Benefits of Lifestyle Modification in the Pharmacologic Treatment of Obesity

A Randomized Trial

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Background: Weight loss medications are recommended as an adjunct to diet and exercise modification but seem to be prescribed as a monotherapy by many physicians. This practice is likely to be associated with suboptimal weight loss.

Methods: This 1-year, randomized trial compared the effects of sibutramine hydrochloride used alone (ie, the drug-alone group) to sibutramine plus group lifestyle modification, prescribed with either a 5021- to 6276-kJ/d diet (1200-1500-kcal/d diet) (ie, the drug-plus-lifestyle group) or, for the first 4 months, a 4184-kJ/d diet (1000-kcal/d diet (ie, drug-plus-lifestyle with a portion-controlled diet [the combined treatment] group). Participants were 53 women with a mean (±SD) age of 47.2±9.8 years and weight of 101.3±9.7 kg. At baseline, they reported the number of pounds they expected to lose at the end of treatment.

Results: At month 12, patients treated with the drug alone lost (mean±SD) 4.1%±6.3% of their initial body weight compared with significantly (P<.05) larger losses in the drug-plus-lifestyle group of 10.8%±10.3% and the combined treatment group of 16.5%±8.0%. Women in the 2 lifestyle groups achieved a significantly (P<.05) greater percentage of their expected weight loss than those in the drug-alone group and were significantly more satisfied with the medication and with changes in weight, health, appearance, and self-esteem (P<.05 for all). Significant reductions were observed at 12 months in triglyceride and low-density lipoprotein cholesterol levels but systolic and diastolic blood pressure both increased significantly (P<.05 for all).

Conclusion: The addition of group lifestyle modification to the pharmacologic management of obesity significantly improved weight loss and patients’ satisfaction with treatment outcome.

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IN Since November 1997, the Food and Drug Administration has approved 2 medications—sibutramine hydrochloride and orlistat—for the induction and maintenance of weight loss.1 Sibutramine is a combined norepinephrine-serotonin reuptake inhibitor that is associated with increased satiation (ie, fullness) and a resulting reduction in food intake.2-5 Orlistat is a gastric and pancreatic lipase inhibitor that induces weight loss by blocking the absorption of about one third of the fat contained in a meal; the undigested fat (ie, oil) is excreted in stool.6-9 In randomized trials, in which patients were prescribed a modest energy deficit (ie, 2092-2929 kJ/d [500-700 kcal/d]) and encouraged to increase physical activity, both medications were associated with a 7% to 10% reduction in initial body weight during the first 6 months.2,6,7,10 Continued use of sibutramine2,11 and orlistat6,7 therapy was associated with generally favorable maintenance of weight loss at the end of 1 and 2 years, respectively.

In approving these medications, the Food and Drug Administration recommended that they be limited to persons with a body mass index of 30 kg/m2 or more or 27 kg/m2 or more in the presence of obesity-related comorbid conditions (eg, hypertension or diabetes mellitus).12,13 In addition, these agents are recommended only as an adjunct to instruction in diet and exercise modification;14,15 the medications, by reducing appetite (or fat absorption), are thought to facilitate patients’ efforts to adhere to a reduced-energy diet.16,17 In most primary care practices, however, weight loss medications seem to be provided with little or no instruction in diet and exercise (ie, lifestyle) modification. Previous studies18,19 suggest that patients who are provided medication without adequate lifestyle modification may lose less than half as much weight as those treated by
PARTICIPANTS AND METHODS

PARTICIPANTS

Participants were 53 women with the following mean (±SD) values: age, 47.2±9.8 years; weight, 101.3±9.7 kg; height, 164.1±6.0 cm; and body mass index, 37.7±3.6 kg/m². They were selected from more than 300 respondents to advertisements in local newspapers. Participation was limited to women who had a body mass index of 30 to 45 kg/m² and who were free of physical contraindications including types 1 or 2 diabetes mellitus; uncontrolled hypertension (>140/90 mm Hg); a history of cerebrovascular, cardiovascular, kidney, or liver disease; the use of medications known to affect body weight (eg, steroids); pregnancy or lactation; a weight loss of 5 kg or more and/or the use of anorectic agents in the previous 6 months; and the use of selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, or other medications contraindicated with the use of sibutramine.13 Psychosocial contraindications included the following: current psychotherapy; bulimia nervosa; major depression, as suggested by a score higher than 25 on the Beck Depression Inventory24; or other psychiatric illness that significantly disrupted daily functioning.25 Patients with binge eating disorder26 were included.

Respondents were screened by telephone, and those who met the aforementioned criteria were scheduled for a 1-hour meeting with a psychologist (T.A.W. or D.B.S.) who described the nature and requirements of the study; obtained patients’ informed consent, and reviewed applicants’ responses to the screening battery. Women who were free of the psychosocial complications described earlier were referred to their primary care physicians, who conducted a history intake and physical examination to determine that applicants also were free of the physical complications noted above. Physicians forwarded their findings to the project physician (R.I.B.), who had final responsibility for accepting patients into the trial. Participants deposited $600, which covered the costs of medications and all professional fees. A total of $150 was returned for completing study assessments at 6 and 12 months. This study was approved by the University of Pennsylvania’s Committee on Subjects Involving Human Beings, Philadelphia.

PROCEDURES

Fifty-five women were randomly assigned to 1 of 3 treatment groups: (1) drug-alone, (2) drug-plus-lifestyle modification (ie, drug-plus-lifestyle), or (3) drug-plus-lifestyle with a portion-controlled diet (ie, combined treatment). One woman in each of the first 2 groups withdrew prior to the start of the trial, leaving a total of 53 patients. Baseline characteristics of the women in the 3 groups are given in Table 1.

Table 1.

TREATMENT GROUPS

Drug-Alone Group

At week 0 (ie, baseline), these 19 patients met with a physician (R.I.B. or R.P.-W.) who described the 1-year program, including the use of sibutramine treatment and the importance of lifestyle modification. They were instructed to consume a balanced diet of 5021 to 6276 kJ/d (1200-1500 kcal/d), with approximately 15% of the energy from protein, 30% from fat, and 55% from carbohydrates. They were also encouraged to gradually increase their exercise (typically by walking) to 4 to 5 sessions per week for 30 to 40 minutes per session. To aid these efforts, they were given a copy of On Your Way to Fitness,27 a 28-page guide that describes the basics of healthy eating and activity habits. At week 0, patients were prescribed 10 mg once daily of sibutramine hydrochloride that, if tolerated, was increased to 15 mg once daily at week 8. Patients had a total of 10 brief (5- to 10-minute) follow-up visits (at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 52) at which the physician measured their weight, blood pressure (BP), and pulse rate and inquired about side effects. Patients were not asked to keep records of their food intake or physical activity; physicians did not provide lifestyle counseling.

Drug-Plus-Lifestyle Group

The 17 women in this group were prescribed sibutramine and had physician visits on the same schedule as those in the drug-alone group. In addition, during the first 20 weeks, they attended weekly group lifestyle modification sessions, which were conducted by doctoral-level psychologists (T.A.W. or D.B.S.), following the LEARN Program for Weight Control.28 These patients were prescribed the same diet and exercise goals as those in the first group but were given behavioral strategies for achieving these objectives and were asked to keep daily records of their food intake and physical activity for at least the first 16 weeks. Records were reviewed at weekly sessions, as were traditional behavioral topics including stimulus control, slowing the rate of eating, social support, and cognitive restructuring.29 From weeks 24 to 52, participants attended monthly group sessions that focused on the skills needed for the maintenance of weight loss.

Combined Treatment Group

The 17 women in this group received, with one exception, the same treatment as those in the drug-plus-lifestyle group. For the first 16 weeks, they were prescribed a 4184-kJ/d (1000 kcal/d) portion-controlled diet that consisted of 4 servings a day of a nutritional supplement combined with an evening meal of a frozen food entree, a serving of fruit, and a green salad. Each serving of

Continued on next page

the combination of pharmacotherapy plus lifestyle modification.

Our study assessed the benefits of adding lifestyle modification to the pharmacologic treatment of obesity. This is the obverse of the typical design in which the benefits of pharmacotherapy are assessed by comparing lifestyle modification plus placebo with lifestyle modification plus medication.3,6,22 In our study, results of treating obese women with sibutramine alone (ie, the drug-alone group) were compared with those for sibutramine combined with group lifestyle modification (ie, the drug-plus-lifestyle group). (We selected sibutramine because...
the liquid supplement provided 669 kJ (160 kcal) with 14 g of protein, 20 g of carbohydrates, and 3 g of fat (OPTIFAST 800; Novartis Nutrition Co, Minneapolis, Minn). Beginning at week 17, participants gradually decreased their consumption of the liquid supplement, so that by week 20 they were prescribed a 5021- to 6276-kJ/d diet (1200-1500-kcal/d diet) of conventional foods, similar to the patients in the other 2 conditions.

DEPENDENT MEASURES

Weight

Weight was measured at each treatment visit, on the schedule of patients in the drug-alone group (ie, weeks 0, 2, 4, 8, 12, 16). Patients were weighed in light clothing without shoes.

Behavioral Adherence

Adherence to the behavioral program was assessed in the second and third groups by the number of food records patients completed the first 16 weeks. For each week, participants were given a score of 0 to 7, reflecting the number of days that they recorded their food intake. At each meeting, women who reported forgetting to bring their records were asked to do so the next week. If they did not, they were given a score of 0 for the week in question.

Weight Loss Expectations and Satisfaction

Before treatment, but after having been informed of their treatment assignment, patients completed a questionnaire that asked how much weight they expected to lose after 1, 3, 6, and 12 months of treatment. For each month, they recorded the cumulative number of pounds they expected to lose by that time. They also noted the weight loss goal they ultimately hoped to achieve, even if not in this program. At months 3, 6, and 12, participants rated their satisfaction with their weight loss, as well as with changes in their health and energy level, appearance, and self-esteem. Ratings were made on a 1- to 10-point scale in which 1 indicated very dissatisfied and 10 indicated very satisfied. Using the same scale, they also reported their satisfaction with their weight loss, as well as with the medical care they received from the study physicians.

BP and Lipids

Blood pressure and pulse rate were measured on the same schedule as weight using a Dinamap monitor (XL Model 9300; Johnson & Johnson, New Brunswick, NJ), an automated instrument that eliminates potential observer bias in the detection of Korotkoff sounds. On each occasion, 2 readings were taken at 1-minute intervals after the patient had been seated for at least 5 minutes. The levels of triglycerides, total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured at baseline and weeks 8, 26, and 52 following an overnight fast; methods used have been described elsewhere.30

ATTRITION AND STATISTICAL ANALYSES

Attrition

All 17 patients in the combined treatment group completed the study (ie, 0% attrition). By contrast, 6 (31.6%) of 19 patients in the drug-alone group discontinued treatment prematurely, as did 4 (23.5%) of 17 patients in the drug-plus-lifestyle group. χ² Analyses revealed a significantly (P<.05) greater rate of attrition in the drug-alone group than in the combined treatment group, with no other significant differences among conditions. Table 2 lists the time of attrition for each patient, weight loss at the time, and factors associated with discontinuation. Six patients withdrew because of apparent scheduling conflicts and/or dissatisfaction with treatment; the other 4 discontinued participation because of concomitant medical conditions (ie, migraine headache, surgery for a fibroid tumor), increased BP, and reports of heartburn and insomnia.

Statistical Analyses

Differences between conditions in changes in weight (and other measures) were compared using analysis of variance with repeated measures. In cases in which a significant treatment effect was observed, the Tukey honestly significant difference test13 was used to identify differences among the 3 groups. This method, similar to the Bonferroni adjustment,11 sets the experimentwise error rate at P<.05, thus, controlling for the effect of multiple comparisons. Weight data were analyzed in 2 ways. A last-observation-carried-forward (LOCF) analysis was used in which the patient’s body weight at the time of attrition was included at the 6- and 12-month assessments. A more conservative intention-to-treat analysis was also conducted in which participants who discontinued treatment were assumed to gain 0.3 kg/mo after leaving the study. This value was selected based on the 1-year weight regain of approximately 3.0 kg observed in trials of behavior modification.36,32 This calculation may be preferable to the LOCF analysis, which does not account for the weight regain that occurs during long-term obesity trials. For example, a patient who loses 10% of his or her initial body weight during the first 3 months of treatment and then drops out is unlikely to maintain a loss of this size at a 1-year assessment, although a 10% loss would be credited if the LOCF analysis were used.11 All values are expressed as means (±SDs).

it was the only medication approved for long-term use when the study began in September 1998.) Patients in both groups were treated for 1 year and were asked to consume a 5021- to 6276-kJ/d diet (1200-1500 kcal/d diet) and to increase their physical activity. However, only those in the second group (the drug-plus-lifestyle) were provided behavioral strategies for achieving these goals. Patients in the third treatment group (the combined treatment group) also were prescribed sibutramine and group lifestyle modification. During the first 4 months, however, they were also provided a 4184-kJ/d (1000 kcal/d) portion-controlled diet.21 This diet was included to induce larger weight losses.22 A previous study23 suggested that obese women were dissatisf-
fied with the 10% reduction in their initial body weight produced by current behavioral and pharmacologic therapies. We wished to determine whether the inclusion of a portion-controlled diet would increase initial weight losses and, thus, patients' satisfaction with treatment outcome.

## RESULTS

### WEIGHT LOSS

Women in all 3 treatment groups achieved their maximum weight loss (as assessed by the LOCF analysis) at month 6, when the patients in the drug-alone group had lost 3.8%±5.0% of their initial body weight, compared with substantially larger losses of 11.0%±6.7% in the drug-plus-lifestyle group and 17.7%±5.9% in the combined treatment group (Table 3 and Figure 1). (The losses were 5.6±5.0 kg, 11.4±7.1 kg, and 17.9±5.8 kg for the 3 groups, respectively.) Pairwise comparisons (ie, Tukey honestly significant difference test) showed that all 3 groups differed significantly from each other. Thus, patients in the drug-plus-lifestyle group lost significantly (P<.05) more weight than those treated with sibutramine alone. Similarly, women who received combined treatment, which included a 4184-kJ/d (1000-kcal/d) portion-controlled diet, lost significantly (P<.05) more than those in the drug-plus-lifestyle group, who were prescribed a 5021- to 6276-kJ/d (1200-1500 kcal/d) diet (Table 3 and Figure 1).

The benefits of group lifestyle modification persisted at month 12. Patients in the drug-alone group maintained a loss of 4.1%±6.3% of their initial body weight, compared with significantly (P<.05) greater reductions in the drug-plus-lifestyle group of 10.8%±10.3% and in the combined treatment group of 16.5%±8.0%. (The losses were 3.8±6.1 kg, 11.1±10.5 kg, and 16.6±7.5 kg for the 3 groups, respectively.) Differences between the latter 2 treatment groups approached statistical significance (P<.12). (The LOCF and intention-to-treat analyses yielded the same results in all cases, thus only the LOCF results are reported here.)

At month 12, significantly more patients in the drug-plus-lifestyle group, as well as in the combined treatment group, had lost 5% or more or 10% or more of their initial body weight than had those in the drug-alone group (P<.05 for both) (Table 4). In addition, significantly more patients in the combined treatment group than in the drug-plus-lifestyle group achieved losses of 10% or more or 15% or more of their initial body weight (P<.05 for both). Thus, at the end of 1 year, the 4184-kJ/d (1000-kcal/d) portion-controlled diet was superior to the conventional 5021- to 6276-kJ/d (1200-1500 kcal/d) diet in promoting weight losses of 10% or more or 15% of initial body weight.

### BEHAVIORAL ADHERENCE AND WEIGHT LOSS

During the first month, women in the lifestyle groups completed more than 85% of their daily food records. For the total 4-month period, patients in the combined treatment group completed 78.9%±19.6% of the possible records, which was significantly (P<.05) greater than the 60.1%±26.1% completed by women in the drug-plus-

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**Table 1. Participants' Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Drug-Alone Group (n = 19)</th>
<th>Drug-Plus-Lifestyle Group (n = 17)</th>
<th>Combined Treatment Group (n = 17)</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>46.3±7.8</td>
<td>41.4±11.9</td>
<td>40.1±8.8</td>
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<tr>
<td>Weight, kg</td>
<td>98.6±9.6</td>
<td>103.5±8.3</td>
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<tr>
<td>Height, cm</td>
<td>164.1±6.0</td>
<td>162.8±5.8</td>
<td>164.1±10.3</td>
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<tr>
<td>BMI, kg/m²</td>
<td>36.7±3.4</td>
<td>39.2±3.7</td>
<td>37.2±3.3</td>
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<tr>
<td>Age at onset of obesity, y</td>
<td>17.7±10.5</td>
<td>14.7±9.9</td>
<td>13.5±9.0</td>
</tr>
</tbody>
</table>

* All values are expressed as the mean ± SD. There were no significant differences among the 3 groups. Drug-alone group indicates the participants who received sibutramine treatment alone; drug-plus-lifestyle group, participants who received sibutramine treatment and attended weekly group lifestyle modification sessions for the first 20 weeks; and the combined treatment group, participants who received sibutramine treatment, attended weekly group lifestyle modification sessions for the first 20 weeks, and ate a 4184-kJ/d (1000-kcal/d) diet for the first 16 weeks. For more detailed information see the “Treatment Groups” subsection of the “Participants and Methods” section.

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**Table 2. Summary of Attrition for 10 Participants**

<table>
<thead>
<tr>
<th>Participant No.</th>
<th>Reason for Discontinuation</th>
<th>Week of Attrition</th>
<th>% Weight Loss at Attrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Severe acid reflux, heartburn, and insomnia</td>
<td>20</td>
<td>−13.5</td>
</tr>
<tr>
<td>2</td>
<td>Increase in blood pressure from 131/78 to 162/92 mm Hg; patient wished to discontinue</td>
<td>24</td>
<td>+0.8</td>
</tr>
<tr>
<td>3</td>
<td>Scheduling problems</td>
<td>36</td>
<td>+6.7</td>
</tr>
<tr>
<td>4</td>
<td>Lost to follow-up, dissatisfied with treatment</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Lost to follow-up, dissatisfied with treatment</td>
<td>16</td>
<td>−2.3</td>
</tr>
<tr>
<td>6</td>
<td>Scheduling problems</td>
<td>8</td>
<td>−5.3</td>
</tr>
</tbody>
</table>

* Mean ± SD number of weeks attended was 21.3±8.5; mean ± SD percent reduction in initial weight at time of attrition was −2.3%±6.2%. Drug-alone group indicates the participants who received sibutramine treatment alone.

†Mean ± SD number of weeks attended was 22.5±12.1; mean ± SD percent reduction in initial weight at attrition was −5.8%±4.6%. Drug-plus-lifestyle group indicates participants who received sibutramine treatment and attended weekly group lifestyle modification sessions for the first 20 weeks.
lifestyle group. Partial correlation analyses, which controlled for the effect of treatment condition, revealed a strong positive relationship between weight loss and the completion of food records. For example, the greater the total number of records women completed in the first 2 months, the greater their weight loss at month 2 (r = .53, P < .001). Similarly, the greater the total number of records completed in the first 4 months, the greater the weight loss at month 4 (r = .57, P < .001), month 6 (r = .55, P < .002), and month 12 (r = .41, P < .03).

Additional analyses, which included patients in all 3 treatment groups, revealed the importance of early weight loss. Partial correlation analyses, controlling for treatment condition, showed that the greater the weight loss the first month, the greater the loss at month 2 (r = .81, P < .001), month 4 (r = .61, P < .001), month 6 (r = .53, P < .001), and month 12 (r = .33, P < .02). Women who discontinued treatment prematurely tended (P < .07) to lose less weight the first month than did those who completed the full program (3.0% ± 1.9% vs 4.3% ± 1.8%, respectively).

**WEIGHT LOSS EXPECTATIONS AND SATISFACTION**

Patients in all 3 treatment groups expected to lose large amounts of weight, as shown in Figure 2. By month 6, eg, they expected to reduce their initial body weight by an average of 16.3% ± 4.7%, increasing by month 12 to 25.2% ± 7.7%. Their ultimate goal was to lose 34.4% ± 11.3% of their initial body weight. There were no significant differences among the 3 groups in the size of expected weight losses for any period.

There were, however, marked differences among groups in patients’ achievement of their expected weight losses. At month 12, for example, women in the drug-alone group achieved only 21.9% ± 22.5% of their expected end-of-treatment weight loss, as compared with a significantly (P < .05) greater 60.7% ± 59.1% for the women in the drug-plus-lifestyle group and 66.2% ± 34.8% for the women in the combined treatment group (with no differences between the latter 2 groups). Partial correlation analyses (controlling for treatment condition) showed that the greater the percentage of their expected

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>Drug-Alone Group</th>
<th>Drug-Plus-Lifestyle Group</th>
<th>Combined Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LOCF</td>
<td>ITT</td>
<td>LOCF</td>
</tr>
<tr>
<td>2</td>
<td>4.0 ± 2.7</td>
<td>4.0 ± 2.7</td>
<td>5.6 ± 3.0</td>
</tr>
<tr>
<td>4</td>
<td>5.4 ± 4.3</td>
<td>5.4 ± 4.2</td>
<td>9.6 ± 5.0</td>
</tr>
<tr>
<td>6</td>
<td>5.8 ± 5.0</td>
<td>5.5 ± 5.2</td>
<td>11.0 ± 6.7</td>
</tr>
<tr>
<td>12</td>
<td>4.1 ± 6.3</td>
<td>3.6 ± 6.5</td>
<td>10.8 ± 10.2</td>
</tr>
</tbody>
</table>

*Data show the percentage of patients meeting various weight loss criteria at month 12. Patients who dropped out were counted as treatment failures (ie, they did not meet the criteria at month 12 for a 5%-9.9% reduction). Drug-alone group indicates the participants who received sibutramine treatment alone; drug-plus-lifestyle group, participants who received sibutramine treatment and attended weekly group lifestyle modification sessions for the first 20 weeks; and the combined treatment group, participants who received sibutramine treatment, attended weekly group lifestyle modification sessions for the first 20 weeks, and were prescribed a 4184-kJ/d (1000-kcal) diet for the first 16 weeks. For more detailed information see the “Treatment Groups” subsection of the “Participants and Methods” section.*
end-of-treatment weight loss patients achieved, the greater their reported satisfaction at month 12 with changes in their weight ($r=0.72$, $P<.001$), health and energy ($r=0.67$, $P<.001$), appearance ($r=0.71$, $P<.001$), and self-esteem ($r=0.62$, $P<.001$). Figure 3A-D shows that at the 3-, 6-, and 12-month assessments, women in the combined treatment group were significantly more satisfied with changes in their weight, health and energy level, appearance, and self-esteem than were those in the drug-alone group ($P<.05$ for all). Women in the drug-plus-lifestyle group were similarly more satisfied at 3 and 6 months with their changes in weight and appearance and at 12 months were significantly more satisfied than women in the drug-alone group on all 4 measures ($P<.05$ for all). No significant differences in satisfaction were observed between the 2 lifestyle conditions.

At no time during the study were there any significant differences among the 3 groups in reported satisfaction with the medical care provided by the study physicians; ratings were uniformly high throughout treatment (8.7±1.4 at month 12 for the 3 groups combined). By contrast, there were marked differences in satisfaction with sibutramine therapy. As shown in Figure 4, women in the 2 lifestyle groups were significantly ($P<.05$) more satisfied with sibutramine at months 6 and 12 than were patients treated with sibutramine alone. In the drug-alone group, satisfaction with the medication declined significantly ($P<.05$) from month 3 to month 12, while ratings remained generally positive (and statistically unchanged) in the 2 other groups.

BP, LIPIDS, AND MEDICATION DOSE

Blood Pressure

Table 5 gives the changes in BP, pulse rate, and lipid and lipoprotein levels for the 43 women who completed the full 1-year study. Data were collapsed across the 3 groups after analyses revealed no significant differences among groups, at the end of treatment, in changes on any of these variables. As listed in Table 5, small, but statistically nonsignificant increases, were observed in systolic BP (SBP) and diastolic BP (DBP) during the first few months. By month 12, however, both values had increased significantly ($P<.05$ for both) above baseline, SBP by 5.0±13.3 mm Hg and DBP by 6.1±8.1 mm Hg. These mean increases may well have been higher if the medication dose had not been tapered from 15 mg/d to 10 mg/d in 4 patients and discontinued altogether in a fifth patient (in the drug-plus-lifestyle group), all of whom had increases in SBP or DBP of 15% or more of baseline values in response to the 15-mg/d dose. (No patient was allowed to remain on this dosage for $>1$ week with a pulse rate $>100$ beats per minute.) No significant correlations were found, at any assessment period, among changes in weight, BP, or pulse rate. In addition, there were no significant differences among treatment conditions, at any time, in the changes in BP or pulse rate.

Lipids and Lipoproteins

Collapsing across the 3 groups, significant reductions were observed in the levels of triglycerides, LDL-C, and TC beginning at month 2 ($P<.05$ for all). These reductions, combined with significant increases in the level of HDL-C at months 6 and 12, resulted in significant reductions in the TC/HDL-C ratio, indicative of a reduced risk of cardiovascular disease ($P<.05$ for all). At the 1-year assessment, a positive relation ($r=0.40$, $P<.02$) was found between weight loss and the reduction in the TC/HDL ratio. Thus, patients who lost more weight tended to have greater reductions in the risk of cardiovascular disease. The correlations between 1-year weight loss and changes in the levels of triglycerides ($r=0.25$) and LDL-C ($r=0.27$) were in the expected direction but did not reach statistical significance.

At month 2, women in the combined treatment group had significantly greater reductions in TC, LDL-C, and HDL-C levels than did those treated with sibutramine alone. There were no other statistically significant dif-
ferences among the 3 groups at this time or at the 6- and 12-month assessments.

Medication Dose and Weight Loss

In addition to the 8 women noted above who took reduced doses of sibutramine hydrochloride (ie, 10 mg/d) because of increased BP or pulse rate, doses were reduced in 2 additional women because of reports of disturbed sleep and in a third woman because of reports of severe heartburn. These 11 women were evenly distributed across the 3 groups. Analysis of covariance, controlling for the effect of treatment group, showed that mean weight loss of these 11 patients did not differ significantly at month 12 from that of patients who received full doses of sibutramine hydrochloride (ie, 15 mg/d) (mean losses, 10.4%±9.5% vs 12.5%±9.8%, respectively).

COMMENT

This study’s principal finding was that lifestyle modification significantly improved the pharmacologic treatment of obesity. After 1 year, women treated with sibutramine plus lifestyle modification lost 10.8% of their initial body weight, more than twice as much as those treated with sibutramine alone. The addition to the group lifestyle intervention of a 4184-kJ/d (1000-kcal/d) portion-controlled diet increased weight loss even further to 16.5%. To our knowledge, this is one of the largest mean weight losses reported in a randomized trial of weight loss medications.

A second major finding was that the obese women in our study had very unrealistic weight loss expectations. Before treatment, participants in all 3 groups expected to lose the equivalent of 25% of their initial body weight by the end of the year. They anticipated this despite having been informed verbally, in the initial interview, that participants in all 3 groups should expect to lose approximately 5% to 15% of their initial body weight. Moreover, they maintained these expectations even after having been informed of their treatment assignment and having signed a consent form that stated, in 2 separate places, that they could expect to lose 5% to 15% of their initial body weight. Participants hoped ultimately to lose the equivalent of 34% of their initial body weight, a figure strikingly similar to that reported by women in a diet and exercise clinical trial who were asked to identify their “dream” weight.23

Data on weight loss expectations have 3 important implications for practice. First, more effort must be devoted to informing obese persons of the health benefits of a 5% to 15% reduction in their initial body weight. These benefits have been summarized by several inve-
tigators and scientific panels. Second, physicians who prescribe anorectic agents must try throughout treatment to correct the patient’s unrealistic weight goals. This is particularly true after the first 4 to 6 months of treatment when weight loss, in most patients, slows and then stops. Women in our study clearly did not anticipate the weight loss plateau that occurred at this time; this plateau is a hallmark of all behavioral and pharmacologic therapies for obesity. Third, the findings clearly revealed the adverse effects of unmet expectations. Participants in the drug-alone group, who were less successful in meeting their weight loss goals, were less satisfied with the medication and with the changes in their health and energy level, appearance, and self-esteem. By contrast the greater the percentage of expected weight loss participants achieved, the greater their satisfaction with changes in their weight and the other outcomes.

Our findings clearly showed that group lifestyle modification improved the pharmacologic treatment of obesity. We, like others, believe that lifestyle modification provides obese persons strategies to manage the external food environment. These strategies include shopping from a list, storing foods out of sight, controlling portion sizes, avoiding fast food restaurants, and keeping food records. By contrast, centrally acting weight loss medications, including sibutramine, seem to modify the internal environment by increasing satiation or by decreasing hunger or preoccupation with food. Such medications may reduce the obese person’s responsiveness (or vulnerability) to the pervasive food triggers encountered throughout the day. Our findings, however, suggest that anorectic agents are likely to be most effective when combined with the individual’s efforts to manage the external environment. Persons who are prescribed medication alone, without behavioral counseling, seem to be at greater risk of discontinuing treatment prematurely, as they did in our study, because of disappointment with their results. Although participating in a structured program of lifestyle modification required more time and effort from participants in our study, these costs seemed to yield substantial benefits, in terms of patients’ increased satisfaction with changes in their weight, health and energy levels, and psychosocial outcomes.

Two additional points should be noted. First, we are unable to identify which components of the lifestyle modification program contributed to our participants’ improved results. It is possible, eg, that the greater frequency of clinic visits alone increased weight loss in the participants in the drug-plus-lifestyle group compared with those in the drug-alone group. One behavioral component, however, that seemed to be particularly important was keeping food records, as shown in other studies. The more food records women in the 2 lifestyle modification groups kept during the first 4 months, the greater their weight loss both short- and long-term. The second point is that many physicians may believe that they are unprepared to help patients modify their eating and activity habits. We have previously shown, in patients treated by weight loss medications, that 10 brief physician counseling visits (of 15 minutes each) were as effective as 32 group behavior modification sessions (of 75 minutes each) in inducing weight losses of approximately 15% of initial body weight. This study also found a strong correlation between weight loss and completion of food records.

The largest mean weight losses were obtained by women in our combined treatment group who consumed a 4184-kj/d (1000-kcal/d) portion-controlled diet for the first 4 months. At 1 year, they maintained a loss of 16.5% of their initial body weight—a reduction similar to that recently reported by Apfelbaum et al. Patients in that study were treated for a first month by a very low-calorie diet, providing 837 to 3347 kJ/d (200-800 kcal/d), on which they lost approximately 7.5 kg. Participants who were subsequently assigned to sibutramine treatment lost an additional 5.2 kg during the ensuing year, whereas those who received placebo gained 0.5 kg. These findings, with those from other recent trials, suggest that sibutramine and orlistat treatment may significantly improve the long-term maintenance of weight loss. Additional studies are needed to determine whether medication will facilitate the maintenance of the larger losses of 15% to 25% of initial body weight that are typically produced by the 12- to 16-week consumption of a very low-calorie diet. This would be a very important finding, given that patients typically regain 35% to 50% of their weight loss in the year following treatment by a very low-calorie diet.

Our study was designed explicitly to determine whether lifestyle modification would improve the results of pharmacotherapy. The investigation did not examine whether medication would improve the results of group lifestyle modification, on either a short- or long-term basis. Thus, for example, it is possible that women in our combined treatment group would have lost 16.5% of their initial body weight at the end of 1 year without taking sibutramine. Future studies should compare the
effects of medication alone with lifestyle modification alone with the combination of the 2 therapies. The results of a study by Craighead et al\textsuperscript{18} suggested that medication and lifestyle modification had additive effects. Patients treated for 6 months with fenfluramine alone lost approximately 7% of their initial body weight, while those treated with lifestyle modification alone lost approximately 11%. Patients who received the 2 therapies together lost a significantly greater 16% of their initial body weight. These changes are greater than the increases of 2 to 3 mm Hg noted in previous studies.\textsuperscript{10,11,13} Results of a study by Craighead et al\textsuperscript{18} suggested that medication alone with lifestyle modification provides a model for assessing the combined effects of lifestyle modification and weight loss medication. Investigations are needed to determine if the promising effects of such combined therapy are maintained for 2 years or longer, a question not answered by the study by Craighead et al or by our investigation.

Weight losses in our study were associated with significant long-term (ie, 1-year) improvements in the levels of triglycerides, TC, and LDL-C, and the TC/HDL-C ratio. These findings confirm the health benefits of modest weight losses.\textsuperscript{15,33-37} By contrast, SBP and DBP increased by 5 and 6 mm Hg, respectively, at the end of the year, despite participants having lost more than 10% of their initial body weight. These changes are greater than the increases of 2 to 3 mm Hg noted in previous studies.\textsuperscript{10,11,13} and cannot be definitively interpreted in the absence of a placebo-control condition. We note, however, that Hansen et al\textsuperscript{7} recently reported, in participants treated for 8 weeks with 15 mg/d of sibutramine hydrochloride, that DBP increased by 7.1 mm Hg, which was significantly greater than the 0.8–mm Hg increase observed in placebo-treated control subjects. (No significant increases were observed in SBP.) These findings, with ours, underscore the importance of ensuring that sibutramine treatment is used only with appropriate subjects and that BP and pulse rate are monitored regularly.

CONCLUSIONS

Results of our study indicate that primary care physicians who prescribe weight loss medications will need to help their obese patients set more realistic weight reduction goals, particularly after the first 4 to 6 months of treatment. In addition, patients will achieve the best outcome by combining weight loss medication with efforts to modify their eating and activity habits. For many patients, keeping a daily food record and increasing daily physical activity would seem to be excellent first steps.

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