

Pharmacologic options for the treatment of obesity

MIKI L. CAMPBELL AND MONICA L. MATHYS

Obesity is a chronic disease with an increasing prevalence worldwide.¹⁻⁵ Reports in the United Kingdom have found a 15% increase in the overweight and obese population between the years of 1980 and 1992⁴ and within the past decade the prevalence has doubled.² Similar increases have been observed in Sweden,⁶ the Netherlands,⁷ and other developed and developing countries.¹ The United States is no exception to these troubling statistics. The National Heart, Lung, and Blood Institute reported that the percentage of obese people in the United States rose from 12.8% in 1976–80 to 22.5% in 1988–94, resulting in an estimated 97 million overweight adults.⁸ Other sources state that one of every three U.S. adults is overweight or obese.⁹⁻¹³ The most current data, released by the National Institutes of Health (NIH), state that more than 50% of Americans are overweight or obese, while 20% are obese as defined by a body mass index (BMI) of ≥ 30 kg/m².⁸

Obesity is associated with increased morbidity and mortality and is estimated to result in approximately 300,000 deaths yearly.¹² Secondary comorbidities associated with this chronic disease include hypertension, heart disease, type 2 dia-

Abstract: Past and current drug therapies for weight loss are discussed.

More than 50% of Americans can be categorized as overweight or obese. Obesity is associated with increased mortality and with comorbidities such as hypertension, hyperglycemia, dyslipidemia, coronary artery disease, and certain cancers. According to guidelines for identification, evaluation, and treatment of obesity, patients with a body mass index (BMI) of ≥ 30 kg/m² should attempt to lose weight. Patients with a BMI of ≥ 25 kg/m² plus two or more risk factors or patients with an excessive waist circumference plus two or more risk factors should also attempt to lose weight. The initial goal is a 10% weight reduction in six months achieved through lifestyle changes. If lifestyle changes alone are not effective, then drug therapy may be indicated. Pharmacotherapeutic options for obesity have decreased over the past few years. Fenfluramine, dexfenfluramine, and phenylpropranolamine have been withdrawn because of severe adverse effects, leaving only sympathomimetics, sibutramine, and orlistat as anorectics with FDA-approved labeling. Phentermine has been shown to cause a 5–15% weight loss if given daily or intermittently. Compared with sibutramine and orlistat, phentermine is cheaper, and specific formulations allow once-daily administration. However, phentermine is indicated only for short-term treatment, and

tolerance often develops. Common adverse effects associated with phentermine are dry mouth, insomnia, increased blood pressure, and constipation. Sibutramine increases norepinephrine and serotonin levels in the CNS and should not be taken with many antidepressants because of the risk of increased norepinephrine and serotonin levels. Its use is also contraindicated in patients with cardiovascular disease. Orlistat is not systemically absorbed; therefore, it does not cause the systemic adverse effects or drug interactions of phentermine and sibutramine. Orlistat has a cholesterol-lowering effect not seen with other diet medications. However, the three-times-daily administration and frequent gastrointestinal effects limit its use.

Sibutramine, phentermine, and orlistat have both positive and negative properties. Choosing among the medications will depend on concurrent disease states and medications, ease of administration, and cost.

Index terms: Anorexics; Antidepressants; Contraindications; Costs; Dexfenfluramine hydrochloride; Dosage schedules; Drug interactions; Fenfluramine hydrochloride; Mechanism of action; Obesity; Orlistat; Phentermine; Phenylpropranolamine; Product withdrawal; Sibutramine hydrochloride; Toxicity

Am J Health-Syst Pharm. 2001; 58:1301-8

betes mellitus, dyslipidemia, stroke, gallbladder disease, osteoarthritis, sleep apnea, and breast, prostate, en-

dometrium, and colon cancers.¹⁴ Although the exact relationship between obesity and hypertension is

MIKI L. CAMPBELL, PHARM.D., is Pharmacist, Target Stores, Minneapolis, MN. MONICA L. MATHYS, PHARM.D., is Assistant Professor of Pharmacy Practice, College of Pharmacy, Midwestern University, Glendale, AZ.

Address correspondence to Dr. Mathys at the College of Pharma-

cy, Midwestern University, 19555 North 59th Avenue, Glendale, AZ 85308 (mmathy@arizona.midwestern.edu).

Copyright © 2001, American Society of Health-System Pharmacists, Inc. All rights reserved. 1079-2082/01/0702-1301\$06.00.

not known, estimates from population studies suggest that at least 75% of hypertension is directly associated with obesity.¹⁵ There is substantial evidence in the literature that blood pressure increases with weight gain, decreases with weight loss, and is responsible for the activation of the sympathetic nervous system, which can ultimately lead to changes in renal structure and function.^{8,15} Lipoprotein metabolism is also affected by obesity. Weight gain results in increased levels of triglycerides and low-density-lipoprotein (LDL) cholesterol and decreased levels of high-density-lipoprotein (HDL) cholesterol. Weight loss has the opposite effect on lipoprotein levels.^{8,15} Obesity has similar effects on insulin-receptor sensitivity in type 2 diabetes mellitus. More than 50% of the variance in insulin sensitivity is directly related to obesity.¹⁵ As weight increases, so does insulin resistance; with weight loss comes improved glycemic control.^{8,15-17}

The economic burden of obesity is substantial. A report published in 1994 estimated the cost of medical expenses and loss of income related to obesity in the United States to exceed \$68 billion.¹⁸ In addition, more than \$30 billion each year is spent on diet food, programs, and products to shed unwanted weight.¹⁹

National guidelines

In June 1998, NIH established clinical guidelines for the identification, evaluation, and treatment of obesity.⁸ These guidelines define overweight persons as having a BMI of 25–29.9 kg/m² and obese persons as having a BMI of 30 kg/m² or greater. The guidelines also state that persons 18 years of age or older with a BMI of 25 kg/m² or more are at risk for secondary comorbidities, such as hypertension, type 2 diabetes mellitus, heart disease, and hyperlipidemia.

Three components are examined when assessing a patient for obesity: BMI, waist circumference, and absolute risk status. BMI is an indicator of

relative weight for height and is calculated as weight (in kilograms) divided by height (in meters) squared (nonmetric formula: [weight (in pounds)/height (in inches)²] × 703). The BMI weight classifications are listed in Table 1. Waist circumference is directly related to abdominal fat content. Excessive abdominal fat relative to total body fat has been proven to be an independent predictor of morbidity. A patient's absolute risk status must also be determined. The following three groups include individual risk factors, as put forth by NIH's guidelines:

1. Those with preexisting comorbidities, such as type 2 diabetes mellitus, established coronary heart disease, other atherosclerotic diseases, and sleep apnea. Any patient with one of these diseases is considered at very high risk for complications of the disease and mortality.
2. Those with cardiovascular risk factors, including hypertension (systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg or taking antihypertensive medications), dyslipidemia (LDL cholesterol concentration, ≥160 mg/dL, or HDL cholesterol concentration, <35 mg/dL), impaired fasting glucose concentration (110–125 mg/dL), cigarette smoking, family history of premature heart disease (myocardial infarction or sudden death at ≤55 years of age in father or a brother or ≤65 years of age in mother or a sister), and age (men, ≥45 years, and women, ≥55 years or postmenopausal). Patients with three of the above cardiovascular risk factors may be considered at high absolute risk.
3. Those with other diseases, such as gynecologic abnormalities, osteoarthritis, gallstones, and stress incontinence.

NIH recommends that any patient with a BMI of ≥30 kg/m², a BMI ranging from 25 to 29.9 kg/m² with two or more of the above risk factors, or an excessive waist circumference

Table 1.
Weight Classification Based on Body Mass Index (BMI)⁸

Classification	BMI (kg/m ²)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25.0–29.9
Obesity class	
I	30.0–34.9
II	35.0–39.9
III	≥40.0

(>102 cm for men and >88 cm for women) plus two or more of the above risk factors should attempt to lose weight. The initial goal should be a 10% weight reduction in six months, which can be accomplished with lifestyle changes, such as decreased caloric intake, increased physical activity, and behavior therapy. If lifestyle changes alone are not enough to meet a patient's therapeutic goal, then drug therapy may be indicated. Before prescribing an anti-obesity medication, clinicians should be informed of the different classes of antiobesity drugs currently available, including their pharmacology, adverse effects, contraindications, and any potential drug interactions.

Antiobesity medications

Drugs recently withdrawn. Fenfluramine hydrochloride and its isomer, dexfenfluramine hydrochloride, increased satiety by elevating serum levels of serotonin in the central nervous system (CNS). This was accomplished by two separate mechanisms. Both drugs inhibited the reuptake of serotonin in the CNS and, when metabolized to norfenfluramine, increased the release of serotonin at the receptor sites.²⁰

Fenfluramine was proven to cause a moderate weight loss when used as monotherapy. However, it was also found that, by combining small doses of fenfluramine with small doses of phentermine, the efficacy of the combined therapy was as great as either agent alone, but adverse effects were fewer.²¹

Dexfenfluramine was proven to cause an average weight loss of 10%

in obese patients. Because of its success in clinical trials, FDA approved dexfenfluramine in April 1996.²⁰ With this approval, approximately 85,000 prescriptions were written per week in the United States, and fenfluramine and fenfluramine-phentermine use also increased. Many of these prescriptions were written for patients mildly overweight or for losing a few pounds rather than for true morbid obesity. When a number of trials showed that dexfenfluramine caused a continuous weight loss over one year, the drug was indicated for the long-term treatment of obesity.²²

The widespread use of fenfluramine and dexfenfluramine had been prominent in Europe since the early 1990s.²⁰ During this period of increased use, many case studies of dexfenfluramine-induced pulmonary hypertension were reported throughout Europe. Fenfluramine-induced pulmonary hypertension had been reported as early as 1981.²³ The International Primary Pulmonary Hypertension Study (IPPHS), a case-control study, found that use of anorectics, mainly derivatives of fenfluramine, was associated with a 10-fold increase in the risk of primary pulmonary hypertension compared with control patients.²⁴ Patients taking anorectics for more than three months had a 23-fold increase in risk compared with control patients.

Pulmonary hypertension was not the only serious adverse effect reported with fenfluramine use. Many reports of cardiac valve abnormalities were also blamed on the two drugs. In the summer of 1997, FDA requested a voluntary withdrawal of fenfluramine and dexfenfluramine.²⁵

The pharmacologic action of fenfluramine-containing products is theorized to be the cause of the pulmonary and valvular problems. Not only do fenfluramine and dexfenfluramine inhibit the reuptake of serotonin in the CNS, but their active metabolite, norfenfluramine, increases the release of serotonin by ac-

tivating serotonin receptors. Serotonin is a potent vasoconstrictor and can lead to vessel narrowing in the lungs.²⁰ Furthermore, high serotonin levels are to blame for histological changes in the cardiac valves of patients previously taking fenfluramine-containing products.

Phenylpropanolamine, a synthetic catecholamine, was an active ingredient in nonprescription weight-loss products. Appetite suppression occurred by stimulating the release of norepinephrine and dopamine in the hypothalamic feeding center in the brain.²⁶ Since the late 1970s, many published and FDA reports have linked phenylpropanolamine use to hemorrhagic stroke. Because of the number of these reports, researchers from Yale University, FDA, and manufacturers of phenylpropanolamine joined together to create the Hemorrhagic Stroke Project, a case-control study designed to determine the correlation between phenylpropanolamine use and risk of hemorrhagic stroke.²⁷ The study concluded that an increased risk of hemorrhagic stroke does exist for women who take appetite suppressants containing phenylpropanolamine. Although the risk of hemorrhagic stroke was low among phenylpropanolamine users, FDA requested that drug companies discontinue the marketing of phenylpropanolamine-containing products.²⁸ The request was made because the benefits of phenylpropanolamine did not justify the risk for serious adverse effects.

Current therapies. *Sympathomimetics.* Sympathomimetics suppress appetite by stimulating the release of norepinephrine and dopamine in nerve terminals in the hypothalamic feeding center. Other effects caused by sympathomimetics, such as decreased gastric secretion and increased energy, may also contribute to decreased appetite and weight loss.²⁶ Benzphetamine, diethylpropion, mazindol, phendimetrazine, and phentermine are the sympathomimetics approved for weight reduction in the United

States. However, phentermine is most often prescribed.

Clinical trials have found phentermine to work similarly if given daily or intermittently, with weight loss being 5–15% of initial body weight in 60% of patients.^{29,30} Patients achieve a more significant weight loss when taking phentermine in conjunction with a hypocaloric diet than when using a hypocaloric diet alone.³¹ However, the weight loss seen with phentermine is usually only 0.5 kg more per week than in patients receiving placebo, and tolerance usually develops.²⁶ Since the longest reported trial involving phentermine was 36 weeks,²⁹ the drug is indicated only for short-term treatment of obesity. Phentermine therapy should be limited to patients with a BMI of $>30 \text{ kg/m}^2$, or $>27 \text{ kg/m}^2$ if comorbidities exist.³²

The most commonly reported adverse effects of phentermine are nervousness, dry mouth, constipation, and hypertension. As a result of these adverse effects, phentermine's use is contraindicated in patients with moderate to severe hypertension and in those with cardiovascular disease. Phentermine should also be used cautiously in patients with anxiety disorders and other agitation conditions because of its stimulant effect. The pharmacology and chemical structure of phentermine are closely related to amphetamines. Therefore, phentermine may be physically and psychologically addictive. Patients with a history of drug abuse should not be started on phentermine therapy.

Cardiac valve abnormalities and pulmonary hypertension associated with patients taking phentermine have been reported.³³ However, most of these patients were also taking fenfluramine or dexfenfluramine in combination with phentermine. Although the cardiac and pulmonary adverse effects are thought to be due to the fenfluramine derivatives, researchers cannot totally exclude phentermine as a cause. Therefore, phentermine recipients should be

warned to discontinue therapy immediately if dyspnea, angina, syncope, or decreased exercise tolerance occurs and to contact a physician. Physicians are then advised to perform cardiac and pulmonary evaluations.

Phentermine should not be taken with, or within two weeks of discontinuing, monoamine oxidase inhibitors (MAOIs) because of the risk of marked sympathomimetic effects, specifically hypertensive crisis.²⁶ Tricyclic antidepressants combined with phentermine can lead to increased norepinephrine stimulation, resulting in hypertension and cardiac arrhythmias. It is recommended that patients taking selective serotonin reuptake inhibitors not take phentermine because pulmonary hypertension and cardiac valve abnormalities are associated with combining phentermine and serotonergic drugs. Phentermine may decrease the hypotensive effect of clonidine, guanethidine, and methyldopa and augment the metabolic effect of thyroid hormones.

The usual dosage of phentermine is 8 mg three times daily or 15–37.5 mg once daily.³³ Patients taking 8 mg three times daily should be told to take each dose 30 minutes before meals, with the last dose being taken at least four to six hours before bedtime to prevent insomnia.²⁶ Patients taking the drug once daily should take the dose before breakfast or one to two hours after breakfast.

Sibutramine. Sibutramine hydrochloride inhibits the reuptake of norepinephrine, serotonin, and dopamine in the CNS, with the inhibition of norepinephrine and serotonin being three times greater than that of dopamine. Sibutramine's two active metabolites are also inhibitors of norepinephrine and serotonin reuptake. This increase in norepinephrine and serotonin in the CNS leads to increased satiety, resulting in decreased caloric intake. The results of one study led some researchers to theorize that sibutramine may also increase resting metabolic rate. How-

ever, this finding is not consistent with other study results.²⁶

Clinical trials have shown that sibutramine causes significantly more weight loss than placebo.^{34–38} Weight loss has been observed in patients receiving sibutramine even when patients do not follow lifestyle modifications or a hypocaloric diet. However, patients are more likely to lose 5–10% of initial body weight or reach their goal weight when sibutramine is combined with lifestyle changes and a hypocaloric diet.³⁴ Studies have shown sibutramine to result in a peak weight loss after approximately six months and this weight loss to be maintained for at least one year.^{34–36} Because sibutramine's effects last at least 12 months, the drug is indicated for long-term treatment of obesity.

In one trial, 40% of patients receiving sibutramine lost 5% or more of their baseline body weight, compared with 8–10% of patients taking placebo, at the end of one year of treatment; 13% of patients receiving sibutramine lost 10% or more of their baseline body weight, versus 5% of the population receiving placebo.³⁵ One small trial showed that as many as 86% of patients taking sibutramine plus a very-low-calorie diet lost 5% or more of initial body weight after one year, compared with 55% of patients receiving placebo; 75% of sibutramine recipients had maintained all of their weight loss, compared with 42% in the placebo group.³⁶ Studies have also shown weight loss resulting from sibutramine to have a positive effect on glucose; uric acid; HDL, triglyceride, and LDL levels; and waist circumference.^{34,35,38}

Sibutramine studies found that sibutramine-treated patients had a significant increase in systolic and diastolic blood pressure of approximately 1–3 mm Hg and an increase in heart rate of 4–5 beats/min compared with patients who took placebo.³² Patients with a history of poorly controlled hypertension, coronary artery disease, heart failure, arrhyth-

mias, or stroke should not be started on sibutramine. Patients who are considered safe candidates for sibutramine therapy should have their pulse and blood pressure taken before therapy begins and periodically throughout therapy. Patients who have hypertension or tachycardia may need to decrease their dose or discontinue therapy completely. Other common adverse effects of sibutramine include dry mouth, anorexia, insomnia, and constipation.

Sibutramine has not been shown to cause cardiac valve abnormalities or primary pulmonary hypertension, as was previously observed with fenfluramine and dexfenfluramine. Although sibutramine inhibits serotonin reuptake similarly to the fenfluramines, it does not have the additional action of stimulating the release of serotonin from nerve terminals.²⁶

Sibutramine should not be taken with, or within two weeks of discontinuing, MAOIs because of the risk of increased norepinephrine activity, which can lead to hypertensive crisis, or excess serotonin activity, which can lead to serotonin syndrome. Combined use of selective serotonin reuptake inhibitors and sibutramine may also increase a patient's risk of serotonin syndrome. Other medications known to increase blood pressure (e.g., decongestants) should not be taken concomitantly with sibutramine. Sibutramine is metabolized by cytochrome P-450 isoenzyme 3A4. Metabolism may be inhibited by ketoconazole and erythromycin. However, the clinical significance of these interactions is small.

Sibutramine is indicated for management of obesity and maintenance of weight loss for patients with a baseline BMI of ≥ 30 kg/m², or ≥ 27 kg/m² if other risk factors exist.³² Sibutramine should be used in combination with a reduced-calorie diet. Patients should be started on 10 mg daily in the mornings. The dosage may be increased to 15 mg daily in patients who do not lose more than four pounds within four weeks.

However, clinicians should keep in mind that the patient's blood pressure and pulse should be checked routinely after the change in dosage.

Orlistat. Unlike other antiobesity drugs, orlistat inhibits gastric, carboxylester, lipoprotein, and pancreatic lipase.³² Orlistat forms a covalent bond with the active serine residue site of these lipases, causing them to be inactive. When the lipases become inactive, they cannot hydrolyze dietary fat into absorbable triglycerides. Decreased fat absorption leads to decreased caloric intake, resulting in weight loss. The complete action of orlistat occurs in the gastrointestinal tract, and very little of the drug is absorbed systemically.

In recent years, three large, randomized, double-blind, placebo-controlled trials have been published regarding the efficacy of orlistat.³⁹⁻⁴¹ During the first year of all three trials, patients were given orlistat or placebo and started on hypocaloric diets. During the second year, patients in both treatment and placebo groups were changed to eucaloric diets in order to maintain the weight loss. All three trials found a significant decrease in body weight in the orlistat group (an average weight loss of 9%) compared with the placebo group (5%) at the end of year 1. In addition, all trials found significantly less weight gain during the weight maintenance period.

After one year, 30–65% of patients taking orlistat lost 5% or more of their baseline body weight, versus 30–43% of the placebo group. The percentage of patients losing 10% or more of their baseline body weight ranged from 28% to 38% in the orlistat group and from 11% to 24% in the placebo group. After year 2, 18–34% of patients taking orlistat maintained their ≥10% weight loss, compared with 6–17.5% of placebo recipients.

In addition to weight loss, these trials found a reduction in risk factors associated with obesity, such as hypertension, hyperglycemia, hypercholesterolemia, and excessive waist

circumference. Two studies observed significant decreases in insulin levels in orlistat-treated patients over two years,^{40,41} while the third found decreases in both fasting glucose levels and insulin levels at two years.³⁹ A study by Hollander et al.¹⁷ investigated the effect of orlistat combined with a mild hypocaloric diet on type 2 diabetes mellitus. As in previous trials, significantly more weight loss occurred in the orlistat group than in the placebo group. In addition, the diabetic patients taking orlistat for one year had significantly lower fasting glucose levels and hemoglobin A_{1c} levels than the placebo group. Fasting insulin levels were not significantly different between the two groups. All patients randomized in this trial were taking a second-generation sulfonylurea (glyburide or glipizide). A decrease in sulfonylurea dosage occurred in 43% of patients taking orlistat, versus 28% of the placebo group.

In all three trials, there was a significant decrease in total-cholesterol and LDL levels in the orlistat groups versus placebo.³⁹⁻⁴¹ The improvement in total and LDL cholesterol was considered to be independent of weight loss. It is believed that orlistat's ability to reduce lipid absorption decreases the amount of dietary lipid and fatty acids delivered to the liver, resulting in upregulation of hepatic LDL-cholesterol receptors.⁴² Unlike other antiobesity medications, orlistat prescriptions are covered by Medicaid with prior approval because the states recognize it as a drug that can produce serum cholesterol reductions not related to weight loss.⁴³

Orlistat is not systemically absorbed; therefore, it does not cause the same adverse effects as other antiobesity drugs. Gastrointestinal symptoms are the most common because of increased fat excretion.³² Adverse effects, such as abdominal pain, oily spotting, fecal urgency, flatulence with discharge, fatty stools, fecal incontinence, and increased defeca-

tion, are experienced by 95% of orlistat users. The majority of these patients no longer have adverse gastrointestinal effects after four weeks of use, but a small percentage do continue to have adverse effects for six months or longer. Patients can decrease gastrointestinal symptoms by complying with a low-fat diet (<30% of total daily calories). Although orlistat is contraindicated in patients with cholestasis, to date it has not been proven to cause gallstone formation. Its use is also contraindicated in patients with malabsorption syndrome. Some patients taking orlistat have had increases in urinary oxalate levels. Therefore, orlistat should be used cautiously in patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis.

FDA approval of orlistat was first delayed when Phase III studies and follow-up data indicated an increased frequency of breast cancer in orlistat-treated patients.^{38,42} Eleven patients taking orlistat were found to have breast cancer during or after completion of the study, compared with three patients taking placebo. After these results were reviewed by an independent panel, it was determined that nine of these cases existed before the trial began. The final conclusion was that 3 orlistat-treated patients (0.4%) and 2 placebo-treated patients (0.35%) possibly developed breast cancer after treatment was started.

Absorption of lipid-soluble vitamins (A, D, E, and K) and beta carotene may decrease during orlistat therapy.⁴⁴ Therefore, patients should be encouraged to take a multivitamin daily while taking orlistat. The multivitamin should be taken two hours before or after the orlistat dose. Warfarin pharmacokinetics appear to be unaltered when warfarin is taken concomitantly with orlistat.⁴⁵ However, because orlistat decreases the absorption of vitamin K, warfarin's anticoagulant effect may increase over time.⁴² Because dietary fat is known to increase cyclosporine ab-

sorption, the opposite would be expected to occur with a decrease in dietary fat resulting from orlistat therapy. Although drug interaction studies involving cyclosporine and orlistat have not been published, six cases of patients with subtherapeutic cyclosporine concentrations thought to be caused by orlistat therapy have been reported.⁴⁶

One small study showed that orlistat used concomitantly with pravastatin increases the lipid-lowering effect of pravastatin.³² A modest increase in serum pravastatin levels does occur when pravastatin is taken with orlistat. However, the additive lipid-lowering effect is thought to occur because of orlistat's mechanism of action rather than an alteration in pravastatin pharmacokinetics. Small studies have shown that orlistat does not alter the pharmacokinetics of digoxin, glyburide, extended-release nifedipine, oral contraceptives, and phenytoin.^{32,47,48}

When combined with a reduced-calorie diet, orlistat is indicated for the long-term treatment of obesity for patients with a BMI of ≥ 30 or ≥ 27 kg/m² if other comorbidities exist.^{26,32}

Orlistat is also indicated for reducing the risk of weight regain after weight loss. It is recommended that patients take 120 mg three times daily with, or up to one hour after, each meal containing fat. If a meal is missed or contains no fat, the dose can be skipped. Patients should be counseled about the importance of taking a multivitamin daily, which is absorbed best if taken two hours before or after an orlistat dose. Patients should also be reminded to comply with a low-fat diet to decrease the adverse effects.

Prescribing considerations

Many weight-loss trials have shown that even a modest weight reduction decreases cardiovascular risk factors and obesity comorbidities.^{16,39-41,49} Obesity management guidelines recommend setting an initial goal of 5–10% weight loss and maintaining that weight loss rather than trying to reach one's ideal body weight.⁸ If lifestyle changes, such as diet, exercise, and behavior modification, fail to decrease a patient's weight by 5–10% within six months, the addition of a pharmacologic agent may be an effective choice for

obese patients, especially those with such risk factors as hyperlipidemia, hypertension, and diabetes. Although drug therapy results in only a 5–15% weight loss in most patients, this small weight loss can improve a patient's health significantly.¹⁹

If drug therapy is being considered for a particular patient, clinicians must evaluate concurrent disease states and medication use before making a decision. For example, if an obese patient also has a history of depression and is taking a selective serotonin-reuptake inhibitor, then sibutramine should not be the agent of choice. Also, sibutramine should not be prescribed for patients with cardiovascular disease because of its effect on blood pressure. Likewise, if an obese patient has a history of nephrolithiasis, then orlistat would not be the drug of choice. Patients who cannot comply with a low-fat diet should not be started on orlistat because of the risk of gastrointestinal adverse effects. The adverse effects and contraindications of antiobesity drugs are listed in Table 2.

Patients choosing drug therapy must keep in mind that obesity is a

Table 2.
Characteristics of Antiobesity Medications

Characteristic	Phentermine	Sibutramine	Orlistat
Indicated for long-term treatment	No	Yes	Yes
Adverse effects	Nervousness, dry mouth, constipation, hypertension, tachycardia	Hypertension, tachycardia, dry mouth, anorexia, insomnia, constipation	Abdominal pain, oily spotting, fecal urgency, flatulence with discharge, fatty stools, fecal incontinence, increased defecation, increased urinary oxalate
Contraindications ^a	Severe hypertension, coronary artery disease, heart failure, arrhythmias, stroke, or history of drug abuse. Use with caution in patients with anxiety disorders.	Severe hypertension or poorly controlled hypertension, heart failure, coronary artery disease, arrhythmias, or stroke	Malabsorption syndrome and cholestasis. Use with caution in patients with history of nephrolithiasis.
Drug–drug interactions	Monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin-reuptake inhibitors, drugs that increase blood pressure or heart rate, clonidine, guanethidine, methyl dopa, thyroid hormones	Monoamine oxidase inhibitors, selective serotonin-reuptake inhibitors, drugs that increase blood pressure or heart rate, ketoconazole ^b , erythromycin ^b	Fat-soluble vitamins, beta-carotene, and possibly cyclosporine

Continued on next page

Table 2 (continued)

Characteristic	Phentermine	Sibutramine	Orlistat
Patient instructions	Take 8 mg t.i.d. 30 min before meals. Last dose should be taken 4–6 hr before bedtime. Take once-daily formulations before breakfast or 1–2 hr after breakfast.	Take once daily in the mornings. Have blood pressure and pulse checked regularly.	Take one capsule t.i.d. with each meal. If meal is missed or contains no fat, then dose can be skipped. Take a multivitamin daily 2 hr before or after dose. Comply with a low-fat diet.
Cost	\$1.30/day (based on 37.5 mg every day)	\$2.96/day (based on 10 mg every day)	\$3.93/day (based on 120 mg t.i.d.)

^aNone of these medications should be used in patients with a history of anorexia nervosa or bulimia.

^bInteractions do not appear to be clinically significant.

chronic disease. Therefore, drug therapy may need to be continued long-term to keep the patient from regaining weight.⁵⁰ For clinically obese patients, phentermine would probably not be an appropriate first-line agent, since it has been proven to work for only a short period and because most patients develop tolerance to its therapeutic effects. Because sibutramine and orlistat have been studied for their long-term efficacy and the therapeutic effects of these two drugs appear to last at least one year, these two drugs should be considered as first-line drug therapy when treating obesity. Choosing between these drugs will depend on the patient's concurrent disease states and medications, ease of administration, and cost.

Conclusion

Sibutramine, phentermine, and orlistat have both positive and negative properties. Choosing among the medications will depend on the patient's concurrent disease states and medications, ease of administration, and cost.

References

- World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation on obesity. Geneva, Switzerland: 1998.
- Bray GA. Obesity: a time bomb to be defused. *Lancet*. 1998; 352:160-1.
- Foreyt J, Goodrick K. The ultimate triumph of obesity. *Lancet*. 1995; 346:34-5.
- Nutrition and Physical Activity Task Force. London: Her Majesty's Stationery Office; 1995.
- Prescott-Clark P, Primates P. Health survey for England 1995. London: Her Majesty's Stationery Office; 1997.
- Kuskowa-Wolk A, Bergstrom R. Trends in body mass index and prevalence of obesity in Swedish women 1980-89. *J Epidemiol Community Health*. 1993; 47:195-9.
- Seidell JC. Time trends in obesity: an epidemiological perspective. *Horm Metab Res*. 1997; 29:155-8.
- Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. *Arch Intern Med*. 1998; 158:1855-67.
- Kuczmarski RJ, Flegal KM, Campbell SM et al. Increasing prevalence of overweight among US adults. *JAMA*. 1994; 272:205-11.
- Flegal KM, Carroll MD, Kuczmarski RJ et al. Overweight and obesity in the United States: prevalence and trends, 1960-1994. *Int J Obes Relat Metab Disord*. 1998; 22:38-47.
- Manson JE, Willett WC, Stampfer MJ et al. Body weight and mortality among women. *N Engl J Med*. 1995; 333:677-85.
- McGinnis JM, Foege WH. Actual causes of death in the United States. *JAMA*. 1993; 270:2207-12.
- Eckel RH, Krauss RM, for the American Heart Association Nutrition Committee. American Heart Association call to action: obesity as a major risk factor for coronary heart disease. *Circulation*. 1998; 97:2099-100.
- Pi-Sunyer FX. Medical hazards of obesity. *Ann Intern Med*. 1993; 119:655-60.
- Krauss RM, Winston M. Obesity: impact on cardiovascular disease. *Circulation*. 1998; 98:1472-6.
- Heymsfield SB, Segal KR, Hauptman J et al. Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch Intern Med*. 2000; 160:1321-6.
- Hollander PA, Elbein SC, Hirsch IB et al. Role of orlistat in the treatment of obese patients with type 2 diabetes: a 1-year randomized double-blind study. *Diabetes Care*. 1998; 21:1288-94.
- Wolf AM, Colditz GA. The cost of obesity: the U.S. perspective. *Pharmacoeconomics*. 1994; 5(suppl 1):34-7.
- National Task Force on the Prevention and Treatment of Obesity. Long-term pharmacotherapy in the management of obesity. *JAMA*. 1996; 276:1907-15.
- Langleben D. Relearning the lessons of history: anorexia and pulmonary hypertension. *Chest*. 1998; 114:55S-7S.
- Weintraub M, Hasday JD, Mushlin AI et al. A double-blind clinical trial in weight control: use of fenfluramine and phentermine alone and in combination. *Arch Intern Med*. 1984; 144:1143-8.
- Guy-Grand B, Apfelbaum M, Crepaldi G et al. International trial of long-term dexfenfluramine in obesity. *Lancet*. 1989; 2:1142-5.
- Douglas JG, Munro JF, Kitchin AH et al. Pulmonary hypertension and fenfluramine. *Br Med J*. 1981; 283:881-3.
- Abenheim L, Moride Y, Brenot F et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. *N Engl J Med*. 1996; 335:609-16.
- Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: U.S. Department of Health and Human Services interim public health recommendations, November 1997. *MMWR Morb Mortal Wkly Rep*. 1997; 46:1061-6.
- USP DI—volume I: drug information for the health care professional. 21st ed. Englewood, CO: Micromedex; 2001.
- Kernan WN, Viscoli CM, Brass LM et al. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med*. 2000; 343:1826-32.
- Food and Drug Administration. Washington, DC: U.S. Department of Health and Human Services 2000 Nov 6. (Talk Paper T00-58.)
- Munro JF, MacCuish AC, Wilson EM et al. Comparison of continuous and intermittent anorectic therapy in obesity. *Br Med J*. 1968; 1:352-4.
- Truant AP, Olon LP, Cobb S. Phentermine resin as an adjunct in medical weight reduction: a controlled, randomized, double-blind prospective study. *Curr Ther Res Clin Exp*. 1972; 14:726-38.
- Langlois KJ, Forbes JA, Bell GW et al. A

- double-blind clinical evaluation of the safety and efficacy of phentermine hydrochloride (Fastin) in the treatment of exogenous obesity. *Curr Ther Res Clin Exp*. 1974; 16:289-96.
32. Schrefer J, ed. Mosby GenRx: a comprehensive reference for generic and brand prescription drugs. 11th ed. St. Louis: Mosby; 2001.
 33. McEvoy GK, ed. AHFS drug information. Bethesda, MD: American Society of Health-System Pharmacists; 2000.
 34. Wadden TA, Berkowitz RI, Sarwer DB et al. Benefits of lifestyle modification in the pharmacologic treatment of obesity. *Arch Intern Med*. 2001; 161:218-27.
 35. McMahon FG, Fujioka K, Shingh BN et al. Efficacy and safety of sibutramine in obese white and African American patients with hypertension: a 1-year, double-blind, placebo-controlled, multicenter trial. *Arch Intern Med*. 2000; 160:2185-91.
 36. Apfelbaum M, Vague P, Ziegler O et al. Long-term maintenance of weight loss after a very-low-calorie diet: a randomized blinded trial of the efficacy and tolerability of sibutramine. *Am J Med*. 1999; 106:179-84.
 37. Hanotin C, Thomas F, Jones SP et al. Efficacy and tolerability of sibutramine in obese patients: a dose-ranging study. *Int J Obes Relat Metab Disord*. 1998; 22:32-8.
 38. McNeely W, Goa KL. Sibutramine: a review of its contribution to the management of obesity. *Drugs*. 1998; 56:1093-124.
 39. European Multicentre Orlistat Study Group. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. *Lancet*. 1998; 352:167-72.
 40. Davison MH, Hauptman J, DiGirolamo M et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA*. 1999; 281:235-42.
 41. Hauptman J, Lucas C, Boldrin MN et al. Orlistat in the long-term treatment of obesity in primary care settings. *Arch Fam Med*. 2000; 9:160-7.
 42. Cada DJ, Baker DE, Levien T. Orlistat. *Hosp Pharm*. 1999; 34:1195-213.
 43. National Association of Chain Drug Stores. Fast facts—Medicaid and Xenical. *Chain Pharm Pract Memo*. 2000; 4(6):4.
 44. Collazo-Clavell ML. Safe and effective management of the obese patient. *Mayo Clin Proc*. 1999; 74:1255-60.
 45. Zhi J, Melia AT, Guerciolini R et al. The effect of orlistat on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers. *J Clin Pharmacol*. 1996; 36:659-66.
 46. Colman E, Fossler M. Reduction in blood cyclosporine concentrations by orlistat. *N Engl J Med*. 2000; 342:1141-2. Letter.
 47. Melia AT, Mulligan TE, Zhi J. The effect of orlistat on the pharmacokinetics of phenytoin in healthy volunteers. *J Clin Pharmacol*. 1996; 36:654-8.
 48. Melia AT, Mulligan TE, Zhi J. Lack of effect of orlistat on the bioavailability of a single dose of nifedipine extended-release tablets in healthy volunteers. *J Clin Pharmacol*. 1996; 36:352-5.
 49. Stevens VJ, Obarzanek E, Cook NR et al. Long-term weight loss and changes in blood pressure: results of the trials of hypertension prevention, phase II. *Ann Intern Med*. 2001; 134:1-11.
 50. Atkinson RL. A 33-year-old woman with morbid obesity. *JAMA*. 2000; 283:3236-43.