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Obesity: An Update

Editorial Introduction

In this issue of JPSW, Deb Dunham and Stacy Savaske present an overview of new medical therapies for the management of obesity. Since the withdrawal of fenfluramine and dexfenfluramine from the market, two new agents have been marketed in this area. While evidence supporting the long-term safety and effectiveness of these new agents are certainly needed, we are faced with health policy question that may not wait for the results of additional trials. From a policy perspective, we have on one hand strong evidence that obese patients who lose weight have better overall health including a reduced risk of heart disease, stroke, and a variety of other conditions. Avoiding these outcomes by treating obesity may result in lower health care resource consumption later in life, and it is possible that the expense associated with obesity medications will produce a positive net cost-offset in certain patient groups. On the other hand, the policy debate should focus on the question of whether obesity is a condition that is best managed with medications. Clearly, exercise and diet modification are two critically important components of weight management which are required for sustained weight loss, regardless of medication use. If patients are unwilling to behave differently with respect to diet and physical activity, the incidence of obesity-related disorders will likely **not be** reduced, and no cost off-set will be realized.

Payers making decisions regarding coverage for obesity

treatments consider both of these perspectives and also consider the relatively low likelihood that obese patients will suffer expensive health events while covered by their policies. Payers generally choose not to cover obesity drugs for fear of negative patient selection that might occur if they become the only payer in a given community who chooses to cover them (obese patients are likely to self-select the one payer in a community that covers obesity medications). Along with obesity, patients often bring other very expensive comorbid conditions, including diabetes, hyperlipidemia, and musculoskeletal disorders to their insurance carrier. In the final analysis, the risk of negative patient selection is considered higher than the risk of obesity-related complications that could be avoided through weight loss, and the decision to not cover the drugs is made. A community standard that calls for universal coverage of these agents will be necessary before obesity medications will be routinely covered by individual third-party payers.

It is unclear how we will resolve this complex health policy debate. As we reach our decision, however, pharmacists should remain abreast of the obesity literature (particularly with respect to long-term safety and effectiveness trials), and bear in mind that it is extremely unlikely that a medication will ever eliminate the need for patients to make lifestyle changes to manage their weight.

—Lee Vermeulen

Obesity is a major public health problem, affecting approximately 97 million American adults.^{1,2} It is second only to smoking as a preventable cause of death in the United States. Obesity increases the risk of illness from hypertension, lipid disorders, coronary disease, stroke, Type 2 diabetes mellitus, gallbladder disease, osteoarthritis, sleep apnea, respiratory problems, and post-surgical complications. The prevalence has greatly increased over the last four decades. In 1960 the percentage of overweight and obese adults in the United States was 43.3%; by 1991 this number had increased to 54.9%.³ The percentage of obese Americans jumped from 12.0% in 1991 to 17.9% in 1998.⁴ The health and economic burdens of obesity are immense. Obesity is a major risk factor for several diseases including type 2 diabetes mellitus, coronary heart disease, dyslipidemias, stroke, and hypertension. The risk of hypertension for moderately obese

men is increased 2-fold compared to non-obese men. The risk of Diabetes is increased 3-fold in obese men compared to non-obese men. Risks for coronary heart disease and stroke increase from 34.9% to 41.8% and 13.9% to 16.2%, respectively.⁵ Obesity is also a risk factor for excess mortality. The number of obesity-related deaths in the US is estimated to be 280,000 per year.⁶ Each year more than \$30 billion are spent on diet foods, prescription diet aids, and weight loss programs.⁷ Excess medical expenses and lost income account for another \$70 billion annually.⁸

Most obesity is primary; secondary obesity accounts for

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only a small percentage of cases.² Metabolic disorders associated with obesity include Prader Willi syndrome, hypothyroidism, and Cushing's syndrome. Iatrogenic causes include glucocorticoids, thiazolidinediones, valproic acid, tricyclic antidepressants, oral contraceptives, and anticonvulsants. For the majority of patients, their weight results from a complex interplay of genetics, environmental, societal, and behavioral factors.^{2,9} Genetics are estimated to contribute up to 70% of the variance in body mass index (BMI). Support for a genetic component comes from animal research showing defects in a specific gene (the obesity or "ob" gene) that results in obese mice and from studies in monozygous twins reared apart demonstrating similarities in weight and body fat distribution.^{10, 11} Environmental factors include a sedentary lifestyle, an abundant food supply, increased reliance on fast foods, and increased consumption of high-fat foods.^{2,9}

For many individuals, being overweight is not a curable disease. Each year an estimated 15% to 35% of the population resolve to lose weight; less than 5% of those patients actually succeed.¹² Lifestyle changes and pharmacological treatment have been shown to decrease weight, but once treatment is stopped, the weight is often regained.^{1,2,9} The last few years have seen a change in our view of the appropriate treatment of obesity. Where we once considered short-term or intermittent treatment appropriate, clinicians are coming to view obesity as a chronic condition that requires chronic therapy much like hypertension or diabetes.^{13,14} Additionally, two new drugs have been approved for the long-term management of obesity, and a national set of guidelines addressing weight management by the primary care practitioner has been created.

Treatment Guidelines

In 1998, the National Institutes of Health National Heart, Lung, and Blood Institute published Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.¹⁵ This document provides evidence-based recommendations on the management of overweight and obesity for primary care practitioners.

Assessment

Management of the overweight/obese patient begins with assessment of the degree of excess weight, evaluation of weight distribution, determination of additional risk factors, and evaluation of the patient's motivation and resources for weight loss. Body mass index is the recommended method for determining the amount of excess fat because it is simple, practical, and inexpensive. Body mass index is determined by dividing the weight in kilograms by the height in meters squared ($BMI = \text{weight in kg} / \text{height in m}^2$). In patients with either excess muscle mass, such as body builders, or those with diminished muscle mass, like the elderly, BMI may be inaccurate. Once the baseline BMI has been determined, progress can

Table 1. Obesity Classifications

	Obesity Class	BMI (kg/m ²)
Underweight		<18.5
Normal		18.5-24.9
Overweight		25-29.9
Obese	I	30-34.9
Moderate Obesity	II	35-39.9
Extreme Obesity	III	≥40

be monitored by weight changes alone. The degree of obesity can then be classified based on BMI (see Table 1 above)

Additionally, the patient's fat distribution should be determined. Fat distribution is typically either gluteofemoral (gynecoid or "pear-shaped") or central (android or "apple-shaped"). Central obesity is associated with an increased risk for diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, and death independent of the patient's BMI. The NHBLI guidelines recommend using waist circumference to measure fat distribution. The waist circumference cutoff points for excess abdominal fat are 102 cm (40 inches) and 88 cm (35 inches) in men and women, respectively. These numbers are valid only in patients with a BMI of no more than 35 kg/m²; at greater BMIs these numbers lose their predictive value.

The extent and nature of comorbid conditions should also be evaluated. Patients with established coronary heart disease, atherosclerotic disease, type 2 diabetes, or sleep apnea are at very high risk for disease complications and mortality. The presence of these conditions affects the decision to treat and should be treated simultaneously with any weight loss initiatives.

Finally, the patient's motivation and available resources should be considered. Since the weight loss requires substantial effort by the patient, no program will succeed unless the patient is ready and able to commit to the necessary efforts. An understanding of the patient's past history of weight loss attempts can be useful in determining what future treatment approaches might succeed. Other things to consider include the patient's support system and understanding of their disease—does he or she have friends and family who will support or sabotage a weight-loss attempt? Does the patient understand the health risks associated with their obesity? Do they understand the goals of a weight-loss program and realize that a cosmetic level of thinness is unlikely to be achieved? Are they willing to make the lifestyle changes necessary for successful weight loss? Do they have the time and resources to devote to this endeavor? For patients who are not motivated to lose weight, it is still necessary to treat their comorbid conditions.

Treatment

The decision to treat obesity factors in the patient's BMI,

waist circumference, and comorbidities. Treatment is recommended in all patients who are obese (BMI ≥ 30 kg/m²) and in patients who are overweight (BMI between 25 and 29.9 kg/m²) or with a large waist circumference and who have two or more risk factors (see Table 2 below).

The initial goal of treatment is to reduce body weight by approximately 10% of baseline. The guideline suggests a period of 6 months as a reasonable timeline. If the patient loses the desired pounds, further weight loss can be attempted if needed. Initial treatment consists of a low-calorie diet, increased physical activity, and behavioral modifications. If the patient does not lose an adequate amount of weight after 6 months, pharmacotherapy may be considered. For severely obese patients (BMI ≥ 40 kg/m²), surgery may be an option. The complete text of the guideline is available at: http://www.nhlbi.nih.gov./nhlbi/cario/obes/prof/guidelns/ob_home.htm.

Pharmacotherapy

Drugs available for the treatment of obesity work by two possible mechanisms: decreasing food intake and reducing nutrient absorption. Orlistat (Xenical[®]) is the only anti-obesity agent which works by decreasing nutrient absorption; all of the other agents focus on suppressing food intake. Table 3 provides a list of weight loss drugs approved for use in the US.

Anorexiant – First Generation

The anorexiant work by either decreasing appetite or increasing satiety.¹⁶ These agents affect neurotransmitter activity in the central nervous system, particularly the hypothalamus. Appetite is mediated by norepinephrine, while serotonin affects satiety. Elevations of norepinephrine levels in the lateral lobe of the hypothalamus suppress appetite, decreasing a person's desire for food. The noradrenergic agents include the amphetamines, phentermine, diethylpropion, phendimetrazine, mazindol, phenylpropanolamine, and ephedrine. The average weight loss seen with the noradrenergic appetite suppressants is 5% to 10%. These drugs are central nervous system stimulants. Common side effects include ner-

vousness, anxiety, insomnia, headache, tremor, talkativeness, hypertension, tachycardia, palpitations, pallor or flushing, nausea, vomiting, diarrhea, dry mouth, and anorexia. With the exception of phenylpropanolamine, each of these drugs is a controlled substances due to their high potential for abuse. The amphetamines in particular can lead to substance abuse and addiction problems.

The serotonergic drugs increase serotonin levels in the hypothalamic ventromedial nucleus, decreasing the amount of food absorbed and increasing the interval between feeding.¹⁷ Fenfluramine, a racemic mixture, was the original serotonergic agent for weight loss in the US. In 1996, the Food and Drug Administration approved dexfenfluramine (Redux[®]), the D-isomer of fenfluramine. Dexfenfluramine quickly became one of the most prescribed drugs in the US. These agents increase serotonin levels by inhibiting post-synaptic reuptake and stimulating the release of serotonin.^{18,19} Fenfluramine and dexfenfluramine were voluntarily removed from the US market because of concerns regarding valvular defects and pulmonary hypertension.

Because serotonergic and noradrenergic anorexiant affect different sites of the food drive (i.e., ‘hunger or appetite’ vs ‘satiety or fullness’), combining these drugs has an appealing logic. The combination of a serotonergic and noradrenergic agent would be expected to affect both appetite and satiety. In 1992, Weintraub et al published the results of a long-term study that found the combination of the serotonergic drug, fenfluramine with the noradrenergic phentermine successfully maintained weight loss for up to 3 years.²⁰ The combination, commonly referred to as “fen/phen” rapidly became very popular. The withdrawal of fenfluramine meant it was not possible to get combined noradrenergic/serotonergic with approved anorexiant.

Sibutramine

With the approval of sibutramine (Meridia[®]), there is now an appetite suppressant with combined noradrenergic/serotonergic activity. Originally investigated as an antidepressant,

Table 2. Treatment Recommendations Based on BMI, Waist Circumference, and Risk Factors

BMI kg/m ²	Excess Abdominal Fat? (Waist Circumference Female: > 88 cm Male: > 102 cm)	Risk Factors Present? (Diabetes, hypertension, dyslipidemia, coronary heart disease, sleep apnea)	Treat?
≥ 25	No	No	No
≥ 25	No	Yes	Yes
≤ 25	Yes	No	No
≤ 25	Yes	Yes	Yes
≥ 30	No	No	Yes

sibutramine was approved by the FDA for both weight loss and maintenance of weight loss.²¹ In clinical trials sibutramine produced a dose-related weight loss.^{22,23}

Most of the clinical effects of sibutramine are attributed to two active metabolites, M1 and M2.²⁴ Sibutramine and its metabolites suppress appetite and induce a sense of fullness by inhibition of norepinephrine and serotonin reuptake inhibition. Unlike fenfluramine and dexfenfluramine, sibutramine does not stimulate release of these neurotransmitters.²¹ Sibutramine has limited effect on dopamine activity so it is unlikely to be a substance of abuse. This observation has been confirmed in studies in rats and in human volunteers with a history of substance abuse.²⁴ Even though sibutramine appears to have limited abuse potential, it has been classified as a schedule IV substance by the Food and Drug Administration.

Sibutramine is rapidly absorbed from the gastrointestinal tract after oral administration.^{21,24,25} The time to peak plasma concentrations is 1.2 hours. The oral bioavailability is 77%. Following oral administration, sibutramine undergoes extensive first-pass metabolism by CYP450 3A4 to two active metabolites.²⁴ Peak plasma levels of the metabolites, M1 and M2, are reached in 3 and 4 hours, respectively. Food decreases the time to peak levels, but does not change the area under the curve. As a result, sibutramine may be taken with or without meals.²⁵ The metabolites have relatively long half-lives (14 and 16 hours, respectively) which allow for once-a-day dosing. Sibutramine, M1, and M2 are highly bound to plasma proteins (97%, 94%, and 94%, respectively).²¹ The active metabolites undergo further metabolism to inactive metabolites, which are then excreted in the urine and feces.

Weintraub et al tested the effect of sibutramine 5 mg and 20 mg, and placebo on weight loss.²² The study was conducted over an 12-week period that included Thanksgiving, Christmas and New Year's. Medication was added to caloric restriction, behavior modification, and exercise after a 4-week placebo run-in period. The 55 patients ranged from 130% to 180% of ideal body weight. There was a significant dose response relationship. The weight lost was 1.4 ± 2.1 kg, 2.9 ± 2.3 kg, and 5.0 ± 2.7 kg for placebo, sibutramine 5 mg, and sibutramine 20 mg, respectively. Sibutramine was superior to placebo at both doses ($p < 0.05$ for sibutramine 5 mg and 20 mg vs placebo) and sibutramine 20 mg was superior to sibutramine 5 mg ($p < 0.005$). Sleep disturbances and irritability were the most frequently reported adverse effects.

In a multi-center dose ranging study, 236 patients with a BMI of 27 to 40 kg/m² were randomized to daily doses of sibutramine 5 mg, sibutramine 10 mg, sibutramine 15 mg, or placebo.²⁶ All patients also received advice on diet and behavior modification. The mean weight loss at the end of the 12-week study was 2.4 ± 0.5 kg, 5.1 ± 0.5 kg, 4.9 ± 0.5 kg, and 1.4 ± 0.5 kg for sibutramine 5 mg, 10 mg, 15 mg, and placebo,

respectively. The changes in weight were similar for sibutramine 5 mg and placebo, while the differences between placebo and sibutramine 10 mg and 15 mg were statistically significant ($p < 0.01$). The percentage of patients losing more than 5% of their baseline body weight was significantly greater for sibutramine 10 mg (49%) and 15 mg (55%) than placebo (19%), ($p < 0.001$). Adverse effects and withdrawal rates were similar across the four groups.

In a dose-ranging study, 173 patients were randomized to treatment with placebo or sibutramine 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, or 30 mg per day in a 24-week double-blind trial.²⁷ The mean BMI at baseline was 34 kg/m². There was a dose-dependent reduction in body weight ranging from 0.9 kg in the placebo group to 6.5 kg in the 30 mg group. The amount of weight lost with doses of 10 mg, 15 mg, 20 mg, and 30 mg were significantly greater than placebo ($p < 0.01$ at all levels).

In a multi-center expansion of the previous study, 1047 patients were randomized to 24 weeks of treatment with placebo or sibutramine 1 mg, 5 mg, 10 mg, 15 mg, 20 mg or 30 mg.²³ A 2-week placebo run-in period was included during which patients began a regimen of diet, exercise, and behavior modification. Weight loss was dose-related and statistically significant compared to placebo at all sibutramine doses. At 24 weeks, the percent weight loss from baseline for the 683 patients completing the study was: placebo, 1.2%; 1 mg, 2.7%; 5 mg, 3.9%; 10 mg, 6.1%; 15 mg, 7.4%; 20 mg, 8.8%; and 30 mg, 9.4% ($p < 0.05$ vs placebo at all doses). Patients who lost weight also demonstrated increases in serum high density lipoprotein cholesterol and decreases in serum triglycerides, total cholesterol, low density lipoprotein cholesterol, and uric acid. The most frequently reported adverse effects were dry mouth, insomnia, and anorexia. Slight increases in heart rate and blood pressure were observed in a few individuals.

The effects of sibutramine on maintaining weight loss following a very low calorie diet (VLCD; 220-800 kcal/day) were evaluated in a 12-month, double-blind, placebo-controlled trial.²⁸ Eligible patients had a baseline BMI ≥ 30 kg/m² and completed a 4-week VLCD. Only 159 of the original 205 patients completed the diet phase. These patients were randomized to receive treatment with sibutramine 10 mg per day or placebo. Patients randomized to the sibutramine group lost an average of 7.7 kg after 4 weeks on the VLCD compared to 7.4 kg in the placebo group. In an intent-to-treat analysis, the mean weight loss at the end of the study was 5.2 ± 7.5 kg for patients in the sibutramine group and 0 ± 0.5 kg in the placebo group ($p < 0.04$). At 12 months, 75% of subjects in the sibutramine group maintained 100% of the weight loss achieved with a very-low-calorie diet, compared with 42% in the placebo group ($p < 0.001$). When compared with their weight prior to the VLCD, 86% of patients in the sibutramine group had lost at least 5% of their weight, compared with only 55%

of those in the placebo group ($p < 0.001$). A weight loss of at least 10% was reported in 54% and 23% of the sibutramine and placebo patients, respectively ($p < 0.001$).

Jones et al examined the effects of long-term treatment with sibutramine in 485 obese patients with a mean baseline BMI of 33 kg/m².²⁹ Patients were randomized to receive placebo, sibutramine 10 mg, or sibutramine 15 mg. At 12 months, the mean amount of weight lost was 1.8 kg, 4.8 kg, and 6.1 kg in the placebo, sibutramine 10 mg, and sibutramine 15 mg groups, respectively ($p < 0.01$ vs placebo). Weight loss plateaued at 2 months in the placebo patients, but continued until 5 to 6 months among the sibutramine recipients. A weight loss of at least 5% from baseline was reported in 29% with placebo, 56% with sibutramine 10 mg, and 65% with sibutramine 15 mg. The percent of patients who lost at least 10% of their baseline weight were 8%, 30%, and 39%.

Sibutramine and dexfenfluramine were compared in a 12-week, multicenter, double-blind study.³⁰ A total of 226 patients with a baseline BMI of at least 27 kg/m² were randomized to treatment with sibutramine 10 mg daily or dexfenfluramine 15 mg twice daily. At the end of 12 weeks the mean weight loss was 4.5±0.4 kg in the sibutramine group and 3.2±0.3 kg in the dexfenfluramine group ($p < 0.05$). Heart rate increased significantly in sibutramine-treated patients (3.6 beats per minute), compared to a decrease in the dexfenfluramine-treated patients (-0.9 beats per minute). The rates of other adverse effects were similar between the two groups.

The most frequently reported adverse effects associated with sibutramine use are headache (30% vs 18.6%, sibutramine vs placebo), dry mouth (17.2% vs 4.2%), anorexia (13.0% vs 3.5%), constipation (11.5% vs 6.0%), and insomnia (10.7% vs 4.5%).^{21,24,25} Paradoxically, increased appetite was reported by 8.7% of patients treated with sibutramine in clinical trials.²⁵ Hypertension and tachycardia may present a problem for some patients. According to the manufacturer, mean increases in heart rate of 4 to 5 beats per minute and blood pressure of 1 to 3 mmHg have been seen with sibutramine use. In one subset of patients, the heart rate increase by greater than 10 beats per minute in 16% to 28% of patients; 15% to 20% experienced an increase of 10 mmHg in diastolic blood pressure; and 6% to 13% experienced an increase of 15 mmHg in systolic blood pressure.

There is limited drug interaction information for sibutramine.²⁵ However, because of its mechanism of action and site of metabolism, the potential for drug interactions does exist. To avoid the risk of serotonin syndrome, the manufacturer recommends avoiding sibutramine in patients taking other serotonergic drugs, such as triptans, dihydroergotamine, mep-eridine, pentazocine, fentanyl, and lithium. At least 2 weeks should lapse between treatment with sibutramine and monoamine oxidase inhibitors. The manufacturer also recommends using caution when prescribing sibutramine in patients taking

medications which may raise heart rate or blood pressure (i.e., pseudoephedrine, phenylpropanolamine).

Sibutramine is indicated for weight loss of maintenance of weight loss in patients with a body mass index (BMI) of at least 30 kg/m² or with a BMI of 27 kg/m² in the presence of concomitant risk factors such as diabetes, hypertension, and dyslipidemias. As with all other drugs for managing obesity, sibutramine should be used as part a comprehensive management program consisting of a low-calorie diet, exercise, and lifestyle changes. The recommended starting dose is 10 mg per day, with or without food. If the patient does not experience a weight loss of 4 pounds after 4 weeks of therapy at the 10 mg level, the dose may be increased to 15 mg once daily. Patients who do not lose at least 4 pounds after 4 weeks at the higher dose are unlikely to respond to continued therapy. Doses greater than 15 mg per day are not recommended.

Orlistat

Orlistat (Xenical®) is the first of a new class of weight loss agents that promotes weight loss by drug-mediated inhibition of nutrient absorption.³¹ Orlistat is a nonabsorbable, reversible inhibitor of lipases. Its activity is exerted in the lumen of the stomach and small intestine by binding to gastric and pancreatic lipases and inactivating them so that they cannot hydrolyze triglycerides into absorbable free fatty acids and monoglycerides. Orlistat is minimally absorbed, and can inhibit dietary fat absorption by approximately 30%.³²

Orlistat is approved for obesity management including weight loss and weight maintenance when used in conjunction with a reduced calorie diet, and to reduce the risk for weight regain after prior weight loss.³² It is indicated for obese patients with an initial BMI greater than or equal to 30 kg/m² or greater than or equal to 27 kg/m² in the presence of other risk factors. Orlistat is contraindicated in patients with chronic malabsorption syndrome or cholestasis, because of the risk of potentiating these diseases states and increased risk of malnutrition.

In clinical studies, orlistat has been shown to be effective for weight loss and in reducing cardiovascular and diabetes mellitus risk factors.³³⁻³⁵ A randomized, double-blind, placebo controlled study examined the effects of orlistat over two years in 892 obese patients.³³ After the initial lead in period of a controlled-energy diet and placebo administration to assess weight loss potential and compliance, subjects were randomized to placebo or orlistat 120 mg three times daily. The controlled diet was continued throughout the study. After the first year, the orlistat group was re-randomized to either placebo, orlistat 60 mg three times daily, or orlistat 120 mg three times daily. A total of 403 subjects completed the full duration of the study, and the completion rate was not significantly different among the treatment groups. While all groups lost weight, the orlistat 120 mg group achieved a more rapid and greater weight loss. Treatment with orlistat 120 mg three

times daily for 2 years produced an average of $7.6\% \pm 0.9\%$ weight loss from initial body weight, compared to $4.2\% \pm 0.8\%$ and $4.5\% \pm 0.9\%$ for those switching from orlistat 120 mg to placebo after year 1, and those on placebo for 2 years, respectively. Of the patients completing the full duration of study, 34.1% in the orlistat 120 mg group maintained a weight loss of over 10%, compared to only 17.5% of subjects in the placebo group. There was a significantly greater lowering of blood pressure ($p = 0.002$), mean waist circumference ($p < 0.05$), total and low-density lipoprotein cholesterol levels ($p < 0.001$), fasting serum insulin levels ($p = 0.04$), less of an increase in serum glucose levels ($p = 0.001$) in the 120mg orlistat treatment group.

Hollander et al evaluated the efficacy of long-term use of orlistat in obese patients with type 2 diabetes mellitus.³⁴ In this multicenter, 57-week, double-blind study, 391 patients were randomized to receive orlistat 120 mg orlistat or placebo three times a day with a mildly hypocaloric diet. All patients had BMIs of 28 to 40 kg/m² with clinically stable diabetes controlled by oral sulfonylureas. After 1 year of treatment, patients in the orlistat group lost an average of $6.2 \pm 0.45\%$ of initial body weight compared to $4.3 \pm 0.49\%$ in the placebo group ($p < 0.001$). Significantly more orlistat patients lost at least 5% of their initial body weight (49% vs 23%; $p < 0.001$). Orlistat was also associated with significant improvements in hemoglobin A_{1c} ($p < 0.001$) and fasting glucose ($p < 0.001$) and in significant reductions in doses of oral sulfonylureas required to maintain glycemic control ($p < 0.001$). Orlistat therapy also resulted in significant improvements in various lipid parameters compared to placebo (reductions in total cholesterol, $p < 0.001$; LDL cholesterol, $p < 0.001$; triglycerides, $p < 0.05$; apolipoprotein B, $p < 0.001$; and the LDL-to-HDL cholesterol ratio, $p < 0.001$).

Sjostrom et al conducted a double-blind trial of the efficacy and safety of long-term use of orlistat in 743 patients with baseline BMIs of 28 to 47 kg/m².³⁵ Following a 4-week, single-blind, placebo lead-in period on a restricted diet (600 kcal/day deficit), the 688 patients who completed the lead-in were randomized to treatment with orlistat 120 mg three times a day or placebo with a restricted diet. In the second phase of the study, patients were randomly reassigned to orlistat or placebo with a weight maintenance diet. At the end of year 1, the average weight loss in the orlistat group was 10.3 kg (10.2%) compared to 6.1kg (6.1%) in the placebo group ($p < 0.001$). During the second year, the patients who remained on orlistat regained only half the amount of weight regained by those switched to placebo. Patients who switched from placebo to orlistat lost an average of 0.9 kg, compared with an increase of 2.5 kg in those who remained on placebo ($p < 0.001$). Total cholesterol, low-density lipoprotein (LDL) cholesterol, LDL/HDL ratio, and concentrations of glucose and insulin de-

creased more in the orlistat group than in the placebo group. With the exception of gastrointestinal adverse events, the adverse drug reaction profiles were similar.

Systemic adverse effects are negligible.³² In clinical trials the majority of adverse effects with orlistat were gastrointestinal (GI) related, and these also were similar to other studies.³¹⁻³⁵ At least one GI event occurred in 79% of patients, compared to 59% in the placebo group. Seven types of GI events have been identified with orlistat: flatus with discharge, oily spotting, fecal urgency, fatty/oily stool, oily evacuation, fecal incontinence, and increased defecation. These effects appear to decrease with time, and are related to the amount of dietary fat intake. Vitamin D and E levels decreased significantly ($p = 0.001$ and $p = 0.003$, respectively), but these levels were still within the reference range. Other studies have shown decreased beta-carotene levels, but these decreases were insignificant.^{33,34}

To date, there are few reported drug interactions with orlistat. Since changes in absorption occur with variations in dietary intake, cyclosporine levels should be monitored with the onset of orlistat therapy.³² Decreased absorption of supplemental fat-soluble vitamins has also been shown, and administration times should be separated. No changes in the INRs of warfarin patients have been noted, but clinicians should be careful and monitor the INR since the absorption of vitamin K may be altered. Additive decreases in lipids have been shown with patients taking pravastatin concomitantly with orlistat, and plasma concentrations of pravastatin have increased by as much as 30%. Patients should be monitored for adverse effects of pravastatin.

The recommended dose of orlistat is 120 mg three times daily with each meal containing fat, to be taken during or up to one hour after the meal.³² Doses above 120 mg three times daily have not shown additional benefit. Patients should be advised to adhere to dietary guidelines, and the manufacturer provides a detailed patient handout that advises patients on the recommended daily grams of fat included in a 30% fat diet. Since there is a risk of a decreased absorption of fat-soluble vitamins while taking orlistat, patients should be counseled on taking a multivitamin containing fat-soluble vitamins at least 1 hour before or after administration of orlistat. Orlistat is minimally (<1%) absorbed, and dose adjustments need not be made in renal or hepatic insufficiency.

Conclusion

Until such time as we can prevent or cure diabetes, we need to ask if it is reasonable to expose patients to the risks and aggravations of treatment for an average weight loss of at most 10%. Does such a modest amount confer any benefits in the obese patient? Surprisingly, the answer is yes. Goldstein conducted a literature review to determine if there were health benefits with modest weight loss.³⁶ It was found that beneficial

effects do occur in most obese patients with modest complications of obesity, including improved glycemic control, a decrease in blood pressure, and a rise in high-density lipoprotein levels. There was a continuum of benefit as weight loss increased, and more benefits were seen in heavier individuals. These effects were seen with as small of a decrease as 5% to 10% of their baseline body weight. Another review of the short term medical benefits with a 5% to 10% weight loss showed increased insulin sensitivity, increased insulin secretion by islet cells, decreased hepatic glucose production, improved glycosylated hemoglobin (as weight loss is maintained), a decrease in blood pressure in the absence of sodium restriction,

an increase in HDL levels, improved pulmonary function, improved low back pain, and a decrease in the pain and disability associated with osteoarthritis.³⁷

Reducing obesity is a major challenge on both an individual and population level. Patients may lose weight, but seldom manage to maintain their weight loss. The number of obese and overweight Americans continues to climb and so do the number of dollars spent to treat obesity and obesity-related diseases. Clearly further research is needed to identify strategies and programs for prevention, treatment, and maintenance of obesity. ■

References available on request.

Table 3. Available Anti-Obesity Drugs

Generic	Usual Dose	Schedule	Cost Per 30-Day Supply (AWP)
NORADRENERGIC AGENTS			
Amphetamine*	5-10 mg 30-60 mins ac	CII	
Dextroamphetamine* (Dexedrine®)	5-10 mg 30-60 mins ac SR 10-15 mg Q AM	CII	\$22.10-\$25.47
Methamphetamine* (Desoxyn®)	5 mg, 30 min ac SR 10-15 mg Q AM	CII	\$64.57-\$99.90
Benzphetamine (Didrex®)	25-50 mg QD-TID	CIII	\$11.30-\$22.59
Phentermine (Fastin®, Ionamin®, Adipex-P®)	8 mg TID 30 min ac 15-37.5 mg Q AM	CIV	\$7.85-\$36.77
Diethylpropion (Tenuate®)	25 mg TID one hour ac and in midevening if needed for night hunger SR 75 mg QD in midmorning	CIV	\$33.46-\$41.36
Phendimetrazine (Prelu-2®)	35 mg BID or TID one hour ac SR 105 mg QD in midmorning	CIII	\$31.40-\$10.75
Mazindol (Sanorex®)	1 mg TID one hour ac or 2 mg QD, one hour before lunch	CIV	\$73.43-\$138.83
Phenylpropanolamine (Dexatrim®, Accutrim®)	25 mg TID 30 min ac 75 mg Q AM	OTC	\$0.81-\$6.51
SEROTONERGIC AGENTS			
Fenfluramine (Pondimin®)	Withdrawn from market		
Dexfenfluramine (Redux®)	Withdrawn from market		
NORADRENERGIC/SEROTONERGIC			
Sibutramine (Meridia®)	10 mg or 15 mg Q AM	CIV	\$87.00
LIPASE INHIBITORS			
Orlistat (Xenical®)	120 mg TID no more than one hour ac	Rx	\$118.80

*Note: Because of their high abuse potential, amphetamines are not recommended for weight control.

Key: ac = before meals; Q AM = daily in the morning; TID = three times a day; BID = twice daily