Pharmacologic and Surgical Management of Obesity in Primary Care: A Clinical Practice Guideline from the American College of Physicians

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This guideline is based on the evidence report and accompanying background papers developed by the Southern California Evidence-Based Practice Center. The American College of Physicians nominated this topic to the Agency for Healthcare Research and Quality Evidence-Based Practice Center program as part of a concerted effort to complement the guidelines of the U.S. Preventive Services Task Force. The College recommends that all clinicians refer to the Task Force recommendations as part of an overall strategy for managing overweight and obesity, which should always include appropriate diet and exercise for all patients who are overweight or obese. The intent of this guideline is to provide recommendations based on a review of the evidence on pharmacologic and surgical treatments of obesity. The target audience is all clinicians caring for obese patients, defined as a body mass index of 30 kg/m^2 or greater. This guideline is not intended to be used by commercial weight loss centers or for direct-to-consumer marketing by manufacturers and does not apply to patients with body mass indices below 30 kg/m^2.

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Numerous reports in the recent medical literature underscore the alarming increase in the prevalence of obesity and overweight in the U.S. population (1–4). Obesity is currently defined as a body mass index (BMI) of 30 kg/m^2 or greater, and a BMI between 25 and 29.9 kg/m^2 is termed overweight. One study estimates the combined prevalence of obesity and overweight to be over 64% of the U.S. adult population, with 4.7% reported as extreme obesity, that is, a BMI of 40 kg/m^2 or greater (4). The prevalence of persons older than 18 years of age with a BMI of 30 kg/m^2 or greater increased 5.6% in just 1 year from 2000 to 2001 (2). Each year, an estimated 300 000 U.S. adults die of obesity-related causes (5), and the direct cost of obesity and physical inactivity has been estimated at 9.4% of U.S. health care expenditures (6). In response to the increase in obesity, treatments for obesity have become both more numerous and more commonly used.

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, dexfenfluramine, and phenylpropanolamine internationally and diethylpropion and phentermine in Europe). Since then, other drugs have become available, such as sibutramine and orlistat. Bariatric surgery has also increased; surgeries performed in California, for example, rose from 1134 in 1996 to 6304 in 2000, an almost 6-fold increase (7).

METHODS

This guideline is based on the evidence report (8) and accompanying background papers (9, 10) developed by the Southern California Evidence-Based Practice Center (EPC). The American College of Physicians (ACP) nominated this topic to the Agency for Healthcare Research and Quality EPC program as part of a concerted effort to complement the guidelines of the U.S. Preventive Services Task Force. The Task Force issued recommendations on screening for obesity in 2003 (11, 12). Specifically, it recommends that clinicians screen all adult patients for obesity and offer intensive counseling and behavioral interventions to promote sustained weight loss for obese adults. The ACP recommends that all clinicians refer to the Task Force recommendations as part of an overall strategy for managing overweight and obesity, which should always include appropriate diet and exercise for all patients who are overweight or obese (13–15). The **Figure** displays an algorithm for suggested management of obesity. The intent of this guideline is to provide recommendations based on a review of the evidence on pharmacologic and surgical treatments of obesity. The target audience is all clinicians caring for obese patients, defined as those with a BMI of 30 kg/m^2 or greater. This guideline is not intended to be used by com-

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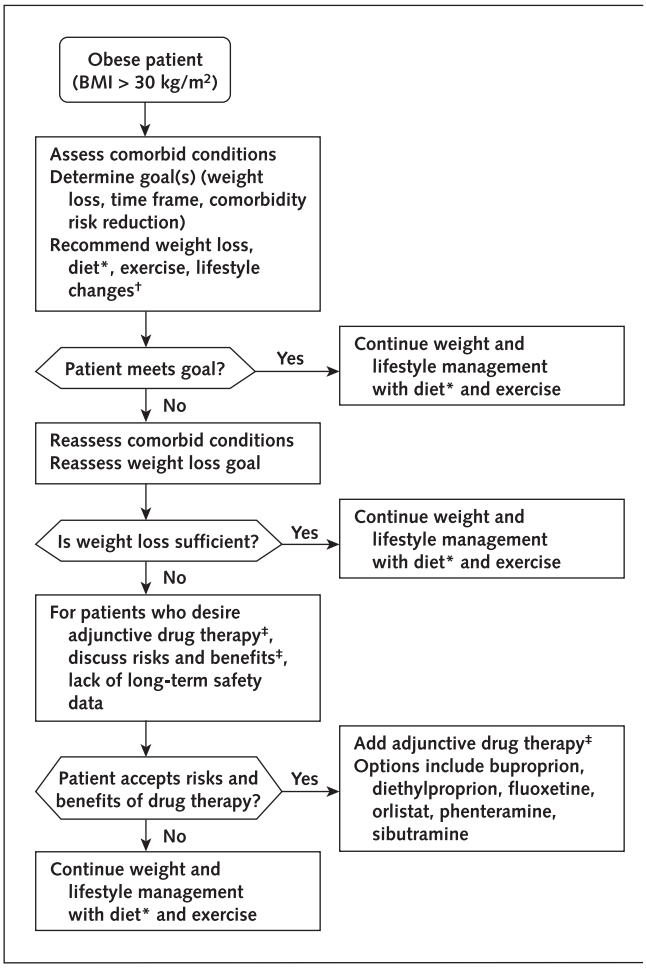
Figure. **Algorithm for managing obesity.**



BMI = body mass index. *References 13–15. †U.S. Preventive Services Task Force recommendations (11, 12). ‡Assess side effects and efficacy; no data are available past 12 months except for orlistat.

mercial weight loss centers or for direct-to-consumer marketing by manufacturers. The target patient populations vary according to the intervention under consideration, since pharmacologic and surgical trials have used different selection criteria with differing BMIs and comorbid conditions. This guideline does not apply to patients with BMIs below 30 kg/m^2.

RECOMMENDATIONS

Recommendation 1: Clinicians should counsel all obese patients (defined as those with a BMI ≥30 kg/m^2) 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 U.S. 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 (16). In other studies, similar amounts of weight loss positively influenced other obesity-associated cardiovascular risk factors, such as lipid levels and hypertension (17, 18). 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/m^2 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 2 categories—appetite suppressants and lipase inhibitors—on the basis of their mechanisms of action. The **Table** lists the medications reviewed, their side effects, and their Drug Enforcement Administration status. The background paper on pharmacologic treatment of obesity (9) provides a detailed description of the review of the evidence on these drugs.

Sibutramine

In 2004, Arterburn and colleagues (19) published the results of a high-quality meta-analysis of sibutramine in patients with a mean age range of 34 to 54 years who had a BMI of 25 kg/m^2 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 (19). 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.

Table. **Medications Used for Weight Loss**

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

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

Orlistat

The EPC performed a meta-analysis of 29 studies of orlistat (9). 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/m^2. 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 (20) 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 (20) assessed the use of diethylpropion 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.

Fluoxetine

Nine studies of fluoxetine treatment reported weight loss outcomes (9). 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/m^2. 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 (21). 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 (9). 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 (22); 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/m^2 (23). 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 (24), 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.

SUMMARY OF THE EVIDENCE FOR SURGICAL TREATMENT OF OBESITY

Bariatric surgery was first performed in the early 1960s, and its use has increased dramatically, particularly in recent years. With this escalation in the number of procedures, there have also been reports of high postoperative complication rates (25–29). A variety of surgical procedures are used to treat obesity. One commonly performed procedure is the Roux-en-Y gastric bypass (RYGB), which generates weight loss by limiting gastric capacity and causing mild malabsorption. Biliopancreatic bypass, which combines a limited gastrectomy with a long Roux limb intestinal bypass, also generates weight loss primarily through malabsorption. A common technique, particularly outside of the United States, is the laparoscopic adjustable gastric band. This device is positioned around the uppermost portion of the stomach, restricting its capacity. The band is adjustable to allow tailoring of the gastric pouch size to an individual's need, and weight is lost through meal volume restriction. Finally, vertical banded gastroplasty, performed more commonly in the past, involves stapling the upper stomach to create limited gastric capacity.

The EPC review focused on randomized, controlled trials; controlled clinical trials; and cohort studies that assessed the use of surgery with a concurrent comparison group of medical treatment or other surgical techniques (10). The main outcomes of interest analyzed were weight loss, mortality, and complication rates. Data for weight-related comorbid conditions such as diabetes, hypertension, sleep apnea, and lipid levels were extracted when available. In addition, each study was examined to determine whether it reported data on adverse events other than death.

Weight Loss and Maintenance

No current randomized, controlled trials that compared bariatric surgery (using procedures used today) with a nonsurgically treated control group were found. Numerous reports from an observational study, the Swedish Obese Subjects (SOS) study, were identified (30–35). In the intervention portion of this study, obese adults (BMI $\geq$ 34 kg/m^2 for men and $\geq$ 38 kg/m^2 for women) were assessed in 2 groups: those who voluntarily underwent bariatric surgery and a group of matched controls treated medically. Patients were matched on 18 variables, including sex, age, height, and weight. The average age of enrolled patients was 47 years. Two thirds were women, and the average baseline BMI was 41 kg/m^2. At 8 years of follow-up, average weight loss was 20 kg for surgically treated patients and average weight did not change for medically treated patients. Patients treated with RYGB lost more weight than those treated with vertical banded gastroplasty or banding procedures. The SOS study recently reported 10-year follow-up data, which continued to show a sustained improvement in weight loss for surgically treated patients compared with controls (36). However, a strong caveat must be made when reviewing this observational study in which the surgical group was composed of self-selected volunteers. Although the controls were matched for many important factors, selection bias cannot be ruled out, and other unknown or undetected differences

between the groups may have influenced the differences in response to treatments.

Comorbid Conditions

A series of reports from the SOS study suggests that patients undergoing surgery experience some improvements in or prevention of comorbid conditions associated with obesity when compared with similar patients undergoing medical therapy. At 24 months after surgery, the incidence of hypertension, diabetes, and lipid abnormalities was markedly lower in the surgery group (adjusted odds ratios, 0.02 to 0.38) (35). At 8 years, the effect of surgery on the reduction in diabetes risk remained (odds ratio, 0.16), while the effect on reduction in risk for hypertension did not persist (odds ratio, 1.01) (36). In the subset (6%) of patients who underwent gastric bypass and lost more weight than the 94% of patients who underwent vertical banded gastroplasty or gastric banding, decreases in both systolic (8.3 mm Hg) and diastolic (6.7 mm Hg) blood pressure persisted (37). Additional reports from the SOS study report a small benefit of surgery in reducing sleep apnea and symptoms of dyspnea and chest pain and improving quality of life (31, 33). Differences were related to the degree of weight loss. A more recent report on the 10-year follow-up data from the SOS study found no differences in incidence of hypertension and hypercholesterolemia between the surgical and control groups at 2 and 10 years (38). This study did find statistically significant differences in rates of recovery from hypertension, diabetes, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, and hyperuricemia both at 2 and 10 years in favor of the surgically treated group. There was no difference between the groups in rates of recovery from hypercholesterolemia at 2 and 10 years. The data collection and analysis of mortality and incidence of myocardial infarction, stroke, and cancer are still ongoing. The SOS study is the only identified study that compares comorbid conditions between surgically treated patients and a concurrent nonsurgical control group.

Comparing Surgical Procedures

Five randomized, controlled trials were identified that compared weight loss between or among surgical procedures and reported enough data for pooling (10). The results of all of these studies support the conclusion that gastric bypass produces weight loss superior to that produced by gastroplasty procedures. In 2 other randomized, controlled trials, the weight lost using vertical banded gastroplasty compared with laparoscopic adjustable gastric banding was 14 kg more at 12 months of follow-up but only about 3 kg more at 36 months of follow-up. No difference in net weight loss was seen in the pooled results from all studies combined.

Mortality

Early mortality rates for RYGB range from 0.3% (95% CI, 0.2% to 0.4%) for case series data to 1.0% (95% CI, 0.5% to 1.9%) in controlled trials. Adjustable gastric banding had an associated early mortality rate of 0.4% (95% CI, 0.01% to 2.1%) for controlled trials and 0.02% (95% CI, 0% to 0.78%) for case series data. No statistically significant differences in mortality were seen among procedures. Early mortality rates following bariatric surgery are 1% or less in published controlled trials and case series data (which come from a specific clinic or surgeon performing procedures on patients enrolled in a research study). Recently, there have been several assessments of 30-day or inpatient mortality in unselected patients. A 2003 report on more than 62 000 procedures performed in the state of Washington between 1987 and 2001 stated that the 30-day mortality rate as assessed by using administrative data was 1.9% (39). Another report on data from the California inpatient database of 6232 gastric bypass cases found an in-hospital mortality rate of 0.3% (40). A review of administrative data from Pennsylvania on 4685 gastric bypass patients found the in-hospital mortality rate to be 0.6% (25).

Relationship of Surgical Volume and Mortality

Several studies have reported that a significant learning curve is associated with these surgical techniques. One study (39) found that surgeons who had performed fewer than 20 procedures had patient mortality rates of 5%, compared with rates near 0% for those who had performed more than 250 procedures. Another study found a 10% anastomotic leak rate following laparoscopic RYGB in the first 50 cases and 0% in the subsequent 100 to 150 cases (41), while another study reported a 3% leak rate in the first 300 cases and a 1% rate thereafter (42). One study reported that operative time for laparoscopic gastric bypass stabilized after 150 cases (43), while another reported a major complication rate of 12.5% in the first 100 cases and 2.7% for 100 to 150 cases (28). Although 4 of these 5 studies are case series, they support the hypothesis that a technical learning curve exists.

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