonisamide was well tolerated: fatigue was the only adverse event occurring at a significantly higher rate with zonisamide than with placebo.

### Cannabinoid Receptor Antagonists

The endocannabinoid system comprises CB<sub>1</sub> and CB<sub>2</sub> receptors and is involved in the regulation of energy balance, food intake, and lipid and glucose metabolism. Whereas CB<sub>2</sub> receptors are found primarily in the immune system, CB<sub>1</sub> receptors are present in the brain, GI tract, adipose tissue, heart, pituitary gland, and adrenal glands. The cannabinoid receptor antagonists are a novel class of agents that act centrally by blocking CB<sub>1</sub> receptors, thereby suppressing appetite. Moreover, they probably also act peripherally, increasing thermogenesis and, therefore, energy expenditure.

Rimonabant, a selective CB<sub>1</sub> receptor antagonist, has been evaluated as a weight loss agent in 4 large, multicenter, randomized, placebo-controlled clinical trials of patients who were either obese or overweight with  $\geq 1$  comorbidity such as diabetes, dyslipidemia, or hypertension.<sup>66</sup> All patients in these studies were prescribed a hypocaloric diet to achieve a daily deficit of 600 kcal and were advised to increase their activity level. They were then randomized to receive rimonabant (5 or 20 mg/d) or placebo for 1 year. The pooled ITT population included 5580 patients without diabetes and 1047 with diabetes. Pooled 1-year data from the studies showed that in patients without diabetes, rimonabant 20 mg/d resulted in significant reductions from baseline in body weight (mean, 6.5 kg), waist circumference (6.4 cm), triglycer-

ide levels (6.9%), fasting insulin levels (0.6  $\mu\text{U/mL}$ ), and homeostasis model assessment of insulin resistance (0.2) and an increase in HDL-C levels (16.4%) versus placebo (all,  $P < 0.001$ ).

Among overweight or obese patients with untreated dyslipidemia,<sup>67</sup> those who received rimonabant 20 mg/d had significant reductions (last observation carried forward) in the proportion of small LDL particles ( $P = 0.002$ ), plasma leptin levels ( $P < 0.001$ ), and CRP levels ( $P = 0.02$ ) and greater increases in plasma adiponectin levels ( $P < 0.001$ ) compared with those receiving placebo. In overweight and obese patients with diabetes who were treated with rimonabant,<sup>68</sup> HbA1c levels were significantly lower ( $P < 0.0001$ ) than were those in patients receiving placebo, and a higher proportion of patients in the rimonabant group reached the target HbA1c goal of  $< 6.5\%$  or  $< 7.0\%$  ( $P < 0.0001$ ). Regression analysis of the changes in HDL-C, triglyceride, adiponectin, and HbA1c levels in the 4 trials showed that 45% to 57% of these effects could not be explained by weight loss alone, suggesting that rimonabant might have a direct pharmacologic effect in peripheral tissues.<sup>66</sup>

Across the 4 studies,<sup>66</sup> nausea, dizziness, diarrhea, depression, anxiety, and insomnia were reported more frequently in the rimonabant 20-mg group than in the placebo group. Serious adverse events occurred more commonly in the rimonabant group than in the placebo group. In total, 13.8% of patients receiving rimonabant 20 mg and 7.2% of patients receiving placebo discontinued treatment because of adverse events. More patients discontinued treatment because of depressive mood disorders, nausea, anxiety, and dizziness in the rimonabant 20-mg group than in the placebo group.

Although rimonabant was approved for use in Europe, it has been withdrawn from the market because of safety concerns. In the United States, the new drug application for rimonabant failed to gain FDA approval owing to safety concerns regarding rare cases of suicidal ideation associated with the use of this drug. Investigations of taranabant, another cannabinoid receptor antagonist, have been halted in light of similar safety concerns.

### Antidiabetic Agents for Weight Loss

Exenatide, a long-lasting analogue of the hormone incretin (glucagon-like peptide 1), enhances glucose-dependent insulin secretion by pancreatic  $\beta$ -cells, suppresses inappropriately elevated glucagon secretion, slows gastric

emptying, and reduces food intake. Exenatide is indicated as adjunctive therapy in patients with type 2 DM who have not achieved adequate glycemic control despite treatment with metformin, a sulfonylurea, a thiazolidinedione, or a combination of these agents. Clinical trials of exenatide have shown that it can cause modest weight loss in addition to reducing HbA1c in patients with type 2 DM. This is in contrast to the weight gain that often accompanies treatment with insulin and most other antidiabetic agents. In an open-label extension study<sup>69</sup> of 217 patients with type 2 DM who were unable to achieve adequate glycemic control on oral medication alone (metformin and/or sulfonylurea), exenatide 10 µg added as adjunctive therapy reduced HbA1c levels by 1.0% (SD, 0.1%) and resulted in a mean (SD) weight loss of 11.68 (0.88) lb at 3 years ( $P < 0.0001$ ). A 24-week, randomized, double-blind, placebo-controlled trial<sup>70</sup> of exenatide monotherapy in 232 drug-naïve patients with type 2 DM demonstrated a statistically significantly greater weight loss of 6.1 and 6.8 lb with exenatide 5 and 10 µg twice daily injections, respectively, versus 3.2 lb with placebo. HbA1c levels were reduced by 0.7% and 0.9% in the exenatide 5-µg and 10-µg groups, respectively. Exenatide is thought to cause weight loss as a result of nausea, which is a common side effect, and by delayed gastric emptying, an increased feeling of fullness, and decreased food intake. Exenatide is not currently approved as a weight loss drug for obese patients with type 2 DM.

## SURGICAL OPTIONS

Surgical treatment of obesity, or *bariatric surgery*, is a treatment option for morbidly obese patients—those with a BMI  $\geq 40$  kg/m<sup>2</sup> or a BMI  $\geq 35$  kg/m<sup>2</sup> and significant obesity-related comorbidities.<sup>18</sup> Because bariatric surgery is associated with certain risks and complications, patients should be carefully selected for these procedures (Table IV).<sup>71</sup> Bariatric surgery could be carefully considered for severely obese adolescents who have failed to lose weight after participating in a comprehensive lifestyle program for at least 6 to 12 months *if they have reached skeletal and developmental maturity*. It could also be considered for patients aged  $\geq 65$  years primarily to improve quality of life, as the surgery by itself is unlikely to increase their lifespan. Bariatric surgery should be performed in centers of excellence in obesity management. The multidisciplinary teams of

**TABLE IV. CRITERIA FOR BARIATRIC SURGERY.**

BMI $\geq 40$ kg/m <sup>2</sup> or $\geq 35$ kg/m <sup>2</sup> with significant obesity-related comorbidities
Age 16 to 65 years
Acceptable operative risks
Documented failure to achieve long-term weight loss with nonsurgical approaches
Psychological stability and realistic expectations
Well-informed and motivated patient with commitment to long-term lifestyle changes
Supportive family/social environment
Commitment to long-term follow-up
Resolution of alcohol/substance abuse
Absence of active psychosis, untreated severe depression

BMI = body mass index.  
Adapted with permission from: Schneider BE, Mun EC. Surgical management of morbid obesity. *Diabetes Care*. 2005;28:475–480.<sup>71</sup>

physicians at these specialized centers are able to assess patients before surgery, and they have experience in diagnosing and managing complications unique to these operations. These centers have an established track record of acceptable outcomes and offer long-term follow-up care.

Bariatric surgery comprises malabsorptive and restrictive procedures. Malabsorptive procedures involve shortening the length of the small intestine by creating a bypass from the duodenum to a distal part of the small intestine. The decreased length of the small intestine reduces the time during which digestion and absorption of nutrients can occur, resulting in negative energy balance and weight loss.<sup>71,72</sup> The degree of malabsorption is determined by the length of the diversion limb. Malabsorptive procedures include jejunoileal bypass (rarely performed today) and biliopancreatic diversion with or without a duodenal switch. Restrictive procedures reduce the storage capacity of the stomach, resulting in early satiety and eventually decreased caloric intake. The most common restrictive procedures include a vertical banded gastroplasty and a laparoscopic adjustable gastric band.

The Roux-en-Y gastric bypass, the most common bariatric procedure performed in the United States, has both malabsorptive and restrictive components.<sup>73</sup> It involves the creation of a gastric pouch that is separated from the rest of the stomach, thereby reducing the capacity of the stomach, and the formation of a Roux-en-Y limb—connection of this smaller stomach directly to the

**KEY POINT**

**Bariatric surgery comprises malabsorptive and restrictive procedures. Malabsorptive procedures involve shortening the small intestine to reduce digestion time and absorption of nutrients, whereas restrictive procedures reduce the storage capacity of the stomach, resulting in early satiety and decreased caloric intake.**

middle portion of the small intestine—to reduce the functional length of the small intestine. The procedure can be done laparoscopically or through open surgery.<sup>72</sup>

Transoral gastroplasty, or *TOGA*, is an incision-free endoscopic approach to bariatric surgery that involves passing a set of flexible staplers through the mouth into the stomach to create a restrictive pouch that limits the amount of food that can be eaten. This procedure gives the patient a feeling of fullness after ingesting a small meal, resulting in weight loss. The procedure is currently in the experimental stage. It is being performed at a handful of obesity centers in the United States and is available only through clinical trials to those who qualify.

Bariatric surgery is a highly effective treatment approach that results in a reduction in BMI of 10 to 15 kg/m<sup>2</sup> and a mean weight loss of 20 to 40 kg.<sup>23,74</sup> As expected, the considerable weight loss from bariatric surgery is associated with significant positive effects on overall mortality in both diabetic and nondiabetic obese individuals. In a cohort of nondiabetic morbidly obese patients (mean BMI, 50 kg/m<sup>2</sup>),<sup>75</sup> those who underwent bariatric surgery had an 89% reduction in mortality compared with those who did not undergo surgery. The mortality rate among morbidly obese patients with diabetes who underwent bariatric surgery was 9% versus 28% among those who did not undergo surgery.<sup>76</sup> The decrease in mortality in those who underwent surgery was primarily due to a reduction in the number of cardiovascular deaths.

According to a meta-analysis conducted by Buchwald et al,<sup>23</sup> bariatric surgery resulted in the resolution of hypertension in 62% of patients, the resolution of obstructive

sleep apnea in 86% of patients, and recovery from type 2 DM in 77% of patients. The mechanisms for recovery from diabetes are not completely understood, but alterations in gut hormone secretion with consequent sustained reductions in food intake and enhanced insulin secretion are thought to play a role, in addition to significant weight loss.<sup>77–79</sup> Bariatric surgery is associated with positive effects on insulin sensitivity, incidence of diabetes, lipid profile, and blood pressure, and it may help resolve conditions such as obstructive sleep apnea and polycystic ovary syndrome.<sup>72</sup> In nondiabetic obese patients undergoing bariatric surgery, total cholesterol and LDL-C levels are reduced,<sup>23</sup> and insulin sensitivity improves significantly.<sup>80,81</sup>

Following bariatric surgery, particularly gastric bypass, iron and vitamin deficiencies (eg, vitamin B12, vitamin D) are very common owing to the new anatomy of the GI tract and the resulting reduced absorption of nutrients.<sup>72</sup> Patients should be routinely placed on daily supplemental vitamin therapy to avoid these deficiencies. Gallstones are also a frequent side effect and may occur in up to 71% of patients.<sup>72</sup> Some surgeons routinely perform a cholecystectomy at the time of the bariatric operation regardless of symptoms or presence of stones. Mortality associated with bariatric surgery ranges from 0.1% to 4.6%, is higher in men than in women, and occurs more frequently with malabsorptive procedures.<sup>72</sup> Pulmonary embolism, sepsis, and anastomotic leaks are the leading causes of death following gastric bypass surgery.<sup>72</sup>

It is important to keep in mind that morbidly obese patients have little physiologic reserve, and any postoperative complication can be potentially life threatening. Additionally, obese patients may not manifest all of the classic symptoms of illness such as fever, leukocytosis, or abdominal pain. Thus, diagnosis of complications requires a high index of suspicion. Of the commonly measured objective parameters, an elevated heart rate may be the most reliable indicator of physiologic abnormality.

**CONCLUSIONS**

The growing prevalence of overweight and obesity around the globe threatens to overwhelm our health care systems with conditions such as diabetes and heart disease. Overcoming barriers to achieving treatment goals and designing and implementing strategies to address the threat of an obesity pandemic are among the foremost public health challenges of our time. Centers of excel-

lence in obesity management represented by multidisciplinary teams can provide comprehensive programs derived from evidence-based medicine for the treatment of obesity. A lifestyle-based weight loss program that includes dietary changes, increased physical activity, and behavioral therapy is the cornerstone of treatment for overweight and obesity. Pharmacotherapy may be added if lifestyle interventions alone are insufficient. For morbidly obese individuals, bariatric surgery may be an appropriate option when combined with long-term lifestyle modifications.

## ACKNOWLEDGMENT

The authors wish to thank Viji Anantharaman for her writing and research assistance in the preparation of this manuscript.

## REFERENCES

- Ogden CL, Carroll MD, McDowell MA, et al, for the Division of Health and Nutrition Examination Surveys. Obesity among adults in the United States—no statistically significant change since 2003–2004. NCHS Data Brief. November 2007. US Dept of Health and Human Services, Centers for Disease Control and Prevention.
- York DA, Rössner S, Caterson I, et al, for the American Heart Association. Prevention Conference VII: Obesity, a worldwide epidemic related to heart disease and stroke: Group I: Worldwide demographics of obesity. *Circulation*. 2004;110:e463–e470.
- US Dept of Health and Human Services, National Institutes of Health, Weight-control Information Network. Statistics related to overweight and obesity. <http://win.niddk.nih.gov/statistics/index.htm#preval>. Accessed April 21, 2009.
- James PT, Rigby N, Leach R, for the International Obesity Task Force. The obesity epidemic, metabolic syndrome and future prevention strategies. *Eur J Cardiovasc Prev Rehab*. 2004;11:3–8.
- Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world—a growing challenge [published correction appears in *N Engl J Med*. 2007;356:973]. *N Engl J Med*. 2007;356:213–215.
- Lissner L, Heitmann BL. Dietary fat and obesity: Evidence from epidemiology. *Eur J Clin Nutr*. 1995;49:79–90.
- Drewnowski A, Kurth C, Holden-Wiltse J, Saari J. Food preferences in human obesity: Carbohydrates versus fats. *Appetite*. 1992;18:207–221.
- Gates JC, Huenemann RL, Brand RJ. Food choices of obese and non-obese persons. *J Am Diet Assoc*. 1975;67:339–343.
- Cox DN, Perry L, Moore PB, et al. Sensory and hedonic associations with macronutrient and energy intakes of lean and obese consumers. *Int J Obes Relat Metab Disord*. 1999;23:403–410.
- Jebb SA, Moore MS. Contribution of a sedentary lifestyle and inactivity to the etiology of overweight and obesity: Current evidence and research issues. *Med Sci Sports Exerc*. 1999;31(Suppl):S534–S541.
- Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med*. 2006;355:763–768.
- Eckel RH, Krauss RM. American Heart Association call to action: Obesity as a major risk factor for coronary heart disease. AHA Nutrition Committee. *Circulation*. 1998;97:2099–2100.
- Chuang SY, Chou P, Hsu PF, et al. Presence and progression of abdominal obesity are predictors of future high blood pressure and hypertension. *Am J Hypertens*. 2006;19:788–795.
- de Simone G, Devereux RB, Chinali M, et al, for the Strong Heart Study Investigators. Risk factors for arterial hypertension in adults with initial optimal blood pressure: The Strong Heart Study. *Hypertension*. 2006;47:162–167.
- Kissebah AH, Freedman DS, Peiris AN. Health risks of obesity. *Med Clin North Am*. 1989;73:111–138.
- Pouliot MC, Després JP, Nadeau A, et al. Visceral obesity in men. Associations with glucose tolerance, plasma insulin, and lipoprotein levels. *Diabetes*. 1992;41:826–834.
- McLaughlin T, Abbasi F, Lamendola C, Reaven G. Heterogeneity in the prevalence of risk factors for cardiovascular disease and type 2 diabetes mellitus in obese individuals: Effect of differences in insulin sensitivity. *Arch Intern Med*. 2007;167:642–648.
- National Heart, Lung, and Blood Institute in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report*. Bethesda, MD: National Institutes of Health; September 1998. NIH publication 98-4083.
- Wadden TA, Anderson DA, Foster GD. Two-year changes in lipids and lipoproteins associated with the maintenance of a 5% to 10% reduction in initial weight: Some findings and some questions. *Obes Res*. 1999;7:170–178.
- Wing RR, Koeske R, Epstein LH, et al. Long-term effects of modest weight loss in type II diabetic patients. *Arch Intern Med*. 1987;147:1749–1753.
- Knowler WC, Barrett-Connor E, Fowler SE, et al, for the Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.
- Tuomilehto J, Lindström J, Eriksson JG, et al, for the Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344:1343–1350.
- Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: A systematic review and meta-analysis [published correction appears in *JAMA*. 2005;293:1728]. *JAMA*. 2004;292:1724–1737.
- Zeyda M, Stulnig TM. Obesity, inflammation, and insulin resistance—A mini-review. *Gerontology*. 2009;55:379–386.
- Tchernof A, Nolan A, Sites CK, et al. Weight loss reduces C-reactive protein levels in obese postmenopausal women. *Circulation*. 2002;105:564–569.

26. Snow V, Barry P, Fitterman N, et al, for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Pharmacologic and surgical management of obesity in primary care: A clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2005;142:525–531.
27. Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med.* 2009;360:859–873.
28. Shai I, Schwarzfuchs D, Henkin Y, et al, for the Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med.* 2008;359:229–241.
29. Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med.* 2009;169:659–669.
30. Wing RR. Physical activity in the treatment of the adulthood overweight and obesity: Current evidence and research issues. *Med Sci Sports Exerc.* 1999;31(Suppl):S547–S552.
31. Foster GD, Makris AP, Bailer BA. Behavioral treatment of obesity. *Am J Clin Nutr.* 2005;82(Suppl):230S–235S.
32. Wadden TA, Foster GD. Behavioral treatment of obesity. *Med Clin North Am.* 2000;84:441–461, vii.
33. Williamson DA, Perrin LA. Behavioral therapy for obesity. *Endocrinol Metab Clin North Am.* 1996;25:943–954.
34. Fujioka K, Lee MW. Pharmacologic treatment options for obesity: Current and potential medications. *Nutr Clin Pract.* 2007;22:50–54.
35. Nisoli E, Carruba MO. An assessment of the safety and efficacy of sibutramine, an anti-obesity drug with a novel mechanism of action. *Obes Rev.* 2000;1:127–139.
36. Cypess AM, Lehman S, Williams G, et al. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med.* 2009;360:1509–1517.
37. James WP, Astrup A, Finer N, et al. Effect of sibutramine on weight maintenance after weight loss: A randomised trial. STORM Study Group. Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet.* 2000;356:2119–2125.
38. Finer N, Bloom SR, Frost GS, et al. Sibutramine is effective for weight loss and diabetic control in obesity with type 2 diabetes: A randomised, double-blind, placebo-controlled study. *Diabetes Obes Metab.* 2000;2:105–112.
39. Fujioka K, Seaton TB, Rowe E, et al, for the Sibutramine/Diabetes Clinical Study Group. Weight loss with sibutramine improves glycaemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus. *Diabetes Obes Metab.* 2000;2:175–187.
40. Sabuncu T, Ucar E, Birden F, Yasar O. The effect of 1-yr sibutramine treatment on glucose tolerance, insulin sensitivity and serum lipid profiles in obese subjects. *Diabetes Nutr Metab.* 2004;17:103–107.
41. Tankova T, Dakovska G, Lazarova M, et al. Sibutramine in the treatment of obesity in type 2 diabetic patients and in nondiabetic subjects. *Acta Diabetol.* 2004;41:146–153.
42. Hung YJ, Chen YC, Pei D, et al. Sibutramine improves insulin sensitivity without alteration of serum adiponectin in obese subjects with type 2 diabetes. *Diabet Med.* 2005;22:1024–1030.
43. Faria AN, Ribeiro Filho FF, Kohlmann NE, et al. Effects of sibutramine on abdominal fat mass, insulin resistance and blood pressure in obese hypertensive patients. *Diabetes Obes Metab.* 2005;7:246–253.
44. Maggioni AP, Caterson I, Coutinho W, et al, for the SCOUT Investigators. Tolerability of sibutramine during a 6-week treatment period in high-risk patients with cardiovascular disease and/or diabetes: A preliminary analysis of the Sibutramine Cardiovascular Outcomes (SCOUT) trial. *J Cardiovasc Pharmacol.* 2008;52:393–402.
45. Finer N, James WP, Kopelman PG, et al. One-year treatment of obesity: A randomized, double-blind, placebo-controlled, multicentre study of orlistat, a gastrointestinal lipase inhibitor. *Int J Obes Relat Metab Disord.* 2000;24:306–313.
46. Hauptman J, Lucas C, Boldrin MN, et al. Orlistat in the long-term treatment of obesity in primary care settings. *Arch Fam Med.* 2000;9:160–167.
47. Sharma AM, Golay A. Effect of orlistat-induced weight loss on blood pressure and heart rate in obese patients with hypertension. *J Hypertens.* 2002;20:1873–1878.
48. Bakris G, Calhoun D, Egan B, et al, for the Orlistat and Resistant Hypertension Investigators. Orlistat improves blood pressure control in obese subjects with treated but inadequately controlled hypertension. *J Hypertens.* 2002;20:2257–2267.
49. Hanefeld M, Sachse G. The effects of orlistat on body weight and glycaemic control in overweight patients with type 2 diabetes: A randomized, placebo-controlled trial. *Diabetes Obes Metab.* 2002;4:415–423.
50. Miles JM, Leiter L, Hollander P, et al. Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin [published correction appears in *Diabetes Care.* 2002;25:1671]. *Diabetes Care.* 2002;25:1123–1128.
51. Kelley DE, Bray GA, Pi-Sunyer FX, et al. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: A 1-year randomized controlled trial [published correction appears in *Diabetes Care.* 2003;26:971]. *Diabetes Care.* 2002;25:1033–1041.
52. Zanella MT, Uehara MH, Ribeiro AB, et al. Orlistat and cardiovascular risk profile in hypertensive patients with metabolic syndrome: The ARCOS study. *Arq Bras Endocrinol Metabol.* 2006;50:368–376.
53. Muls E, Kolanowski J, Scheen A, Van Gaal L, for the ObelHyx Study Group. The effects of orlistat on weight and on serum lipids in obese patients with hypercholesterolemia: A randomized, double-blind, placebo-controlled, multicentre study. *Int J Obes Relat Metab Disord.* 2001;25:1713–1721.
54. Jacob S, Rabbia M, Meier MK, Hauptman J. Orlistat 120 mg improves glycaemic control in type 2 diabetic patients with or without concurrent weight loss. *Diabetes Obes Metab.* 2009;11:361–371.
55. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study: A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2

- diabetes in obese patients [published correction appears in *Diabetes Care*. 2004;27:856]. *Diabetes Care*. 2004;27:155–161.
56. Wadden TA, Berkowitz RI, Womble LG, et al. Effects of sibutramine plus orlistat in obese women following 1 year of treatment by sibutramine alone: A placebo-controlled trial. *Obes Res*. 2000;8:431–437.
  57. Munro JF, MacCuish AC, Wilson EM, Duncan LJ. Comparison of continuous and intermittent anorectic therapy in obesity. *Br Med J*. 1968;1:352–354.
  58. Li Z, Maglione M, Tu W, et al. Meta-analysis: Pharmacologic treatment of obesity. *Ann Intern Med*. 2005;142:532–546.
  59. Anderson JW, Greenway FL, Fujioka K, et al. Bupropion SR enhances weight loss: A 48-week double-blind, placebo-controlled trial. *Obes Res*. 2002;10:633–641.
  60. Dolfing JG, Wolfenbittel BH, ten Hoor-Aukema NM, Schweitzer DH. Daily high doses of fluoxetine for weight loss and improvement in lifestyle before bariatric surgery. *Obes Surg*. 2005;15:1185–1191.
  61. De Simone G, Supuran CT. Antiobesity carbonic anhydrase inhibitors. *Curr Top Med Chem*. 2007;7:879–884.
  62. Wilding J, Van Gaal L, Rissanen A, et al, for the OBES-002 Study Group. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of topiramate in the treatment of obese subjects. *Int J Obes Relat Metab Disord*. 2004;28:1399–1410.
  63. Stenlöf K, Rössner S, Vercauteren F, et al, for the OBDM-003 Study Group. Topiramate in the treatment of obese subjects with drug-naïve type 2 diabetes. *Diabetes Obes Metab*. 2007;9:360–368.
  64. Toplak H, Hamann A, Moore R, et al. Efficacy and safety of topiramate in combination with metformin in the treatment of obese subjects with type 2 diabetes: A randomized, double-blind, placebo-controlled study. *Int J Obes (Lond)*. 2007;31:138–146.
  65. Gadde KM, Franciscy DM, Wagner HR II, Krishnan KR. Zonisamide for weight loss in obese adults: A randomized controlled trial. *JAMA*. 2003;289:1820–1825.
  66. Van Gaal L, Pi-Sunyer X, Després JP, et al. Efficacy and safety of rimonabant for improvement of multiple cardiometabolic risk factors in overweight/obese patients: Pooled 1-year data from the Rimonabant in Obesity (RIO) program. *Diabetes Care*. 2008;31(Suppl 2):S229–S240.
  67. Després JP, Golay A, Sjöström L, for the Rimonabant in Obesity-Lipids Study Group. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med*. 2005;353:2121–2134.
  68. Scheen AJ, Finer N, Hollander P, et al, for the RIO-Diabetes Study Group. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: A randomized controlled study [published correction appears in *Lancet*. 2006;368:1650]. *Lancet*. 2006;368:1660–1672.
  69. Klonoff DC, Buse JB, Nielsen LL, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin*. 2008;24:275–286.
  70. Moretto TJ, Milton DR, Ridge TD, et al. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naïve patients with type 2 diabetes: A randomized, double-blind, placebo-controlled, parallel-group study [published correction appears in *Clin Ther*. 2008;30:1937]. *Clin Ther*. 2008;30:1448–1460.
  71. Schneider BE, Mun EC. Surgical management of morbid obesity. *Diabetes Care*. 2005;28:475–480.
  72. Bult MJ, van Dalen T, Muller AF. Surgical treatment of obesity. *Eur J Endocrinol*. 2008;158:135–145.
  73. Santry HP, Gillen DL, Lauderdale DS. Trends in bariatric surgical procedures. *JAMA*. 2005;294:1909–1917.
  74. Maggard MA, Shugarman LR, Suttorp M, et al. Meta-analysis: Surgical treatment of obesity. *Ann Intern Med*. 2005;142:547–559.
  75. Christou NV, Sampalis JS, Liberman M, et al. Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese patients. *Ann Surg*. 2004;240:416–423.
  76. MacDonald KG Jr, Long SD, Swanson MS, et al. The gastric bypass operation reduces the progression and mortality of non-insulin-dependent diabetes mellitus. *J Gastrointest Surg*. 1997;1:213–220.
  77. Whitson BA, Leslie DB, Kellogg TA, et al. Enteroendocrine changes after gastric bypass in diabetic and nondiabetic patients: A preliminary study. *J Surg Res*. 2007;141:31–39.
  78. Laferrère B, Teixeira J, McGinty J, et al. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2008;93:2479–2485.
  79. Ferrannini E, Mingrone G. Impact of different bariatric surgical procedures on insulin action and beta-cell function in type 2 diabetes. *Diabetes Care*. 2009;32:514–520.
  80. Ballantyne GH, Farkas D, Laker S, Wasielewski A. Short-term changes in insulin resistance following weight loss surgery for morbid obesity: Laparoscopic adjustable gastric banding versus laparoscopic Roux-en-Y gastric bypass. *Obes Surg*. 2006;16:1189–1197.
  81. Dixon JB, Dixon AF, O'Brien PE. Improvements in insulin sensitivity and beta-cell function (HOMA) with weight loss in the severely obese. Homeostatic model assessment. *Diabet Med*. 2003;20:127–134.

**Address correspondence to:** Christopher P. Cannon, MD, TIMI Study Group, 333 Longwood Avenue, Suite 402, Boston, MA 02115. E-mail: cpcannon@partners.org

## Dialogue Box

### EDITORIAL BOARD

**Do all obese patients develop cardiovascular risk factors?**

### CANNON

Interestingly, no. One of the more intriguing aspects of obesity is that in addition to the cosmetic issue, from a medical perspective, it is important to subcategorize obese patients based on the presence of cardiometabolic risk factors and/or cardiovascular disease. To do this, blood tests designed to provide a quick read on cardiometabolic consequences are generally recommended, including C-reactive protein, fasting plasma glucose, lipid profile, and glycosylated hemoglobin. The next level of assessment involves a search for the presence of vascular disease. Probably the least invasive measure for the heart is the coronary calcium score. Tests measuring carotid artery intima-media thickness and the ankle-brachial index can provide evidence of extra-cardiac vascular disease. If you find evidence of cardiovascular disease, you can inform the patient. This information may provide him or her with a greater incentive for initiating lifestyle changes and/or beginning preventive therapies (eg, lipid-modifying therapies) than would cosmetic issues alone.

### EDITORIAL BOARD

**Can cardiovascular risk in obese patients be accurately gauged by assessing whether their build is “apple” versus “pear” shape?**

### CANNON

From a pathophysiologic perspective, those with visceral obesity are the ones most likely to have the substrate for cardiometabolic consequences. Although waist circumference is a useful measure, I don't know whether its clinical positive predictive value is good enough to be able to confidently say that the heavy patient with a thinner waist doesn't have visceral adiposity and thus wouldn't be someone we'd have to worry about having a higher cardiovascular risk.

### EDITORIAL BOARD

**Would measuring serum adiponectin be helpful in this regard?**

### CANNON

Although the utility of serum adiponectin and other such measures are well developed in the research arena, the big question is how well their utility will translate clinically and when, if ever, they will become ready for clinical use. There's no simple answer. However, at this time, serum adiponectin is not a screening test that we should be thinking about in the office.

### EDITORIAL BOARD

**How does your approach to obesity differ in a patient with newly diagnosed obesity compared with that for a patient with long-standing obesity?**

### CANNON

In the patient recently diagnosed with obesity, my focus is on lifestyle changes as the first step. Although many physicians remain skeptical as to whether anything ever really comes of this approach, in recent years there has been a series of studies which have demonstrated not only that such interventions work for losing weight but also that positive outcomes can be achieved with weight loss and/or exercise. At a minimum, I have obese patients see a nutritionist and I encourage them to make modest changes in their diet. I direct them toward healthier diets they can sustain rather than toward a more radical diet. On the exercise side of the equation, I begin by asking them what they do currently and try to have them build from there. For example, recently I saw a woman who told me she lived on a golf course and that she got out just about every day. I advised her to increase the amount of exercise she does by staying out an extra 10 minutes and to aim to do this at least 5 times a week. For some, I may encourage them to go to the gym, but I make a point not to imply that going to the gym is the only way to carry out an exercise program. For patients with longer-standing obesity for whom lifestyle modification measures have failed and who are

## Dialogue Box

making absolutely no progress, I'm more inclined to suggest a formal weight loss program where surgical and other interventions are considered. In addition to providing more detailed nutrition interventions and pharmacologic therapy, these programs also consider bariatric surgery for morbidly obese patients.

### EDITORIAL BOARD

**There appears to be a movement back toward non-pharmacologic interventions, with an emphasis on the benefits of modest calorie restriction and even modest exercise. To what do you attribute this?**

### CANNON

The movement toward lifestyle interventions is a direct result of studies that have come out in the past year or so showing the benefits of this approach. For example, there have been a couple of studies in patients with diabetes that produced identical results—exercise, diet, or both resulted in incremental benefits on glycemic control. In addition, there have been outcome studies looking at exercise which have shown that, even without weight loss, outcomes are better. These new studies reaffirm the notion that lifestyle modifications actually can work and that we, as physicians, have to work harder at getting patients to embrace them.

An analogy can be drawn with smoking cessation. Even if repeated attempts to get a patient to stop smoking are unsuccessful, it is important to keep trying because someday it might work. For our patients who are obese, we need to adopt a similar approach and continue to preach lifestyle modification.

Then there is the societal factor. The problem of obesity is so widespread and publicized that even food companies are realizing they can't go on promoting fattening foods all the time—hence, the 100-calorie snack packs that are available for almost any kind of snack. A few states, including Massachusetts, now require fast food chains to put calorie counts on their menus. This is an incredibly powerful tool, since having that information so readily available puts into perspective for patients the adverse consequences of eating things that

look tasty. This notion of posting calories represents another societal practice that can help people make better choices.

### EDITORIAL BOARD

**Can you elaborate on the postoperative complications associated with bariatric surgery?**

### KUMAR

The postoperative complications of deep venous thrombosis and pulmonary embolism are relatively common in morbidly obese patients undergoing bariatric surgery, just as they are for obese patients following any major surgical procedure. The diagnosis of venous thromboembolism can be particularly challenging because obese patients don't always develop common clinical manifestations, such as chest pain, and leg edema or tenderness might be difficult to appreciate on physical examination owing to the body habitus. An anastomotic leak can also be very difficult to diagnose, and failure to detect it early can lead to disastrous consequences. Sepsis ranks among the leading causes of morbidity and mortality in this patient population. It is important to be aware that morbidly obese patients have little physiologic reserve, and any of these postoperative complications can be potentially life threatening. Because they don't always develop the traditional symptoms of illness, such as fever, leukocytosis, or abdominal pain, we need to have a very high index of suspicion for early detection of complications. Paying close attention to patient complaints is especially important. It is also important to be aware that on physical examination, the most reliable finding that may signal the presence of an underlying complication is an unexpected tachycardia. If sepsis is suspected, broad-spectrum antibiotics should be started without delay and the possibility of methicillin-resistant *Staphylococcus aureus* infection should not be overlooked.

### EDITORIAL BOARD

**When do you consider bariatric surgery for a patient?**

## Dialogue Box

### **CANNON**

I generally don't think patients should consider an interventional procedure until after they fail both a trial with lifestyle modification managed by me and their primary care provider and medical and pharmacologic therapy managed by our weight management service. That way, if a surgical complication were to

occur, you at least would be comforted by knowing the procedure was done for a good reason. I do not recommend that patients rush into these procedures lightly. They really are best for patients who have cardiometabolic consequences of obesity and/or other consequences and who are really refractory to other therapies.