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Use of Sibutramine and Other Noradrenergic and Serotonergic Drugs in the Management of Obesity

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Drugs that act through noradrenergic and serotonergic mechanisms have historically served as the mainstays of pharmacologic treatments for obesity. This review addresses the following three topics: a brief discussion of older weight loss medications approved for short-term use (benzphetamine, phendimetrazine, diethylpropion, mazindol, and phentermine), as well as over-the-counter adrenergic drugs (phenylpropanolamine and ephedrine); recent clinical studies documenting the safety and efficacy of a new medication for obesity treatment, sibutramine, recently approved by the Food and Drug Administration for long-term use; and recent studies characterizing the valvulopathy associated with fenfluramine and dexfenfluramine, serotonergic medications for obesity which have been removed from the markets.

Key Words: Anorexiant; valvulopathy; pharmacotherapy; noredrenergic, serotonergic; sibutremine.

Introduction

Drugs that act through noradrenergic and serotonergic mechanisms have historically served as the mainstays of pharmacologic treatments for obesity. It has only been since 1998 that the Food and Drug Administration (FDA) approved a medication for a weight loss indication that is not a noradrenergic and/or a serotonergic drug. That drug, orlistat, is a pancreatic lipase inhibitor and reduces dietary fat absorption (see the article by Hauptman in this issue). In addition to orlistat, there is only one other medication currently approved by the FDA for long-term use in obesity management. That drug, sibutramine, is a centrally acting reuptake inhibitor for the monoamines, norepinephrine, serotonin, and, to a lesser extent, dopamine.

This review focuses on sibutramine, with special emphasis on recent publications documenting its clinical trial experiences. The goal is to provide practical guidance for the use of noradrenergic and serotonergic agents in obesity management. Other noradrenergic and serotonergic medications have been FDA approved for short-term use or have been shown to produce weight loss in clinical trials, but have not been given an FDA-approved indication for use in weight loss. Because current guidelines *(1)* sanction the use of medications in obesity management if they are FDA approved for long-term use, these other noradrenergic and serotonergic drugs are discussed only briefly. In 1994 the FDA approved dexfenfluramine for long-term use in obesity treatment. It is the dextro isomer of a serotonergic medication (fenfluramine) that had been in use for over 20 yr. Fenfluramine and dexfenfluramine were removed from the market in 1997 because of their association with cardiac valvulopathy. This review updates evidence describing and quantifying that association.

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Importance of Long-Term Safety in Medicating for Obesity

Obesity is a chronic disease in which health risks are usually remote rather than immediate. It is best compared to hypertension as a treatment paradigm *(2)*, in that blood pressure (BP) can be controlled as long as medication is continued, but when medication is stopped, the condition recurs. Long-term continuous treatment is the standard for hypertension therapy. Similarly, treatments including medication do not cure obesity; they must be maintained to maintain weight reduction. The requirement for long-term treatment and the relative remoteness of health risk from obesity make safety a prime consideration in evaluating the use of medication (or any treatment, for that matter) for obesity. Another aspect relevant to safety and pharmacotherapy is that for less severe degrees of overweight in which short-term pharmacotherapy might play a role in preventing more severe weight gain, the risk:benefit equation is an even more important consideration.

The clinical guidelines recently developed for obesity treatment *(1)* contain the following: "Evidence statement: Weight loss drugs approved by the FDA for long-term use may be useful as an adjunct to diet and physical activity for patients with BMI $\geq$ 30 kg/m^2 with no concomitant obesity-related risk factors or diseases, and for patients with a BMI > 27 kg/m^2 with concomitant obesity-related risk factors or diseases." Still, pharmacologic treatment of obe-

sity is not a routine part of primary care practice, in part because of the stigma associated with "diet pills" *(3)*. The recent experience surrounding the unforeseen toxicity of the popular "phen-fen" regimen is instructive. Significant (16%) long-term weight loss and maintenance for 3.5 yr were demonstrated when fenfluramine and phentermine were combined with lifestyle intervention *(4–8)*. While a small ($n = 121$) set of patients formed this study population, the regimen was well tolerated by patients and made significant advances in clinical practices. Then, in 1997, fenfluramine and dexfenfluramine were associated with the previously unsuspected complication of cardiac valvulopathy *(9)* and were withdrawn from the market. Estimates project that as many as 6 million people *(10)* have been exposed to these medications, attesting to the popular demand for effective obesity treatment. Anorexiant valvulopathy seen with the fenfluramines is discussed in detail later. The lesson from this experience is fresh in the minds of prescribing physicians and regulators. Thus, long-term safety will be an important issue for the future of obesity pharmacotherapy.

Overview of Noradrenergic and Serotonergic Medications

The observation that amphetamine (α-methyl-β-phenylethylamine), an agent developed for narcolepsy, was associated with weight loss led to the development of a number of β-phenylethylamine derivatives used for weight loss. In fact, all the centrally acting medications approved for weight loss, with the exception of mazindol (a tricyclic compound), have had this basic structure. Because β-phenylethylamine is the common structure of dopamine, serotonin, and norepinephrine, the derivatives can have a variety of dopaminergic, serotonergic, or noradrenergic effects. The strong dopaminergic attributes of amphetamine seem responsible for its abuse potential, and derivatives for weight loss have sought to minimize this property. All centrally active medications for weight loss developed to date have had noradrenergic and/or serotonergic properties.

Available Drugs

Table 1 lists the medications used for weight loss that act by noradrenergic and serotonergic mechanisms. Dextroamphetamine (Dexedrine), combined dextroamphetamine/amphetamine (Biphetamine), and methamphetamines (Desoxyn) are classified by the U.S. Drug Enforcement Agency (DEA) as class II agents and are currently indicated only for use in children with behavioral syndromes such as attention deficit disorder. There are no indications for the use of these drugs in obesity because of their abuse potential. Although there are two DEA class III agents, benzphetamine (Didrex) and phendimetrazine (Bontril, Plegine, or Prelu-2), with FDA-approved indications for use over a few weeks in obesity treatment, these drugs should not be used because their class III status indicates moderate abuse potential.

Table 1
Medications Approved for Treatment of Obesity

Noradrenergic and serotonergic drugs approved for long-term use	
Serotonin-norepinephrine reuptake inhibitor	
Sibutramine	(schedule IV)
Noradrenergic drugs approved for short-term use	
Norepinephrine releasers	
Benzphetamine	(schedule III)
Phendimetrazine	(schedule III)
Diethylpropion	(schedule IV)
Norepinephrine reuptake inhibitors	
Phentermine	(schedule IV)
Mazindol	(schedule IV)
Noradrenergic α-1 agonist	
Phenylpropanolamine	(over the counter)

There are three DEA schedule IV medications approved for short-term (a few weeks) use. Diethylpropion (Tenuate, Tepanil) is a norepinephrine releaser. Mazindol (Sanorex, Mazanor), a norepinephrine reuptake inhibitor, stands out by virtue of its tricyclic chemical structure. Phentermine is a norepinephrine reuptake inhibitor marketed under a variety of names (Adipex P, Fastin, Obenix, Oby-Cap, Oby-Trip, Zantryl, Ionamin) and, in the United States, is the most frequently prescribed of the medications approved for short-term use. All three of these medications are no longer patent protected and, thus, are much less expensive than the newer medications approved for long-term use.

A recent review by Bray and Greenway *(11)* contains a comprehensive compilation of the clinical trials documenting efficacy of the older noradrenergic medications. As documented in that review, there is evidence from small, single-center, short-term trials demonstrating efficacy of the three class IV medications (diethylpropion, mazindol, and phentermine). Long-term efficacy data are lacking except for one frequently cited study by Munro et al. *(12)* of intermittent phentermine use. A small (108 patients) group was randomized to receive 36 wk of placebo vs phentermine resin (30 mg/d) vs placebo alternating monthly with phentermine resin. Munro et al. *(12)* interpret the results to show significant weight loss that is comparable with either continuous or intermittent phentermine. This is an intriguing concept, but the dropout rate was 41% in just 36 wk and one should not extrapolate long-term safety and efficacy from this meager data source.

This article is designed to provide a clinical perspective to medicating obese patients. Obesity is a chronic disease requiring a long-term approach. I do not endorse the use of phentermine, mazindol, or diethylpropion for that reason. Safety and efficacy over the long term must be demonstrated in clinical trials before physicians should adopt medications for long-term use. Furthermore, there is little

rationale for a short-term approach to a chronic disease. Interested readers may consult the comprehensive review by Bray and Greenway *(11)*, which catalogs the evidence of clinical trials using phentermine, mazindol, and diethylpropion succinctly and which elucidates the state of our knowledge of adrenergic and serotonergic receptor pharmacology.

Over-the-Counter Adrenergic Drugs for Obesity

Two additional adrenergic sympathomimetic weight loss agents deserve mention. Both are available without a prescription. Phenylpropanolamine (Dexatrim, Acutrim, and others) is sold as an over-the-counter appetite suppressant and decongestant. Ephedrine, usually combined with caffeine, is found in herbal preparations and sports drinks.

Phenylpropanolamine is classified by the FDA as "possibly effective." It is an adrenergic alpha-1 receptor agonist. A review *(13)* of placebo-controlled trials concluded that although weight loss was less than with other prescription noradrenergic agents, phenylpropanolamine did produce significantly more weight loss than did placebo. Because of the ready availability of the drug and because noradrenergic stimulation may cause BP to rise, safety is an issue. A review of existing prospective data *(14)* concluded that there is no increased risk for exacerbating hypertension, provided the dosage guidelines of 75 mg daily are not exceeded.

Ephedrine is an adrenergic drug that stimulates norepinephrine secretion and has been used for treatment of asthma. It also has been used alone or in combination with caffeine for weight loss. Ephedrine and caffeine are found in several herbal preparations that are widely marketed in the United States for treatment of obesity. The thermogenic and food intake inhibiting effects of caffeine and ephedrine, as well as the published clinical trial data supporting their weight loss effects, are reviewed in "Thermogenic Drugs as a Strategy for Treatment of Obesity," by A. Astrup, p. 207. Again, there is a shortage of data to support long-term use. Only one year-long trial with 180 subjects entering and 99 competing has been published *(15)*.

Sibutramine

Sibutramine (marketed as Meridia in the United States and as Reductil elsewhere) is a selective reuptake inhibitor for norepinephrine, serotonin, and, to a lesser extent, dopamine. Its chemical structure is shown in Fig. 1, along with its two active metabolites. It is rapidly absorbed and metabolized in the liver by cytochrome P450 enzymes. It is available as 5-, 10-, and 15-mg capsules and requires only once-a-day dosing. The recommended dose range is 5–15 mg.

When administered to experimental animals, sibutramine reduced food intake *(16)* and produced a 30% increase in energy expenditure *(17)*. In human studies,

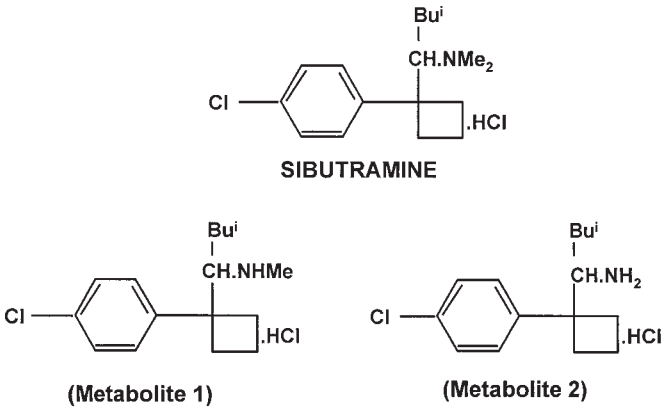

Fig. 1. Chemical structure of sibutramine and its two active metabolites.

sibutramine has also been demonstrated to decrease food intake in obese *(18)* and lean *(19)* subjects. The reduction in food intake has been shown to be an effect on satiety *(20)*, rather than producing anorexia. The effect of sibutramine on human thermogenesis is somewhat controversial. One group of researchers did not find a thermogenic effect of sibutramine in humans *(21)*, but another group reported thermogenic effects in two studies *(22,23)*. The degree of thermogenesis, however, is certainly not comparable to the effect sibutramine produces in animals. The issue of sibutramine's thermogenic effect in humans seems to be resolved by two studies. One is a metabolic chamber study *(23)* in patients whose weight declined on sibutramine to an equal degree as placebo (–2.6 vs –2.5%) despite no energy restriction. There was significantly less reduction in 24-h energy expenditure in the group taking sibutramine compared to placebo. In the second study *(24)*, patients who lost weight on sibutramine (8.1 $\pm$ 3.1%) were compared with those who lost weight on placebo (-5.1 $\pm$ 4.4%). In that study, there was a negative correlation in loss of fat-free mass and decline in resting energy expenditure for the sibutramine patients that was not evident with placebo. Sibutramine limited the decline equivalent to about 100 kcal/d.

In clinical studies *(25–33)*, there is dose-related weight loss with sibutramine. The pattern is one of weight loss that continues for approx 6 mo after the drug is initiated, and maintenance of that loss occurs for the duration of administration—up to 1 yr in these studies.

Two recent sibutramine studies *(30,31)* merit special discussion. Bray et al. *(30)* describe a placebo-controlled, double-blind, randomized, dose-ranging study conducted in seven clinical centers. It is noteworthy for its size: there were 1047 patients randomized, and 683 completed the study. There were statistically significant weight losses for the 5–30 mg/d dosages of sibutramine. At wk 24, the percentages of weight loss from baseline were as follows: 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%. Figure 2 illustrates this dose-response relationship. This trial also demonstrated weight loss–associated improvements in serum lipids and uric acid. The most frequent adverse events were dry mouth, anorexia, and insomnia. Small mean increases in pulse rate and BP were observed with considerable individual variability (*see* below). Note that the behavioral intervention in this trial was relatively weak. There was only one session with a dietitian at the start of the trial, and printed instructional material was dispensed. The percentage of patients who achieved 5% weight loss was dose related. For the 5-, 10-, and 15-mg doses, 25.3, 37.4, and 59.6% achieved this landmark, respectively. Early weight loss (≥4 lb at 4 wk) predicted success. At the 15-mg dose, 70% of those who lost ≥4 lb at 4 wk achieved 5% weight loss at wk 24, compared with 17% achieving 5% weight loss who did not lose 4 lb in the first 4 wk.

The combination of sibutramine with a "stronger" behavioral intervention produces greater weight loss. Apfelbaum et al. *(31)* treated 159 obese subjects with a very low-calorie diet (VLCD) to induce a 7.2% weight loss and then randomized them to receive placebo or 10 mg/d of sibutramine. Weight regain is common after this type of diet, but a behavioral program resulted in weight maintenance of the placebo-treated patients with 6.7% of the initial loss from baseline weight maintained at 1 yr. Subjects on 10 mg of sibutramine lost a total of 13.5% of their weight, an additional loss of 8.3% following cessation of the VLCD (see Fig. 3). The mean reduction in weight from baseline in sibutramine-treated patients is impressive, but the percentage of patients who received significant benefit is even more so. At least a 5% reduction from baseline was achieved by 86% in the sibutramine-treated group (55% in placebo-treated patients). Similarly, at mo 12, 75% of subjects in the sibutramine-treated group maintained at least 100% of the weight loss achieved with VLCD, compared with 42% in the placebo-treated group.

Sibutramine is being marketed in the United States with a no-cost Point of Change program that provides an individually tailored diet and lifestyle prescription by mail to enrolled patients. Because sibutramine promotes satiety, a sensible lifestyle plan that reinforces regular meals and portion control are the strategies most likely to maximize chances for success.

The side effects of sibutramine (insomnia, asthenia, dry mouth, and constipation) are generally mild and transient. The principal concerns have been the increase in BP and pulse rate, which averages 1–3 mmHg for BP and a 4–6 beats/min increase in pulse *(25,27–31)*, although in some individuals the rise in pulse may be above 100 beats/min and BP may rise to borderline levels. For these individuals and those with cardiovascular problems, the use of sibutramine may be inappropriate. It is recommended that BP and pulse be monitored for the first few weeks after starting the medication to identify sensitive individuals. The wise

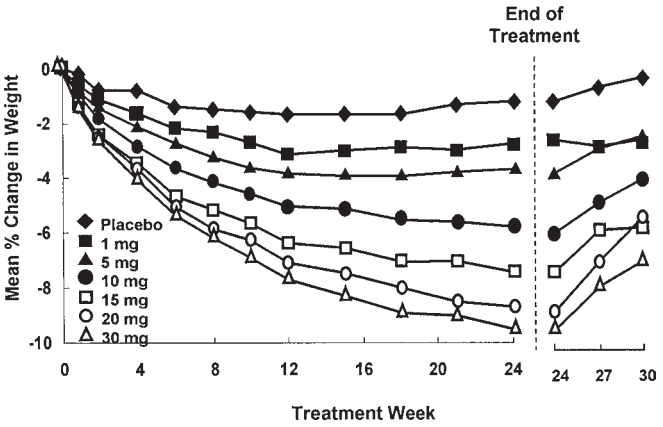

Fig. 2. Weight loss in patients completing 24 wk of sibutramine treatment followed by 6 wk of single-blind placebo wash-out. $p < .05$ vs. placebo for all time points for sibutramine doses 5–30 mg, nonparametric Williams' test. $n = 87–107$ per group. Post-treatment follow-up data are also shown for those patients in whom it was available ($n = 50–61$ per group). (Adapted from ref. *30*, with permission.)

clinician will use clinical judgment and weigh the degree of weight loss that is achieved with sibutramine against the increase in baseline pulse and BP. Many patients will have clinically significant (>5% from baseline) weight loss with no or little increase (or even decrease) in BP or pulse. Those patients may safely continue medication. The drug should be stopped in patients who lack clinically significant weight loss (<5%), or when the physician judges that there are clinically significant increases in BP or pulse rate.

There is no reason to suspect that sibutramine might be associated with valvulopathy, and one study *(34)* has been published that confirms a lack of association. In that study *(34)*, obese diabetics on sibutramine for an average of 7.6 mo had no significant difference in left-sided valvular dysfunction than did placebo-treated patients.

Sibutramine is scheduled by the DEA as class IV (low abuse potential). Indeed, 25- and 75-mg doses of sibutramine were compared to 20 mg of d-amphetamine and placebo in a study in polydrug abusers *(35)*. Sibutramine (25 mg) produced subjective effects indistinguishable from placebo. The 75-mg dose produced unpleasant effects (anxiety, confusion, and decreased vigor). Thus, even higher-than-recommended doses are not likely to be abused.

There is great interest in clinical trials of the use of sibutramine in primary care settings in controlled hypertensive patients and in diabetics. Of particular interest is the Sibutramine Trial in Obesity Reduction and Maintenance. This trial has been conducted in eight European primary care centers and will assess sibutramine use over 2 yr. It has only been reported in abstract form *(36)* thus far.

Recently, the effect of sibutramine in weight loss and glycemic control in diabetic patients has been described by Fujioka et al. *(37)* and McMahon et al *(38),* although a review *(28)* and abstract *(38,39)* are available describing

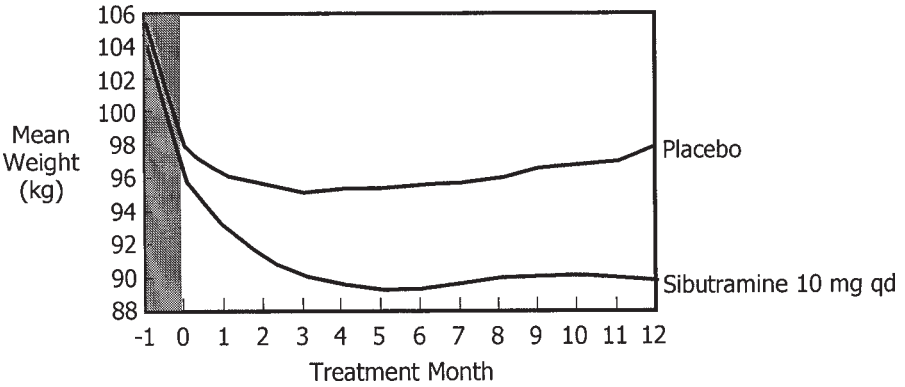

Fig. 3. Subutramine and behavioral intervention following a VLCD. Mean weight in kilograms in 179 patients randomized to 10 mg of sibutramine or placebo following 1 mo of a VLCD. An intention to treat analysis shows significantly greater weight loss at 1 yr for sibutramine-treated patients compared to placebo ($p < 0.004$) for months 1–12. (Adapted from ref. *31*, with permission.)

additional data on sibutramine use in diabetic patients. A recent publication *(37)* describes sibutramine used in a multicenter trial in which diabetic patients were randomized to sibutramine (dose titrated to 20 mg/d) or placebo for 24 wk. Of the 86 placebo-treated patients and 89 sibutramine-treated patients, 71 and 67%, respectively, completed the study. At wk 24, the weight loss for sibutramine-treated patients was –4.5% for those on sibutramine vs 0.5% for those on placebo ($p < 0.001$). Weight loss correlated with improvement in glycemic control, lipid profile, and quality-of-life assessments. In the 33% of sibutramine-treated patients who lost at least 5% from baseline weight, the HbA_{1C} decreased by 0.53% and plasma fasting glucose by 1.4 mmol/L ($p < 0.05$). For those 8% of patients who lost >10% from baseline, the HbA_{1C} decreased by 1.65% and the fasting plasma glucose by 3.8 mmol/L.

A recently published study *(40)* describes sibutramine use in obese patients with hypertension controlled with a calcium channel blocker (with or without a thiazide diuretic). Sibutramine (5–20 mg/d) produced >5% weight loss in 40% and >10% weight loss in 13.4% of the 150 patients randomly assigned to drug treatment compared with 8.7 and 4.3%, respectively, of the 74 patients assigned to placebo. Mean BP (+ 2 mmHg diastolic) and heart rate (+4.9 beats/min) increases were observed with sibutramine. Of the sibutramine-treated patients 5.3% were discontinued for hypertension, compared with 1.4% of those on placebo.

Valvulopathy Associated with Fenfluramine and Dexfenfluramine

The association of valvular heart disease and appetite suppressant use was unsuspected until July 1997, when an article *(9)* posted on the Internet described 24 women who had taken the phentermine and fenfluramine together and who had echocardiographic demonstration of unusual heart valve morphology with predominantly aortic regurgitation. In September 1997, fenfluramine and its isomer, dexfenfluramine, were voluntarily removed from the market. Since then, the clinical manifestations of valvulopathy associated with the fenfluramines and phentermine have emerged through studies taking various approaches to the problem.

Khan et al. *(41)* conducted a case-control study (257 patients, 239 controls) of patients who had participated in clinical trials using dexfenfluramine alone, dexfenfluramine and phentermine, or fenfluramine and phentermine for various periods. Echocardiographic analysis demonstrated that 1.3% of control subjects compared with 22.7% of patients met the case definition for regurgitation (≥mild aortic or ≥moderate mitral regurgitation). A similar approach was taken by Weissman et al. *(42)*, who modified an ongoing clinical trial of dexfenfluramine vs sustained-release dexfenfluramine vs. placebo. The average duration of treatment was only 71–72 d in each group, but there was still a small increase in prevalence of aortic or mitral regurgitation in patients treated with the dexfenfluramine preparations, though the degree of regurgitation was ≤ mild in most cases. A population-based, nested case-control study *(43)* was conducted in the General Practice Research Database located in the United Kingdom. It compared 6532 patients who received dexfenfluramine, 2371 who received fenfluramine, 862 who received phentermine, and 9281 control subjects. There were 11 cases of newly diagnosed cardiac valve disorders in those who used fenfluramine or dexfenfluramine compared with none in the control subjects who had not taken medication. In that study, duration of exposure beyond 4 mo was a risk factor. Wadden et al. *(44)* reported that 6 of 20 patients who completed 2 yr of treatment with fenfluramine and phentermine had echocardiographic evidence of ≤mild aortic and/or ≤moderate mitral regurgitation.

Two incidence studies have been reported *(45,46)* and are important because they document the development of abnormalities in patients who had echocardiograms before exposure to fenfluramine or dexfenfluramine. Wee et al. *(45)* studied 46 patients who took either drug for 14 or more

days. Eight had regurgitation at baseline and two developed regurgitation after exposure. In a larger study, Ryan et al. *(46)* studied 86 patients who fortuitously had echocardiography at the start of a weight loss program. Seven had aortic or mitral regurgitation on echocardiography at baseline. There were 13 new cases of echocardiographic regurgitation, and the development of new regurgitation was correlated with the duration of exposure to fenfluramine or dexfenfluramine.

What is apparent from the cited studies is that the degree of valvular regurgitation is not as severe as one might have guessed from the initial 1997 report. Rather, most cases of regurgitation are discovered by highly sensitive echocardiography in asymptomatic patients. Most of those qualifying as cases are mild aortic regurgitation. Only 30 cases have involved valve operations *(47)*. Furthermore, only patients exposed for more than 4 mo *(43,46)* to fenfluramine or dexfenfluramine seem to have increased risk for regurgitation.

Perhaps the most encouraging aspect of the anorexiant valvulopathy episode is that the mild valve regurgitation may remit. Thus far, only small numbers of patients and early reports have appeared *(48–50)*, but the evidence is strong enough to advise caution in advancing too rapidly to surgery for patients with valvulopathy; it may be best to observe for improvement prior to surgery *(47)*.

Conclusion

After a hiatus of more than 20 yr, in the last 5 yr three new medications have been approved by the FDA for obesity treatment. One of these, dexfenfluramine, a serotonin releaser, was taken off the market in 1997 because of associated valvulopathy. A second, sibutramine, is a reuptake inhibitor of norepinephrine and serotonin—and follows a long line of serotonergic and noradrenergic medications for obesity. However, it comes with the clinical efficacy and safety data that the modern approval process requires. The third, orlistat (discussed in the article by Hauptman in this issue) also comes with abundant clinical data to support its approval, and it is the first agent approved that is not a sympathomimetic drug. Sibutramine and orlistat represent significant advances in developing new medications for obesity. Significant advances have also occurred since the initial reports in understanding the valvulopathy associated with fenfluramine and dexfenfluramine. The constant tension between risk and benefit as related to obesity pharmacotherapy will not abate in the future, and the experience of the last 5 yr is expected to echo in future years. As new approaches *(51)* for obesity treatment are explored and new targets for pharmaceutical intervention are discovered from genetic and physiologic studies, the risk:benefit issue will continue to require exploration. The need for safe and effective pharmacologic intervention will only become more acute in the face of rising rates of overweight and obesity *(52)* because of their attendant risks of morbidity and mortality *(53,54)*.

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