

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

NOVEMBER 17, 2005

VOL. 353 NO. 20

Randomized Trial of Lifestyle Modification and Pharmacotherapy for Obesity

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ABSTRACT

BACKGROUND

Weight-loss medications are recommended as an adjunct to a comprehensive program of diet, exercise, and behavior therapy but are typically prescribed with minimal or no lifestyle modification. This practice is likely to limit therapeutic benefits.

METHODS

In this one-year trial, we randomly assigned 224 obese adults to receive 15 mg of sibutramine per day alone, delivered by a primary care provider in eight visits of 10 to 15 minutes each; lifestyle-modification counseling alone, delivered in 30 group sessions; sibutramine plus 30 group sessions of lifestyle-modification counseling (i.e., combined therapy); or sibutramine plus brief lifestyle-modification counseling delivered by a primary care provider in eight visits of 10 to 15 minutes each. All subjects were prescribed a diet of 1200 to 1500 kcal per day and the same exercise regimen.

RESULTS

At one year, subjects who received combined therapy lost a mean ($\pm$ SD) of 12.1 ± 9.8 kg, whereas those receiving sibutramine alone lost 5.0 ± 7.4 kg, those treated by lifestyle modification alone lost 6.7 ± 7.9 kg, and those receiving sibutramine plus brief therapy lost 7.5 ± 8.0 kg ($P < 0.001$). Those in the combined-therapy group who frequently recorded their food intake lost more weight than those who did so infrequently (18.1 ± 9.8 kg vs. 7.7 ± 7.5 kg, $P = 0.04$).

CONCLUSIONS

The combination of medication and group lifestyle modification resulted in more weight loss than either medication or lifestyle modification alone. The results underscore the importance of prescribing weight-loss medications in combination with, rather than in lieu of, lifestyle modification.

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N Engl J Med 2005;353:2111-20.

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TWO MEDICATIONS, SIBUTRAMINE (Meridia, Abbott Laboratories) and orlistat (Xenical, Roche), are currently approved by the Food and Drug Administration for the induction and maintenance of weight loss.¹⁻⁵ These agents are recommended as an adjunct to a comprehensive program of diet, exercise, and behavior therapy,^{2,3,6} which is known as lifestyle modification and is delivered in weekly group or individual sessions.⁷⁻⁹ Industry-sponsored trials of weight-loss medications typically have included limited programs of lifestyle modification.^{5,10,11}

This randomized trial compared the efficacy of sibutramine alone (as typically prescribed in primary care practice), group sessions of lifestyle modification alone, and the combination of the two therapies. We expected that the combined treatment would result in significantly greater weight loss than either therapy alone because of the potentially complementary mechanisms of action of the two approaches.¹¹ Sibutramine, a serotonin-norepinephrine reuptake inhibitor, appears to modify internal signals that control hunger (the drive to eat) and satiation (fullness).^{4,12} In contrast, lifestyle modification teaches patients to control the external environment involving food — for example, by grocery shopping from a list or recording food intake.⁷⁻⁹ Two studies^{13,14} of fenfluramine (which was withdrawn from the market in 1997 because of its association with valvular heart disease¹⁵) suggested that the effects of lifestyle modification and medication would be additive.

Our study included a fourth treatment group that assessed the efficacy of sibutramine combined with brief lifestyle-modification counseling delivered by primary care providers. We anticipated that this intervention would result in significantly greater weight loss than medication alone and could potentially provide a model for delivering lifestyle-modification counseling in primary care practice.^{16,17}

METHODS

SUBJECTS

The study involved 180 women and 44 men, 18 to 65 years of age, each of whom had a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 to 45. Eligible subjects were free of uncontrolled hypertension (defined by a blood pressure greater than 140/90 mm Hg); cerebrovascular, cardiovascular, renal, or hepatic dis-

ease; and type 1 or 2 diabetes. Women were ineligible if they were pregnant or breast-feeding. The use of medications known to affect body weight, a weight loss of 5 kg or greater in the preceding six months, and the use of selective serotonin-reuptake inhibitors were exclusion criteria. Psychosocial contraindications included bulimia nervosa, substance abuse, clinically significant depression, or current psychiatric care.

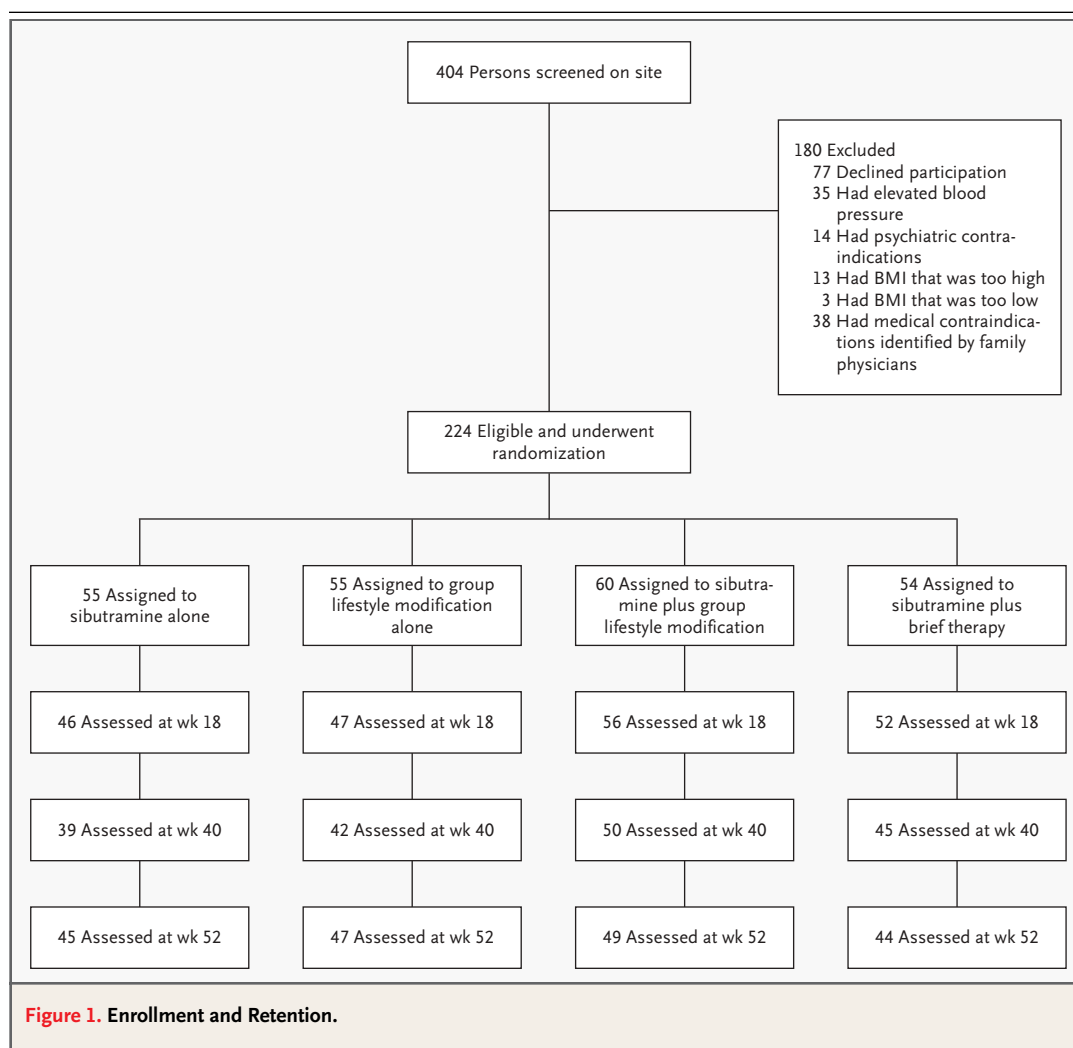
Initially, 404 persons responded to advertisements for the study, completed a telephone interview, and appeared to meet eligibility requirements. They met with a psychologist, who described the study's requirements, obtained written informed consent, and assessed their psychosocial status. Also, height, weight, and blood pressure were measured. As shown in Figure 1, a total of 77 applicants elected not to participate and 65 were excluded because of various contraindications. The remaining 262 persons were referred to their family physicians, who obtained a history and performed a physical examination and electrocardiography to determine whether applicants were free of the physical complications described previously; 38 were deemed by their physicians to have contraindications to participation. The family physicians forwarded their findings to the project physician. The 224 persons who passed the medical-screening tests comprised the final sample (Table 1).

TREATMENT GROUPS

Subjects were randomly assigned to receive one of the four treatments described below. At week 0 (baseline), all subjects were instructed to maintain their usual eating and activity habits. Thereafter, all subjects were prescribed a balanced-deficit diet of 1200 to 1500 kcal per day, with approximately 15 percent of energy derived from proteins, 30 percent or less from fats, and the remainder from carbohydrates. All were encouraged to exercise (walk) 30 minutes a day most days of the week.

Sibutramine Alone

Fifty-five subjects were assigned to receive sibutramine alone. They had eight brief visits (10 to 15 minutes each) with a primary care provider at weeks 1, 3, 6, 10, 18, 26, 40, and 52. During week 1, subjects were given a daily dose of 5 mg of sibutramine (provided by Abbott Laboratories, which otherwise had no involvement in the study), and the dose was increased to 10 mg at week 3 and



to 15 mg at week 6. Subjects received a copy of "On Your Way to Fitness,"¹⁹ a pamphlet that provides tips for healthy eating and activity. They were not instructed to keep records of food intake or activity, and the primary care providers gave only general encouragement. Weight and vital signs were measured at all visits. The primary care providers included three internists and one nurse practitioner, none of whom specialized in obesity management.

Lifestyle Modification Alone

A total of 55 subjects were assigned to receive lifestyle modification alone. They attended weekly group meetings from weeks 1 through 18, sessions conducted every other week from weeks 20 through 40, and a follow-up visit at week 52. Meetings included 7 to 10 subjects, lasted 90 minutes, and were

led by trained psychologists. For the first 18 weeks, sessions followed the LEARN (Lifestyle, Exercise, Attitudes, Relationships, and Nutrition) Program for Weight Control,²⁰ which instructed subjects to complete weekly homework assignments that included keeping daily records of food and calorie intake and physical activity. Records were reviewed at weekly meetings. From weeks 20 through 40, sessions were conducted with the use of the *Weight Maintenance Survival Guide*.²¹

Combined Therapy

Sixty subjects were assigned to combined therapy. They were given the same two treatments as those in the first two groups, but with a slight modification. They received sibutramine, attended medical visits, and attended group sessions of lifestyle coun-

Table 1. Baseline Characteristics of the Subjects.*

Characteristic	Sibutramine Alone (N=55)	Lifestyle Modification Alone (N=55)	Combined Therapy (N=60)	Sibutramine plus Brief Therapy (N=54)
Sex (no. of subjects)				
Female	44	42	49	45
Male	11	13	11	9
Race or ethnicity (no. of subjects)				
White	31	35	42	39
Black	22	18	17	12
Hispanic	2	2	1	3
Age (yr)	42.1±10.2	43.3±9.7	44.2±10.8	44.9±10.1
Weight (kg)	107.9±14.7	105.1±17.0	108.5±18.6	106.0±18.3
Height (cm)	168.0±7.8	167.3±8.4	168.8±9.2	167.5±8.1
Body-mass index	38.2±3.9	37.8±4.2	37.9±4.2	37.6±4.7
Blood pressure (mm Hg)				
Systolic	123.6±16.0	127.3±14.5	126.4±14.0	121.4±14.5
Diastolic	67.9±10.7	70.9±10.5	67.9±9.6	65.5±7.6
Pulse (beats/min)	80.0±10.5	77.6±9.9	79.7±11.0	77.5±11.1
Triglycerides (mg/dl)	125.1±94.1	140.2±151.2	126.8±78.8	132.7±68.2
Cholesterol (mg/dl)				
Total	197.1±38.1	200.7±33.9	196.4±33.6	198.8±30.2
LDL	116.9±30.9	121.7±30.8	113.7±29.4	118.8±27.3
HDL	56.2±14.8	53.4±13.5	57.5±15.8	53.4±12.4
Glucose (mg/dl)	96.1±14.3	94.8±15.1	92.8±11.1	97.3±14.9
Insulin (μU/ml)	18.9±18.3	16.0±9.6	16.8±9.4	19.9±15.0
Insulin resistance†	4.8±5.8	3.9±2.7	3.9±2.2	5.0±4.5

* Plus-minus values are means ±SD. There were no significant differences among the four groups on any of the baseline characteristics. Race or ethnicity was self-reported. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for insulin to picomoles per liter, multiply by 6. LDL denotes low-density lipoprotein, and HDL high-density lipoprotein.

† The degree of insulin resistance was determined with the use of the homeostasis model of insulin resistance.¹⁸ Scores ordinarily range from 0 to 15, with higher scores indicating greater insulin resistance, and are calculated as the product of the fasting plasma insulin level (in microunits per milliliter) and the fasting plasma glucose level (in millimoles per liter), divided by 22.5.

selling that followed a version of the LEARN Program for Weight Control²² that was adapted to include sibutramine.

Sibutramine plus Brief Therapy

A total of 54 subjects received sibutramine and met with a primary care provider (10 to 15 minutes per session) on the same schedule as subjects in the group given sibutramine alone. They also were given the two treatment manuals^{21,22} and were instructed to complete homework assignments, including daily food-intake and activity records, which they reviewed during visits with the primary care providers. (Additional details about treatment im-

plementation are provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org.)

OUTCOMES

A digital scale (model 6800A, Detecto) was used at all treatment visits to measure subjects' weight while they were dressed in light clothing. Behavioral adherence during the first 18 weeks was assessed in the three groups receiving lifestyle-modification therapy by counting the number of food-intake records completed. For each week, subjects received a score of 0 to 7, reflecting the number of days they completed a record. Completion of food-intake rec-

ords has been shown to correlate positively with weight loss.^{16,23,24}

Levels of triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, glucose, and insulin were measured at baseline and at weeks 18, 40, and 52 after an overnight fast (Quest Diagnostics). Insulin sensitivity was estimated with the use of the homeostasis model of insulin sensitivity.²⁴ Blood pressure and pulse were measured by research assistants with an automated monitor (Dinamap, model 9300, Johnson & Johnson) on the same schedule as the visits to primary care providers. On each occasion, two readings were taken at one-minute intervals after subjects had been seated for at least five minutes.

ATTRITION

Thirty-nine subjects (17 percent) did not complete the one-year study. This number includes anyone who attended the first treatment visit but did not return. There were no significant differences in attrition among the four groups (Fig. 1). Most of those who dropped out did so because they were dissatisfied with treatment (22 subjects) or had scheduling conflicts (5 subjects). Twelve withdrew because of medical complications. The complications included two pregnancies reported at week 6 of the program; the data on these two women were excluded from the analysis because of the likelihood that they were pregnant at the start of the study.

STATISTICAL ANALYSIS

The sample size was selected to provide the study with a statistical power of 80 percent to detect a 4-kg difference in weight loss at week 52 among those receiving combined therapy as compared with both those receiving sibutramine alone and those receiving lifestyle modification alone. Similar statistical power was available to detect a 4-kg difference between those in the group given drug plus brief therapy and those given sibutramine alone. Preliminary analysis revealed no significant differences among the four groups in baseline characteristics (Table 1). Differences in weight and other outcomes among groups at weeks 18, 40, and 52 were compared with the use of analysis of variance with repeated measures. In cases of a significant treatment effect, Tukey's honestly significant difference test²⁵ was used to identify differences among the four groups.

Data were examined for the 222 subjects who

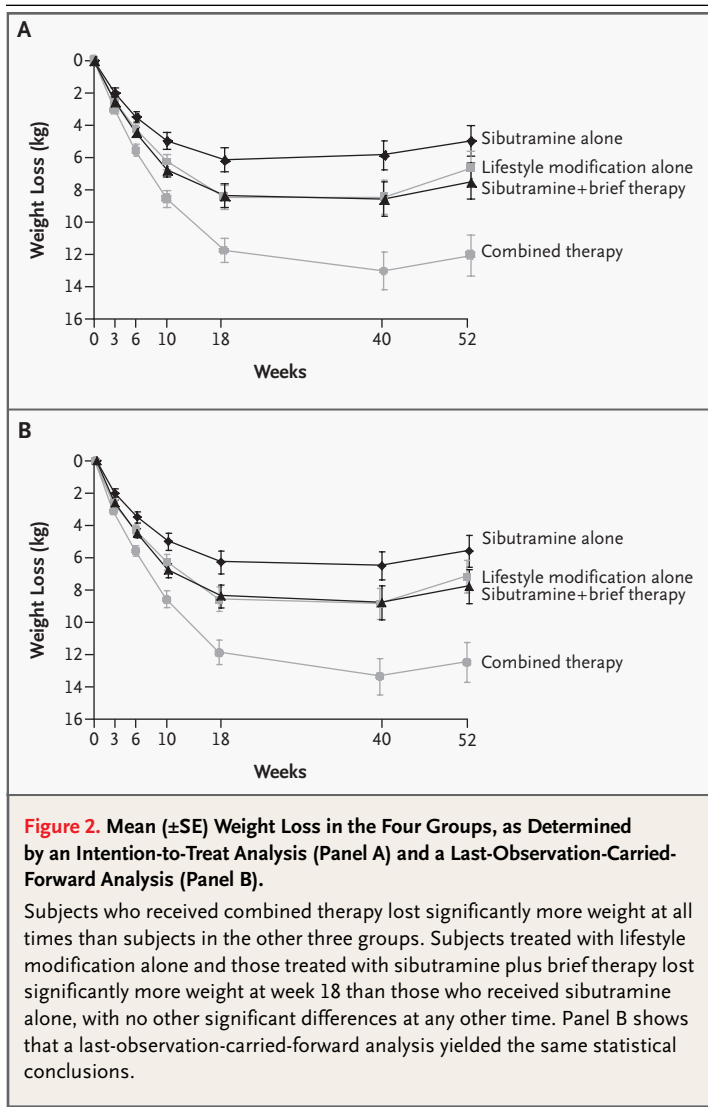
began treatment (excluding the 2 women who were thought to be pregnant before the study began) with the use of the last-observation-carried-forward analysis, a more conservative method than examining only those who completed treatment. An even more conservative intention-to-treat analysis was used for weight change; subjects who discontinued treatment were assumed to have regained 0.3 kg per month after leaving the study.²⁴ Chi-square tests were performed to compare percentages of subjects in each group who lost 5 percent or more of their initial weight. Partial-correlation analysis, which controlled for the effect of treatment group, was used to examine predictors and correlates of weight loss. Data were analyzed with the use of SPSS software (version 11).²⁵

This study was approved by the institutional review board of the University of Pennsylvania and was conducted from January 2000 to August 2003. The authors were solely responsible for designing the study, securing funding, treating subjects, collecting and analyzing the data, and writing the manuscript.

RESULTS

WEIGHT LOSS

At one year, subjects who received combined therapy lost a mean ($\pm$ SD) of 12.1 ± 9.8 kg, whereas those receiving sibutramine alone lost 5.0 ± 7.4 kg, those treated by lifestyle modification alone lost 6.7 ± 7.9 kg, and those receiving sibutramine plus brief therapy lost 7.5 ± 8.0 kg. Subjects in the group receiving combined therapy lost significantly more weight at 1 year, as well as at weeks 18 and 40, than those in the other three groups ($P < 0.001$ by the intention-to-treat analysis) (Fig. 2A). In addition, subjects in the group treated by lifestyle modification alone and those in the group given sibutramine plus brief therapy lost significantly ($P = 0.05$) more weight at week 18 than those in the group given sibutramine alone; there were no other significant differences among these three groups at week 40 or 52. Results of the last-observation-carried-forward analysis yielded the same statistical conclusions (Fig. 2B). An analysis of covariance that controlled for the effects of initial weight, age, sex, and race or ethnicity also yielded the same statistical conclusions, with one exception; at week 18, the weight losses in the group treated by lifestyle modification alone and the group given sibutramine plus brief therapy were superior ($P = 0.05$) to those



in the group given sibutramine alone in the last-observation-carried-forward analysis but not in the intention-to-treat analysis.

At one year, significantly more subjects in the combined-therapy group (73 percent) lost 5 percent or more of their initial weight than did those in the group given sibutramine alone (42 percent), the group treated by lifestyle modification alone (53 percent), and the group given sibutramine plus brief therapy (56 percent) ($P=0.05$). More subjects in the combined-therapy group (52 percent) also lost 10 percent or more of their initial weight than did those in the three other groups (26 percent, 29 percent, and 26 percent, respectively; $P=0.004$).

BEHAVIORAL ADHERENCE

The mean ($\pm$ SD) number of food-intake records completed during the first 18 weeks (126 days) of the study was 88.4 ± 32.7 in the group treated by lifestyle modification alone, 91.5 ± 35.9 in the combined-therapy group, and 61.0 ± 40.0 in the group given sibutramine plus brief therapy. Subjects in the first two groups completed significantly more records than did those in the third group ($P<0.001$). Partial-correlation analysis that controlled for treatment group showed that the more records subjects completed, the more weight they lost at week 18 ($r=0.29$, $P<0.001$), week 40 ($r=0.22$, $P=0.01$), and week 52 ($r=0.31$, $P<0.001$).

The importance of recording food intake was further revealed by examining those in the highest and lowest thirds of adherence in the combined-therapy group and the group treated by lifestyle modification alone. In both groups, subjects in the highest third of adherence lost more than twice as much weight as those in the lowest third of adherence (Fig. 3). Those, for example, in the combined-therapy group who recorded food intake frequently lost more weight than those who did so infrequently (18.1 ± 9.8 kg vs. 7.7 ± 7.5 kg, $P=0.04$).

SERUM CHEMISTRY

No significant differences in changes in cardiovascular risk factors were observed among the four groups at any time. Table 2 shows the results for week 52. Combining the four groups, significant reductions were observed in levels of triglycerides ($P=0.003$), glucose ($P<0.001$), and insulin and in insulin resistance ($P<0.001$ for both comparisons). Levels of total cholesterol also declined ($P=0.02$), whereas HDL cholesterol increased ($P=0.003$). Partial-correlation analysis that controlled for treatment group showed that weight loss at week 52 was correlated with decreases in triglyceride levels ($r=0.31$, $P<0.001$), insulin levels ($r=0.28$, $P<0.001$), and insulin resistance ($r=0.24$, $P=0.006$) and with increases in HDL cholesterol levels ($r=0.26$, $P=0.004$).

BLOOD PRESSURE AND PULSE

At week 18, systolic and diastolic blood pressure both decreased more in the group treated by lifestyle modification alone than in the group given sibutramine alone or the group given sibutramine plus brief therapy ($P<0.001$ for both comparisons) (Table 3). Diastolic blood pressure increased by approximately 3 mm Hg in the group given sibutra-

mine alone and the group given sibutramine plus brief therapy. At one year, there were no significant differences among groups in the changes in either systolic or diastolic blood pressure. Changes in pulse paralleled changes in blood pressure (Table 3). Partial-correlation analysis that controlled for the treatment group indicated that weight loss at week 52 was correlated with decreases in systolic blood pressure ($r=0.33$, $P<0.001$), diastolic blood pressure ($r=0.22$, $P=0.004$), and pulse rate ($r=0.15$, $P=0.05$).

MEDICATION REDUCTION ON THE BASIS OF CARDIOVASCULAR STATUS

Thirty-four subjects taking sibutramine (14 in the group given sibutramine alone, 12 in the combined-therapy group, and 8 in the group given sibutramine plus brief therapy) received reduced doses in response to an increase in systolic or diastolic blood pressure of 10 mm Hg or more above baseline or an increase in the pulse rate of 15 percent or more. These criteria were selected a priori to minimize increases in blood pressure and pulse reported previously with the use of sibutramine.⁴ Reducing the daily dose from 15 mg to 10 mg typically caused the elevated values to return to baseline.

ADVERSE EVENTS

Twelve subjects discontinued treatment because of adverse events that included breast cancer, chronic inflammatory polyneuropathy, preexisting attention-deficit disorder treated with bupropion at week 12, hepatitis C, Lyme disease, back injury (in two), heart palpitations, facial rash, and pregnancy (in three, which includes the two women who were excluded from the data analysis). The only adverse events judged to be potentially related to the use of sibutramine were the heart palpitations and facial rash, both of which remitted after withdrawal of the medication. The three full-term pregnancies yielded healthy infants with normal Apgar scores. There were no significant differences among the groups in the rate of adverse events.

DISCUSSION

We found that the combination of group lifestyle-modification counseling and pharmacotherapy resulted in an average loss of 12.1 kg at one year—a loss approximately double that of the groups receiving either sibutramine alone (5.0 kg) or lifestyle-

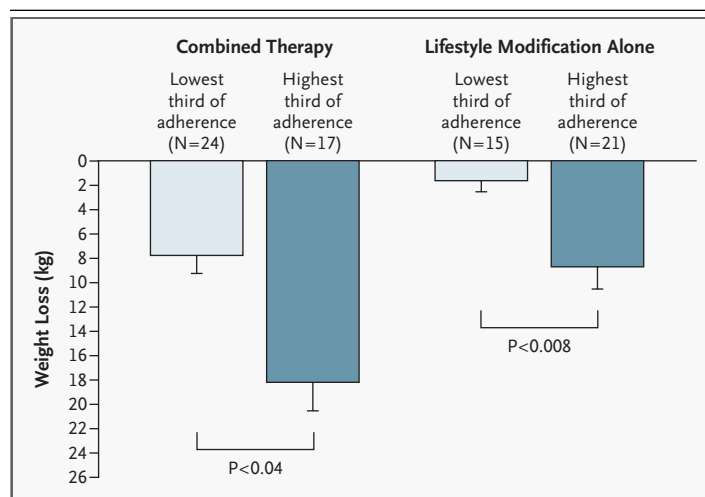


Figure 3. Mean ($\pm$ SE) Weight Loss at One Year in the Combined-Therapy Group and the Group Treated by Lifestyle Modification Alone among Subjects in the Lowest and Highest Thirds of Adherence for Completing Food-Intake Records during the First 18 Weeks.

In the combined-therapy group and the group treated by lifestyle modification alone, the 24 and 15 subjects in the lowest third of adherence completed 54.5 ± 21.9 and 40.5 ± 27.4 food-intake records, respectively, whereas the 17 and 21 subjects in the highest third of adherence completed 122.3 ± 4.2 and 120.1 ± 3.6 records, respectively (of a possible 126 daily records). Within each treatment group, differences in weight loss between subjects in the lowest third of adherence as compared with those in the highest third of adherence were significant as determined by Wilcoxon rank-sum tests. In the combined-therapy group, the 19 subjects in the middle third of adherence completed 100.7 ± 9.6 records and lost 12.2 ± 9.8 kg, whereas in the group treated by lifestyle modification alone, the 19 subjects in the middle third of compliance completed 100.3 ± 8.5 records and lost 8.7 ± 7.2 kg.

modification counseling alone (6.7 kg). Nearly twice as many subjects in the combined-therapy group as in the monotherapy groups lost 10 percent or more of their initial weight, a prespecified benchmark for success.⁶ These findings, which are based on all enrollees (not just those who completed treatment), provide strong support for recommendations that weight-loss medications be used only as an adjunct to a comprehensive program of diet, exercise, and behavior therapy.⁶ These results also confirm previous reports of the benefits of lifestyle modification used alone for inducing clinically and statistically significant weight loss.^{9,26} Subjects treated by lifestyle modification alone had significantly greater weight loss than those who received sibutramine alone during the first 18 weeks.

We cannot identify the components of group lifestyle modification that contributed most to the increased weight loss when combined with sibutra-

Table 2. Changes in Cardiovascular Risk Factors at Week 52 in the Four Groups, as Determined by a Last-Observation-Carried-Forward Analysis.*

Variable	Sibutramine Alone (N=53)	Lifestyle Modification Alone (N=53)	Combined Therapy (N=58)	Sibutramine plus Brief Therapy (N=53)	All Groups Combined (N=217)
Triglycerides (mg/dl)	-12.0±54.5	-31.6±109.1	-33.9±58.4	-12.6±45.6	-22.8±71.3†
Cholesterol (mg/dl)					
Total	-3.4±30.2	-2.7±28.6	-7.9±18.2	-1.1±20.3	-3.9±24.7‡
LDL	-2.2±25.9	+1.0±25.3	-4.6±16.6	+0.5±21.2	-1.4±22.4
HDL	+0.9±9.6	+0.8±8.0	+2.7±9.8	+0.9±7.4	+1.4±8.8†
Glucose (mg/dl)	-0.6±11.7	-4.2±8.3	-3.0±12.1	-3.6±12.4	-2.8±11.3§
Insulin (μU/ml)	-0.5±10.9	-4.3±6.5	-6.2±7.9	-5.4±16.2	-4.2±11.2§
Insulin resistance¶	-0.3±2.7	-1.1±1.8	-1.5±1.9	-1.5±4.9	-1.1±3.1§

* Plus-minus values are means ±SD. There were no significant differences among the four groups as determined by analysis of variance. Acceptable baseline serum chemistry values were not obtained in two subjects in the group given sibutramine alone, the group treated with lifestyle modification alone, and the combined-therapy group and in one subject in the group given sibutramine plus brief therapy. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for glucose to millimoles per liter, multiply by 0.05551.

† P=0.003 for the comparison with baseline values.

‡ P=0.02 for the comparison with baseline values.

§ P<0.001 for the comparison with baseline values.

¶ The degree of insulin resistance was determined with the use of the homeostasis model of insulin resistance.¹⁸ Scores ordinarily range from 0 to 15, with higher scores indicating greater insulin resistance, and are calculated as the product of the fasting plasma insulin level (in microunits per milliliter) and the fasting plasma glucose level (in millimoles per liter), divided by 22.5.

mine therapy. However, keeping daily food-intake records during the first 18 weeks correlated positively with weight loss at all assessments. A secondary analysis showed that subjects in the combined-therapy group who were in the top third of record-keeping lost 18.1 kg, as compared with only 7.7 kg for those in the bottom third. These observations underscore the importance of patients' efforts to modify their eating behavior, rather than relying solely on medication.^{11,16,23,24}

The group given sibutramine plus brief therapy was included to determine whether practitioners might provide effective lifestyle counseling during a limited number of visits of 10 to 15 minutes each, intended to simulate patterns of primary care practice. Subjects in this group lost significantly more weight at week 18 than did those who received sibutramine alone. Thus, it appears that practitioners may be able to provide brief, effective weight-loss counseling. However, the superiority of this approach faded after week 18, when the frequency of visits was reduced.

Treatment with sibutramine plus brief therapy appeared to be as effective in inducing and maintaining weight loss as lifestyle modification alone, which required participation in 30 group sessions of 90 minutes each. Future studies comparing these

two therapeutic strategies should include an economic analysis to weigh savings in patients' time and travel against the costs of medication and physicians' visits.²⁷ Studies also must include a thorough evaluation of the status of the patients' general health. At both weeks 18 and 40, we found significant differences between these two groups in changes in systolic and diastolic blood pressure. The difference in diastolic blood pressure was attributable, in part, to a slight rise in blood pressure, as reported previously,^{4,28,29} in subjects in the group given sibutramine plus brief therapy. These increases were minimized by selectively reducing the dose of sibutramine in 34 subjects from the three groups that included drug therapy. Analysis of other cardiovascular risk factors revealed clinically significant improvements in triglyceride levels and insulin resistance, as estimated by the homeostasis model of insulin sensitivity.³⁰

Our goal was to compare the efficacy of two well-established therapies for obesity — lifestyle modification and pharmacotherapy — and to determine whether the two in combination would be more effective than either treatment alone. We intentionally did not conduct a placebo-controlled trial, since the efficacy of sibutramine has been established in more than a dozen such trials.²⁸ We

Table 3. Changes in Blood Pressure and Pulse during One Year of Treatment in the Four Groups, as Determined by a Last-Observation-Carried-Forward Analysis.*

Variable	Sibutramine Alone (N=53)	Lifestyle Modification Alone (N=55)	Combined Therapy (N=60)	Sibutramine plus Brief Therapy (N=54)
Systolic blood pressure (mm Hg)				
Week 18	+0.5±11.2†	-8.5±12.1	-4.5±12.2	-0.2±11.0†
Week 40	-2.9±11.7	-6.8±12.2	-4.0±12.8	+1.1±11.7‡
Week 52	-1.8±13.9	-3.8±13.2	-5.8±15.0	-0.4±10.0
Diastolic blood pressure (mm Hg)				
Week 18	+2.6±7.6§	-2.2±8.4	+0.5±7.9	+3.1±7.1¶
Week 40	+0.9±8.5	-1.7±8.2	+0.7±7.8**	+4.7±8.1
Week 52	+0.7±9.4	-1.1±8.8	-0.2±9.3	+2.6±7.2
Pulse (beats/min)				
Week 18	+0.5±9.9†	-6.4±10.4	-0.5±9.6††	+2.3±10.5†
Week 40	+1.9±10.4	-2.6±8.5	+1.1±12.7	+3.4±10.4‡‡
Week 52	+1.1±12.3	-1.7±8.7	+0.5±10.8	+2.0±10.7

* Plus-minus values are means ±SD. Significant differences were determined by Tukey's honestly significant difference test²⁵ for all possible pairwise comparisons. Baseline blood-pressure measurements were not obtained in two subjects in the group given sibutramine alone.

† P<0.001 for the comparison with lifestyle modification alone.

‡ P=0.02 for the comparison with lifestyle modification alone.

§ P=0.005 for the comparison with lifestyle modification alone.

¶ P=0.003 for the comparison with lifestyle modification alone.

|| P=0.002 for the comparison with sibutramine plus brief therapy.

** P=0.05 for the comparison with sibutramine plus brief therapy.

†† P=0.004 for the comparison with lifestyle modification alone.

‡‡ P=0.03 for the comparison with lifestyle modification alone.

wished to assess the efficacy of group lifestyle modification alone as customarily delivered. The inclusion of a placebo with this treatment could potentially have undermined subjects' efforts to adhere to diet and exercise recommendations and, thus, limited their weight loss.^{11,31,32}

Our findings strongly suggest that the best weight-loss results will be obtained when medication is used as an adjunct to a comprehensive program of diet, exercise, and behavior therapy. Further research is needed to identify effective methods of providing lifestyle counseling in primary care and community settings.³³

Supported by grants (DK56124 and DK065018) from the National Institute of Diabetes and Digestive and Kidney Diseases.

Dr. Wadden reports having received consulting fees from Abbott Laboratories, Merck, Pfizer, and Sanofi-Aventis; lecture fees from GlaxoSmithKline, Roche Laboratories, and Johnson & Johnson; grants from Abbott Laboratories, GlaxoSmithKline, Johnson & Johnson, Merck, and Regeneron; and royalties from American Health Publishing. Dr. Berkowitz reports having received consulting fees from Abbott Laboratories, Johnson & Johnson, Roche Laboratories, Sanofi-Aventis, and Shionogi USA; lecture fees from Abbott Laboratories and Roche Laboratories; and grants from Abbott Laboratories and Knoll Pharmaceutical. Dr. Sarwer reports having received lecture fees from Abbott Laboratories. During the conduct of the study, Dr. Osei worked full time at the University of Pennsylvania but since has moved to GlaxoSmithKline. Dr. Stunkard reports having received grants from Pfizer.

We are indebted to Drs. George Bray and Ken Fujioka for serving as consultants to the study; to Shirley Wang, Rebecca Rothman, and Suzanne MacDonald for their many contributions in coordinating the recruitment, assessment, and treatment of study subjects; and to Johanna Brock for her editorial assistance.

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