

Combining Behavioral and Pharmacological Treatments for Obesity

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Abstract

Weight-loss medications are currently recommended for use only as an adjunct to diet, exercise, and behavior modification. Little, however, is known about the benefits of combining behavioral and pharmacological therapies or about the mechanisms that would make these combined approaches more effective than either used alone. This article reviews the effects of adding pharmacotherapy (i.e., principally sibutramine and orlistat) to a modest program of lifestyle modification. Studies revealed that the addition of medication typically improved short- and long-term weight loss compared with lifestyle modification alone. The best results, however, were obtained when medications were combined with an intensive, group program of lifestyle modification. The two approaches may have additive effects; behavioral treatment seems to help obese individuals control the external (i.e., food-related) environment, whereas pharmacotherapy may control the internal environment by reducing hunger, cravings, or nutrient absorption. The article examines possible methods of sequencing behavioral and pharmacological therapies and offers suggestions for future research.

Key words: weight-loss medications, sibutramine, orlistat, behavior therapy, obesity

Introduction

The Food and Drug Administration (FDA), as well as an expert panel convened by the National Heart Lung and Blood Institute, has recommended that weight-loss medications be used only as an adjunct to a comprehensive pro-

gram of lifestyle modification that includes diet, physical activity, and behavior therapy (1). A common hypothesis is that medication should help facilitate adherence to lifestyle modification. By reducing appetite or nutrient absorption, medications may make it easier for patients to adhere to a low-calorie diet. Surprisingly little, however, is known about the specific benefits of combining these therapies, or how and when they should be combined. This paper reviews evidence from randomized control trials that compare the effects of lifestyle modification, pharmacotherapy, and their combination. The potential mechanisms of action of combination therapy are explored, and ways to maximize the benefits of this approach are discussed.

Lifestyle Modification

Lifestyle modification generally consists of a combination of dietary modification, exercise, and behavior therapy. Women who wish to lose weight are usually encouraged to eat 1200 to 1500 kcal/d and men are encouraged to eat 1500 to 1800 kcal/d. Instruction is provided in consuming a well-balanced, low-fat diet, as suggested by the Food Guide Pyramid (2). In addition, patients may be instructed to select foods high in fiber to enhance satiety and nutrition. They are also encouraged to gradually increase their physical activity to 30 min/d, most days of the week (3). Adherence to diet and exercise recommendations is promoted through the use of behavioral techniques (4), including recording caloric intake and physical activity and limiting the places and activities associated with eating and inactivity (i.e., stimulus control). Instruction is also provided in cognitive restructuring to prevent relapse. Adherence to these weight-control behaviors may be facilitated by the use of reinforcement contingencies (e.g., monetary or social support) (5).

Weight Loss

Comprehensive behavioral programs, providing weekly group treatment of 20 to 26 weeks, produce mean losses of 8 to 10 kg (~9% of initial body weight) and are associated with attrition of ~15% to 20%. By contrast, less intensive interventions that provide patients with treatment manuals and minimal or no therapist contact produce weight losses of only 1 to 5 kg over 6 months (6–8).

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The well-documented problem with lifestyle modification is weight regain after treatment termination. On average, in the year after treatment, patients regain ~30% to 35% of their weight loss. Approximately 3 to 5 years after therapy, 50% or more of participants have returned to their baseline weight (9,10). These results are not entirely discouraging considering that most obese people, left untreated for 3 to 5 years, would probably gain 0.5 to 1 kg per year (11).

Mechanisms of Action

Reducing energy intake is the key to short-term weight loss; the greater the energy deficit, the greater the loss (12,13). Attending treatment sessions and keeping food records are consistently related to weight loss (1,5–6), probably because they facilitate adherence to energy restriction. Whereas increased physical activity may contribute modestly to short-term weight loss (14), the role of other components of lifestyle modification, including stimulus control, problem-solving, cognitive-restructuring, and reinforcement contingencies, is unclear. During treatment, cognitive restraint (i.e., cognitive control of eating) and self-efficacy increase; however, these variables are only modestly correlated with weight loss (15,16).

The maintenance of weight loss is facilitated by patients engaging in high levels of physical activity (17–22). Frequent patient-provider contact also prevents weight regain (23–26). Behavioral-maintenance therapy, however, seems only to delay rather than to prevent weight regain. Attendance of maintenance sessions declines over time, and once treatment is terminated, patients regain weight (23). As others have suggested (27), it may be asking too much for overweight individuals to exert continuous control in the face of unremitting biological factors and an environment that supplies an abundance of ready-made high-calorie, high-fat foods, as well as a multitude of energy-saving devices. Interventions are needed that make the day-to-day work of weight control *easier* and more sustainable. Pharmacotherapy may be helpful in this regard.

Pharmacotherapy

Historically, anorectic agents have induced weight loss by influencing central nervous system (CNS) receptors associated with eating and appetite regulation. Noradrenergic (e.g., amphetamines) and serotonergic (e.g., fenfluramines) agents, for example, were associated with reports of decreased hunger and increased satiety, respectively (28). Studies also reported macronutrient-specific effects of CNS agents (29–31), although the data were contradictory (32–34).

The history of weight-loss agents has been marked by several adverse experiences. In 1997, for example, fenfluramine and dexfenfluramine were withdrawn from the market because of their association with valvular heart disease

(35). Two medications, sibutramine and orlistat, are currently approved by the FDA for long-term use in obesity management. Sibutramine is a CNS agent that inhibits the reuptake of norepinephrine and serotonin. By contrast, orlistat is a gastric and pancreatic lipase inhibitor that works by blocking the absorption of about one-third of the fat contained in a meal; the undigested fat is excreted in stool (36). The medications seem to be generally safe and effective when used with appropriate persons under medical supervision. The clinical use of these medications has been described by several investigators (28,37,38).

Sibutramine

Weight Loss. Sibutramine, in conjunction with dietary therapy, induces weight losses of 4% to 12% of initial body weight, which are 3 to 9 percentage points greater than those produced by placebo. Losses have been sustained for up to 2 years with continuous therapy (39,40). Sibutramine has also been found to induce weight loss independent of subjects' efforts to diet and lose weight (41).

Mechanisms of Action. Sibutramine has been shown to reduce energy intake, particularly at lunchtime (42). This may be because peak plasma concentration occurred at this time, after early morning dosing (41,42). Preliminary research did not find that the medication altered macronutrient selection (41,42); however, further studies are needed. Research on the appetite-altering effects of sibutramine has yielded mixed findings; 6-month studies showed reductions in hunger and increases in fullness (43,44), but shorter-term studies found no such effect (45–48). Studies also were divided concerning whether the medication has a thermogenic effect (47,48); it seems to be very weak, if present.

Orlistat

Weight Loss. Orlistat, in conjunction with a reduced-calorie diet, produces weight losses of 5% to 13% of initial body weight. These losses are 2 to 6 percentage points greater than those associated with placebo. Weight losses are generally well-maintained for up to 2 years, although modest weight regain was observed in patients while they remained on medication (49,50).

Mechanisms of Action. Unlike sibutramine, orlistat does not affect the CNS and is unlikely to have a direct effect on appetite (51). It induces weight loss principally by blocking the absorption of about one-third of the fat consumed in a meal. However, orlistat also could affect food preference through aversive conditioning. Specifically, individuals may learn to eat less fat to avoid aversive gastrointestinal side-effects that include increased defecation, soft stools, fatty/oily evacuation, and oily spotting (50,52,53). In anecdotal reports, patients noted that orlistat acted as a “watchdog” for dietary compliance (54). Consistent with this hypothesis, one report (55) found that fat intake was generally higher in the placebo group than in orlistat-treated partici-

pants, but differences between groups were not statistically significant. Another study found similar fat intake in placebo- and orlistat-treated groups (52). Thus, further research is needed to determine orlistat's effects on food preferences.

Why Is Medication Recommended Only as an Adjunct to Diet, Exercise, and Behavior Therapy?

There are several reasons for recommending that pharmacotherapy be added to a program of lifestyle modification. First, growing evidence shows that a program of modest physical activity can reduce the risk of cardiovascular disease, independent of weight status (56,57). Similarly, behavioral treatment encourages patients to eat a low-fat, low-cholesterol diet, which, by itself, may reduce the risk of coronary artery disease (58). These important benefits would be lost if weight loss were induced by medication alone.

Second, without lifestyle modification, pharmacotherapy alone might result in suboptimal short- and long-term weight losses. Larger weight losses are desirable because they are generally associated with greater improvements in weight-related health complications (59). They are also eagerly desired by obese individuals (60).

Third, adding pharmacotherapy to lifestyle modification fits well with a stepped-care approach in which the least aggressive intervention is tried first and, if unsuccessful, is augmented by more aggressive interventions. In this model, lifestyle modification is the cornerstone of weight management, in part, because it is less expensive and has fewer side-effects than pharmacotherapy. The next section reviews research on the effects of adding pharmacotherapy to lifestyle modification.

Does the Addition of Pharmacotherapy Improve the Results of Lifestyle Modification?

Most studies of pharmacotherapy compare the effects of placebo plus lifestyle modification with medication plus the same program of lifestyle modification. These placebo-drug studies appropriately test the efficacy of the medication. The use, however, of placebos in these trials limits their assessment of lifestyle modification as delivered in clinical practice. A placebo could diminish the effectiveness of the lifestyle-modification program by reducing participants' involvement in behavioral treatment (61). Nonetheless, the placebo-controlled trials reviewed below do provide an assessment of whether adding medication generally improves on the results of diet and exercise modification.

Tables 1 and 2 summarize the results of double-blind placebo controlled trials of 6 months or more that used sibutramine or orlistat. Participants were overweight or obese (i.e., body mass index ≥ 25 kg/m²) adults and were

predominantly women. Most trials included relatively weak programs of lifestyle modification, in part, to better reveal the effects of the medications (28). Diet and exercise modification was typically initiated during a 2- to 4-week single-blind run-in period, after which subjects were randomized into the double-blind phase of the study. The diets generally contained 30% fat and were designed to produce a mild hypocaloric deficit of 500 to 600 kcal/d. Unless otherwise noted, data in the tables reflect weight change beginning after the run-in period. Data from subjects who completed the trials are reported, unless otherwise noted in the text.

Induction of Weight Loss

As indicated in Table 1, sibutramine produced mean weight losses that were 3 to 9 kg greater than placebo when both interventions were combined with a low-intensity program of lifestyle modification. These findings demonstrate sibutramine's efficacy and suggest that the medication can improve a modest program of lifestyle modification administered with a placebo.

Studies of orlistat plus lifestyle modification produced weight losses that were 2 to 6 kg greater than those resulting from placebo plus lifestyle change (Table 2). Thus, similar to sibutramine, orlistat seems to improve results produced by minimal lifestyle modification therapy (with placebo).

Whether these medications would have the same weight-loss enhancing effect when combined with a more comprehensive lifestyle-intervention program is unknown. Comprehensive lifestyle-modification programs provide weekly group treatment and specific instruction in diet, exercise, and behavioral strategies. By contrast, the low-intensity interventions used in most of the studies of sibutramine and orlistat provided little (e.g., monthly) or no contact with a weight-loss practitioner and only general recommendations for modifying eating and exercise habits. Three studies of fenfluramine (62–64), as well as one of the fenfluramine-phentermine combination (65) (summarized in Table 3), found that medication, combined with a comprehensive program of lifestyle modification, produced significantly greater weight loss than the same behavioral program used alone or combined with placebo. However, the potential benefits of adding medication to a comprehensive lifestyle-modification program cannot be fully determined until such studies are conducted with medications approved for long-term use. In addition, comparison conditions are required, including lifestyle modification without a placebo pill (66).

Weight-Loss Maintenance

Pharmacotherapy's greatest benefit may be in facilitating the long-term maintenance of weight loss. Placebo-controlled trials of this issue generally provided the same frequency of follow-up visits as used in behavioral treatment (i.e., monthly or quarterly follow-up visits). In this way, the

Table 1. Randomized double-blind controlled trials of sibutramine and lifestyle modification for obesity

Reference	Randomized/ completed (n)	Dose (mg/QD)	6-Month weight loss (kg)	1-Year weight loss (kg)	2-Year weight loss (kg)	Number of counseling visits
Apfelbaum et al. (67)	81/54	SIB 10	~12.7 ^{a*}	~12.7 (12%) ^{a*}	—	3 in 6 months; total, 5 over 1 year; dietitian provided advice
	78/45	PL	~ 9.0 ^{b*}	~7.6 (7%) ^b		
Bray et al. (76)	173/147	SIB 15	7.3 (7.5%) ^b	—	—	1 in 6 months; dietitian provided advice
		SIB 20	8.3 (8.8%) ^b			
		PL	0.5 (0.2%) ^a			
Bray et al. (77)	152/98	SIB 15	7.0 (7.4%) ^b	—	—	1 in 6 months; dietitian provided advice
		SIB 20	8.2 (8.8%) ^b			
		PL	1.3 (1.2%) ^a			
Cuellar et al. (43)	35/22	SIB 15	10.4 (11.8%) ^{a†}	—	—	7 in 6 months; physician provided minimal dietary counseling
	34/9	PL	1.3 (1.4%) ^{b†}			
Dujovne et al. (94)	162/114	SIB 20	4.9 (4.9%) ^{a†}	—	—	1 in 6 months (additional sessions, as needed); individual dietary counseling
	160/105	PL	0.6 (0.6%) ^{b†}			
Fanghanel et al. (44)	55/40	SIB 10	7.5 (8.7%) ^{a‡}	—	—	8 in 6 months; psychologist provided tailored advice
	54/44	PL	3.2 (3.8%) ^{b‡}			
Fujioka et al. (95)	89/60	SIB 20	4.4 (4.5%) ^a	—	—	8 in 6 months; individual dietary counseling
	86/60	PL	0.4 (0.5%) ^b			
James et al. (40)	352/204	SIB 10–20	—	~11.0§	10.2 (10%) ^{b§}	12 in year 1; total 24 in 2 years; monthly sessions with a dietitian with the option of returning every 2 weeks
	115/57	PL	—	~ 7.0§	4.7 (4.6%) ^{a§}	
McMahon et al. (68)	150/79	SIB 20	~4.4	4.4 (4.7%) ^{a‡}	—	1 in 6 months; dietary advice
	74/41	PL	~0.5	0.5 (0.7%) ^{b‡}		

Superscripts that differ (a and b) are significantly different ($p < 0.05$). Percentage weight loss is provided in parentheses to aid interpretation.

* Treated by very-low-calorie diet for first month during which participants lost approximately 7.5 kg; data in the table reflect weight losses from baseline, representing 13 months of treatment.

† Data reflect values from last-observation-carried-forward analysis.

‡ Sibutramine initiated after 2 weeks of a low-calorie diet and a 1.4 kg loss; data reflect weight losses from baseline.

§ Randomization and placebo initiated after 6 months of dieting plus sibutramine, during which patients lost about 11 kg; data in the table reflect weight loss from baseline.

QD, once daily; SIB, sibutramine; PL, placebo.

Table 2. Randomized double-blind controlled trials of orlistat and lifestyle modification for obesity

Reference	Randomized/ completed (n)	Dose (mg/TID)	6-Month weight loss (kg)	1-Year weight loss (kg)	2-Year weight loss (kg)	Number of counseling visits
Davidson et al. (70)	657/458 223/133	ORL 120 PL	—	8.7 (8.8%) ^a 5.8 (5.8%) ^b	7.6 (7.6%) 4.0 (4.0%)	18 in 1 year; total 24 in 2 years; dietary and exercise advice; 4 behavioral modification sessions/year
Finer et al. (71)	114/73 114/66	ORL 120 PL	~9.0 ^a ~6.6 ^b	8.8 (8.8%) ^a 5.5 (5.5%) ^a	—	10 in 6 months; total 16 in 1 year; dietary advice
Hauptman et al. (49)	210/14 212/122	ORL 120 PL	—	7.9 (7.9%) ^{a*} 4.1 (4.2%) ^{b*}	5.1%* 1.7%*	5 in 1 year; total 9 in 2 years; physician provided brief dietary and exercise advice; video-administered behavioral guidance
Hollander et al. (69)	163/139 159/115	ORL 120 PL	(~6.0%) (~3.5%)	(6.3%) ^a (4.2%) ^b	—	9 in 6 months; total 18 in 1 year; dietitian provided dietary and exercise advice; a minimum of 4 sessions included behavioral advice
James et al. (96)†	23/9 23/11	ORL 120 PL	8.6 (8.4%) 5.5 (5.7%)	(8.4%) (2.6%)	—	6 in 6 months; total 8 in 1 year; dietitian and obesity nurse provided dietary and exercise advice
Karhunen et al. (86)	45/36 45/36	ORL 120 PL	11.2 ^a 8.7 ^b	13.1 ^a 8.6 ^b	—	~3 in 6 months; total 4 in 1 year; dietitian provided dietary counseling
Rossner et al. (72)	244/181 243/158	ORL 120 PL	(~8.5%) (~6.5%)	9.8 (10.2%) ^a 4.3 (4.5%) ^b	(7.8%) (4.5%)	8 in 6 months; total 16 in 2 years; dietitian provided dietary and behavioral advice
Sjöström et al. (51)	343/284 340/260	ORL 120 PL	—	10.3 (10.2%)* 6.1 (6.1%)*	(~8%)* (~4%)*	16 in 1 year; total 24 in 2 years; dietitian provided dietary and behavioral advice
Van Gaal et al. (97)	120/97 123/96	ORL 120 PL	(9.8%) ^b (6.5%) ^a	—	—	14 in 6 months; dietitian provided advice
Zavoral (98)	1561/1107 1119/722	ORL 120 PL	—	(9.2%)* (5.8%)*	—	Inconsistent across sites; nonstandardized instruction in dietary, exercise, and behavioral advice

Superscripts that differ (a and b) are significantly different ($p < 0.05$). Percentage weight loss is provided in parentheses to aid in interpretation.

* Data reflect values from last-observation-carried-forward analysis.

† p values were not reported.

TID, three times daily; ORL, orlistat; PL, placebo.

Table 3. Short-term randomized controlled trials evaluating current or former anti-obesity medications and lifestyle modification

Reference	Treatment groups	Randomized/ completed (n)	Number of counseling visits	Weight loss (kg)
Brightwell and Naylor (66) (at 8 weeks)	1) Lifestyle mod + placebo (PL)	1) 20/15	1) 3	1) 2.0 (2.0%) ^a
	2) Lifestyle mod + med (phentermine)*	2) 20/15	2) 3	2) 7.5 (8.3%) ^b
Brownell and Stunkard (64) (at 16 weeks)	1) Lifestyle mod alone	1) 43/39	1) 16	1) 7.1 (8.0%) ^a
	2) Lifestyle mod + med (fenflur)†	2) 69/62	2) 16	2) 10.8 (10.9%) ^b
Craighead (63) (at 16 weeks)	1) Med alone (fenflur)†	1) 16/13	1) 7	1) 4.8 (6.6%) ^a
	2) Lifestyle mod alone	2) 16/15	2) 16	2) 5.7 (7.7%) ^a
	3) Lifestyle mod + med (fenflur)†	3) 14/13	3) 16	3) 6.9 (8.8%) ^b
Craighead et al. (62) (at 26 weeks)	1) Med alone (fenflur)‡	1) 10/9	1) 7	1) 6.0 (7.3%) ^a
	2) Lifestyle mod alone	2) 40/33	2) 26	2) 10.9 (12.0%) ^b
	3) Lifestyle mod + med (fenflur)‡	3) 34/31	3) 26	3) 15.3 (15.6%) ^c
Wadden et al. (73) (at 24 weeks)	1) Med alone (SIB)§	1) 19/13	1) 7	1) 5.6 (5.8%) ^{a¶}
	2) Lifestyle mod + med (SIB)§	2) 17/13	2) 20	2) 11.4 (11.0%) ^{b¶}
	3) Lifestyle mod + LCD + med (SIB)§	3) 17/17	3) 20	3) 17.9 (17.7%) ^{c¶}
Weintraub et al. (65) (at 34 weeks)	1) Lifestyle mod + PL	1) 54/49	1) 14	1) 4.6 (4.9%) ^a
	2) Lifestyle mod + med (fen-phen)**	2) 58/54	2) 14	2) 14.3 (15.6%) ^b
Weintraub et al. (99) (at 24 weeks)	1) Lifestyle mod + PL	1) 18/10	1) 3	1) 4.4 (5.0%) ^a
	2) Lifestyle mod + med (phentermine)††	2) 20/14	2) 3	2) 10.0 (11.0%) ^b
	3) Lifestyle mod + med (fenflur)††	3) 19/8	3) 3	3) 7.5 (8.4%) ^b
	4) Lifestyle mod + med (fen-phen)††	4) 21/13	4) 3	4) 8.4 (10.1%) ^b

Superscripts that differ (a, b, and c) are significantly different ($p < 0.05$). Percentage weight loss is provided in parentheses to aid in interpretation.

* Medication dosage was 30 mg/d.

† Medication dosage was up to 160 mg/d.

‡ Medication dosage was up to 120 mg/d.

§ Medication dosage was up to 15 mg/d.

¶ Data reflect values from last-observation-carried-forward analysis.

** Medication dosage was 60 mg/d of phentermine and 15 mg/d of fenfluramine.

†† Medication dosages were: 30 mg/d of phentermine; 60 mg/d of fenfluramine; and 30 mg/d of fenfluramine plus 15 mg/d of phentermine.

Lifestyle mod, lifestyle modification; med, medication; PL, placebo.

results are generalizable to trials of lifestyle modification; however, the use of a placebo remains a potential confounder.

In studies of 1- and 2-year durations, sibutramine (10 to 20 mg/d) produced an average weight loss of 7 to 10 kg, which was 5 kg greater than placebo plus lifestyle modification. Patients maintained 100% of their 6-month weight losses at 1 year (40,67,68), and 90% of their 1-year loss at 2 years (40) (Table 1).

More studies have evaluated the long-term effects of orlistat. In 1-year studies, weight loss averaged 6 to 10 kg, equal to a 4-kg placebo-subtracted weight loss (49,51,69,72).

In 2-year studies (49,51,70), weight losses averaged 5 to 8 kg, which were also ~4 kg greater than placebo. Across studies, patients maintained nearly 100% of their 6-month weight loss at 1 year and ~75% of this loss at 2 years. The medication, compared with placebo, reduced the rate of weight regain but did not prevent it entirely.

In summary, long-term studies of sibutramine and orlistat demonstrate that the medications significantly improve long-term weight loss compared with placebo when combined with standard monthly or quarterly treatment visits. However, additional research, particularly with sibutramine, is needed to assess the long-term efficacy (≥ 2 years) of

these medications. It is also unclear whether medication would improve results on a more comprehensive behavioral weight-maintenance program (with biweekly patient visits) as described by Perri et al. (23).

Does Adding Lifestyle Modification Improve the Results of Pharmacotherapy?

Clearly, pharmacotherapy improves results of a modest program of lifestyle modification, but does adding lifestyle modification improve on the results of pharmacotherapy alone? This may seem like an inappropriate area of inquiry, given that pharmacotherapy is only recommended as an adjunct to a comprehensive lifestyle-modification program. In clinical practice, however, weight-loss medications are often used alone.

Earlier studies of formerly approved weight-loss agents examined the effects of medication alone compared with a comprehensive program of lifestyle modification and the combination of the two therapies (62,63). Craighead et al. (62) found that individuals treated with fenfluramine in monthly, routine office visits lost an average of 6 kg in 26 weeks; patients treated with weekly group lifestyle modification alone lost 11 kg. However, patients treated with both medication and group lifestyle modification lost a significantly greater amount—15 kg. Thus, the addition of lifestyle modification improved the results obtained with treatment by pharmacotherapy alone (and vice versa). A similar study (63) of only 16 weeks reached the same conclusions, although weight losses for all three groups were smaller than in the 26-week investigation.

Only one study of currently approved medications examined whether adding lifestyle modification improved the results obtained by medication alone. In a 1-year trial, Wadden et al. (73) examined the effect of 15 mg/d of sibutramine combined with three interventions. Patients in the medication-alone group were instructed to consume a diet of 1200 to 1500 kcal/d and to walk ~150 min/wk; they were not, however, provided any instruction in behavior change. Persons in the medication plus lifestyle-modification group received the same diet and exercise prescription but attended weekly group treatment sessions for the first 5 months and monthly sessions for the remainder of the year. Patients in a third group received the same behavioral intervention but for the first 4 months were prescribed a 1000-kcal/d portion-controlled diet. After 6 months, patients in the medication-alone group lost only 5.8% of initial weight compared with significantly greater losses of 11.0% and 17.7% for participants in the second and third groups, respectively. Similar findings were found at 1-year follow-up. These findings illustrate that lifestyle modification improves the pharmacological treatment of obesity. This study, however, did not include a lifestyle-

modification-alone group, which precludes determination of whether pharmacotherapy improves on comprehensive lifestyle modification treatment.

Clearly, additional research on sibutramine and orlistat (as well as agents to be discovered) is needed to determine whether greater intensity of lifestyle modification improves the efficacy of these medications, as suggested by the study by Wadden et al. (73). The use in current placebo-controlled trials of low-intensity lifestyle programs may simulate practice in a primary-care setting and ensure that any adjunct behavioral treatment does not mask the effects of the drug. However, it is possible that the medication's effects are enhanced by more aggressive lifestyle interventions.

How Could Combining Medication and Lifestyle Modification Result in Better Weight Control than Either Approach Used Alone?

As reviewed above, weight-loss medications seem to improve on the effects of low-intensity and possibly comprehensive lifestyle modification programs. An important question is how the combination of lifestyle modification and pharmacotherapy could be more effective than either approach alone. Three possible ways are discussed.

Additive Hypothesis

First, it is possible that the treatments act additively. Each treatment may target a unique set of variables, and combined, target more variables and result in greater weight loss. Behavioral treatment teaches patients to control the external environment. Patients are instructed to control external prompts to eat by storing food out of sight, shopping from a list, avoiding fast-food restaurants, and keeping records of everything eaten. By contrast, medication would seem to modify principally biological variables that affect hunger, fullness, palatability, or fat absorption.

Studies of formerly approved medications support these hypotheses. Investigations that compared fenfluramine and lifestyle modification found that patients who received behavior therapy showed significantly greater improvements in eating habits, cognitions, and adherence to their eating schedule (63,74). They also reported greater control of their weight and felt that the program was more helpful, compared with patients treated by fenfluramine alone (63,74). By contrast, studies of the fenfluramine-phentermine combination found that it was associated with greater improvements in hunger (65) and evening fullness (65), and with reduced difficulty with dietary adherence (65), compared with behavioral treatment alone. The withdrawal of medication also resulted in increased hunger and decreased fullness (65). These studies suggest that medication and lifestyle modification targeted different variables.

A recent study of sibutramine reported similar findings (75). In an 18-week trial, sibutramine (15 mg/d) combined

with intensive lifestyle modification (i.e., weekly group behavioral treatment) was compared with sibutramine plus minimal lifestyle intervention (i.e., monthly physician visits) and with an intensive lifestyle-modification-alone group. At the end of treatment, patients treated with sibutramine plus minimal lifestyle modification reported significant reductions in hunger and craving but no increases in their practice of weight-control behaviors (e.g., exercising, eating vegetables, following a meal plan). By contrast, those treated with intensive behavior modification alone reported little change in appetite but significant increases in their practice of weight-control behaviors. Participants who received combined treatment (i.e., medication plus behavior therapy) seemed to reap the benefits of both approaches. They reported significant improvements in both appetite and their practice of weight-control behaviors. Based on these findings, behavioral and pharmacological treatments seem to target different variables; thus, an additive effect seems plausible.

Synergistic Hypothesis

A second possibility is that medication and behavioral treatment act synergistically and enhance one another's efficacy. A synergistic effect would occur if the weight loss produced by combined treatment was greater than the sum of the weight losses produced from medication therapy and lifestyle modification alone. This hypothesis is suggested by examining the placebo-subtracted weight losses (an indication of medication efficacy) in studies of sibutramine. Specifically, in studies that prescribed 15 mg/d of sibutramine, the most intensive lifestyle-modification program, which included on-going dietary counseling sessions (43), resulted in a 9-kg placebo-subtracted weight loss, whereas the two studies that used less intensive lifestyle-modification therapy (76,77) resulted in 7 and 6 kg placebo-subtracted weight losses, respectively. Thus, the greater intensity of lifestyle-modification treatment may have improved the medication's efficacy. This possibility, however, was only suggested; it was not apparent for studies of sibutramine with 10 mg or 20 mg or in studies of orlistat.

There are a number of ways synergistic effects could occur. For example, behavioral treatment could enhance the effects of medication by improving medication adherence; self-monitoring, cue control, and similar behavioral techniques could facilitate the behavior of taking medication. Conversely, by suppressing appetite, anorectic agents could facilitate adherence to lifestyle modification, including patients' dietary and possibly exercise compliance. Improved appetite control could make it easier for patients to adhere to behavioral goals such as eating a low-calorie, low-fat diet and recording their food intake. It is also possible that medication could blunt the palatability and reduce food value (78), thereby making it easier for patients to adhere to an appropriate calorie level.

Compensatory-Effects Hypothesis

A third possibility is that combination treatment has compensatory effects. Each treatment may prevent the untoward effects produced by the other. For example, medication could counteract the declines in resting energy expenditure (REE) and leptin that are associated with dieting and weight loss, and which ultimately slow weight loss. It might be possible to use medications such as leptin to reverse the decline in REE that occurs with energy restriction and weight loss (79).

Ultimately, additive, synergistic, and/or compensatory interactions may differ depending on the medication and lifestyle intervention used and the particular outcome variable of interest (e.g., appetite vs. REE). In addition, new medications are likely to have new mechanisms of action. Clearly, multiple dimensions of therapeutic efficacy will need to be considered in evaluating how treatments interact to enhance weight loss.

Options for Combining Medication and Lifestyle Modification

Another important question is when and how best to combine medication and lifestyle modification to maximize weight loss and long-term weight control. A stepped care approach suggests that lifestyle modification should be prescribed first, with pharmacotherapy provided only to those individuals who are unsuccessful, for example, in losing 10% of initial body weight or in improving control over a risk factor (e.g., type 2 diabetes). Similarly, with a stepped approach, those who lost 10% would only be prescribed medication if they began to regain weight (for example, >2 percentage points of their initial loss). Whereas this approach is logical from the standpoints of both safety and cost, some patients might benefit from receiving both lifestyle modification and pharmacotherapy from the outset of treatment. This is particularly true of individuals who reported a history of difficulty in losing weight by diet and exercise alone. Patients with a marked history of weight loss and regain (i.e., weight cycling) also might wish to begin taking medication as soon as they reached a weight-loss plateau (e.g., >1 month). Given the significant weight regain that occurs with the withdrawal of either lifestyle modification or medication, the great majority of patients will require long-term treatment of some kind. At present, investigators know little about how best to prescribe lifestyle modification and medication to maximize both short- and long-term outcomes. There are at least four possible options, in addition to that of stepped care.

Concurrent Administration

One approach is to introduce both treatments from the outset and maintain both interventions long-term. Studies that evaluated this approach typically reduced the frequency

of lifestyle counseling visits after the first 6 to 12 months, and therefore, did not provide definitive assessments of the possible benefits of this approach. Investigations with orlistat found that ~60% to 75% of the weight lost during the first year of treatment was maintained at the end of the second year (while patients remained on medication), resulting in a 5% to 8% weight loss at this time (49,51,70,72). The one long-term (i.e., 2-year) investigation of sibutramine that used this approach found that participants maintained ~90% of their maximal weight loss (11%), which was achieved at 6 months (40).

Similarly, data from formerly approved agents, including fenfluramine and dexfenfluramine, also revealed beneficial weight loss effects of simultaneously administering medication and lifestyle modification (80–82). Whereas these data provide support for the concurrent administration of therapies, some have questioned whether this method is necessary, particularly when an aggressive dietary intervention, such as a very-low-calorie diets (VLCD), is used (83). Medication is unlikely, for example, to augment weight loss when prescribed concurrently with a VLCD, but it does increase costs substantially.

Lifestyle Modification Followed by Pharmacotherapy

A second option is to boost the induction of weight loss by using the medication after lifestyle treatment has been initiated. Apfelbaum et al. (67) evaluated the effects of this approach by adding sibutramine after an initial month of treatment with a VLCD (providing 200 to 800 kcal/d), during which patients lost ~7.5 kg. Patients who were subsequently assigned to sibutramine lost an additional 5.2 kg during the ensuing year, whereas those who received a placebo gained 0.5 kg. These findings suggest that adding medication after a brief course of VLCD may facilitate larger weight losses. It is unclear, however, whether the medication would have induced additional weight loss if patients had lost 15 to 20 kg by adhering to a VLCD for 2 to 3 months, as these diets are commonly prescribed.

Studies of formerly approved medications also evaluated the short-term effects of adding pharmacotherapy after lifestyle modification (63,66). In a study by Craighead (63), one group received fenfluramine during the second half (weeks 9 to 16) of a 16-week lifestyle-modification program; in another group, medication was included only in the first half (i.e., weeks 1 to 8) of the program. At the end of the 16 weeks, those who received medication during the latter half of the program lost 9.3 kg, which was significantly more than either the behavior therapy alone group (5.7 kg) or the group that received medication during the first but not second half of treatment (5.6 kg). Thus, adding medication during the second 8 weeks of treatment increased weight losses by ~3.5 kg. In contrast, an earlier 24-week study of phentermine found that starting medication after 8 weeks of placebo and a program of modest

lifestyle modification seemed to benefit only a subgroup of “slow losers” (66). Further studies are needed to determine if medication will reliably induce further weight loss in persons originally treated by lifestyle modification alone.

Medication for Weight Maintenance

Another option is to introduce pharmacotherapy later in treatment to facilitate the maintenance rather than induction of weight loss. With this approach, consistent with stepped care, medication could be introduced at a specific time-point when the rate of weight loss typically slows (e.g., 6 months), after patients had met a weight-loss criterion (e.g., 7% to 10% loss), or as a rescue strategy after patients had regained weight (e.g., 2% or more).

Two studies of orlistat evaluated the effect of adding medication after a specific period of time. Hill et al. (84) randomly assigned obese subjects who had lost $\geq 8\%$ of their initial body weight (by diet and exercise alone) to placebo or orlistat, which was administered for 1 year in combination with a weight-maintenance diet. At the end of the year, participants treated with medication regained less weight than did placebo-treated subjects (32.8% vs. 58.7% regain of lost weight, respectively). Similarly, Sjöström et al. (51) randomly assigned patients who lost 5 kg during the previous year to receive orlistat or placebo during a second year. During year 2, patients on orlistat lost an additional 0.9 kg, compared with a mean regain of 2.5 kg in patients who continued on placebo. Overall, these and other (85) studies suggest that adding medication after treatment by diet and exercise may minimize weight regain while reducing the duration of exposure to medication and its potential side-effects.

Two studies compared the approaches of prescribing medication to induce weight loss and continuing it for the long-term vs. using medication for weight maintenance only. One found that mean weight loss of patients who received orlistat continuously for 2 years did not differ significantly from that of patients who began the medication at year 1 (51). The other study also reported that participants who began orlistat after 1 year of treatment by lifestyle modification alone achieved the same weight loss at the end of 2 years as participants who had received medication for the entire 2 years (86). It is unclear why later medication administration resulted in similar weight losses as continuous combined treatment. There seems to be a limit to the total amount of weight loss that is typically produced by current medications. Patients treated late by pharmacotherapy seem to catch up with those treated early and in whom weight loss has plateaued.

Intermittent Use of Medication

A final approach is to administer medication and/or lifestyle modification intermittently. Studies have shown inter-

mittent pharmacotherapy to be as (87,88) or almost as effective (89) as continuous medication. Munro et al. (90), for example, compared the effects of continuous and intermittent treatment with phentermine. One group received alternating 4-week supplies of active and placebo pills; a second group received continuous placebo, and the third received continuous phentermine. After 36 weeks, the alternating therapy with phentermine and placebo was as effective as continued daily treatment with phentermine, and both were superior to placebo. The authors concluded that there seemed to be no advantage in taking the medication continuously, because intermittent treatment was as effective, cheaper, and possibly safer.

Similarly, intermittent therapy was found to be as effective as continuous therapy in a recent study of sibutramine. Wirth and Krause (88) randomized participants to sibutramine administered continuously, sibutramine used intermittently with placebo, or placebo given alone for 48 weeks. All groups received brief dietary counseling from their physician. After 1 year, there were no significant differences in weight losses between the intermittent vs. continuous treatment groups (7.8 kg vs. 7.9 kg, respectively). In addition, the percentage of patients who experienced adverse events was similar in all groups. These findings again suggest that intermittent use of medication could save costs without sacrificing efficacy.

Weintraub et al. (89) reported findings similar to those of Munro et al. (90) but came to a different conclusion. In this study, although the end-of-treatment weight losses were similar with intermittent and continuous therapies, continuous medication (i.e., phentermine and fenfluramine) was judged preferable to intermittent therapy, primarily because of the adverse side effects that occurred when medication was reinitiated. Additional problems included weight gain, difficulty in adherence, and decreased appetite control during periods without medication.

In summary, adding medication to boost weight loss and/or promote weight maintenance may be a more effective and less costly option than prescribing both medication and lifestyle modification from the outset of treatment. Whereas it is possible that some patients (e.g., those with a history of unsuccessful weight-loss attempts or weight cycling) would reap more benefit from being offered medication and lifestyle modification concurrently, the effects of such patient characteristics on treatment outcome need to be investigated. Further research is also needed to fully assess the relative benefits of treatments administered intermittently or at specific time-points to maximize weight loss and maintenance. Findings may differ depending on the medication used and its specific side-effect profile. Studies are also needed to determine whether medications may be used to prevent weight gain during high-risk periods, including the winter holidays and times of acute stress.

Potential Pitfalls of Combined Treatments

Some practitioners have voiced concerns that medication may undermine lifestyle modification (91). For example, if medication reduces hunger, patients may not be motivated to practice strategies such as eating at regular intervals or eating high-fiber foods to prevent hunger and enhance satiety. Failure to practice these behaviors could undermine weight control in the long-term, particularly if medication was discontinued or its effects waned over time.

The use of medication may also convey the message that obesity is “biological” in origin and that personal efforts to change this “disease” process are futile. Such sentiments could reduce weight-control self-efficacy and receptiveness to lifestyle modification, which teaches patients to see themselves as active participants in solving their problems. Similarly, medication may foster external attributions for success. When patients lose weight, they may attribute their success completely to the medication, and not to their own efforts, thus further undermining self-efficacy. Conversely, it is possible that the failure of medication to produce adequate weight loss could be ascribed to internal causes, such as inadequate personal self-control. The small but significant number of medication nonresponders may feel guilty or hopeless that the medication is not working and withdraw from weight-management efforts.

Although there is no evidence that, when used together, medication and lifestyle modification limit one another’s effectiveness, researchers and practitioners should be sensitive to the potential drawbacks of combined therapy. Investigators also should evaluate potential adverse behavioral (e.g., completion of fewer food diaries) and psychological (e.g., decreased self-efficacy, motivation, self-esteem) effects of combining treatments. Practitioners should inform patients how the medication and the patient’s own efforts to modify diet and activity habits potentially complement each other to produce a better outcome.

Treatment and Research Implications

Treatment Implications

The data reviewed in this article clearly indicate that medications, when added to a low-intensity program of lifestyle modification, improve both the induction and maintenance of weight loss compared with lifestyle modification alone. Whereas it is likely that combining pharmacotherapy with more intensive lifestyle modification will improve results, data with currently approved agents are lacking.

Research Implications

There are a number of key unresolved issues that require future research. Foremost is the need for randomized control trials that include adequate control conditions.

		Lifestyle Modification	
		- (minimal)	+ (intensive)
Medication	- (no)	1. Placebo plus Minimal Lifestyle Modification	2. Placebo plus Intensive Lifestyle Modification
	+ (yes)	3. Medication plus Minimal lifestyle Modification	4. Medication plus Intensive Lifestyle Modification

Figure 1: Research design for evaluating the effects of combined behavioral and pharmacological treatment.

Research Design. The most rigorous test of combination treatment would require a 2×2 design in which minimal lifestyle modification was administered with placebo and medication, and intensive lifestyle modification was also provided with placebo and medication (see Figure 1). These four groups would provide several comparisons.

First, it is important to measure independent treatment effects to evaluate the relative contribution of each therapy to combined treatment. Thus, the model includes groups that assess whether intensive lifestyle-modification treatment is, in fact, more effective than a minimal lifestyle intervention program (i.e., comparison of cell #2 with cell #1) and whether medication is, in fact, superior to placebo (i.e., comparison of cell #3 with cell #1). The comparison of medication and placebo is relatively straightforward, although consideration must be given to the dose of the medication to be used and whether it may be increased because of poor response either early or late in treatment. In addition, the use of placebos that produce side-effects would also be helpful, as double-blind procedures are often not maintained in medication trials because therapists and patients can discover a patient's treatment conditions through observation of side effects (92).

Selection of the lifestyle interventions presents more choices. As described previously, intensive lifestyle modification usually consists of 16 to 26 sessions of weekly group treatment that is provided by a dietitian, psychologist, or other health practitioner. This approach produces excellent weight loss that may be increased further by the use of a meal replacement (100). Low-intensity lifestyle modification, by contrast, could take a number of forms, ranging from 4 to 6 visits a year with a primary-care practitioner who provided brief diet and exercise counseling to weekly (or biweekly) visits of 5 to 10 minutes at which patients were weighed by a medical technician and praised for keeping food records. (Frequent weigh-ins alone could account for the success of intensive lifestyle modification.) Investigators may want to design minimal lifestyle interventions that can be implemented in primary-care practice.

Protocols used in most industry-sponsored trials have included relatively few visits, consistent with primary-care practice.

After the separate effects of medication and lifestyle intervention have been examined, one of the central questions concerning combined treatment may be addressed: does adding medication improve on the effects of intensive lifestyle modification alone? This question is answered by comparing weight losses and changes in health in the groups that receive intensive lifestyle modification combined with placebo (cell #2) vs. medication (cell #4). Results of previous studies lead us to predict that medication plus intensive lifestyle modification will induce significantly larger weight losses (and improvements in health) than placebo plus the same program of lifestyle modification. Perhaps the more important question is whether the first therapy will be more effective than the second in maintaining improvements in weight and health one or more years after weekly group treatment has been discontinued.

Some have argued that it is inappropriate to test behavioral interventions in combination with a placebo (61,91). Treatment is not administered this way in clinical practice, and the placebo could undermine the effectiveness of behavior therapy by not meeting patient's expectations. The addition of a fifth treatment cell, intensive lifestyle modification alone, corrects for this possible shortcoming. If no differences were consistently found between this treatment condition and intensive lifestyle modification with placebo, the fifth cell could be eliminated.

The 2×2 design also addresses the question of whether intensive lifestyle modification improves on the results of pharmacotherapy. This is revealed by the comparison of treatment cell # 3 with cell #4. Intensive lifestyle modification may be required to obtain the best results with most medications. As noted earlier, Wadden et al. (73) found that sibutramine plus minimal lifestyle instruction produced a weight loss less than one-half as large as that resulting from sibutramine combined with intensive group behavior modification. By contrast, some medications may be so potent that maximal weight loss may be achieved with only minimal lifestyle modification, as was suggested by a study of the fenfluramine-phentermine combination (93).

The relative and combined effects of lifestyle modification and pharmacotherapy will not be known until studies similar to those described above are conducted. We note that the cost of conducting trials that included four or five treatment conditions could be prohibitive. For studies in which the efficacy of medication, relative to placebo, has already been demonstrated, an alternative would be a three-group design that compared 1) medication plus minimal lifestyle modification, 2) medication plus intensive lifestyle modification, and 3) intensive lifestyle modification alone. The design would address several issues concerning methods of maximizing the benefits of behavioral and pharma-

cological interventions. The results of these three-group designs could inform the design of second-generation studies. Future studies should fully describe the components of each treatment condition, including the intensity of lifestyle intervention, the training of individuals who delivered the therapy (e.g., psychologist, dietitian), and the frequency, duration, and content of treatment sessions.

Mechanisms of Action. The means by which combined treatment potentially enhances monotherapy (i.e., pharmacotherapy or lifestyle modification alone) needs to be determined. As a prelude to doing so, it will be important to better understand the specific variables that are associated with eating and inactivity, both in the short- and long-term. For example, it is unclear whether hunger and craving do, in fact, contribute to overeating and weight gain in most obese individuals. If found to be the case, investigators would want to evaluate whether treatments had an effect on these variables. The effects of medications, as well as behavioral interventions, on variables including food preoccupation, macronutrient selection, dietary restraint, hedonic ratings of food, food preferences, cognitions, and activity level need to be investigated. Possible effects of medication on optimism and expectations for success should also be evaluated. Once independent treatment effects are identified, the ways in which combined treatments work could be better determined. Obtaining information about treatment mechanisms is critical for the development of efficient and effective lifestyle-modification interventions. Depending on the medication(s) used, the content of lifestyle-modification treatments will likely need to be modified to maximize the effects of the medication. We have outlined a number of possibilities to explain the interaction of medication and lifestyle modification. These mechanisms should be tested empirically.

Matching Patients to Treatment. Whether various subtypes of obese patients do better with different interventions has not been studied adequately. Some patients may be resistant to weight loss with a particular medication and need more intensive lifestyle treatment or an alternative medication. The characteristics of treatment responders and nonresponders need to be clarified more fully. Perhaps patients in whom emotional complaints override somatic ones might find behavioral treatment most useful. Patients who complain of hunger or cravings might find pharmacotherapy most useful. Other variables such as gender, body-fat distribution, stress, degree of obesity, age, and medical conditions need to be evaluated in relation to various treatment outcomes. Research on patient-treatment matching is needed.

Dissemination. Finally, investigators will need to identify methods by which combination treatment can be delivered in an economical and widespread fashion. There are a number of promising new methods for disseminating behavioral treatment, including internet-administered inter-

ventions (101). Perhaps both medical and behavioral professionals need to be involved for combination treatment to be most effective. However, training medical practitioners and other medical staff to provide brief lifestyle counseling might be an equally or even more efficient means of providing combination care (93).

Summary and Conclusions

FDA-approved weight-loss medications improve the results of low-intensity programs of lifestyle modification for weight management. In addition, long-term use of medication facilitates the maintenance of weight loss. At present, however, investigators know little about how best to combine lifestyle modification and medication to maximize short- and long-term improvements in weight and health. Research is needed to determine the types of lifestyle interventions that maximize the effects of orlistat and sibutramine, as well as of medications to be discovered. Understanding the optimal means of combining behavioral and pharmacological therapies is critical to improving the management of obesity in both primary-care practice and in specialty clinics.

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