Introduction

Obesity is growing at alarming rates and has recently been cited as one reason that the current generation will be the first to not enjoy a longer life span than previous generations. Obesity is defined as a body mass index (BMI) of 30 kg/m\(^2\) or greater, while a person with a BMI between 25 and 29.9 kg/m\(^2\) is termed overweight. Morbid obesity, or clinically severe obesity, is defined as having a BMI greater than 40 kg/m\(^2\).

Obesity spares no organ system and is associated with an increased risk of many diseases, including:

- Diabetes mellitus type 2 (DM2)
- Cardiovascular conditions (hypertension, dyslipidemia, coronary heart disease, cardiomyopathy)
- Obstructive sleep apnea (OSA)
- Nonalcoholic steatohepatitis (NASH)
- Osteoarthritis (OA)
- Some types of cancer

In 1991, the NIH consensus panel concluded that weight loss surgery is the only effective treatment for long term weight loss in severely obese patients – those with a BMI greater than 40kg/m\(^2\) or patients with a BMI greater than 35kg/m\(^2\) with associated comorbidities. The Centers for Medicare and Medicaid Services (CMS) has agreed with the NIH and will provide coverage for beneficiaries undergoing bariatric surgery.

The primary care physician plays an integral role in treating obesity, both prior to and after weight loss surgery. Careful patient selection and pre-operative evaluation as well as consistent follow-up all require participation from a primary care physician. In some cases where insurance carriers require medically supervised weight loss therapy prior to authorizing surgery, a primary care physician becomes vital in providing the necessary therapy for these patients.
WEIGHT LOSS SURGERY

Weight-loss surgery (WLS) is currently the most effective intervention for the treatment of severe obesity in terms of magnitude as well as duration of weight loss. The degree to which severe obesity impairs quality of life as well as health cannot be underestimated. This impairment may impart a sense of desperation such that patients may not fully appreciate the potential risks of WLS. Careful discussions regarding the balance of benefits versus risks are required, which should be reflected in the informed consent process.

• WLS produces average losses of 45-70% of excess weight (actual - ideal weight),1 in contrast to the approximately 10% loss from initial weight with nonsurgical approaches.2,3

• WLS results in improvements in many obesity-related comorbidities and disease states, resulting in an increased quality of life and reduction in mortality.1, 4-21

Understanding the Procedures

Surgical procedures for weight loss range from purely restrictive, to restrictive with a modest degree of malabsorption, to primarily malabsorptive.

FIGURE 1

The current, purely restrictive procedure of choice is the laparoscopic adjustable gastric band (LAGB). A fluid-filled band is placed around the stomach, and the degree of restriction can be adjusted.

Patients who have BMI >50 kg/m^2, who are older, and who have multiple comorbid conditions should undergo surgery by experienced surgeons in high-volume centers with multi-disciplinary programs that can provide around-the-clock airway management and resuscitative care.
by inflation of the band with saline through a subcutaneous port.

**FIGURE 2**
Roux-en-Y gastric bypass (GBP) is currently the most popular procedure performed in the United States. In this operation, a 15-mL gastric pouch is created, the jejunum is resected and the distal portion anastomosed to the pouch, and the proximal jejunal limb is then re-anastomosed to create a roux limb. The roux limb may be of variable length, with longer limbs associated with greater malabsorption.

**FIGURE 3**
The more malabsorptive procedures, biliopancreatic diversion (BPD) with or without duodenal switch, create substantial degrees of malabsorption.

**Risks**
Short-term complications of WLS procedures vary, with rates of serious complications and mortality highest in BPD and revisional surgeries, intermediate with GBP, and lowest with LAGB. Other factors associated with increased complication rates are higher BMI, age, and male gender. Comorbid conditions such as DM2, OSA, and hypertension have been associated only inconsistently with complications or early mortality after surgery.

Approximately two thirds of early postoperative mortality after GBP is associated with anastomotic leaks and pulmonary emboli. In addition, limited surgeon experience and low hospital/procedure volume are strongly associated with complications and mortality.

**Contraindications for Bariatric Surgery**
- Unstable or severe coronary artery disease
- Severe pulmonary disease
- Portal hypertension with gastric or intestinal varices
- Conditions that seriously compromise anesthesia
- Wound healing problems
- Inability to comprehend basic principles of WLS
- Unable to follow postoperative instructions
Who Should Be Referred for Surgery?
Patient selection criteria from the 1991 National Institutes of Health Consensus Development Conference on Gastrointestinal Surgery for Severe Obesity provide the basis for WLS candidacy. The fundamental criterion is body mass index (BMI) ≥40 kg/m² or BMI ≥35 kg/m² in the presence of significant comorbidities. There remains no specific guidelines for the extent to which patients must try to control weight by non-surgical means before consideration of WLS.

### Selection Criteria for Bariatric Surgery
- BMI >40 kg/m²
- BMI >35 kg/m² and significant comorbidities
- Well informed and motivated
- Failure to achieve weight control with nonsurgical approaches
- Acceptable operative risk

Preoperative Evaluation
Patients often present for preoperative evaluation with undiagnosed weight-related comorbidities.

Severely obese patients in general receive less preventive medical care than their lean counterparts, and WLS patients often present for preoperative evaluation with undiagnosed weight-related comorbidities.

Pre-operative evaluation by primary care physicians for conditions that may influence surgical outcomes or that are commonly associated with obesity is recommended. Listed here are several of the issues to be considered in patients considering WLS.

**OBSTRUCTIVE SLEEP APNEA**
Sleep studies conducted in patients presenting for WLS suggest that prevalence of OSA is between 35% and 71%. The adverse effects of OSA extend well beyond daytime fatigue, and OSA is associated with pulmonary HTN, transient cardiac ischemia, arrhythmias, traffic accidents, and mood disturbances. OSA also increases the risk of anesthesia-related perioperative complications.

**BENEFITS ASSOCIATED WITH THE TREATMENT OF OSA INCLUDE:**
- Reduced airway mucosal edema
  - Improved responsiveness to hypercapnia and hypoxemia
  - Reduced baseline hypoxemia
  - Decreased ventilation perfusion mismatch and shunt
  - Possible weight loss

Clinical predictors of OSA such as questionnaires or anthropometrics have yielded inconsistent predictive power in extremely obese persons; thus they cannot replace the need for formal polysomnography in the diagnosis of this disorder. Overnight polysomnography should routinely be included as part of the preoperative assessment for patients who have witnessed episodes of sleep apnea, significant daytime somnolence, or other suggestive symptoms, especially in the presence of coexisting hypertension, lower extremity edema, and cardiac disease.

**THROMBOEMBOLIC DISEASE**
Persons with morbid obesity are at high risk for venous thromboembolism in comparison to leaner individuals. Although the absolute incidence of deep vein thrombosis (DVT) and pulmonary emboli (PE) after WLS is low, PE accounts for 25% to 67% of early postoperative mortality.
**Risk Factors for DVT/PE Include:**
- history of a prior thromboembolic event or hypercoagulable state
- use of oral contraceptives
- central fat distribution
- smoking
- female gender
- increased age
- venous stasis or insufficiency
- OSA

Unless contraindicated, WLS patients should receive perioperative venous thromboembolism prophylaxis by both mechanical methods and unfractionated or low-molecular weight heparin. Preoperative inferior vena cava filter (IVCF) placement should be considered for patients at very high risk for DVT or PE.\(^{(31, 50)}\)

**Liver Disease**
Nonalcoholic fatty liver disease (NAFLD) and the progression to NASH are associated with obesity and DM2.\(^{51-54}\) Intraoperative liver biopsy samples from WLS patients show high rates of liver disease:\(^{51, 55-59}\)

- 65-89% had steatosis
- 10-56% had NASH
- 1-51% had fibrosis
- Up to 6% had cirrhosis

Intraoperative liver biopsy at the time of WLS should be considered for patients with hepatic dysfunction for diagnostic purposes or for establishing the extent of disease, especially in those with DM2, insulin resistance, or hyperferritinemia.

In patients with cirrhosis, the decision about whether to proceed with WLS should be made in consideration of overall patient health, the physical and histological appearance of the liver, and whether evidence of portal hypertension or ascites is present.

**Preoperative Weight Loss**
In many WLS centers, patients are encouraged to lose weight before surgery. The rationale for this is two-fold:

- Diet and lifestyle changes leading to weight loss are considered to be reflective of the lifelong changes necessary after WLS.
- Modest weight loss may reduce surgical risk and improve outcome.

Losses of just 5-10% of initial weight are known to improve obesity-related OSA, hypertension, lipid abnormalities, and glycemic control.\(^{52-64}\) However, no published prospective studies have demonstrated that preoperative weight loss reduces perioperative complications. (Busetto et al\(^{(65)}\) reported significantly shorter operating room times and lengths of stay after preoperative weight loss by use of an intragastric balloon in patients with BMI >50.) Reduction in visceral adipose tissue as well as liver volume or fat is observed with
weight loss in the range of achievable surgery.66 Despite the absence of evidence that preoperative weight loss reduces complications or predicts long-term weight outcome, it seems prudent to encourage at least modest preoperative weight loss (i.e., 5-10% of initial weight) in WLS patients, especially those with a BMI >50 kg/m² and those with obesity-related comorbidities. In selected patients such as those with higher BMI or uncontrolled comorbid conditions, greater degrees of weight loss may be requested.

MEDICALLY SUPERVISED WEIGHT LOSS
Aside from providing modest weight loss prior to surgery, some bariatric programs and insurance companies require that a prospective weight loss surgery patient participate for some period (3 to 24 months) in a medically supervised weight loss program. While requirements vary, it is recommended to follow professional guidelines for weight loss, National Heart, Lung, and Blood Institute (NHBLI), The American Association of Family Practitioners (AAFP) and the American College of Physicians (ACP) have presented guidelines for the treatment of obesity.

One of the key aspects for a medically supervised weight loss in this context is documentation. It is important to follow all HIPPA rules, and in some cases it may be appropriate to enlist the patient in maintaining documentation to satisfy the requirements of a particular program or insurance carrier. In general, all of the office notes from the supervising physician, including proof of dietary supervision and recorded weigh-ins are required. Documentation of obesity related comorbidities and their progression may also be required.

Therapies

DIETARY, LIFESTYLE AND BEHAVIOR MODIFICATIONS
Any effective weight loss program should involve a combination of diet modification, increased physical activity, and behavior therapy. Clinicians should counsel all obese patients (defined as those with a BMI >30 kg/m²) on lifestyle and behavioral modifications such as appropriate diet and exercise to promote sustained weight loss.

The patients’ goals for weight loss should be individually determined (these goals may encompass not only weight loss but also other parameters, such as decreasing blood pressure or fasting blood glucose levels).

Most overweight and obese people should adopt long-term nutritional adjustments to reduce caloric intake. Dietary therapy includes instructions for modifying diets to achieve this goal. Moderate caloric reduction is the goal for the majority of cases; however, diets with greater caloric deficits are used during active weight loss. In general, diets containing 1,000 to 1,200 kcal/day should be selected for most women; a diet between 1,200 kcal/day and 1,600 kcal/day should be chosen for men. The patient should maintain a dietary log to present to the supervising physician.
Increased physical activity is important in efforts to lose weight because it increases energy expenditure and plays an integral role in weight maintenance. For the obese patient, activity should generally be increased slowly, with care taken to avoid injury. A wide variety of activities and/or household chores, including walking, dancing, gardening, and team or individual sports, may help satisfy this goal. All adults should set a long-term goal to accumulate at least 30 minutes or more of moderate-intensity physical activity on most, and preferably all, days of the week.

Behavior therapy is a useful adjunct to planned adjustments in food intake and physical activity. Specific behavioral strategies include the following: self-monitoring, stress management, stimulus control, problem-solving, contingency management, cognitive restructuring, and social support. Evidence supports the recommendation that weight loss programs should employ a combination of low-calorie diets, increased physical activity, and behavior therapy.

**Postoperative Care**

**POSTOPERATIVE VOMITING**

It should be stressed that vomiting is never normal after WLS and is not an intended effect of WLS. Postoperative vomiting is often caused by eating too much or too fast, especially in patients soon after WLS. Procedure-specific indications are as follows:

**LAGB INDICATIONS**

The restriction imposed by gastric banding and gastric bypass dictates that small bites be taken, food chewed extensively, and small portions consumed. Although vomiting may most often be ascribed to behavioral issues, anatomic and other complications do occur. In LAGB patients, vomiting may indicate that band tightness should be reduced or that a complication such as band slippage has occurred.

**GBP INDICATIONS**

In GBP patients, vomiting may indicate stricture or ulceration at the gastrojejunostomy ("marginal ulceration") or bowel obstruction. For diagnosis of ulcer, upper gastrointestinal contrast studies are seldom useful, and endoscopy by a gastroenterologist familiar with GBP anatomy is recommended. Stricture and bowel obstruction are often first assessed by upper GI contrast studies followed by endoscopy if indicated.

Cholelithiasis should be suspected in patients with nausea, vomiting, or abdominal pain who have not undergone cholecystectomy. Internal hernia is more likely to present after substantial weight loss, is often associated with vague symptoms, and is difficult to diagnosis by available radiological studies. If other etiologies of vomiting, pain, or other symptoms are excluded, surgical exploration may be warranted to diagnose and repair internal hernia.

**CONSEQUENCES OF POST-OPERATIVE VOMITING**

Post-operative vomiting may lead to dehydration and can result in uncommon but potentially serious problems, such as protein energy malnutrition and thiamine deficiency.

- Protein energy malnutrition is most likely to occur with malabsorptive procedures such as BPD and distal GBP but may occur in any situation with prolonged poor intake.
- Symptomatic thiamine deficiency has occurred in patients without preoperative risk factors or concurrent alcohol abuse and has developed as early as 1 week to 2 months after WLS.

All WLS patients with protracted vomiting should be treated with supplemental thiamine in addition to usual micronutrient supplementation.
Vomiting is never normal after weight loss surgery.

MANAGEMENT OF COMORBID CONDITIONS
In some WLS patients, postoperative weight loss is rapid. It is not uncommon for patients treated for DM2 to demonstrate dramatic reductions in need of medications as soon as 1-2 weeks after surgery, and such patients may require weekly or bimonthly monitoring. Patients taking antihypertensive medications may also experience hypotension, although the rapidity of blood pressure reduction after WLS appears to be slower than that with DM2. Patients with OSA appear to demonstrate slower improvement despite improved daytime symptoms, however. It is recommended that patients continue use of continuous positive airway pressure for at least 3-6 months after WLS and then undergo follow-up polysomnography to re-assess OSA status.

MICRONUTRIENT SUPPLEMENTATION
Micronutrient deficiency occurs because of a decrease in food intake, malabsorption, and complications such as vomiting. Risk of deficiency is least with purely restrictive procedures, intermediate with GBP (and varies with length of roux limb), and greatest with BPD. GBP patients are at risk for development of deficiencies of iron, vitamins B₁₂, vitamin D, and folic acid and may have be at increased risk for metabolic bone disease. Patients with BPD are at risk for the above nutrient deficiencies as well deficiencies of fat soluble vitamins and are at greater risk for metabolic bone disease.

Table 1 below lists recommendations for supplementation and treatment of micronutrient deficiencies after GBP. Iron deficiency has been observed in 20-49% of GBP patients and is most likely to occur in menstruating women.²⁻⁵ Ferrous sulfate (640 mg/day) has been shown to prevent iron deficiency but may not always be tolerated because of gastrointestinal side effects. Addition of small doses of vitamin C (e.g., ≤250 mg) with iron supplements may improve absorption.⁷⁻⁶ Vitamin B₁₂ deficiency has been found in about 35% (range 25-75%) patients after gastric bypass.⁷⁻⁵ Supplementation with oral crystalline B₁₂ (up to 1000 mcg) has been found to prevent deficiency in some but not all patients. Patients who have symptomatic vitamin B₁₂ deficiency should always be treated with parenteral therapy. Folic acid deficiency is generally prevented by regular multivitamin use⁸⁻⁰ and deficiencies should evoke consideration of noncompliance with supplementation or alcohol abuse. BPD and to a lesser extent GBP have been associated with hypovitaminosis D, impaired calcium absorption, elevated markers of bone turnover, and osteopenia.⁸¹⁻⁸³
All WLS patients should be screened preoperatively for micronutrient deficiencies, particularly of iron, vitamin \( B_{12} \), and vitamin D, which are not uncommon in the general population. Assessment of micronutrient status should be repeated 6 months after surgery and at least annually thereafter. Postoperative micronutrient assessment should include assessment of iron, vitamin \( B_{12} \), folate, and vitamin D status. Persistent vomiting may be associated with additional micronutrient deficiencies, especially of thiamine. All WLS patients should take a daily multivitamin and calcium supplement with added vitamin D. Other recommendations are found in Table 1.

**Long-Term Follow-Up Required**

To maintain weight loss after WLS, patients need to maintain lifelong vigilance to prevent return to patterns that contributed to weight gain, and need also to maintain appropriate diet and physical activity. Some patients experience a sense of invincibility during the rapid weight loss that occurs early after GBP and BPD. However, approximately 1-2 years after WLS, patients commonly experience increased desire to eat, increased cravings, and tendencies to return to pre-WLS eating and lifestyle patterns. Furthermore, the rapid and dramatic weight loss with WLS necessitates far-reaching psychological and emotional adjustments. These adjustments are facilitated by individual and group counseling by mental health providers familiar with WLS. A multidisciplinary team of physicians, nutritionists, and psychologists is best equipped to address the medical, nutritional, and behavioral long-term care needs of WLS patients.

**ALTERNATIVE THERAPY**

**Pharmacotherapy**

Although lifestyle changes and interventions can be helpful for many obese individuals, without recurrent and ongoing follow-up appointments with their healthcare provider, it is not uncommon for most of the weight lost to be regained over

<table>
<thead>
<tr>
<th>Drug</th>
<th>Monitoring</th>
<th>Recommended</th>
<th>Supplementation Treatment of Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivitamin</td>
<td>Yes</td>
<td>N/A</td>
<td>MVI</td>
</tr>
<tr>
<td>Iron</td>
<td>Serum Fe, Fe saturation</td>
<td>As in MVI</td>
<td>PO: 120-200 elemental Fe daily in divided doses</td>
</tr>
<tr>
<td>Calcium</td>
<td>Bone Mineral Density</td>
<td>1200-1500 mg per day in divided doses</td>
<td></td>
</tr>
<tr>
<td>Vitamin ( D )</td>
<td></td>
<td>Calcium supplements</td>
<td>Vitamin D 50,000 units limited duration, then monthly maintenance</td>
</tr>
<tr>
<td>Folate</td>
<td>RBC folate</td>
<td>400-1,000 mg/day</td>
<td>1000 mg/day</td>
</tr>
</tbody>
</table>

**TABLE 1: RECOMMENDATIONS FOR MICRONUTRIENT SUPPLEMENTATION AFTER GASTRIC BYPASS SURGERY**
the course of several years. These poor, long term results and the recognition that obesity is a chronic disease requiring lifelong management, have led to the development of pharmacological approaches that may minimize weight regain and enhance the long-term results.

Pharmacotherapy, approved by the FDA for long-term treatment, can be a helpful adjunct for the treatment of obesity in some patients. These drugs should be used only in the context of a treatment program that includes the elements described previously—diet, physical activity changes, and behavior therapy.

Pharmacologic therapy can be offered to obese patients who have failed to achieve their weight loss goals through diet and exercise alone.

A doctor–patient discussion of the drugs’ side effects, the lack of long-term safety data, and the temporary nature of the weight loss achieved with medications MUST occur before initiating therapy.

Pharmacotherapy is currently limited to those patients who have a BMI ≥ 30, or those who have a BMI ≥ 27 if concomitant obesity-related risk factors or diseases exist. However, not all patients respond to a given drug. If a patient has not lost 4.4 pounds (2 kg) after 4 weeks, it is not likely that this patient will benefit from the drug. The decision to add a drug to an obesity treatment program should be made after consideration of all potential risks and benefits and only after all behavioral options have been exhausted.

Pharmacologic treatment has received great attention from clinicians and patients. However, as of 1997, 5 drugs had been removed from the U.S. and international markets because of efficacy and safety concerns:

- Fenfluramine (Phen-fen)
- Dexfen-fluramine and Phenylpropanolamine (internationally)
- Diethylpropion and Phentermine (in Europe)

Since then, other drugs have become available, such as Sibutramine and Orlistat.

**Recommendations**

**RECOMMENDATION 1**

Clinicians should counsel all obese patients (defined as those with a BMI ≥ 30 kg/m²) on lifestyle and behavioral modifications such as appropriate diet and exercise, and the patient’s goals for weight loss should be individually determined (these goals may encompass not only weight loss but also other parameters, such as decreasing blood pressure or fasting blood glucose levels).

The United States Preventive Services Task Force recommends that clinicians offer all obese patients intensive counseling and recommends behavioral interventions, such as diet and exercise, to promote sustained weight loss. Moreover, the Task Force states that although there is no direct evidence that behavioral interventions decrease mortality or morbidity from obesity, changes in intermediate outcomes due to modest weight loss, such as improved glucose metabolism, lipid levels, and blood pressure, provide indirect evidence of health benefits. Since these intermediate outcomes may be of as much importance to a patient as the actual amount of weight lost, the ACP felt that they should also be considered when setting desired goals for a weight loss regimen.

**RECOMMENDATION 2**

Pharmacologic therapy can be offered to obese patients who have failed to achieve their weight loss goals through diet and exercise alone. However, there needs to be a doctor–patient discussion of the drugs’ side effects, the lack of long-term safety data, and the temporary nature of the weight loss achieved with medications before initiating therapy.

The amount of extra weight loss attributable to weight loss medications is modest (<5 kg at 1 year). However, in trials studying the effects of diet and exercise in obese patients with impaired glucose tolerance, similar amounts of weight loss significantly decreased progression to type 2 diabetes mellitus. In other studies, similar amounts of weight loss positively influenced other obesity-associated cardiovascular risk factors, such as lipid levels and hypertension. Therefore,
although trials of weight loss drugs have not looked at these outcomes, the benefits found with weight loss through diet and exercise may also be attributed to the weight loss attained with medications. All of these drugs have side effects, however, and long-term safety and efficacy data are lacking, so patients need to understand these cautions when considering their use. There is no evidence of mortality benefits from this level of modest weight loss.

**RECOMMENDATION 3**

For obese patients who choose to use adjunctive drug therapy, options include sibutramine, orlistat, phentermine, diethylpropion, fluoxetine, and bupropion. The choice of agent will depend on the side effects profile of each drug and the patient’s tolerance of those side effects.

According to meta-analysis, the pooled amounts of weight lost with these drugs were 4.45 kg at 12 months for sibutramine, 2.89 kg at 12 months for orlistat, 3.6 kg at 6 months for phentermine, 3.0 kg at 6 months for diethylpropion, 3.15 kg at 12 months with fluoxetine, and 2.8 kg at 6 to 12 months with bupropion. There are no data to determine whether one drug is more efficacious than another, and there is no evidence for increased weight loss with combination therapy. There are no data about weight regain after medications are withdrawn, underscoring the need for sustained lifestyle and behavioral modifications. There are no long-term (>12 months) studies of efficacy or safety to inform the decision to continue treatment beyond 1 year; thus, the decision to continue should be a shared discussion between the physician and patient.

**RECOMMENDATION 4**

Surgery should be considered as a treatment option for patients with a BMI of 40 kg/m² or greater who instituted but failed an adequate exercise and diet program (with or without adjunctive drug therapy) and who present with obesity-related comorbid conditions, such as hypertension, impaired glucose tolerance, diabetes mellitus, hyperlipidemia, and obstructive sleep apnea. A doctor–patient discussion of surgical options should include the long-term side effects, such as possible need for reoperation, gall bladder disease, and malabsorption.

Lifestyle modification through diet and exercise should always be recommended for all obese patients. In addition, patients need to be continuously educated regarding diet and exercise, and it should be clear that after a surgical procedure patients cannot resume their previous eating habits. There is no evidence at present to answer the question of whether one procedure is better than another. In addition, weight loss through surgery has not been shown to reduce cardiovascular morbidity or mortality.

**RECOMMENDATION 5**

Patients should be referred to high volume centers with surgeons experienced in bariatric surgery.

Bariatric surgery is an elective procedure that has a reported mortality rate ranging from 0.3% to 1.9% and an evident learning curve for the operator. Better outcomes for surgical patients depend not only on the skills of individual surgeons and their teams but also on the capacity of the systems of care, from the perioperative period until the transfer back to primary care. The surgical literature shows that high-volume centers have better surgical outcomes. Although there are no high-quality volume–outcome studies in bariatric surgery, we feel that high-volume centers should be preferred whenever feasible.
Summary of the Evidence for Pharmacologic Treatment

Drugs used for weight loss can be divided into two categories on the basis of their mechanisms of action:

1. Appetite suppressants (Sibutramine, Phenteramine, Diethylpropion, Bupropion, Fluoxetine, Sertraline,)
2. Lipase inhibitors (Orlistat)

The table below lists the medications reviewed, their side effects, and their Drug Enforcement Administration (DEA) status. The background paper on pharmacologic treatment of obesity provides a detailed description of the review of the evidence on these drugs.

### SIBUTRAMINE

In 2004, Arterburn and colleagues published the results of a high-quality meta-analysis of Sibutramine in patients with a mean age range of 34-54 years who had a BMI of 25 kg/m² or greater. They concluded that Sibutramine was more effective than placebo in promoting weight loss in overweight and obese adults at all time points assessed, with an average increased weight loss of 4.5 kg at 1 year compared with placebo. Dietary interventions were a co-intervention in nearly all primary studies, and exercise and behavior modification were each interventions in about one quarter of the studies.

### ORLISTAT

The EPC performed a meta-analysis of 29 studies of Orlistat. The average age of patients enrolled in these studies was 48 years. Seventy-three percent were women, and the average BMI was 36.7 kg/m². Diet was a co-intervention in all 29 studies, and 18% of studies included exercise co-interventions. The pooled mean weight loss for Orlistat-treated patients was 2.59 kg at 6 months and 2.89 kg at 12 months.

### PHENTERMINE

A recent meta-analysis assessed the use of Phentermine for weight loss in obese individuals. The authors concluded that Phentermine use, in addition to lifestyle interventions, resulted in statistically significant but modest weight loss. The pooled mean weight loss was 3.6 kg.

### DIETHYLPROPION

A recent meta-analysis assessed the use of Diethyl-propion for weight loss in obese individuals. The duration of treatment with Diethylpropion varied from 6 to 52 weeks. The authors concluded that Diethylpropion use, in combination with lifestyle interventions, was associated with a modest pooled weight loss of 3.0 kg, which was of borderline statistical significance.

### MEDICATIONS USED FOR WEIGHT LOSS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibutramine*†</td>
<td>Appetite suppressant: combined norepinephrine and serotonin reuptake inhibitor</td>
<td>Modest increases in heart rate and pressure nervousness insomnia</td>
</tr>
<tr>
<td>Phentermine*†</td>
<td>Appetite suppressant: sympathomimetic amine</td>
<td>Cardiovascular, gastrointestinal</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>Appetite suppressant: sympathomimetic amine</td>
<td>Palpitations, tachycardia insomnia, gastrointestinal</td>
</tr>
<tr>
<td>Orlistat*</td>
<td>Lipase inhibitor decreased absorption of fat</td>
<td>Diarrhea, flatulence bloating, abdominal pain, dyspepsia</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Appetite suppressant: mechanism unknown</td>
<td>Paresthesia, insomnia, central nervous system effects</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Appetite suppressant: selective serotonin reuptake inhibitor</td>
<td>Agitation, nervousness, gastrointestinal</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Appetite suppressant selective serotonin reuptake inhibitor</td>
<td>Agitation, nervousness, gastrointestinal</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Mechanism unknown</td>
<td>Paresthesia, changes in taste</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Mechanism unknown</td>
<td>Somnolence, dizziness, nausea</td>
</tr>
</tbody>
</table>

*Approved by the U.S. Food and Drug Administration for weight loss.
†Drug Enforcement Administration schedule IV.
**FLUOXETINE**

Nine studies of Fluoxetine treatment reported weight loss outcomes. The doses used for weight loss are higher (60 mg) than those used for depression (20 mg). The average age of patients in the studies was 48 years, and the average BMI was 35.5 kg/m². In 78% of the studies, diet was a co-intervention; 12% of studies included exercise as a co-intervention. The pooled weight loss in Fluoxetine-treated patients was 4.74 kg at 6 months and 3.15 kg at 12 months.

**SERTRALINE**

The EPC identified only 1 small study of Sertraline, which did not have statistically significant results. Recommendations cannot be made on the basis of 1 small study.

**BUPROPION**

The EPC identified 3 articles for a pooled analysis of the efficacy of Bupropion for weight loss. In these studies, the average age of enrolled patients was 43 years. Eighty-one percent were women, and the average weight was 94.3 kg. Two of the 3 studies included diet as a co-intervention, and 1 study included exercise. The pooled weight loss in the Bupropion-treated patients was 2.77 kg at 6 to 12 months.

**TOPIRAMATE**

The EPC identified 6 studies for analysis of the efficacy of Topiramate for weight loss. Only 1 of these studies was published; the rest had been published only as abstracts at the time of the EPC’s analysis. Recommendations cannot be made on the basis of only 1 published study.

**ZONISAMIDE**

The EPC identified 1 small eligible study that assessed the efficacy of 16 weeks of Zonisamide therapy for weight loss in patients with a mean BMI of 36 kg/m². Although the findings were statistically significant, recommendations cannot be made on the basis of a single small study.

**LENGTH OF THERAPY AND COMORBID CONDITIONS**

The optimal duration of treatment has not yet been determined. Data from randomized, controlled trials have examined only up to 12 months of therapy; thus, more long-term clinical trials need to be performed to answer this question. A recently published study demonstrated efficacy and safety in a 4-year trial of Orlistat, but the question of side effects, particularly the possibility of rare adverse events, remains unanswered for most of these drugs. There are no long-term data on whether these drugs decrease morbidity or mortality from obesity-related conditions.
REFERENCES AND ADDITIONAL READING


