CLINICAL DILEMMAS

Antiobesity Drugs: Should They Be Used in the Treatment of Obesity?

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Obesity remains an escalating problem in the United States despite medical efforts to contain this disease. Data from the National Center for Health Statistics report that the prevalence of obesity has risen in the United States from 25.4% during 1976 to 1980 to 33.3% during 1988 to 1991.[1] In fact, based on prevalence data reported since the mid-1960s, it has been estimated that the entire US population will be obese by the year 2230.[2] This epidemic is worrisome in that obesity costs our society approximately $51 billion per year (1995 estimate) in direct health care costs, which are associated with the increased frequency of comorbid medical and psychiatric conditions. This does not include the effects of reduced social status, educational achievement, and employment opportunities.[3,4] Because of these staggering statistics, there have been heightened efforts to control this epidemic, including renewed interest in appetite suppressants and other antiobesity agents, which are used in conjunction with conventional medical treatment and diet education, exercise training, and lifestyle modification. This article reviews appetite suppressants both from a historical perspective and from a current use perspective. A rationale for the continued use of antiobesity agents in the management of obesity also is presented. Finally, strategies for medical treatment of obesity are outlined.

BACKGROUND

In the aftermath of the "fen-phen" fiasco, it is illuminating to review similar pharmacotherapeutic events in the history of the medical treatment of obesity, even including "fad" diets. As early as 1893, thyroid extract was the first drug reported to be used against obesity, when clinicians attempted to treat obese persons for "low metabolism." This effort was abandoned when it was reported that the thyroid medication produced hyperthyroidism in patients, along with the resultant catabolism of bone and muscle.[5]

Dinitrophenol, which uncouples oxidative phosphorylation, was also used but discontinued after patients developed neuropathies and cataracts. Amphetamines began to be used in 1937 as a "cure" for obesity but slowly fell into disfavor when their addictive potential was realized. Amphetamines are centrally acting agents that primarily release norepinephrine and cause release of dopamine, which in increased concentrations in the synaptic cleft are associated with abuse potential.[5] The use of amphetamines and other inappropriate drugs, such as digitalis and diuretics, in clinical practice for the treatment of obesity was curtailed in 1967 after several deaths were reported. The misuse and addictive potential of amphetamines and other β-phenethylamines prompted the Drug Enforcement Agency (DEA) to schedule appetite suppressants as controlled substances. In 1971, aminorex, a drug used against obesity in Europe, was withdrawn from the market after numerous cases of pulmonary hypertension were associated with its use. Even certain marketed "diet" regimes caused deaths; for example, in 1978, several deaths were reported to be associated with the use of very-low-calorie diets, which use collagen as the major source of protein in a liquid base.[6] Controversy arose yet again in the early 1990s as diet clinics promoting liquid diets were criticized for precipitating attacks of cholecystitis in obese patients who lost weight rapidly on these programs.

Although phentermine (an adrenergic agent) and fenfluramine (a serotonergic agent) were approved for short-term use as antiobesity agents by the Food and Drug Administration (FDA) in 1972, their use was curtailed chiefly because of the bad press that "diet drugs" received because of amphetamine use in the United States. The use of anorexiants in obesity management was reexamined chiefly because of the results of studies by Weintraub and colleagues.[7] These studies reported that the combination of phentermine and fenfluramine was effective in producing weight losses of 7.7 to 14.1 kg during a 3-year period when used in conjunction with diet counseling, exercise, and behavior modification.[8] The combination fen-phen appeared to be safe with minimal

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side effects and, in fact, the side effects of each drug used independently were minimized when used in conjunction with each other. The timing of the publication of these studies[9] coincided with the news of the results of the National Health and Nutrition Examination Surveys (NHANES III), which announced that the prevalence of obesity had risen dramatically in the United States and was of epidemic proportions. In 1996, there was a sudden increase in the number of prescriptions written for phentermine and fenfluramine, which peaked at 11 million and 7 million, respectively, and an increase in pressure to develop and test new antiobesity agents.[10] Further optimism followed the FDA approval of dexfenfluramine (Redux; Wyeth-Ayerst Laboratories, St Davids, Division of American Home Products Corp, Philadelphia, PA) in April 1996, the first new drug approved for the treatment of obesity since the early 1980s.

However, by the fall of 1997, it was clear that these three drugs were associated with three different problems: primary pulmonary hypertension (PPH), neurotoxicity, and cardiac valvulopathies. A report published in the *New England Journal of Medicine* in 1996 determined an odds ratio of 23 (1 case per 35,714 patient-years) for PPH in patients using appetite suppressants for 3 months.[11] There were also reports of neurotoxicity, which manifested in patients as forgetfulness and memory loss, while they were taking dexfenfluramine or fenfluramine. The forgetfulness and memory loss were apparently reversible on cessation of the drugs.[10] Finally, in July 1997, 24 women were reported as having developed an unusual form of valvular heart disease during treatment with the combination fen-phen.[12] By September 15, 1997, the FDA had evidence that 92 of 291 study participants receiving either fenfluramine or dexfenfluramine alone, or in combination with phentermine, had evidence of valvular pathology by echocardiography. This number included 80 reports of aortic regurgitation of mild or greater severity and 23 reports of moderate or greater mitral regurgitation. Approximately 77% of these positive cases were asymptomatic. Based on echocardiogram reports from five independent surveys, the prevalence of valvular lesions in people taking these appetite suppressants was similar, ranging from 30.0% to 38.3%. The prevalence in those exposed to the drugs for <3 months was 22%, in those exposed for 3 to 5 months was 22%, and in those exposed for >6 months was 35%. Even though this report from the distributor (Wyeth-Ayerst Laboratories) included an editorial observing that these data reflected a preliminary analysis of pooled information rather than results of a formal clinical investigation, both fenfluramine and dexfenfluramine were removed from the market. There was no evidence of abnormal cardiac pathology associated with the use of phentermine alone and, therefore, phentermine is still available. Based on available data, the FDA has been significantly criticized as a result of its behavior regarding the handling of these drugs and their recall.[13] Definitive studies are currently under way.

In the aftermath of these reports, it has been recommended that an echocardiogram be performed on all patients exposed to fenfluramine or dexfenfluramine who exhibit cardiopulmonary signs or symptoms. An echocardiogram also is recommended for those patients exposed to fenfluramine or dexfenfluramine who are asymptomatic before undergoing invasive medical or dental procedures for which antimicrobial endocarditis prophylaxis is recommended by the American Heart Association.[14]

Because of the sobering revelations of cardiac valvular abnormalities, the risk of primary pulmonary hypertension, and the potential for neurotoxicity with use of the available medications for weight loss, the marketing of a new generation of antiobesity agents was delayed. The FDA approval ofsibutramine (Meridia; Knoll Pharmaceutical Co, Mount Olive, NJ), a norepinephrine and selective serotonin reuptake inhibitor (SSRI), was delayed until late 1997 and has been prescribed since March 1998. In addition, a new drug application for orlistat (Xenical; Roche Laboratories, Basel, Switzerland), a pancreatic lipase inhibitor, was withdrawn but resubmitted. Orlistat produces weight loss through the malabsorption of dietary fat; however, studies have shown a possible association of its use with breast neoplasms.[14]

A clinical study presented at the American College of Cardiology[15] showed no significant increase in the prevalence of clinically relevant heart valve regurgitation after 2 to 3 months of taking Redux. The randomized, double-blind, multicenter study involved 1072 patients who were part of a trial of a new sustained-release form of Redux, which was never marketed. The trial of this new drug compared the sustained-release form to both Redux and placebo, and was stopped in September 1997 as a result of the manufacturer's voluntary withdrawal of Redux from the market. At the time the trial was stopped, patients had been treated with drug or placebo for a median of 77 days. Echocardiograms were performed on all 1072 patients and showed mild or greater aortic regurgitation in 5.0% of patients treated with Redux, 5.8% of patients treated with sustained-release dexfenfluramine, and 3.6% of placebo-treated patients. Findings also included moderate or greater mitral regurgitation in 1.7%, 1.8%, and 1.2%, respectively. Mild or greater aortic regurgitation, moderate or greater mitral regurgitation, or both occurred in 6.5%, 7.3%, and 4.5%, respectively. None of the differences between drug and placebo groups were statistically significant. This particular study demonstrated that there is but a small difference in prevalence of valvular regurgitation among patients who took Redux and those who took placebo. This is reassuring for patients who took Redux for 2 or 3 months. However, studies are still needed to explore combination therapy and duration of therapy.

Undaunted, medical efforts to control obesity

Table 1. Adrenergic agents and drug enforcement agency schedule

Schedule III	Phendimetrazine (Prelu-2,* Bontril,† Plegine,‡ X-Trozine)
	Benzphetamine (Didrex)
Schedule IV	Diethylpropion (Tenuate,§ Tepanil)
	Mazindol (Mazanor,‡ Sanorex)
	Phentermine HCl (Fastin,‖ Adipex-P)
	Phentermine resin (Ionamin¶)
Over-the-counter	Phenylpropanolamine (Acutrim, Dexatrim)
	Ephedrine (not approved for obesity treatment)

*Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT.
†Carnrick Laboratories, Cedar Knoll, NJ.
‡Wyeth-Ayerst, Philadelphia.
§Hoechst Marion Roussel, Kansas City, MO.
‖SmithKline Beecham, Pittsburgh, PA.
¶Medeva Pharmaceuticals, Rochester, NY.

must continue in the face of what is now a major national and international epidemic. Obesity is associated with diseases causing the highest rates of morbidity and mortality in the United States: diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, gallbladder disease, some cancers, osteoarthritis, and sleep apnea. Obesity has now been characterized as a disease in and of itself and, as clinicians, we are obligated to treat it using the available armamentarium. The dismal success rates of medical approaches that focused solely on behavior modification of diet and exercise prompt the continued use of antiobesity agents as adjuncts to conventional treatment. Obese patients with associated comorbidities are likely to benefit from a modest 5% to 10% weight loss, which is the recommended goal of obesity management and is attainable with the use of antiobesity agents.[16]

AVAILABLE DRUG OPTIONS AS ADJUNCTS IN OBESITY THERAPY

Three different mechanisms can be used to classify drug treatments for obesity: (1) treatments that reduce food intake (anorexiants), (2) treatments that alter metabolism either before or after absorption, and (3) treatments that increase energy expenditure (thermogenesis).

The appetite suppressants currently available fall into category 1. Medications that are anorexiants act either on the central catecholaminergic neurotransmitter system or the serotonergic system to increase satiety.[5,17] Noradrenergic drugs act by releasing norepinephrine or by blocking its reuptake into neurons by activating β-adrenergic and dopaminergic receptors within the hypothalamus. Table 1 lists these compounds, which are all derivatives of β-phenethylamine except for Mazindol (Wyeth-Ayerst Laboratories). All the drugs listed except Mazindol are chemically related to amphetamine; however, modification of the basic structure has led to decreased abuse potential, while retaining its appetite-suppressing effects. These drugs release norepinephrine from stores in presynaptic vesicles—except for Mazindol, which is a tricyclic compound—and block reuptake of norepinephrine into presynaptic terminals.

Of the agents listed in Table 1, phentermine is the one most prescribed in the past few years, chiefly because of the results of the Weintraub study and the popular combination of fen-phen. Phentermine used alone has not been associated with cardiac valvular defects and remains available for use as a single agent for a short term (3 months). It is available as phentermine HCl and phentermine resin. The resinate is absorbed more slowly and blood levels reach a lower, later, and flatter peak, which is likely to result in more consistent and sustained blood levels compared with phentermine HCl.[14]

The two adrenergic agents that are available over-the-counter are phenylpropanolamine and ephedrine. They have been used both alone or in combination with other agents in obesity treatment, although ephedrine is not approved for this purpose. The FDA issued a warning to consumers in April 1996 concerning the potential for deleterious effects on the nervous system and heart after reports of deaths from ephedrine-containing compounds and "herbal" remedies. Side effects of adrenergic agents can include dry mouth, constipation, alertness, disturbed sleep, increased blood pressure, headaches, and palpitations.

Serotonergic drugs suppress hunger by activating the serotonin system in the hypothalamus. *d,l*-Fenfluramine and its dextroisomer, dexfenfluramine, are β-phenethylamines that are chemically related to the noradrenergic compounds in Table 1. These drugs are strictly serotonin releasers and act to increase the concentration of serotonin in the neuronal cleft. Fluoxetine is a selective SSRI that is approved for treating depression but not obesity. It has been shown to be somewhat effective in producing weight loss; this is dose dependent at doses ranging from 10 to 80 mg/d. However, weight tended to be regained after 20 weeks despite continued therapy[18] Fluoxetine, and the related antidepressants sertraline and paroxetine, have shown greater efficacy in the treatment of binge-eating disorders and other obsessive-compulsive syndromes and, thus, have a place in the treatment of this kind of obesity.[19] Table 2 summarizes the previously approved serotonergic medications.

NEW AGENTS

Sibutramine (Meridia) was approved by the FDA in late 1997 and has been available since March 1998. Sibutramine is a β-phenethylamine, which acts as a reuptake inhibitor for both norepinephrine and serotonin. It therefore has some of the properties of both serotonergic and noradrenergic agents. It does not act as a serotonin-releasing agent, however, as do fenfluramine and dexfenfluramine. Side effects of sibutramine can include small increases in heart rate and blood pressure, dry mouth, insomnia, and asthenia. The experience with

Table 2. Serotonergic agents

Schedule IV	*d, l*-Fenfluramine (Pondimin*,†)
	Dexfenfluramine (Redux*,†)
Antidepressants‡	Fluoxetine (Prozac§)
	Sertraline (Zoloft‖)
	Paroxetine (Paxil¶)

*Withdrawn from the market September 15, 1997.
†Wyeth-Ayerst Laboratories, St Davids, Philadelphia, PA.
‡Not approved for obesity treatment.
§Dista Products Co, Division of Eli Lilly, Indianapolis, IN.
‖Pfizer, New York.
¶SmithKline Beecham Pharmaceuticals, Pittsburgh, PA.

this drug reveals no increase in incidence of primary pulmonary hypertension or any association with cardiac valvular disease or neurotoxicity.[20] In a 1-year study, patients who received 15 mg sibutramine daily plus dietary counseling lost an average of 9.5 pounds.[21] Table 3 lists the most commonly prescribed anorexiant drugs (through September 1997) and includes the new agent sibutramine as a comparison.

Orlistat tetrahydrolipostatin (Xenical) is a selective inhibitor of pancreatic lipase, which falls under the category of drugs that alter metabolism and, if approved, will be the first of its class of drugs to be used in the treatment of obesity under FDA approval. It acts locally in the gastrointestinal tract to block gastric and pancreatic lipase and, therefore, causes malabsorption of fat. Approximately one third of digested fat is excreted in the stool of patients taking orlistat.[22] A dose of 120 mg three times per day is associated with an 80% maximal effect with minimal adverse side effects. This dose of orlistat used with a diet program consisting of 1800 kcal/d, with 30% of kilocalories as fat (65 g), would result in a caloric loss of 200 fat calories per day via stool. The addition of orlistat to a conventional diet program would increase weight loss by approximately 1 pound every 2 weeks if used in this manner.

For example, in a 12-week study, following a 4-week, single-blind, run-in period of diet alone, patients eating a mildly hypocaloric diet and taking orlistat lost an average of 3.9 pounds.[23]

Orlistat is most often associated with gastrointestinal side effects including flatulence, diarrhea, fatty stools, and fecal incontinence. These side effects are minimized by adhering to a diet consisting of no more than 30% of calories as fat.

The FDA application for orlistat was voluntarily withdrawn pending further evaluation of a possible association with breast neoplasms and has been recently resubmitted.

MANAGEMENT STRATEGIES

Clinicians are now better able to offer reasonable medical therapy for their obese patients because of a new perspective on the disease brought about by recent advances in knowledge of the genetic link between body weight and satiety such that we no longer view obesity as a "lack of will power." We now better understand the powerful forces preventing some obese people from losing weight and the even greater forces preventing the maintenance of that weight loss.[24,25] This should always be kept in mind by clinicians in a reputable weight loss program.

We have also realized the benefits of moderate weight losses of 5% to 10% of initial body weight in decreasing health risks such that we no longer require patients to achieve an "ideal" body weight based on actuarial tables.[16] This has been a setup for failure in many weight loss programs in the past and a source of frustration for many patients.

Table 3. Antiobesity drugs

Generic	Phentermine	Fenfluramine	Dexfenfluramine	Sibutramine
Trade name	Ionamin*	Pondimin†	Redux†	Meridia‡
	Fastin§			
	Adipex P‖			
Transmitter	Adren	Serotonin	Serotonin	Adren
				Serotonin
Dose (mg)	15–30	20–60	15 (BID)	5–20
	30			
	37.5			
Side effects	GI	GI	GI	GI
	CNS	CNS	CNS	CNS
	CV			CV
FDA	Approved	Withdrawn	Withdrawn	Approved

BID, two times per day; GI, gastrointestinal; CNS, central nervous system; CV, cardiovascular; FDA, Food and Drug Administration.
*Medeva Pharmaceuticals, Rochester, NY.
†Wyeth-Ayerst Laboratories, St Davids, Philadelphia, PA.
‡Knoll Pharmaceuticals Co, Mount Olive, NJ.
§SmithKline Beecham, Philadelphia.
‖Gate Pharmaceuticals, Sellersville, PA.

EVALUATION OF THE OBESE PATIENT

The body mass index (BMI), weight in kilograms divided by height in meters squared (kg/m^2), is more helpful in assessing weight-related health risks than ideal weight-for-height and currently is used to determine appropriate modes of obesity treatment as recommended by the American Obesity Association and Shape Up America![26] There is a curvilinear relationship between BMI and mortality that is often described as being J- or U-shaped. Significant increases in mortality and morbidity are associated with BMI >27; and, therefore it has been deemed appropriate that those patients who have a BMI >27 and who have obesity-related comorbidities, such as type II diabetes, hypertension, and dyslipidemia, be considered for pharmacotherapy treatment, especially if they have been unable to lose weight by diet and exercise alone. Consideration should also be given to other risks for obesity-related disease, such as family history of obesity and recent significant weight gain. Patients with BMI >30 who have not been able to achieve sustained weight loss with a hypocaloric diet and increased physical activity are candidates for pharmacotherapy even without comorbidities. Evaluation of the obese patient should involve determination of the patient's BMI-related health risk so that treatment options for which the patient is eligible can be identified. Table 4 can be used to predict health risk based on BMI.

The risk for each BMI category is adjusted to a higher level by other factors such as smoking, hypertension, elevated total or low-density lipoprotein (LDL) cholesterol, and reduced high-density lipoprotein (HDL) cholesterol. After BMI and risk of obesity are evaluated in the initial visit, the appropriateness of various medical treatments or even surgical treatments can be determined. Table 5 presents health risk category and treatment options available.

A moderate deficit diet corresponds to 1200+ kcal/d for women and 1400+ kcal/d for men. A low-calorie diet corresponds to 800 to 1200 kcal/d for women and 800 to 1400 kcal/d for men. A very-low-calorie diet corresponds to <800 kcal/d for both men and women.

Increased physical activity should be gradual and can be incorporated into a patient's daily routine.

Table 4. BMI and risk categories

BMI	Health risk	Risk adjusted for comorbid conditions or other factors
<25	Minimal	Low
25 to <27	Low	Moderate
27 to <30	Moderate	High
30 to <35	High	Very high
35 to <40	Very high	Extremely high
>40	Extremely high	Extremely high

BMI, body mass index. From Shape Up America! and the American Obesity Association.[25]

Table 5. Health risk and treatment options

Health risk	Treatment options
Minimal and low	Healthful eating and moderate deficit diet Increased physical activity Lifestyle change strategies
Moderate	All the above plus low-calorie diet
High and very high	All the above plus drugs All the above plus very-low-calorie diet
Extremely high	All the above plus surgical intervention

From Shape Up America! and the American Obesity Association.[25]

A comprehensive behavior modification program such as the LEARN for Weight Control[27] can help a patient make the permanent lifestyle changes that are necessary to incorporate more physical activity and a healthier eating pattern into their lives.

DURATION OF DRUG TREATMENT

The lifestyle modifications described in the preceding section are obviously long term. What about treatment with antiobesity agents? When fenfluramine and phentermine were approved by the FDA in 1972, it was for short-term use up to 3 months, whereas dexfenfluramine was approved in 1996 for use up to 1 year, as is the case for sibutramine. In selecting drug therapy for patients, a single agent should be selected first. However, in the case of patients already on an SSRI antidepressant such as fluoxetine, the addition of phentermine has shown efficacy in producing weight losses that are similar to those produced by the combination fen-phen.[28] In general, failure to lose at least 4 pounds in the first 4 weeks on any antiobesity agent is a signal that the patient is unlikely to benefit from further drug treatment and should discontinue that particular drug. In a few cases, nonresponders may benefit from an increased dosage as long as doses do not exceed the recommended range. Weight loss achieved with antiobesity agents typically plateaus after 6 months of therapy. Patients may attempt dose reduction at that time with a goal of maintaining a loss of 10% below baseline weight, or they may stop medication entirely and maintain weight loss through lifestyle changes. Treatment with antiobesity agents may be resumed whenever weight gain exceeds 5% of body weight.[5] For patients who have trouble maintaining weight loss during times of stress or at holidays, intermittent drug therapy provides another viable option.

THE FUTURE AND COMBINATION DRUG THERAPY

Orlistat tetrahydrolipostatin (Xenical), if approved, will be the first antiobesity agent that acts peripher-

ally, not centrally, and may be approved for use of more than 1 year. It may be tempting to combine this agent with a centrally acting drug, but there is no experience with the concomitant use of orlistat with appetite suppressants. The issue of combination drug therapy should be approached with caution; lessons were learned after using fen-phen without FDA approval for this combination. Similarly, some practitioners also combined dexfenfluramine with phentermine.

There also has been no experience with the use of sibutramine in combination with other agents, and, because sibutramine affects two different central pathways, its use in combination with other appetite suppressants should be discouraged unless studies indicate efficacy and safety.

Previously, the use of fenfluramine or dexfenfluramine with an SSRI antidepressant was not recommended because of the risk of precipitating the "serotonin syndrome." This syndrome is manifest by tachycardia, hypertension, and confusion and can lead to cardiovascular collapse and death.[29] However, in a patient already taking an SSRI, a trial of phentermine could be considered. After examining the reports of valvular heart disease with fen-phen, some experts advise obtaining a baseline echocardiogram before taking phentermine with an SSRI and repeating the echocardiogram after 3 months of treatment.[14]

The 1990s have heralded an explosion in obesity research, and as we realize the complex biochemical pathways involved in the control of hunger, satiety, and energy balance, we begin to understand that obesity is a disease that should be treated just as we treat other diseases. Antiobesity agents on the horizon include gut peptides, β-3 adrenergic agents, antineuropeptide Y, and long-acting cholecystokinin. Also anxiously awaited is the peptide leptin, which has been shown to reduce body weight and body fat in rodents with obesity. Leptin acts to reduce food intake, perhaps by reducing levels of neuropeptide Y, which is a potent stimulant to food intake.[30]

CONCLUSION

Obesity research in the 1990s has illuminated the truth that obesity is a disease and most often is not the result of a person's lack of will power but is due to the combination of a complex genetic system and an environment that has allowed this genetic predisposition to be expressed. The result is a national epidemic that has spread to other industrialized nations around the world. The medical community has an obligation to treat this disease with the armamentarium available, as long as we first "do no harm." The risks and benefits of antiobesity agents should be weighed carefully in each individual patient. The recommendations discussed in this article provide guidelines for the use of diet education, exercise therapy, lifestyle modification, and antiobesity agents in the medical treatment of obesity. The future holds great promise for obesity treatment as a new generation of antiobesity agents is waiting in the wings.

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