REVIEW

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How to help your patients lose weight: Current therapy for obesity

ABSTRACT

Obesity is epidemic and dangerous. Weight loss is difficult but worth the effort. Although new weight-loss drugs are available, there are no magic bullets: to lose weight and keep it off, people must eat less and exercise more. This article presents a practical approach on how physicians can help their patients lose weight through diet, behavior modification, and adjunctive pharmacologic therapy.

KEY POINTS

An appropriate initial goal is to lose 5% to 10% of one's baseline weight over 3 to 6 months.

Drug therapy should not be used in isolation, but it can be an adjunct to diet, exercise, and behavior modification if a patient is committed and able to make necessary changes in eating and activity, and if the patient has a BMI of 30 or higher or a BMI greater than 27 with weight-related comorbid conditions.

Anorectic therapy is unlikely to succeed and should be stopped if the patient does not lose at least 4 lb in the first 4 weeks of therapy. Orlistat is unlikely to be of benefit if patients do not lose at least 3% of their baseline weight by 12 weeks.

Because obesity is a chronic disease, drug treatment should be continued indefinitely. The physician and patient must understand the intention to treat long-term.

The weight loss plan devised should improve upon previous plans: for example, implementing a regular, convenient exercise program that had not been included in the past, or offering pharmacotherapy.

*Disclosure: The author has indicated that he serves on the speaker's bureau of Roche Pharmaceuticals.

THIS GUIDE COVERS how to assess obese patients, set reasonable goals, plan diet and exercise therapy, and appropriately prescribe newer agents approved for this indication. Along the way we explode some popular myths and give practical suggestions.

OBESITY IS EPIDEMIC

In the United States, 29% of men and 44% of women are trying to lose weight at any given time.[1] Despite these efforts, the chronic disease that is obesity is more prevalent than ever.[2]

The body mass index (BMI) quantifies weight across a range of body sizes.[3,4] It is calculated as the weight in kilograms divided by the square of the height in meters. Alternatively, one can use a readily available nomogram (FIGURE 1). The normal range is 18.5 to 24.9 kg/m^2.

Obesity, defined as a BMI of 30 or higher, is present in about 18% of the US population.[2] Data from the early 1990s showed that 55% of women and 63% of men are overweight (BMI 25 to 29.9) or obese.[5]

DANGERS OF OBESITY

Mortality and morbidity increase progressively with a BMI greater than 25 and more steeply with a BMI greater than 30.[6–12] The more overweight a person is, the more likely he or she is to have type 2 diabetes, hypertension, dyslipidemia, coronary artery disease, stroke, obstructive sleep apnea, cor pulmonale, daytime sleepiness without sleep apnea, gout, lower extremity degenerative joint disease, low back pain, lower extremity venous insufficiency, gastroesophageal reflux disease, nonalcoholic steatohepatitis, cholelithiasis, or polycystic ovary syndrome.[4,5,13–15]

Obese persons have a higher mortality rate from cancers of the biliary tract, ovary, endometrium, and cervix in women and from cancers of the colon and prostate in men.[16]

An estimated 300,000 deaths each year in the United States are attributable to obesity—and this is a conservative figure.[17]

Obese persons are also more likely to have impaired quality of life and disability,[18,19] and their health care costs are more than 25% higher compared with the nonobese.[20]

Lower body fat vs central body fat

But not all obese persons carry the same risk of adverse outcome. In persons with a BMI less than 35, gluteofemoral or lower body adiposity is not as worrisome as is abdominal or centrally distributed fat. Waist circumference has been shown to be an independent risk factor for the diseases associated with obesity. A waist circumference greater than 40 inches in men or 35 inches in women places the patient at high risk.[3]

Patients with a BMI less than 35 should have their waist measured at the narrowest area between the lowest rib and the iliac crest. The "waist" does not always correspond to the level of the umbilicus.

Patients with a BMI of 35 or greater are at high risk irrespective of waist measurement. In these patients, it is not necessary to record the waist measurement, as this information would not affect prognosis.

MODEST WEIGHT LOSS IS BENEFICIAL

Do obese patients who lose weight live longer? Although there are no prospective randomized trials proving that weight loss reduces mortality, considerable indirect data support such a conclusion. One large, prospective, observational study in nonsmoking women found a 20% reduction in all-cause mortality in those who had intentionally lost weight.[21]

Weight loss also appears to reduce the likelihood of developing type 2 diabetes and reduces risk factors for coronary artery disease. Loss of 5% to 10% of baseline weight usually leads to lower triglycerides, blood pressure, and left ventricular mass.[22] Persons with type 2 diabetes often have dramatic reductions in blood glucose levels. Improvements can be expected in HDL cholesterol, low back pain, lower extremity arthralgias, obstructive sleep apnea, and gastroesophageal reflux. Moreover, modest weight loss (ie, 5% to 10% of baseline) often allows one to reduce or discontinue medications prescribed for conditions exacerbated by obesity.[3,4]

Nomogram for body mass index

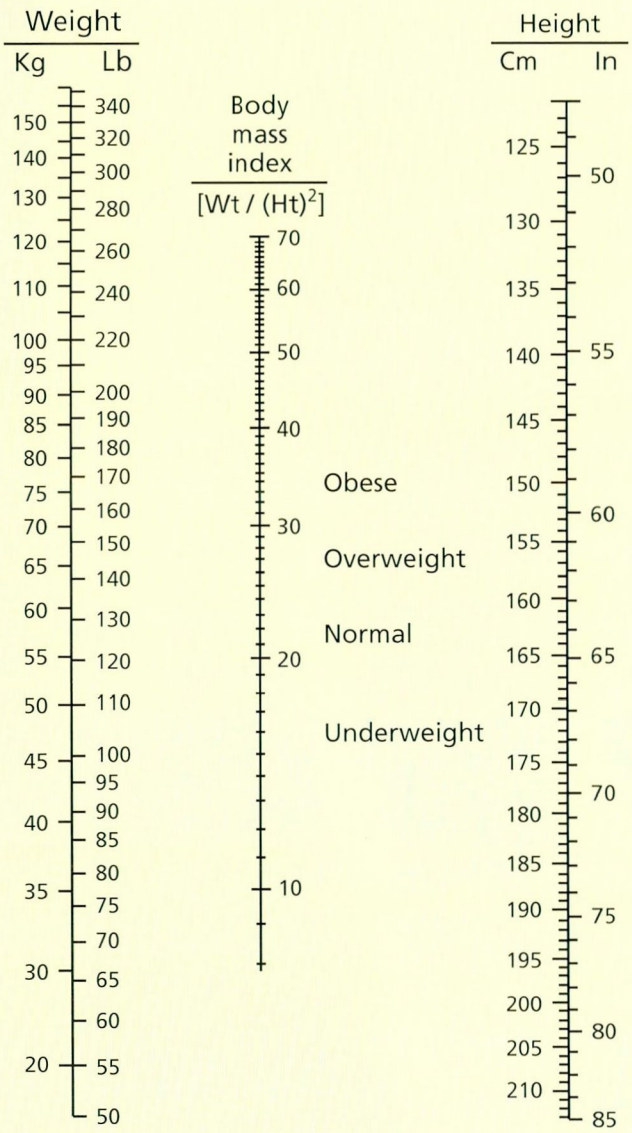

FIGURE 1. Weight classifications according to body mass index (BMI). To find the BMI, use a straight edge to connect the patient's weight and height.

ADAPTED FROM BRAY GA. CLASSIFICATION AND EVALUATION OF THE OBESITIES. MED CLIN NORTH AM 1989; 73:161.

HOW TO ASSESS OBESE PATIENTS

Because weight loss requires considerable effort, appropriate candidates must be committed to change and have realistic expectations. The clinician should try to determine the patient's readiness for change and whether the time is right for such change. Changes in behavior should be attempted when the chances for success are optimal. Does the patient have reason and motivation for losing weight at this time? Does he or she have support for this effort at home or at work? Does he or she have the motivation and time for regular, scheduled exercise? If so, chances for success are improved.

Conversely, does the patient have substantial life stresses (eg, a recent move, a new job) that cannot be modified? If so, the present may seem a poor time for intervention. For these patients, indeed for many obese patients, preventing further weight gain may be a reasonable option.

Perform a history and physical examination

Screen *all* obese patients for depression

All obese patients for whom treatment is contemplated need a thorough history and physical examination to clarify the severity of obesity and the comorbid conditions that can be expected to improve with weight loss.

Obtain a **weight history** and include previous weight-loss efforts. Keep in mind that substantial weight gain may be associated with pregnancy, major life stresses, reduced physical activity, tobacco cessation, depression and certain medications (eg, glucocorticoids, valproate, and some antipsychotic agents).

The **family history** should elucidate any family history of obesity and associated disorders (eg, diabetes, coronary artery disease).

Identify the **eating pattern** for a typical day, as well eating in response to certain emotional states.

The **exercise history** and obstacles to exercise should be assessed.

Screen all obese patients for **depression**, which is common in this setting. Obesity should not be invoked as a "reason" for depression or used as an excuse not to treat depression. Screening questions for depression that are simple, nonthreatening, and validated[23] include:

- "Do you have problems getting to sleep or staying asleep, or are you sleeping too much?"
- "Do you have problems feeling tired a lot or having little energy?"
- "Have you lost pleasure or interest in things?"
- "Do you often feel sad and down?"

Patients who are troubled with these symptoms on most days have depression and need to be further evaluated.

Recommended laboratory studies are:

- Fasting lipids
- Fasting glucose
- Alanine aminotransferase
- Aspartate aminotransferase.

In addition, it is reasonable to obtain a thyroid-stimulating hormone level to screen for hypothyroidism. Cushing syndrome is uncommon but easily missed; if suspected, a 24-hour urine sample should be obtained to measure free cortisol and creatinine. Overnight dexamethasone suppression testing may also help in this setting.

WHAT ARE REALISTIC GOALS?

The initial goal is to lose 5% to 10% of the baseline weight.[3] This goal needs to be discussed openly because obese patients often have unrealistic expectations of magically achieving a "dream" weight.

The weight loss plan devised should improve upon previous plans: for example, implementing a regular, convenient exercise program that had not been included in the past, or offering pharmacotherapy.

Advise the patient that it may take 3 to 6 months to reach the initial weight-loss goal. Furthermore, any therapy instituted or changes made will need to be continued to keep the lost weight off. Reverting to previous behavior, going back to old eating habits, or stopping effective medication will all lead to gaining weight back.

PRESCRIBE DIET THERAPY

To lose weight, obese patients must change their food intake. Patients may protest, "But I eat very little!" The best response to this

claim is a nonchallenging "I'm sure you do, but you've got to eat less if you want to lose weight." Obese persons have been documented to eat more than they report, especially more fat; this is termed underreporting. In contrast, when they keep a food diary they tend to eat less than they do when not keeping a food diary; this is termed undereating.[24,25] The calorie intake and metabolic rate (and in turn, daily energy expenditure) of most obese persons are not low.

For weight loss, calorie expenditure must exceed intake

The resting energy expenditure[26] in kilocalories can be estimated using the following formulae:

- In men: 10 × (current weight in kg) + 900
- In women: 7 × (current weight in kg) + 800

Multiplying the results by 1.2 gives an estimate of 24-hour calorie requirements for a sedentary lifestyle.

A calorie deficit of 500 to 1,000 kcal/day leads to loss of about 1 to 2 lb/week. Weight loss may plateau at about 6 months, primarily owing to decreased energy expenditure.

Patients should consume at least 800 kcal/day. There is no clear benefit from diets containing less than 800 kcal/day, ie, the so-called very-low-calorie diets.[27–29]

If less than 1,000 calories per day are consumed, care should be taken to provide enough protein of high biologic value, at least 0.8 gm/kg of ideal body weight per day. (To calculate the ideal body weight in this setting, take the patients height in meters, square it, and then multiply times 24—the result would be the patient's weight at a body mass index of 24.) Adequate protein intake preserves lean body mass. Consultation with a dietitian may be indicated. However, very few patients need to reduce calorie intake to less than 1,000 calories per day to lose weight.

Weight loss will occur only if calorie intake is less than expenditure. No special foods alter this fact. Diets should be balanced to provide essential nutrients consistent with the food pyramid and accepted dietary guidelines (eg, from the American Heart Association, American Diabetes Association, and American Dietetic Association).

Limit fats, not just calories

No more than 30% of the total calorie intake should come from fats. Excess calories from fat are more likely to lead to fat accumulation than are excess calories from carbohydrates, because fat is stored as fat with little energy needed for storage. Carbohydrates, on the other hand, must first be converted to fat for storage. This biochemical transformation requires substantial energy, about 20% of the excess carbohydrate calories consumed.[30]

Patients who count both fat and total calorie intake rather than calories alone are more successful at weight loss.[31,32] Fat is much more calorie-dense than carbohydrate, containing 9 calories per gram vs 4 per gram.

Provide an eating plan

Making new food choices is challenging for obese patients who have established their eating habits and preferences over years. Written, detailed meal plans aid weight-loss efforts. Low-calorie frozen entrees can also help.[33,34] No foods need be strictly forbidden, although some patients find it difficult to control the quantity of certain foods. Such foods may be best avoided until restraint and coping techniques are enhanced.

Aim for a calorie deficit of 500 to 1,000 kcal/day

Olestra, a sucrose polyester, may be of some benefit in reduced-calorie meal plans. Well-performed short-term studies demonstrated an overall reduction in calorie and fat intake when olestra-containing snacks replaced conventional fat snacks.[35,36] There are no long-term data showing reduced calorie intake with olestra snacks, however.

Diet fads and myths

High-fat, low-carbohydrate diets, which are receiving renewed interest by the public, lack evidence of long-term benefit. Multiple studies showed that people take in more calories when they consume fat ad lib than when they consume carbohydrates ad lib. Some studies showed weight loss with low-fat (30% of calories) and ad lib carbohydrate intake.[37] In addition, high-fat low-carbohydrate diets are unbalanced, and people do not adhere to them well in the long term.

High-protein intakes are given to those few patients prescribed less than 800 calories per day. One such approach to this protein-

sparing modified fast is the use of natural foods such as lean fish, fowl, or red meat with little or no carbohydrate. Other approaches use a commercially available mixed formula powder that is reconstituted with liquid. These formulas may differ in their carbohydrate content. No scientific evidence supports any particular very-low-calorie diet over another. Great care must be taken to ensure that adequate vitamin and mineral intake is provided on these diets.

Drinking lots of water. Another popular recommendation that has no demonstrated benefit in weight loss is to drink 6 to 8 glasses of water daily. No changes in calorie intake have been shown with increased water consumption before meals.[38]

Number and size of meals per day. In terms of weight loss, there is no proven advantage to eating three meals per day vs fewer meals. Many obese persons habitually skip breakfast, eat a small lunch, and then eat from supper until bedtime. Although patients may be more inclined to eat breakfast if they were to stop eating in the evening, an obese person should never be advised to eat when he or she is not hungry.

Any activity is better than none at all

WHY EXERCISE IS ESSENTIAL

Dietary changes are not enough; exercise is essential. An obese person should exercise regularly because:

- Those who exercise regularly have greater cardiorespiratory fitness and appear to be at reduced risk of cardiovascular events and mortality.[39]
- Regular exercise, by increasing the calorie deficit, may modestly increase the amount of weight lost when coupled with reduced calorie intake.
- Exercise during weight loss helps retain muscle that would be lost if the person were not to exercise.[40]
- Exercise is perhaps the most important predictor of long-term maintenance of weight loss.[41,42]

Prescribing exercise

The American College of Sports Medicine and the Centers for Disease Control and Prevention recommend 30 minutes or more of moderately intense physical activity such as brisk walking at least 5 days per week.[43] Fewer than 25% of US adults get this much exercise, and about another 25% are completely sedentary. Only 20% of obese men and 15% of obese women engage in this degree of activity in addition to calorie restriction during their weight-loss efforts.[1]

It is unreasonable, however, to expect sedentary obese persons to move from inactivity to this amount of exercise. Any activity is better than none at all. As with any behavioral change, small steps are more easily accomplished. For example, have your patient start walking three to four times a week for 10 minutes, and over the ensuing weeks gradually increase the duration and frequency. Consider exercise stress testing to assess for coronary artery disease in sedentary patients at high risk, such as those with type 2 diabetes.

Exercise does not have to be vigorous to be of value for weight loss. However, a recent study[44] suggested that people may need to exercise longer and harder than the current recommendations if they wish to keep lost weight off: 60 to 80 minutes per day of moderately intense exercise or 35 minutes per day of vigorous exercise may be needed. The total duration of exercise, weekly and daily, is more important for weight loss than whether it is done in short (10-minute) bouts throughout the day or one longer period of 40 minutes.[45]

Discuss a realistic exercise program with your patient. The exercise chosen should be convenient and acceptable to your patient. Patients appear more likely to exercise when they have access to home equipment.[45] Options include walking (outside or in an indoor shopping mall), riding a stationary cycle, walking on a treadmill, or performing low-impact aerobic exercise with a video or in a class. Those who plan to walk outdoors must have an alternative for inclement weather, otherwise they'll have an excuse for not exercising up to half the year in some parts of the United States.

Although daily activity should be distinguished from scheduled aerobic exercise, all activity is of value.[46] For example, parking the car farther away from the building entrance, taking the stairs, walking the dog, or cleaning the house are all helpful in weight management.

Muscle strengthening using resistive weight training is less well studied in obesity management. This form of exercise does appear to be of value in maintaining lean body mass.[47] However, data are insufficient to show benefit in the other three aspects for which aerobic exercise is clearly beneficial (reducing cardiovascular risk, increasing weight loss, or maintaining weight loss).

BEHAVIOR MODIFICATION

Current treatments for obesity all require some modification of behavior for success. The changes in eating and activity described above can only be accomplished with awareness and understanding sufficient to modify one's current lifestyle.[48]

Books and manuals. A variety of approaches have been used. Workbooks and self-help manuals are available. In one study (in which patients also received an antiobesity medication), 15-to-20-minute visits with a physician were as effective as a more-intensive, more-frequent traditional group approach to behavior modification.[49] In both interventions, patients used the *LEARN Manual for Weight Control*.[50] This is a very useful, practical workbook that can be used with patients in a group or one-on-one interactions. On the other hand, pharmacotherapy without guidance in making lifestyle changes is less effective than the combination of both methods.

Food diary. Self-monitoring is one method used in behavior modification. One type of self-monitoring—keeping a food diary has been proven to increase weight loss.

TABLE 1 lists other cognitive and behavioral techniques that may enhance weight-loss efforts.

TABLE 1

Behavioral and cognitive techniques for weight loss

Keep a food diary
Grocery shop when not hungry
Shop from a list
Start a walking program
Eat smaller portions
Don't "clean your plate"
Do nothing else while eating
Leave the table after eating
Reduce fat and calorie intake
Wait 5 minutes before another helping of food
Distinguish hunger from cravings
Avoid using "never" and "always"; expect lapses
Set realistic short-term goals
Park far from your destination
Watch less TV and spend less time at the computer

ADAPTED FROM BROWNELL KD. THE LEARN PROGRAM FOR WEIGHT CONTROL 6TH ED. DALLAS: AMERICAN HEALTH PUBLISHING CO, 1994.

USE PHARMACOTHERAPY AS AN ADJUNCT

Pharmacotherapy for obesity can be considered for a patient who:

- Is committed and able to make changes in eating and activity necessary for weight loss, *and*
- Has a BMI of 30 or greater or a BMI greater than 27 with weight-related comorbid conditions.[3,28]

Drug therapy should be used as an adjunct to diet, exercise, and behavior modification; it should not be used in isolation. Some state medical boards place additional restrictions on prescribing drugs for obesity. No drugs for weight loss should be prescribed during pregnancy or lactation.

Treat depression before giving antiobesity drugs

Treat depression before beginning medication for obesity. Depression impairs function and, if untreated, impedes weight-loss efforts.[51] Of the antidepressants, bupropion appears least likely to be associated with weight gain; indeed, it often causes modest weight loss. Nefazodone, venlafaxine, and most of the selective serotonin reuptake inhibitors are better choices in obese patients than are tricyclic antidepressants.

Duration of drug therapy. Decades ago, when the FDA originally approved the older anorectic agents, they were to be used only for "a few weeks." However, we now understand that obesity is a chronic disease. To be effective, drug treatment for obesity should be continued indefinitely.[52] Short-term use makes no physiologic sense. The physician and patient must understand the intention to treat long-term, assuming a good response is demonstrated. When a medication for a chronic condition is

TABLE 2

Prescription agents for obesity

GENERIC NAME	DEA SCHEDULE*	MECHANISM OF ACTION	MAXIMUM DAILY DOSE
Benzphetamine	III	Promotes norepinephrine release	150 mg
Phendimetrazine	III	Promotes norepinephrine release	210 mg
Diethylpropion	IV	Promotes norepinephrine release	75 mg
Phentermine	IV	Promotes norepinephrine release	37.5 mg
Mazindol	IV	Inhibits norepinephrine reuptake	3 mg
Sibutramine	IV	Inhibits norepinephrine, serotonin reuptake	15 mg
Orlistat	Unscheduled	Inhibits intestinal lipase activity	360 mg (120 mg three times a day)

*DEA, Drug Enforcement Administration
Schedule III: Less potential for abuse than with schedule I drugs (eg, heroin, marijuana) or schedule II drugs (eg, codeine, fentanyl, meperidine, morphine) and having a currently accepted medical use; still, abuse of these drugs may lead to moderate or low physical dependence or high psychological dependence; examples of other schedule III drugs are acetaminophen with codeine, acetaminophen with oxycodone
Schedule IV: Less potential for abuse than with schedule III drugs but dependence is still possible; examples of other schedule IV drugs are pentazocine, benzodiazepines, phenobarbital, chloral hydrate, and paraldehyde

If a patient does not lose 4 lb in 4 weeks, stop the drug

stopped, the condition for which it was prescribed will reappear; high blood pressure recurs when an antihypertensive is stopped. Likewise, weight is usually regained when the antiobesity drug is discontinued. No drugs "cure" obesity.

The balance of risk vs benefits must be addressed when anorectic agents are prescribed. One placebo-controlled study with double-blind and open-label periods showed benefit of anorectic agents in a small group of patients followed for more than 3 1/2 years.[53] The efficacy of these agents was demonstrated repeatedly when the patients regained weight after the drugs were stopped and resumed losing weight when back on drug therapy.

As with other medications, patient responses to antiobesity agents are quite mixed. In general, failure to achieve the initial goal of a weight loss of 5% to 10% of the baseline weight within 3 to 6 months is an indication to stop the medication. However, a plateau in weight after 6 to 9 months is expected and is not cause for stopping the drug.

Currently available prescription medications for obesity work via one of two mechanisms, as discussed below. Six anorectic agents, which result in reduced food intake, are currently available (TABLE 2).

Sibutramine

Sibutramine (Meridia), the newest of the anorectic agents, has been extensively studied for up to 2 years of treatment. However, it has not been shown to be any more effective than other anorectic agents currently available. Sibutramine acts by inhibiting reuptake of norepinephrine and serotonin in the central nervous system without promoting the release of these neurotransmitters.

Effectiveness. In a multicenter study,[54] 1,047 patients were randomized to receive differing doses of sibutramine or placebo for 24 weeks. Only 683 patients completed the study; this high (35%) dropout rate is common in obesity studies. All patients received counseling in diet, exercise, and behavioral change. At baseline, the mean BMI was 34.5. In an analysis that included all patients randomized including those who dropped out (a so-called "last observation carried forward" [LOCF] analysis), the group receiving placebo lost 0.9% of their baseline weight, compared with 4.7% in the sibutramine 10-mg group and 5.8% in the 15-mg group.

An analysis of patients who actually completed 24 weeks of treatment showed more favorable results. Of those taking sibutramine

10 mg, 60% lost 5% of their baseline weight and 17% lost 10% of their baseline weight. Of those taking 15 mg, 67% lost 5% of their baseline weight and 35% lost 10% of their baseline weight. Of those receiving placebo, 20% lost 5% and none lost 10%.

However, even among patients taking sibutramine 15 mg—the maximum recommended dose—30% of patients did not lose even 5% of their baseline weight. The initial response to treatment can identify this group early. Patients who do not lose at least 4 lb over the first 4 weeks of treatment (20%–25% of the group in the studies) are not likely to lose 5% by 6 months (83% of this group did not) and should therefore stop the drug after 4 weeks.

Studies showed that sibutramine retains its effectiveness in responders for up to 2 years. Most of these data are not yet published. In one published 12-month study,[55] sibutramine was substantially more effective than placebo in maintaining weight lost after 4 weeks of a very-low-calorie diet.

Adverse effects. The most common adverse effects of sibutramine are dry mouth, constipation, and insomnia. No evidence of abuse potential is seen.[56] Dose-dependent mean increases of 3 to 4 mm Hg in both systolic and diastolic blood pressure occur. Dose-dependent heart rate increases averaging 6 beats per minute also occur. These changes may be more substantial in some patients but infrequently necessitate stopping the drug.

Echocardiography has shown no increase in cardiac valvular abnormalities with sibutramine,[57] unlike that seen with fenfluramine and dexfenfluramine, serotonin-releasing agents withdrawn from the market in 1997.[58] Whether this is because sibutramine has a somewhat different mechanism of action (inhibiting norepinephrine and serotonin reuptake rather than promoting serotonin release, as with the earlier agents) is not known.

Primary pulmonary hypertension is a rare disorder that has been associated with anorectic agents, especially fenfluramine derivatives. The background incidence of this disorder in the general population is estimated at 1 to 2 cases per million persons per year.[59] Patients treated with fenfluramine or dexfenfluramine had an estimated incidence of 25 cases per million persons treated per year.[59] No increase in the incidence of primary pulmonary hypertension has been seen thus far with sibutramine.

Contraindications to the use of sibutramine include coronary artery disease, congestive heart failure, stroke, arrhythmia, severe liver or kidney disease, uncontrolled hypertension, and seizure disorders. Other contraindications include treatment with serotonergic migraine medications, monoamine oxidase inhibitors, or other medications active in the central nervous system, including antidepressants and other anorectic agents. There are no data on safety and efficacy in patients younger than 16 years, and few data for those older than 65 years.

Dosage. Sibutramine is available as 5-mg, 10-mg, and 15-mg capsules. The usual starting dose is 10 mg. The 5-mg dose is reserved for those with side effects at the 10-mg dose. The maximum recommended dose is 15 mg/day.

Cost. The average wholesale price in the United States is $2.90 for a 10-mg capsule, and $3.75 for the 15-mg capsule.

Support program. The manufacturer provides a telephone and newsletter-type support program to patients taking sibutramine.

Older anorectic agents

Other anorectic agents (TABLE 2)[52] are far less costly than sibutramine. Most of these drugs, however, were studied only in small trials lasting no more than 12 weeks. One study in 72 patients found that phentermine resin was significantly more beneficial than placebo during 36 weeks of therapy; this was the longest-running monotherapy trial of the older agents. Intermittent therapy (on drug 1 month, off the next) was as effective as continuous therapy. Another study found the combination of phentermine and fenfluramine better than placebo during more than 3 years of therapy.[53]

The combination of ephedrine (an adrenergic agonist, 60 mg/day) with caffeine (600 mg/day) was studied in a limited fashion.[60] This combination is not FDA-approved, but ephedrine-caffeine combinations are sold

Orlistat reduces fat absorption by 30%; the fat passes into the colon

over-the-counter in herbal preparations. Although many people use them, they may lack consistent reliable doses of ephedrine and cause unpredictable adverse cardiovascular effects.

Orlistat

Orlistat (Xenical) acts by a completely different mechanism: inhibiting intestinal lipase activity. Orlistat binds covalently to the active site of the enzyme, making it unavailable to hydrolyze dietary fat in the form of triglycerides. Therefore, 30% of fat is unabsorbed and passes into the colon. There is minimal (< 1%) systemic absorption of the drug.

Effectiveness. Two large placebo-controlled trials documented the efficacy of orlistat use for up to 2 years.[61,62] A total of 1,580 patients were randomized. In both trials the diet was adjusted to maintain weight after 1 year. After 1 year, the orlistat group lost 10.2% of body weight in one study and 8.8% in the other; in comparison, patients in the placebo groups lost 6.1% and 5.8%. Thirty-nine percent of orlistat-treated patients lost more than 10% of their initial weight, compared with 25% of the placebo group. At 2 years, weight loss with orlistat was 7.6% compared with 4.5% with placebo. After 2 years, twice as many patients taking orlistat (34% vs 17%) maintained a weight loss of more than 10%. Likewise, twice as many patients taking orlistat lost at least 5% of their weight (about 50% compared with 25% in the placebo group).

Careful assessment and tailored treatment provide weight losses of 5% to 10%

These and other 1-year studies[63,64] demonstrated less weight regain with orlistat than with placebo, and small but statistically significant improvements in lipids, glycemic control, and blood pressure. Pooled data reveal that patients who lose less than 3% of their initial weight at 12 weeks (approximately 30% of those completing the studies) are unlikely to lose 5% or more of their weight by 52 weeks.

Adverse effects of orlistat relate to its mechanism of action. Patients may experience flatus with discharge, oily spotting, fecal urgency, increased stool frequency, and occasional fecal incontinence. These effects can be avoided by limiting fat in the diet to 30% of calories distributed over three meals. Symptoms are usually minimal and diminish with time as patients modify their diet. Patients need specific dietary instruction and should count how many grams of fat they consume.

No drug interactions have been reported with orlistat. The only contraindications to its use are chronic malabsorption and cholestasis, which are unlikely settings for obesity. Slight decreases in serum levels of fat-soluble vitamins have been seen but usually not below the normal range. However, patients should take a multivitamin supplement daily at least 2 hours before or after taking orlistat.

Dosage. Orlistat 120 mg should be taken no more than three times per day, during or up to 1 hour after each main meal. There is no benefit to increasing the dosage above 360 mg/day, and there is no reason to take a dose if a meal contains no fat. If the meal is skipped, the orlistat should be skipped.

Cost is $1.32 per capsule or about $4 a day if taken three times a day.

Support program. The manufacturer sponsors a support program for patients taking orlistat.

BARIATRIC SURGERY

For a small number of severely obese patients for whom repeated attempts at weight loss have failed, surgery may be a reasonable option.[65] Patients with a BMI of 40 or greater or those with a BMI greater than 35 with multiple comorbidities may be appropriate candidates.

The Roux-en-Y gastric bypass procedure appears to be most effective and safest long-term. This procedure divides the stomach into a small proximal pouch and a larger excluded fundus and antrum. The pouch has a capacity of 30 to 60 mL and is attached directly to the jejunum via a narrow anastomosis. The small pouch volume produces early satiety, and the narrow anastomosis delays pouch emptying.

Candidates must be carefully selected and counseled regarding the lifelong changes in eating necessary after surgery. At 5 years,

60% of patients maintain a weight loss of at least 50% of their excess weight. Weight losses of 125 lb are typical. Iron, calcium, and multivitamin supplements are usually required.[66]

More recent approaches have modified the historically less successful vertical banded gastroplasty by using less-invasive laparoscopic adjustable silicone gastric banding. This technique holds promise, but there are few long-term studies.[67]

CONCLUSION

The treatment of obesity remains challenging for patients and their physicians. Careful assessment of patients and tailored treatment can often provide weight losses of 5% to 10%, which will significantly reduce health risks. Hopefully, current intense research efforts will lead to more-effective therapies in the near future for this increasingly common and poorly understood chronic disease.

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