

# Fundamentals of Cardiometabolic Risk Factor Reduction: Achieving and Maintaining Weight Loss with Pharmacotherapy or Bariatric Surgery

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Obesity is a major health problem in the United States and many other countries because of its high prevalence and causal relationship with serious medical comorbidities. The therapeutic options currently available to help obese patients lose weight are: (1) therapeutic lifestyle change (behavioral, dietary, and physical activity modification); (2) pharmacotherapy; and (3) bariatric surgery. Lifestyle modification is the first therapeutic choice; however, achieving a successful long-term weight loss with lifestyle intervention alone is difficult. There is increasing interest, therefore, in the use of pharmacotherapy and surgery to treat obesity. Although there are a number of antiobesity medications available, the only medications approved in the United States for long-term treatment of obesity are sibutramine and orlistat. Use of these medications results in 3% to 5% more weight loss compared with placebo after 1 year. Bariatric surgery is an effective weight loss option for obese patients, but it is restricted to patients who are considered morbidly obese (ie, with a body mass index [BMI]  $\geq 40$  kg/m<sup>2</sup> or a BMI of 35–39.9 kg/m<sup>2</sup> with  $\geq 1$  severe obesity-related medical complication). (*Clinical Cornerstone*. 2008;9[1]:41–51) © 2008 Elsevier. All rights reserved.

The prevalence of obesity continues to increase in the United States and in many other countries worldwide. Data from the 2003–2004 National Health and Nutrition Examination Survey (NHANES)<sup>1</sup> indicate that ~32% of adults in the United States are obese (body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>), which represents a 9% increase in obesity prevalence from NHANES III (1988–1994) data. Moreover, the relative increase in extreme or morbid obesity (BMI  $\geq 40$  kg/m<sup>2</sup>) is greater than the increase in lower BMI subcategories.<sup>2,3</sup>

Intentional weight loss improves many of the medical complications associated with obesity,<sup>4,5</sup> and beneficial effects are evident even with only moderate (5%–10%) weight loss.<sup>6</sup> For example, moderate weight loss can improve glycemic control in patients with type 2 diabetes<sup>7</sup> and prevent the onset of diabetes in high-risk individuals.<sup>8,9</sup> In fact, data from several studies<sup>7,10</sup> suggest

that improvement in insulin sensitivity is directly related to percentage of weight loss and that improvement continues until a weight loss of ~20% to 30% of initial body weight is achieved.

### KEY POINT

**Intentional weight loss improves many of the medical complications associated with obesity, and beneficial effects are evident even with only moderate (5%–10%) weight loss.**

Generally, the major goals of obesity treatment are to decrease body fat and improve appearance, physical function, and medical health. However, removing large amounts (~10 kg) of subcutaneous abdominal fat by liposuction does not improve the metabolic risk factors for coronary heart disease or liver, skeletal muscle, or adipose tissue insulin sensitivity in obese adults with normal oral glucose tolerance or type 2 diabetes.<sup>11</sup> Furthermore, although liposuction removes billions of fat cells, it does not change the size of the remaining adipocytes, nor does it decrease ectopic fat (eg, intrahepatic and intramyocellular lipid content) or visceral fat mass, which may be involved in the pathophysiology of obesity<sup>11</sup>; therefore, fat loss induced by negative energy balance rather than surgical removal is necessary to achieve metabolic benefits.

**KEY POINT**

**Fat loss induced by negative energy balance rather than surgical removal is necessary to achieve metabolic benefits.**

The therapeutic options currently available to help obese patients lose weight by means of a negative energy balance are: (1) lifestyle modification to change eating and physical activity behaviors; (2) pharmacotherapy to decrease food intake or prevent absorption of ingested fat (ie, malabsorption); and (3) bariatric surgery, which results in a decrease in food intake with or without malabsorption.

The primary approach for achieving weight loss is therapeutic lifestyle change, which includes a reduction in energy intake, an increase in physical activity, and behavior therapy to facilitate these changes. Although lifestyle intervention generally achieves a weight loss of ~5% at 1 year,<sup>12</sup> it is difficult for patients to maintain this loss and weight regain usually occurs. The difficulty in achieving successful long-term weight loss by lifestyle intervention alone has led to an increased interest in pharmacotherapy and bariatric surgery to treat obesity.

**PHARMACOTHERAPY FOR WEIGHT LOSS**

The medical indications for pharmacotherapy to treat obesity include a BMI  $\geq 30.0$  kg/m<sup>2</sup> or a BMI between

27.0 and 29.9 kg/m<sup>2</sup> plus an obesity-related medical complication and no contraindications to therapy. There are a number of antiobesity drugs available; however, few drugs have been approved by the US Food and Drug Administration (FDA) for the long-term treatment of obesity (**Table**). Because effective pharmacotherapy for obesity requires long-term if not lifelong treatment, discontinuing drug treatment in patients who have achieved successful weight loss results in rapid weight regain; yet adherence to FDA guidelines prevents long-term use of most antiobesity drugs.<sup>13,14</sup> Sibutramine (approved in 1996) and orlistat (approved in 1999) are the only anti-obesity medications approved for long-term use and the only agents approved by the FDA for the treatment of obesity since 1973.

**KEY POINT**

**Effective pharmacotherapy for obesity requires long-term if not lifelong treatment.**

**Sibutramine**

Sibutramine, an anorexiant that causes weight loss primarily by reducing food intake, inhibits the neuronal reuptake of norepinephrine, serotonin, and dopamine. Several randomized controlled trials (RCTs)<sup>15-21</sup> have evaluated the effect of long-term (1 year) treatment with sibutramine on body weight in obese persons. These studies were conducted in several patient populations,

**TABLE. PRESCRIPTION WEIGHT LOSS MEDICATIONS APPROVED BY THE US FOOD AND DRUG ADMINISTRATION.**

Approved Use	Drug	DEA Schedule
Long-term	Orlistat	None
	Sibutramine	IV
Short-term	Benzphetamine	III
	Diethylpropion	IV
	Phendimetrazine	III
	Phentermine	IV

DEA = Drug Enforcement Administration.

including obese patients with few obesity-related medical complications,<sup>16,17,19</sup> and in obese patients with type 2 diabetes<sup>18,20</sup> or hypertension.<sup>15</sup> Data from 2 meta-analyses<sup>22,23</sup> of long-term RCTs found that subjects treated with sibutramine lost ~4.5% (~4.5 kg) more weight than those who received placebo. In addition, ~2 to 3 times as many subjects randomized to sibutramine lost  $\geq 5\%$  and  $\geq 10\%$  of their initial weight compared with those randomized to placebo.

Intermittent therapy with sibutramine may be just as effective as continuous daily therapy in inducing weight loss. Wirth and Krause<sup>17</sup> found that at the end of 48 weeks, weight loss in subjects who received intermittent therapy (daily sibutramine during three 12-week periods separated by two 6-week intervals of placebo therapy) was equal to that in subjects who received daily sibutramine therapy.

#### KEY POINT

**Intermittent therapy with sibutramine can be just as effective as continuous daily therapy in inducing weight loss.**

Treatment with sibutramine can help maintain weight loss achieved by diet. Apfelbaum et al<sup>22</sup> found that, compared with placebo, 1 year of sibutramine treatment effectively prevented weight regain after weight loss induced by a short-term (4 week), very-low-calorie diet. Moreover, subjects randomized to sibutramine continued to lose weight while those randomized to placebo gained weight. James et al<sup>14</sup> found that treatment with sibutramine effectively maintained weight loss for 18 months in subjects who lost  $\geq 5\%$  of their initial body weight after 6 months of sibutramine therapy. In contrast, those randomized to placebo after 6 months of sibutramine treatment rapidly regained the weight they had lost.

The most common side effects of sibutramine therapy are dry mouth, headache, constipation, and insomnia, all of which are usually mild and transient. Sibutramine also causes a small increase in blood pressure and heart rate, which generally occurs in the first few weeks of treatment and can last as long as the drug is taken.<sup>14,23</sup> In some patients, however, a significant increase in blood

pressure can occur,<sup>14</sup> in which case sibutramine therapy must be discontinued. The risk of increased blood pressure is not greater in patients who have controlled hypertension than in those who do not have hypertension.<sup>15</sup>

#### Orlistat

Orlistat is a synthetic derivative of a product made by the *Streptomyces toxytricini* mold that inhibits mammalian lipases. When taken with a meal, orlistat binds to intestinal lipases and prevents the digestion and absorption of intraluminal triglycerides.<sup>24</sup> The recommended dose, 120 mg with meals TID, blocks the absorption of ~30% of ingested fat in subjects consuming a diet containing ~30% of calories as fat.<sup>25</sup> Increasing the dose of orlistat does not result in a significant increase in fat malabsorption. The percentage of malabsorbed dietary fat induced by orlistat therapy varies considerably; however, no studies have evaluated the reproducibility of treatment or whether relative absorption is affected by the amount of fat consumed.

#### KEY POINT

**When taken with a meal, orlistat binds to intestinal lipases and prevents the digestion and absorption of intraluminal triglycerides.**

A number of long-term (1–4 years) RCTs have evaluated the efficacy of orlistat therapy in initiating and maintaining weight loss. Data from 2 meta-analyses<sup>26,27</sup> show that subjects treated with orlistat lost ~3% (~3 kg) more weight than those randomized to placebo. In addition, about twice as many subjects randomized to orlistat lost  $\geq 5\%$  and  $\geq 10\%$  of their initial body weight compared with those randomized to placebo. In one study, weight loss was 5% greater (11% vs 6%) at 1 year and 3% greater (7% vs 4%) at 4 years for those treated with orlistat compared with those randomized to placebo.

The most common side effects of orlistat therapy are gastrointestinal symptoms associated with fat malabsorption, including abdominal pain, fatty/oily stool, increased defecation, fecal urgency, liquid or soft stool, flatulence, and fecal incontinence. Approximately 79% of subjects treated with orlistat experience  $\geq 1$  gastrointestinal complication compared with 59% of subjects who receive

placebo.<sup>28</sup> Gastrointestinal side effects usually occur early, shortly after initiation of treatment.<sup>13,29</sup> They are of mild or moderate intensity, are limited to 1 or 2 episodes, and tend to resolve spontaneously despite continuing orlistat treatment.<sup>28,29</sup> Approximately 5% of subjects treated with orlistat experience a decrease in serum vitamin D, vitamin E, and beta carotene concentrations to values that are below normal.<sup>13,28,29</sup> All patients treated with orlistat should be given a daily multivitamin supplement; however, the supplement should not be taken when orlistat is ingested. Orlistat can also impair absorption of lipophilic medications, such as cyclosporine<sup>30–32</sup>; therefore, orlistat and lipophilic medications should not be given simultaneously and drug plasma concentration should be monitored, if possible.

#### KEY POINT

**Orlistat can impair absorption of lipophilic medications, such as cyclosporine; therefore, orlistat and lipophilic medications should not be given simultaneously.**

### Potential New Agents: Endocannabinoid Receptor Antagonists

Endocannabinoids have been found to modulate several metabolic functions, including the drive for food ingestion, energy storage, lipogenesis, body weight, and the lipid profile.<sup>33</sup> Overactivation of the endocannabinoid system has been implicated in the development of obesity and dyslipidemia<sup>33</sup>; thus, endocannabinoid receptor antagonism, along with behavior or lifestyle changes, may help reduce body weight, improve lipid profiles, and modify cardiometabolic risk in overweight and obese patients. Rimonabant, the first endocannabinoid receptor antagonist, has been shown in clinical trials<sup>34–37</sup> to increase high-density lipoprotein cholesterol (HDL-C) levels, decrease triglyceride levels, reduce body weight and waist circumference, and improve both peak size of low-density lipoprotein (LDL) particles and the ratio of total cholesterol to HDL-C. The most common side effects of rimonabant therapy are nasopharyngitis, headache, nausea, and dizziness.<sup>34–37</sup> A slightly higher percentage of patients receiving rimonabant than those re-

ceiving placebo experience treatment-related adverse events; however, these events are generally mild and transient and occur in the first months of therapy. Compared with placebo, treatment with rimonabant has been associated with a higher incidence of anxiety and depression leading to treatment withdrawal but a similar or slightly lower incidence of suicidality.<sup>38,39</sup> Although not yet approved for use in the United States, rimonabant has been approved for use in the European Union.

#### KEY POINT

**Endocannabinoid receptor antagonism can help reduce body weight, improve lipid profiles, and modify cardiometabolic risk in overweight and obese patients.**

Taranabant, which is in Phase III clinical trials, also has been shown to reduce body weight and waist circumference and to improve HDL-C, LDL cholesterol, and triglyceride levels versus placebo when used in combination with diet and exercise.<sup>40</sup> Phase III studies investigating doses of  $\leq 2$  mg are ongoing.

### BARIATRIC SURGERY

Bariatric surgery is an effective weight loss option for some obese patients. Proceedings from a National Institutes of Health Consensus Conference,<sup>41</sup> reported in 1991, provided guidelines for bariatric surgery for obese patients. The panel concluded that eligible patients were those who were morbidly obese—defined as those with a BMI  $\geq 40$  kg/m<sup>2</sup> or a BMI of 35 to 39.9 kg/m<sup>2</sup> plus  $\geq 1$  severe obesity-related medical complication (eg, hypertension, type 2 diabetes, heart failure, or sleep apnea). Moreover, potential candidates should be those who have tried to lose weight by way of conventional diet therapy but who have been unsuccessful in losing weight or maintaining the weight loss.

Weight loss induced by bariatric surgery effectively reverses or improves the medical complications associated with obesity, even if patients remain obese.<sup>42</sup> Data from recent prospective and retrospective cohort studies<sup>43,44</sup> also show that bariatric surgery decreases long-

term mortality rates, particularly death from heart disease, diabetes, and cancer.

#### KEY POINT

**Weight loss induced by bariatric surgery effectively reverses or improves the medical complications associated with obesity, even if patients remain obese.**

Currently, the 2 most popular bariatric surgical procedures performed in the United States and the world are the Roux-en-Y gastric bypass (RYGB) and laparoscopic adjustable gastric banding (LAGB). Only a small percentage of US patients actually undergo bariatric surgery. For example, in 2006, it was estimated that 177,600 obese patients were treated with bariatric surgery in the United States, whereas ~15 million (1 in 50) persons are morbidly obese and may be potential candidates for the surgery.<sup>45</sup>

### Roux-en-Y Gastric Bypass

The RYGB procedure is the most common bariatric surgical procedure performed in the United States.<sup>46</sup> The first gastric bypass was reported by Mason and Ito in 1967,<sup>47</sup> and modifications have led to the current RYGB procedure. RYGB involves the construction of a small (15–25 mL) proximal gastric pouch either by stapling across the stomach or by complete transection from the stomach. The pouch empties into a segment of jejunum that is brought up to the pouch as a Roux-en-Y limb. The anastomotic outlet to the Roux limb is restricted to ~1 cm in diameter. This procedure can be performed using either an open or a laparoscopic technique. In addition to gastric restriction, bypass of the upper small intestine causes malabsorption. The degree of malabsorption is presumably related to the length of the Roux limb, but this has not been studied carefully in clinical trials.

On average, after RYGB with a standard 75-cm Roux limb, patients lose ~60% of their excess body weight, which represents ~30% of their actual body weight.<sup>48,49</sup> Weight loss is usually greatest at 1 to 2 years after surgery, and there is often some weight regain before a plateau in body weight is achieved.<sup>42</sup> Some patients do not achieve adequate weight loss after surgery, and others

#### KEY POINT

**On average, after RYGB with a standard 75-cm Roux limb, patients lose ~60% of their excess body weight, which represents ~30% of their actual body weight.**

regain most of the weight lost. It is not possible to determine before surgery which patients will or will not have a successful outcome.

The mechanisms responsible for RYGB-induced weight loss are not precisely known; however, the procedure decreases the intensity of hunger, enhances satiety, and alters food selection and preference.<sup>46</sup> It is likely that a combination of gastric restriction, malabsorption, and neural and neuroendocrine changes contribute to the decrease in body weight.<sup>50</sup>

The perioperative (30-day) mortality rate for patients undergoing RYGB is ~0.5% when the procedure is performed by a surgeon experienced in bariatric surgery, but it is much higher (6.2%) when the procedure is performed by a surgeon who has minimal experience.<sup>51</sup> Data collected from hospitals in the state of Washington found that the risk of death within 30 days of surgery was almost 5 times greater for a surgeon's first 19 procedures than for subsequent procedures. Most perioperative deaths are caused by peritonitis related to an anastomotic leak or by pulmonary embolism.

Complications of RYGB include gastrointestinal or anastomotic leak, hemorrhage, pulmonary embolism, wound infection, staple line disruption, internal or incisional hernias, dumping syndrome (ie, rapid gastric emptying), and nutrient deficiencies, particularly in iron, calcium, folic acid, vitamin D, and vitamin B<sub>12</sub>, which may be prevented with appropriate vitamin and mineral supplementation.<sup>46,52</sup>

### Laparoscopic Adjustable Gastric Banding

LAGB was first performed in patients in the early 1990s and is currently the most popular bariatric surgical procedure performed outside of the United States, particularly in Australia, South America, and Europe.<sup>53</sup> This procedure involves laparoscopic placement of an adjustable gastric band around the upper stomach, forming a

small (~15-mL) gastric pouch. A balloon within the band is connected to a subcutaneous port that can be accessed percutaneously to adjust band circumference by inflating or deflating the balloon with saline. Band circumference can be adjusted as needed, based on the patient's rate of weight loss and gastrointestinal symptoms.

LAGB is associated with fewer and less severe complications than other bariatric surgery procedures.<sup>48,49</sup> The perioperative (30-day) mortality rate for patients undergoing LAGB is ~0.1% and complications include gastric erosion, band prolapse, esophageal dilatation, and local infection.

On average, at 2 years after LAGB, patients lose ~50% of their excess body weight, which represents ~25% of their actual body weight.<sup>48,49</sup> Weight loss continues with additional band adjustment so that after several years, weight loss appears to be similar to that after RYGB. The efficacy of these 2 procedures has not been compared in an RCT.

### KEY POINT

**On average, after LAGB, patients lose ~50% of their excess body weight, which represents ~25% of their actual body weight.**

### CONCLUSIONS

Although lifestyle modification should be the primary approach for treating obesity, making and maintaining effective changes in eating and physical activity behaviors is difficult for most people. Long-term pharmacotherapy and bariatric surgery are additional, effective options for weight loss in properly selected patients.

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## Dialogue Box

### EDITORIAL BOARD

**Is there a way of predicting which obese patients are likely to respond to pharmacologic therapy?**

#### KLEIN

Unfortunately, there is no good way to predict who will respond to drug treatment. The best predictor of success is an early response—within the first 4 to 6 weeks of therapy. If the patient does not lose several pounds during the first month of therapy, it is unlikely that he or she will experience significant weight loss further down the road. This observation has important clinical implications because there really is no need to continue drug therapy in someone who does not respond within the first 1 or 2 months of treatment.

### EDITORIAL BOARD

**Have any trials compared the efficacy of combining sibutramine and orlistat versus using either alone?**

#### KLEIN

Only a few studies have evaluated the combined use of these drugs versus either alone. An added or synergistic effect was not seen, and the weight loss was not greater by combining the 2 drugs than by using 1 drug alone.

### EDITORIAL BOARD

**Since they work by different mechanisms, why would this be the case?**

#### KLEIN

Possibly for several reasons. First, the mechanism of action may not be synergistic—if you eat less food and fat because of sibutramine therapy, you will get less of a beneficial effect with orlistat, which decreases fat absorption. Second, the potential additive effect on weight loss caused by using both drugs together might be so small that it was not detected because of the inadequate sample size in the published trials.

### EDITORIAL BOARD

**Has financial reward ever been studied as an intervention for obesity?**

#### KLEIN

Yes, and the results have been kind of mixed. In some studies, financial reward seemed to make a difference and in others it did not. There are data to suggest that reward might not be as effective as negative reinforcement; that is, rewarding a good behavior might not be as effective as punishing a bad behavior. For example, there is a report of an experience in Shanghai policemen that drives home this point. Obese Shanghai policemen who were offered bonuses to become thinner did not lose weight; however, they all lost weight when they were told they were going to be fired if they did not lose weight.

### EDITORIAL BOARD

**Is the failure of liposuction to reduce cardiovascular risk a reflection of peripheral fat cells being innately different from visceral fat cells?**

#### KLEIN

No, I think it is premature to conclude that the absence of a beneficial metabolic effect of liposuction observed in some studies is due to the removal of the wrong type of fat. It might be that visceral fat is simply a marker of metabolic abnormalities and does not in itself contribute to the metabolic abnormalities. The true test needed to determine whether visceral fat is deleterious is to surgically remove visceral fat and see if that results in a beneficial metabolic effect. Those studies are currently being conducted in obese human subjects, but the results are not yet available. I think the reason that removing subcutaneous fat by liposuction does not provide the same metabolic benefits as diet-induced fat loss is that, although liposuction removes billions of fat cells, it does not change the size of remaining fat cells, decrease intramuscular or intrahepatic fat content, or decrease visceral fat. Losing fat by inducing a negative energy balance, however, eliminates fat and muscle, decreases

## Dialogue Box

visceral fat, and reduces fat cell size. All or at least some of these changes may be necessary to get the desired metabolic benefits.

### EDITORIAL BOARD

**With regard to diet, does it matter if a patient consumes his evening meal late at night just prior to going to bed?**

#### KLEIN

In terms of body weight, energy balance is the key. It doesn't matter when you eat the calories, or when you burn the calories. "Calories in and calories out" ultimately determines body mass. So if you eat the calories at 2:00 in the morning, or 8:00 in the morning, if you eat 5 times a day, or once a day, it doesn't make any difference in terms of energy balance. Having said that, the timing of feeding can result in differences in metabolic health. There are data from some intriguing studies conducted in rodents demonstrating the effects of alternate-day fasting, where rodents are fed ad libitum for 24 hours followed by fasting for 24 hours. The animals overeat during the days they are being fed, so they don't lose weight. Despite maintaining the same body weight, the rats on the alternate-day fasting regimen are metabolically healthier in terms of insulin sensitivity and lipid profile. Similar studies conducted in humans have produced less definitive results because it is very hard to get humans to comply with an alternate-day fasting regimen. However, the rodent data suggest that having a large gap between meals is healthier than our traditional concept of "3 square meals a day."

### EDITORIAL BOARD

**What is the status of rimonabant?**

#### KLEIN

Rimonabant represents a novel approach to treating obesity by blocking endocannabinoid receptors. Data from multiple large clinical trials have demonstrated impressive long-term weight loss efficacy with rimonabant therapy. However, the application for approval in

the United States was rejected by the US Food and Drug Administration because of a concern about neuropsychiatric side effects, including anxiety, depression, and, possibly, suicidal ideation. Current trials looking at endocannabinoid receptor antagonists as a potential therapy for obesity are using more regimented questionnaires and instruments to evaluate psychiatric side effects.

### EDITORIAL BOARD

**You mentioned that lipophilic medications, such as cyclosporine, should not be taken at the same time as orlistat. What about other medications, such as warfarin or oral contraceptives?**

#### KLEIN

Although orlistat clearly affects cyclosporine absorption, it does not affect the absorption of warfarin, digoxin, phenytoin, diphenhydantoin, glyburide, oral contraceptives, furosemide, captopril, nifedipine, or atenolol.

### EDITORIAL BOARD

**What advantages does intermittent therapy with sibutamine offer?**

#### KLEIN

Intermittent therapy is less expensive than continuous therapy. Obesity drugs are usually not covered by insurance, and the cost is about \$100 a month in the United States. If you take the medication every other day instead of every day, you will save \$50 a month.

### EDITORIAL BOARD

**In a patient started on orlistat, is taking a multivitamin sufficient or should they take specified amounts of the fat-soluble vitamins affected?**

#### KLEIN

Any multivitamin usually suffices. Most subjects enrolled in the orlistat clinical trials did not experience deleterious changes in blood vitamin levels, despite taking the drug without any vitamin supplements. A multivitamin supplement should not be taken at the same

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time as orlistat but 2 hours before or after to prevent malabsorption of fat-soluble vitamins.

### **EDITORIAL BOARD**

**In your experience, have you ever had to stop sibutramine treatment because of elevated blood pressures?**

### **KLEIN**

I have not had to stop sibutramine treatment because of increased blood pressure. A significant rise in blood pressure is seen in only a small percentage of people. However, sibutramine does reduce the beneficial blood pressure-lowering effect of weight loss.