

Long-term Pharmacotherapy of Obesity 2000

A Review of Efficacy and Safety

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To clarify the efficacy of antiobesity drugs, this article reviews all long-term (≥ 36 weeks), placebo-controlled trials of obesity pharmacotherapy published since 1960. Since fears of anorexiant-induced heart valve damage preclude many physicians and patients from even considering antiobesity drugs, this area is also reviewed in-depth. Electronic database and manual bibliography search was used to identify all relevant publications. While existing studies are too few and heterogeneous to warrant meta-analysis, their review does provide evidence highly relevant to the safety and efficacy of available anorexiant. Weight loss attributable to obesity pharmacotherapy (ie, in excess of placebo) in trials lasting 36 to 52 weeks was 8.1% or 7.9 kg for those receiving phentermine resin, 5.0% or 4.3 kg for those receiving sibutramine hydrochloride, 3.4% or 3.4 kg for those receiving orlistat, and -1.5% or -1.5 kg for those receiving diethylpropion hydrochloride. Physiologic, pathologic, and epidemiological studies strongly support that anorexiant-induced valvulopathy is attributable to specific serotonergic properties of the fenfluramines that are not present with available weight loss drugs.

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Recent reports including the latest National Health and Nutrition Examination Survey (NHANES III) have focused attention on an alarming recent increase in the prevalence of obesity. The NHANES III¹ (1988-1991) reported that obesity prevalence in the United States had risen from 25% to 33%, a 31% increase since NHANES II (1976-1980). That report was widely cited in a call to arms against obesity by the surgeon general and others amidst predictions that 40% of the US population would be obese by the year 2000 if present trends were unaltered. Although anorectic drugs have been prescribed for more than 40 years, few patients were treated with diet drugs prior to the mid 1990s. At that time an explosion in diet drug prescribing was

fueled by a variety of factors including the publication and publicizing of "the phen-fen [phentermine resin-fenfluramine] study"² and resultant aggressive direct-to-consumer promotion of diet drugs by for-profit weight loss clinics. By 1997 well over 10 million prescriptions for the popular phen-fen regimen had been written³ compared with a mere 60000 fenfluramine prescriptions in 1992.⁴ Our nation's acute interest in medications to treat obesity did not go unnoticed by pharmaceutical manufacturers who broke a 23-year drought in the introduction of new weight loss drugs by bringing 3 new drugs to market in a 2-year period (dexfenfluramine hydrochloride in 1996, sibutramine hydrochloride in 1997, and orlistat in 1998). This explosion in the drug treatment of obesity was abruptly and dramatically curtailed with the September 1997 recall of dexfenfluramine and fenfluramine from the market. That action immediately followed the reporting of results of echocar-

From the University of Rochester School of Medicine and Dentistry, Rochester, NY. Dr Glazer received a \$1000-limited honorarium from phentermine resin manufacturer Medeva Pharmaceuticals in 1998 for a lecture on obesity pharmacotherapy given to their trainees. Lecture content was his standard presentation given in other settings and not influenced in any way by Medeva Pharmaceuticals.

diographic “surveys” of patients using fenfluramines showing that up to one third of these patients had had echocardiographic abnormalities.

The above events have resulted in an atmosphere in which intense interest in and fear of weight loss drugs coexist, a landscape of ambivalence toward drug treatment of obesity perhaps unprecedented in medical therapeutics. Balanced reviews of obesity pharmacotherapy are, therefore, needed to help reconcile the justified interest in treating obesity with drugs with the fear of disastrous adverse effects from such treatment. We need look no farther than our television sets for a striking example of the degree to which conflicting messages about diet drugs are now before us. Moments after one national television advertisement promotes the new drugs (orlistat or sibutramine) a separate advertisement invites past fenfluramine users to participate in a multibillion dollar class action lawsuit.

RATIONALE FOR OBESITY PHARMACOTHERAPY

A growing body of evidence has eroded ingrained misconceptions about obesity that have traditionally been obstacles to the appropriate use of medication in obesity treatment. Of these paradigm shifts that have led to the inclusion of weight loss drugs in current guidelines for obesity treatment,⁵ 3 are most compelling:

- Understanding that obesity is a true disease with genetic determinants (not a “character flaw”).
- Understanding that obesity is a major public health threat (not merely a “cosmetic” issue).
- Understanding that weight regain after stopping medications indicates that obesity is a typical chronic disease (not that drug treatment is a failure).

A genetic contribution to obesity is supported by the findings of greater similarity of body mass index (BMI) between monozygotic vs dizygotic twins and correlation of BMI with biological but not adoptive parents.⁶ In addition, low meta-

bolic rates have shown familial aggregation, greater similarity in monozygotic than dizygotic twins, and correlation with weight gain and BMI.⁷ Recent reviews of obesity’s causes^{8,9} point out that energy homeostasis is vigorously defended by multiple mechanisms whose neuroendocrine and genetic basis are only beginning to be understood. This redundancy in our energy stores’ defense system probably explains the refractoriness of obesity to treatment and further justifies a multifaceted attack on obesity including pharmacotherapy. Separate studies suggest rising obesity in the United States¹⁰ and England¹¹ is due to decreased activity and has occurred despite less caloric intake. The genetically metabolically challenged may, therefore, constitute a disproportionate percentage of the newly obese. Ultimately, the recent rise in obesity must reflect nature and nurture since the US genome could certainly not have changed to the degree of our national girth in recent years.

The review by McGuiness and Foege¹² defining obesity and activity patterns as the second leading killer of Americans and the report of Manson et al¹³ stating that 53% of deaths in obese women (BMI >29 kg/m²) were attributable to their obesity have drawn widespread attention to obesity’s health risks. In men similar increases in cardiovascular¹⁴ and cancer¹⁵ deaths have been attributed to obesity. While controversy about a “J-shaped” body-weight vs mortality curve has persisted, recent studies controlling for smoking status and early death caused by preexisting disease find this relationship to be linear.^{13,14} In addition to the well-known association of obesity with elevation of traditional cardiac risk factors (blood pressure, cholesterol level), obesity also contributes to emerging cardiac risk factors including endothelial dysfunction,¹⁶ hyperinsulinemia, and elevated C-reactive protein.¹⁷ The cost of treating the 50% to 80% of US cases of diabetes mellitus attributable to obesity has been estimated at \$10 billion annually.¹⁸ Obesity-associated respiratory illnesses include asthma, sleep apnea, pickwickian syndrome, and pulmonary

hypertension. Adenocarcinoma of the esophagus and gastric cardia,¹⁹ hepatic necrosis, and cirrhosis²⁰ have recently shown strong correlations with obesity, joining increased rates of cholecystitis, colon cancer, reflux esophagitis, and gastroesophageal reflux disease on the traditional list of gastrointestinal tract complications of obesity. Obesity may be the most potent risk factor for incident knee osteoarthritis²¹ and is a major cause of Social Security Insurance disability claims.¹⁸ Obesity-associated pulmonary embolism is likely an underreported source of obesity-related death since obesity conferred a relative pulmonary embolism risk of 3.4 in the Nurses Health Study²² and almost 120 000 deaths per year are only attributed to pulmonary embolism after autopsy.²³

The widely publicized failure of traditional diet and behavioral therapies in sustaining weight loss continues to provide impetus for obesity pharmacotherapy. In the 6 US studies providing at least 2.5-years’ follow-up of traditional (ie, dietary±behavioral) obesity treatments, weight regain was 61% to 86% at 2.5 to 3.5 years²⁴⁻²⁷ and 75% to 121% at 5 years.^{28,29} These low rates of maintained weight loss are certainly overestimates of the response of the average patient since data are reported only for the fraction of patients (54%-83%) available and willing to participate in follow-up surveys.

MECHANISM OF ACTION

With the exception of orlistat, which blocks absorption of ingested fat by inhibiting pancreatic lipase, available weight loss drugs work by suppressing appetite through central mechanisms and possess no significant thermogenic abilities. Anorectics are classified as noradrenergic (ie, phentermine, mazindol, or diethylpropion hydrochloride) or serotonergic (ie, fenflurmine, dexfenfluramine, or fluoxetine hydrochloride) depending on which neurotransmitter they primarily effect. Sibutramine hydrochloride is a serotonin norepinephrine reuptake inhibitor effecting both serotonin and norepinephrine reuptake. Detailed

reviews of the mechanisms and sites of action of available and future anorectics are presented elsewhere.^{30,31}

STUDY SELECTION: STUDIES OF LONG-TERM OBESITY PHARMACOTHERAPY

Available long-term studies of obesity pharmacotherapy were identified through MEDLINE and bibliographic review of published articles. For this discussion, long-term studies are defined as including 9 months or more of treatment. While selected shorter or open-label studies are cited, only long-term, double-blind, placebo-controlled trials are considered in the comparative analysis. Since results in subjects with diabetes mellitus may differ from the broader patient base, trials limited to diabetic patients are reviewed but excluded from the comparative analysis. With the exception of orlistat, which has data on 742 patients treated for at least 1 year, existing long-term studies on available weight loss drugs contain data on fewer than 300 patients in aggregate.

NORADRENERGIC WEIGHT LOSS DRUGS

While older-generation noradrenergic appetite suppressants are approved for obesity treatment in the United States, obesity experts agree that these schedule II (eg, amphetamine-dextroamphetamine and methamphetamine) and schedule III drugs (eg, benzphetamine hydrochloride and phendimetrazine tartrate) have no current appropriate role in obesity treatment given the availability of newer anorectics (schedule IV) with negligible addiction or abuse liabilities. With the exception of 1 drug company's recent efforts to resurrect phendimetrazine for obesity treatment, the older anorectics have appropriately received little advertisement or use.

Diethylpropion

Introduced in 1960, diethylpropion is available as Tenuate, 25 mg (usually taken 3 times daily) or Tenuate Dospan, 75 mg (extended release, once daily). In the longest

double-blind, placebo-controlled diethylpropion study,³² weight loss at both the 6- and 12-month follow-ups was less in the drug-treated patients than in the placebo-treated patients at 7.0 vs 8.7 kg and 8.9 vs 10.5 kg, respectively. In separate shorter placebo-controlled trials, DeRamos³³ and McKay³⁴ reported weight loss after 6 months of diethylpropion treatment to be 7.8 and 11.7 kg, respectively, compared with 1.9 ($P > .05$) and 2.5 kg ($P < .01$) in placebo-treated patients. Overall, data for long-term diethylpropion treatment are limited to 30 patients at 6 months and 5 patients at 12 months. Although it may have the least stimulant adverse effects among the noradrenergic agents,³¹ a relatively rapid tolerance to its anorectic effects has been observed³⁵ while weight loss beyond 6 months has not.

Mazindol

While mazindol's pharmacological and anorectic actions (ie, inhibition of norepinephrine reuptake) resemble other noradrenergic anorectics, structurally it is related to the tricyclic antidepressants and lacks the phenylethylamine structure of the other noradrenergic anorectics and the fenfluramines. In patients with stable cardiac disease, mazindol treatment has been associated with untoward cardiac events (3 episodes of atrial fibrillation and 2 of syncope in 15 patients receiving mazindol for 12 weeks)³⁶ and significant withdrawals owing to adverse effects.^{37,38} The longest report of mazindol treatment was an open-label observation in which 11 patients treated intermittently for 12.5 months with mazindol, 1 mg/d, lost 14 kg ($P < .05$) compared with a loss of 10 kg in a historical control group treated with diet alone.³⁷ Other long-term data on mazindol are limited to an uncontrolled observation of 12-kg weight loss with 60 weeks' treatment and a higher rate of maintained weight loss for 1 year following a very-low-calorie diet with (53%) than without (20%) mazindol treatment.³⁸ Overall, mazindol's efficacy has not been assessed in a long-term, blinded, placebo-controlled trial and its safety in cardiac patients is suspect.

Phentermine

Phentermine, the still available "phen" of the recent "phen-fen" phenomenon, has been available since the 1960s with a worldwide exposure of more than 50 million prescriptions. It is available in a timed-release resin under the brand name Ionamin (15 or 30 mg) or a more quickly released hydrochloride form (15, 30, or 37.5 mg) in various brands and generic form. In the only long-term, double-blind, placebo-controlled phentermine study, 108 obese women were assigned to receive placebo, continuous phentermine (30 mg/d of phentermine resin), or intermittent phentermine (4 weeks receiving phentermine therapy and 4 weeks not receiving phentermine therapy) for 36 weeks.³⁹ Nondrug treatment in this study was limited to a single dietary instruction in a 1000-kcal diet at study initiation and monthly clinic visits for weigh-ins and prescription renewals. Weight loss was significantly greater ($P < .001$) in patients treated with continuous (12.2 kg) or intermittent phentermine (13.0 kg) than with placebo (4.8 kg). Adverse effects were minor with only 8% of the drug-treated patients and 3% of placebo-treated patients leaving because of perceived stimulant adverse effects such as agitation or insomnia. As with virtually all other studies of obesity pharmacotherapy, most weight loss occurred in the first 6 months. However, in contrast to the weight regain that has been observed despite continued pharmacotherapy with sibutramine⁴⁰ and fluoxetine⁴¹ after 6 months, phentermine-treated patients in this study continued with a slower rate of weight loss between months 6 and 9.

While no other long-term, placebo-controlled data are available for phentermine, several shorter double-blind placebo-controlled studies corroborate the efficacy of phentermine observed in the study by Munro et al.³⁹ In what could be termed the "other" phen-fen study, Weintraub et al⁴² compared weight loss in patients treated with placebo, phentermine, fenfluramine, or the phen-fen combination for 5 months. Weight loss with phenter-

mine in this study was 11.3 kg ($P < .01$ vs placebo) nearly identical to the 11.2-kg loss seen with phentermine at 5 months in the study by Munro et al. In this only published comparison of phen-fen with any other regimen, patients receiving phentermine monotherapy actually lost more weight than those receiving the phen-fen combination (11.3 vs 9.3 kg, $P > .05$). In a shorter 4-month trial,⁴³ weight loss in phentermine-treated patients (8.8 kg, $P < .01$ vs placebo) was consistent with weight loss at the 4-month mark in phentermine-treated patients in the studies by Munro et al³⁹ (10.4 kg) and Weintraub et al⁴² (9.2 kg). In a double-blind comparison of 5 different regimens of phentermine and/or fenfluramine, Steel and Munro⁴⁴ reported 9-month weight loss in phentermine-treated patients to be essentially the same (eg, 12.0 kg) as that seen in the Munro et al³⁹ prior 9-month study. While no placebo group was used in the Steel and Munro⁴⁴ study, the placebo group from the Munro et al study could reasonably serve as historical controls since both studies originated from the same research department and seem to have used the same nondrug treatments. Phentermine adverse effects in the comparative trial were low, with only 1 patient (3%) withdrawing because of phentermine adverse effects compared with 11 withdrawals (8%) because of perceived fenfluramine adverse effects.

Overall, available data suggest that phentermine is well tolerated and efficacious. Comparative studies suggest that its efficacy exceeds monotherapy with the fenfluramines^{42,44} and is comparable to combination therapy with phen-fen.⁴²

Sibutramine

Sibutramine is a serotonin norepinephrine reuptake inhibitor, blocking the reuptake of norepinephrine and serotonin. Since its appetite suppression is completely reversed by adrenergic blockade⁴⁵ and pure selective serotonin reuptake inhibitors (SSRIs) have been shown not to produce long-term weight loss,⁴¹ sibutramine's weight loss effects are primarily mediated by its noradren-

ergic action. Sibutramine is dispensed as Meridia and given at 10 or 15 mg/d, doses shown in a large dose ranging study to optimize weight loss vs adverse effects.⁴⁶

Long-term data on sibutramine for initial weight loss are from a 1-year trial comparing sibutramine at 10 or 15 mg/d to placebo in 485 patients.⁴⁰ The published results gave few details of any supportive treatments. Weight loss at 1 year was 1.8 kg in the placebo-treated group and 4.8 kg and 6.1 kg in the 10- and 15-mg sibutramine-treated groups, respectively ($P < .001$). Sibutramine was well tolerated with 57% of the 173 patients initially assigned to sibutramine therapy completing the study and an overall withdrawal rate of 13% because of adverse effects.

In the other long-term sibutramine study, 160 patients who had been successful in losing at least 13 lb (5.85 kg) on a 4-week very-low-calorie diet were given placebo or 10 mg/d of sibutramine for 1 year.⁴⁷ While providing valuable long-term data, this study is not comparable with others cited thus far because of 2 opposing selection biases. First, the study enrolled only patients who were already successful in losing weight on a low-calorie diet and may, therefore, have been more motivated and success prone than patients enrolled in other drug studies. Second, the usual tendency of patients to rapidly regain weight after rapid weight loss may have made it tougher for patients to lose more weight with or without medications. With these factors in mind, a significant positive effect of sibutramine therapy was noted at 1 year. After 1 year, the 81 sibutramine-treated patients had lost an average of 5.2 kg (in addition to the weight they had lost during the 4-week prestudy diet) compared with an average gain of 0.5 kg in placebo-treated patients ($P = .004$). Sibutramine was well tolerated with 73% of the sibutramine-treated patients completing the full year of treatment compared with 62% of the placebo-treated patients. The number and type of adverse events were similar in both patient groups with only 2 sibutramine-treated and 5 placebo-treated patients actually

withdrawing from the study owing to perceived adverse effects.

Overall, sibutramine has demonstrated effectiveness in producing weight loss in its 1-year studies. While it is generally well tolerated, its effects on heart rate (average increase of 3-4 beats/min) and blood pressure (average increase of 2 mm Hg) may be more than other noradrenergic anorectics.⁴⁸

Orlistat

Orlistat received Food and Drug Administration (FDA) approval for obesity treatment April 23, 1999, making it the newest of the available weight loss drugs. While it also inhibits gastric and carboxylester lipases, its inhibition of pancreatic lipase is responsible for its therapeutic action of blocking the absorption of approximately 30% of ingested fat calories.⁴⁹ Orlistat is available only as Xenical (Hoffmann-LaRoche Inc, Nutley, NJ) and is given at 120 mg 3 times daily, the dose determined to maximize the benefit-adverse effects ratio in separate dose ranging studies.^{49,50}

In patients having type 2 diabetes mellitus, 1 year of orlistat treatment produced a 1.9% greater weight loss (eg, 6.2% vs 4.3%, $P < .001$) than placebo.⁵¹ Long-term data for weight loss with orlistat in nondiabetic subjects is from 2 multicenter, randomized, double-blind, placebo-controlled, 2-year trials.^{52,53} The first (European) study of these compared weight loss in 340 placebo-treated patients with 343 patients receiving orlistat, 120 mg 3 times daily.⁵² Supportive treatment of both groups was dietary instruction (600 kcal/d—deficit for year 1 with eucaloric maintenance in year 2) and monthly clinic visits. One-year weight loss for orlistat-treated patients was 10.3 kg compared with 6.1 kg ($P < .001$) in placebo-treated patients. At the conclusion of year 1, patients were randomly reassigned to medication or placebo for year 2. During year 2, patients switched from placebo to orlistat lost an additional 0.9 kg while patients continuing to take orlistat regained approximately 25% of the weight lost during year 1. Six gastrointestinal tract adverse effects

occurred in at least 10% of the orlistat-treated patients and more frequently than with placebo; oily stool, 31% vs 5%; increased defecation, 20% vs 7%; oily spotting, 18% vs 1%; soft stool, 15% vs 9%; liquid stools, 13% vs 10%; and fecal urgency, 10% vs 3%. Completion rates were high with 83% of the orlistat-treated group and 76% of the placebo-treated group finishing 1 year of treatment.

The similar US multicenter orlistat trial yielded nearly identical results with a 1-year weight loss of 8.8 kg in 657 orlistat-treated patients compared with 5.8 kg in 223 placebo-treated patients ($P < .001$, intent-to-treat analysis).⁵³ At the end of year 1, orlistat-treated patients were randomly reassigned to placebo or orlistat at 60 or 120 mg, 3 times daily, while placebo-treated patients continued receiving placebo. During year 2, weight regain occurred in all 3 patients groups receiving orlistat for year 1 but was less ($P < .001$) for those receiving 120 mg of orlistat (3.2 kg, 35%), than for those receiving either 60 mg of orlistat (4.3 kg, 51%) or placebo (5.6 kg, 63%).

The concern about a possible association of orlistat with breast cancer that postponed FDA approval of orlistat was addressed in the US study during which 3 orlistat-treated patients (0.54%) and 1 placebo-treated patient (0.51%) developed breast cancer. In contrast to the evidence implicating adiposity in breast cancer risk,⁵⁴ a mechanism for an orlistat–breast cancer association is difficult to propose in light of its negligible systemic absorption⁵⁵ and lack of demonstrated carcinogenic or estrogen-stimulating effects.⁵⁶ Because of its inhibition of fat absorption, concerns about deficiencies in fat-soluble vitamins during orlistat treatment were addressed by both multicenter studies. Small decreases in vitamins D and E reached statistical significance in the US trial only while mean levels of these vitamins remained in the reference range in both studies. Vitamin supplements were required in 14.1% of the orlistat-treated and 6.5% of placebo-treated patients in the US study with restoration of normal levels in every case. The manufacturer recommends that patients taking or-

listat use a multivitamin containing the fat-soluble vitamins once daily at least 2 hours prior to an orlistat dose.

Overall, in 2 of the largest and most well-designed trials of obesity pharmacotherapy to date, orlistat has been shown to induce 1-year weight loss of 3 to 4 kg in excess of placebo. Adverse effects are virtually limited to the gastrointestinal tract because of its low absorption with adverse gastrointestinal events leading to the withdrawal of 9.0% and 3.5% of patients from the European and US studies, respectively.

SEROTONERGIC WEIGHT LOSS DRUGS

Selective Serotonin Reuptake Inhibitors

Fluoxetine and sertraline hydrochloride have both been studied for long-term weight loss with neither drug receiving FDA approval for obesity treatment. A 655-patient, 8-week dose ranging study showed that the 60-mg/d dose of fluoxetine hydrochloride was optimal for weight loss, producing a 4.0-kg loss vs 0.6 kg ($P < .001$) in placebo-treated patients.⁵⁷ The long-term data of fluoxetine for weight loss in nondiabetic patients consist of a multicenter US trial by Goldstein et al⁵⁸ in which drug treatment produced no weight loss at 1 year. Maximal weight loss in both groups occurred at 20 weeks and was modestly greater in the fluoxetine-treated group (5.1 vs 2.4 kg, $P < .05$). However, weight regain from that point forward was significantly faster in the fluoxetine-treated group with 52-week weight loss in the fluoxetine-treated and placebo-treated groups being 1.7 kg and 2.1 kg, respectively. Separate analysis of data from the participating centers showed a significant weight loss with fluoxetine treatment at only 1 of the 10 sites, possibly because of greater emphasis on a walking regimen.⁵⁹ It is difficult to attribute lack of fluoxetine effect at the other 9 sites to factors other than fluoxetine itself since the patients enrolled and the supportive treatments used in this study were similar to studies in which other anorectic agents did produce significant weight loss at 1

year. Other long-term data on fluoxetine for weight loss is limited to 2 studies in subjects with diabetes mellitus showing a small advantage in weight loss of 2 to 3 kg ($P < .05$) at 9 to 12 months of fluoxetine treatment.^{60,61} The remaining data on SSRIs for long-term weight loss consist of a study of sertraline hydrochloride, 200 mg/d, given to patients for 1 year to maintain weight loss after an initial very-low-calorie diet.⁶² Sertraline-treated patients regained 70.9% of their lost weight vs a 46.5% regain in the placebo-treated group ($P < .05$). Overall, the modest anorectic effects of SSRIs seem to wear off after about 5 months with no weight loss remaining at 1 year.

Nonselective Serotonin Reuptake Inhibitors

In addition to blocking synaptic reuptake of serotonin, the nonselective serotonergic weight loss drugs fenfluramine and dexfenfluramine stimulate serotonin release both in the central nervous system and from its major peripheral storage pool in platelets and can directly stimulate serotonin receptors.⁶³⁻⁶⁵ Although they are no longer available, a brief look at the long-term studies with fenfluramines is necessary to dispel the common misconceptions and lamentations that fenfluramines, particularly their combination with phentermine (ie, phen-fen), were so uniquely effective that obesity pharmacotherapy ceased to be worthwhile after their removal from the market. Long-term data on fenfluramine is limited to an open-label, 1-year observation in which 176 fenfluramine-treated patients lost 8.2 kg vs 4.5 kg (P value not reported) in patients treated with diet alone.⁶⁶ Long-term data on dexfenfluramine come mainly from the INDEX study, a double-blind, placebo-controlled trial in which 256 patients completing 1 year of dexfenfluramine treatment lost 9.8 kg vs 7.2 kg ($P < .001$) in the placebo-treated group.⁶⁷ A smaller placebo-controlled trial of dexfenfluramine showed a similarly small (eg, 2.7 kg) and nonsignificant increment in weight loss from 1 year of dexfenfluramine treatment.⁶⁸

Combination Therapy

Long-term, double-blind, placebo-controlled data on the initial treatment of obesity with phen-fen is limited to weeks 0 to 34 of the multiphase 190-week long-term weight control study.² Weight loss was 14.2 kg in the 58 phen-fen-treated patients vs 4.6 kg ($P<.001$) in the placebo-treated group.

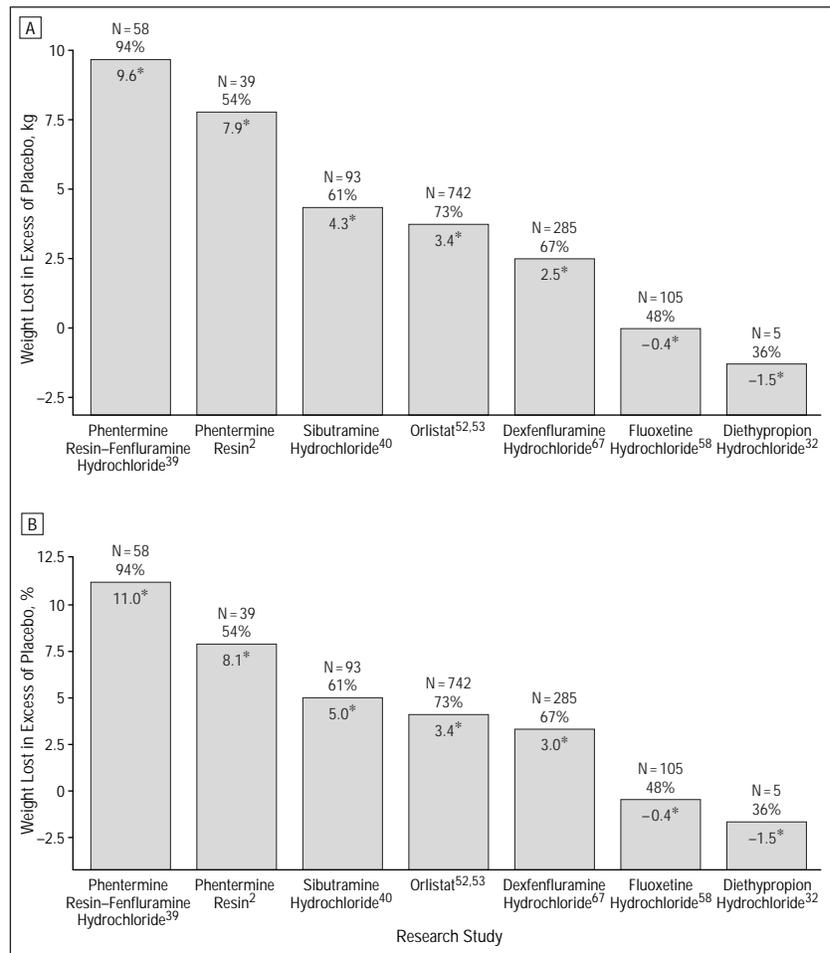
Efficacy of Obesity Pharmacotherapy

The **Figure** shows the weight loss attributable to diet drugs in all long-term, double-blind, placebo-controlled trials to date. In general, the lower the study completion rate, the more reported weight loss may overestimate results for the average patient since study completers are generally those who have lost the most weight. To highlight weight loss attributable to the drugs themselves, weight loss is reported as weight lost in excess of placebo. Percentage weight loss may be a better estimate of comparative efficacy than absolute weight loss as it controls for the tendency of heavier patients to lose more weight than lighter patients.

While available data do not permit definitive comparisons, phentermine resin seems to be the most effective available agent. The apparent weight loss advantage of phen-fen over phentermine in the Figure is mitigated by the slightly greater weight loss with phentermine monotherapy in the only head-to-head comparison of the 2 regimens.⁴² Sibutramine may have a small efficacy edge over orlistat with both of these agents being comparable to, or slightly more effective than, the discontinued dexfenfluramine.

Comparative Cost-effectiveness

Currently phentermine resin, sibutramine, and orlistat are the only drugs approved for obesity treatment in the United States that have demonstrated efficacy in long-term, double-blind, placebo-controlled studies. Their comparative cost efficacy is summarized in the **Table**.



Graphs show weight loss using diet drugs (A) and the percentage of weight loss using diet drugs (B). N indicates the total number of patients completing drug treatment for the referenced trials; percentage, the completion rate for patients assigned to drug treatment in the referenced trials; and the asterisk, $P<.001$ vs placebo. See "References" section for research study source.

SAFETY OF OBESITY PHARMACOTHERAPY

Valvular Heart Disease

On September 15, 1997, the fenfluramines were voluntarily withdrawn from the market. That action resulted from an FDA survey of reports from several independent sites showing asymptomatic valve abnormalities in 32% of 271 phen-fen users and the report by Connolly et al⁶⁹ of 24 cases of symptomatic valvular heart disease associated with phen-fen use. Subsequent reports have clarified the prevalence, incidence, mechanism, and natural history of the effects of these medications on heart valves.

Prevalence of Valvular Regurgitation in Uncontrolled Surveys

In the original FDA survey a case of valvular regurgitation attributable to

anorectic use was defined as at least mild aortic regurgitation (FDA AR) and/or at least moderate mitral regurgitation (FDA MR) since these levels of regurgitation were present in only 1% of the healthy adults aged between 23 and 35 years in the large CARDIA study.⁷⁰ In uncontrolled surveys, this FDA case definition may overestimate the risk of valvular regurgitation attributable to anorectic use since patients in these surveys had a mean age of 48 years where the background prevalence of valvular regurgitation is likely severalfold higher than the CARDIA study's younger reference population.

Since the original FDA survey, 4 additional uncontrolled surveys provide data on the prevalence of echocardiographic findings associated with anorectics. Burger and Sherman⁷¹ noted that the finding of FDA AR in 6.6% of 226 phen-fen-

Comparative Cost Efficacy of Available* Weight Loss Drugs

Medication and Dose†	Weight Loss in Excess of Placebo, ‡ %/kg	Cost, per mo/ per Year§	Cost for 1% Weight Loss, \$	Cost for 1-kg Weight Loss, \$
Phentermine resin, 30 mg/d	8.1/7.9	60/720	89	91
Sibutramine hydrochloride, 15 mg/d	5.0/4.3	116/1392	268	323
Orlistat, 120 mg thrice daily	3.4/3.4	119/1428	433	433

*Diethylpropion is available but was not effective in its only long-term, placebo-controlled study. Mazindol is available and possibly effective (see "Mazindol" subsection of the "Noradrenergic Weight Loss" section) but has no long-term, double-blind, placebo-controlled trials.

†These drugs are available only as the brands Ionamin (phentermine resin), Meridia (sibutramine), and Xenical (orlistat). Phentermine hydrochloride is a non-timed-release phentermine (with no long-term, placebo-controlled studies) that is available as a generic drug or several brands at a cost of \$10 to \$30 per month.

‡Kilograms and percentage lost in excess of placebo are the weighted average for all double-blind, placebo-controlled studies for each drug.

§Prices are the average retail prices quoted by 2 national and 1 regional pharmacy chain for the drugs on the same day.

treated patients in their survey was similar to the prevalence in like-aged normal offspring of the Framingham study. Kancherla et al⁷² reported an FDA AR prevalence of 12% in 200 consecutive patients referred after having used phen-fen or dexfenfluramine for an average of 8 months. Teramae et al⁷³ reported FDA valvulopathy in 60 (31%) of 191 patients referred to Mayo Clinic because of anorectic use. A much smaller survey found FDA AR in 10 of 22 phen-fen users.⁷⁴

Prevalence of Valvular Regurgitation in Case-Controlled Studies

Six case-control studies compared the prevalence of FDA AR and FDA MR in a total of 3505 patients receiving a fenfluramine with (n=1557) or without (n=1672) phentermine to that in 2017 generally well-matched control patients.⁷⁵⁻⁸⁰ In the 5 of these studies containing separate data on FDA AR and FDA MR,⁷⁵⁻⁷⁹ 4 reported FDA AR to be significantly more prevalent in patients (6.3%-25.0%; weighted average, 8.8%) than in controls (1.6%-4.1%; weighted average, 3.5%).⁷⁵⁻⁷⁸ In contrast, FDA MR was not significantly more common in patients than in controls in any of those reports. Much of the variability in FDA AR prevalence between studies^{75,76} and between treatment groups within studies⁸⁰ can be attributed to differences in duration of drug exposure. In the most vigorous analysis to date of the ef-

fect of exposure duration on FDA AR, Jollis et al⁷⁶ reported the prevalence of FDA AR as 4.4% for 0- to 6-months' exposure (relative risk, 1.5; $P>.05$; n=314), 7.0% for 6 to 12 months' (relative risk, 2.4; $P=.002$; n=420), 13.7% for 12 to 24 months' (relative risk, 4.6; $P<.001$; n=317) and 17.4% for longer than 24 months' (relative risk, 6.2; $P<.001$; n=86).⁷⁶

Incidence of Valvular Regurgitation

Two reports provide information on the incidence of FDA AR or FDA MR in patients with echocardiograms before and after diet drug use. Wee et al⁸¹ described 46 patients who had echocardiograms done before (average, 1.9 years) and after (average, 6 months) using a fenfluramine for a mean of 160 days. The lone case of new FDA AR or FDA MR was a 66-year-old man who developed moderate FDA AR (not seen on a prior study 9 years earlier) after 402 days of phen-fen use. While the prevalence of FDA valvulopathy was 8.3% among phen-fen users, use of the methodologic advantage of the cohort design to exclude patients with FDA AR or FDA MR on pre-treatment echocardiograms gave a rate of 2.6% for incident FDA valvulopathy. Ryan et al⁸² reported new FDA AR in 13 (12 patients with mild FDA AR and 1 with moderate FDA MR and FDA AR) of 86 patients with a longer fenfluramine exposure averaging 13.8 months.

Available data strongly suggest that clinically important valvular disease caused by the use of anorectics is rare. The above prevalence studies in more than 3500 patients consistently report a rare prevalence of FDA AR greater than mild, and rare or 0 prevalence of FDA AR greater than moderate. Three of the case-control prevalence studies contained specific comments on clinical valve disease in their patients (N>2800) and noted no clinically significant valvulopathy.^{75,76,79} In the most rigorous published search to date for anorectic-associated clinical valvulopathy, Jick et al⁸³ used a national UK database identifying almost 10000 anorectic-exposed patients. New cases of symptomatic valvulopathy were identified in 8 of 8903 patients exposed to dexfenfluramine or fenfluramine and 0 of 862 phentermine users. Reported symptoms were chest pain or angina in 3 patients, and fatigue, dyspnea, syncope, and palpitations in 1 patient each. Surgical cases and congestive heart failure were absent and the degree of valvular regurgitation was not specified.

Apart from isolated case reports, published data on symptomatic or surgical cases of anorectic-associated valvulopathy are preponderantly from the Mayo Clinic. In May 2000, Mayo Clinic researchers reported an update⁷² of the August 1997 findings by Connolly et al⁶⁹ that reported 24 symptomatic (5 surgical) cases of anorectic-associated valvulopathy. That update included patients referred between June 1997 and December 1997, and identified a total of 92 symptomatic and 5 surgical patients. Twenty of the 24 patients (not specified as surgical or symptomatic) from the original report were included in the update. Given the relatively short 12-month interval from anorectic initiation to symptomatic valvulopathy in the initial report by Connolly et al, the scarcity of reported symptomatic or surgical cases now 2 years after the fenfluramines recall is reassuring. In addition, case reports^{84,85} and the lower prevalence of FDA AR or FDA MR in prevalence studies with a longer elapsed time between anorectic ces-

sation and echocardiography⁷⁷ suggest that the natural history of anorectic valvulopathy is regression. The relatively few clinical cases to date are, therefore, more likely to be the majority that will be detected rather than the tip of the iceberg.

Mechanism

A serotonergic mechanism for anorectic valvulopathy was strongly suggested as early as the initial report by Connolly et al.⁶⁹ Specifically, endocardial fibroplasia seen in heart valves removed from anorectic-exposed patients was described as indistinguishable from the pathologic changes unique to carcinoid syndrome (serotonin excess) and ergotamine toxic reactions (serotonin-agonist effect⁸⁶). Unlike other anorectics, the fenfluramines have shown serotonin agonist effects.⁶³⁻⁶⁵ These agonist properties, rather than their serotonin (5-hydroxytryptamine)-releasing or reuptake inhibition effects, are likely primarily responsible for their demonstrated effects on the aortic valve since circulating serotonin is rapidly metabolized in the lungs. Recently, the fenfluramine metabolite norfenfluramine showed a high affinity for serotonin receptors (5-HT₂) that are highly expressed in heart valves and whose stimulation is known to cause fibroblast hyperplasia.⁸⁷ The serotonin-agonist hypothesis of anorectic-induced valvulopathy would also explain the lack of valve abnormalities in patients treated with SSRIs,⁸⁸ serotonin norepinephrine reuptake inhibitors (sibutramine),⁸⁹ and phentermine monotherapy.^{73,83} In terms of causality, anorectic valvulopathy is, therefore, reminiscent of primary pulmonary hypertension where physiologic,^{90,91} pathologic,^{92,93} and epidemiological⁹⁴ studies support a serotonergic mechanism and causal role for fenfluramines but not phentermine.

COMMENT

Pharmacotherapy Fundamentals

Available data can support the practitioner in an evidence-based approach to long-term obesity pharmacotherapy. While weight loss

attributable to medications is modest (Figure), this degree of weight loss is associated with important health and psychological benefits.⁹⁵⁻⁹⁸ In consideration of recent studies relating BMI to morbidity and mortality, there is general agreement that patients with a BMI exceeding 27 kg/m² with complications or a BMI exceeding 30 kg/m² without complications are potential candidates for weight loss drugs. In addition, weight loss drugs should only be taken by patients (and prescribed by physicians) who fully acknowledge obesity as a true chronic medical disease requiring nothing less than lifelong vigilance toward diet and activity patterns for sustained weight loss. In contrast, patients looking to diet drugs as another quick fix should never be prescribed these medications. A practical questionnaire for detailed assessment of a patient's readiness for aggressive obesity treatment has been developed by Brownell and Wadden⁹⁹ and is available in print or online at <http://www.LearnEducation.com>. Since patients undertaking weight loss programs often have the unrealistic goal of achieving ideal body weight,⁹⁸ expectations should also be addressed up front and an achievable goal (ie, last weight they felt good at, 10%-15% BMI reduction) set.

Of the 3 available weight loss drugs with demonstrated efficacy in long-term placebo-controlled trials, phentermine (resin) has produced the greatest weight loss (8.1% vs placebo) followed by sibutramine (5.0% vs placebo) and orlistat (3.4% vs placebo). These magnitudes of weight loss are supported by level I evidence (randomized, double-blind, placebo-controlled trials) for orlistat (2 studies)^{32,53} and sibutramine (1 study).⁴⁰ While the weight loss figure for phentermine is based directly on 1 long-term level II (double-blind, placebo-controlled) study,³⁹ it is closely corroborated by a long-term level III (blinded comparison with fenfluramine without placebo controls) study⁴⁴ and a shorter level I study.⁴² While no head-to-head data compare the 3 drug choices, cost efficacy would also favor phentermine as initial pharmacotherapy (Table).

Indefinite duration pharmacotherapy, while not FDA approved, is generally agreed to be appropriate for obesity as with other chronic diseases. In all cases, refills of weight loss medications should be limited and contingent on regular (not less than every 1-2 months) visits since weight loss maintenance is critically dependent on follow-up.

Role of Exercise

Patients considering pharmacotherapy must be informed of the evidence implicating deconditioning over obesity itself as the major killer of the obese¹⁰⁰ and of the dismal prognosis for maintaining weight loss without exercise.^{101,102} In light of that evidence, it is appropriate to make initiation and continuation of pharmacotherapy contingent on a patient's progression toward a regular activity regimen. Professional help with building this regimen is invaluable, particularly for those with little exercise experience. Type of exercise must consider the patient's preference, experience, access to facilities, and possible orthopaedic limitations. For patients considering home exercise machines, a treadmill may be more efficient in burning calories at given levels of perceived effort than a stationary bike or stair stepper¹⁰³ and mitigates the impact of walking on harder surfaces. Ultimately, the best form of exercise is the one that the patient finds enjoyable and sustainable. A daily exercise energy expenditure of 200 to 300 kcal, corresponding to a 2- to 3-mile walk (any speed) or 35 minutes of vigorous (eg, swimming, stair climbing, or jogging) activity has demonstrated optimal effectiveness in weight loss maintenance.^{101,104} The misconception that exercise must reach an aerobic threshold (often unattainable for the obese) to be beneficial is being replaced by the understanding that the goal of exercise for weight loss is total calories burned per week rather than achieving some threshold of exercise intensity. This true goal may be achieved by short frequent exercise bouts in patients whose time or physical conditioning limits initial exercise duration.

Role of Dietary Therapy

Commitment to an ongoing program of caloric restriction should also be a prerequisite to using weight loss drugs. Enrollment in a formal dietary program should be strongly encouraged and is nearly essential for patients with limited nutritional knowledge. While individual patients may experience short-term success on any diet, physicians must educate patients that, ultimately, it is caloric restriction and not, contrary to popular diet book titles, diet composition that determines weight loss. Specifically, low-carbohydrate diets have not produced greater weight loss than isocaloric low-fat diets in the metabolic ward¹⁰⁵ or in the community.^{106,107} In addition, low-carbohydrate diets lack the lipid-lowering effects of the lower-fat diets^{106,107} endorsed by the American Heart Association and American Diabetes Association.

Role of Obesity Surgery

Although weight loss drugs produce clinically important weight loss, the magnitude of weight loss with pharmacotherapy is rarely sufficient to bring the morbidly obese down to a healthy weight. Gastroplasty or gastric banding procedures, which produce early satiety by reducing stomach volume and influencing neurohormonal regulation of hunger, result in loss of 30% to 40% of excess weight. Bypass procedures also produce a mild malabsorptive effect by adding the bypass of an initial length of small intestine and are becoming the preferred procedure owing to superior weight loss. Average initial weight loss with modern gastric bypass surgery is 60% of excess weight.¹⁰⁸ Moreover, long-term maintenance of weight loss which is unusual with medical therapies is common after gastric bypass. At 4- to 5-years' follow-up, weight loss maintenance is 50% to 58% of excess weight.¹⁰⁹⁻¹¹¹ In 1 study of 608 patients who underwent bypass surgery and had 97% follow-up, maintenance of excess weight loss was 55% at 10 years and 49% at 14 years.¹¹¹

Dramatic reversal of obesity-related disability and medical com-

plications often follows gastric bypass surgery. For example, long-term normalization of glucose metabolism has been reported in 83% of patients with non-insulin-dependent diabetes mellitus and 98% of patients with impaired glucose tolerance.¹¹² At East Carolina University, annual mortality was 1% in patients undergoing gastric bypass surgery compared with 4.5% in similar patients referred for but not receiving surgery due to personal preference or insurance issues.¹¹¹ This mortality reduction is severalfold greater than the 1% annual mortality reduction associated with coronary artery bypass grafting in patients with stable angina.¹¹³

Established criteria for consideration of obesity surgery are BMI exceeding 40 kg/m² (or >35 kg/m² with complications from obesity), failure of aggressive medical therapy, stable psychiatric status, and an understanding of the need for lifetime lifestyle modification. As with pharmacotherapy, obesity surgery is likely underused as most patients meeting (and exceeding) the above criteria are never formally considered for surgery.

Role of Pharmacotherapy

Available evidence indicates that weight loss drugs have a definite role alongside diet and exercise in the battle against one of our nation's most pressing health problems. In contrast, the common misconception that obesity pharmacotherapy was dead (or at least in critical condition) after the fenfluramines recall is not supported by the evidence. Rather, that evidence indicates that the obesity drugs that we have are at least as effective as the drugs we have lost and are unassociated with the rare, but potentially serious, adverse effects that have received so much recent publicity.

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