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# Behavior Therapy and Sibutramine for the Treatment of Adolescent Obesity

## A Randomized Controlled Trial

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**A**DOLESCENT OBESITY IS RAPIDLY becoming a national public health problem. The prevalence of this disorder increased from 5% to 11% from the 1980s to 1994 and to 15.5% by 2000.<sup>1-3</sup> This increase has been accompanied by a dramatic increase in type 2 diabetes mellitus and related health complications.<sup>4-11</sup> There has been relatively little controlled research on the treatment of adolescent obesity. A comprehensive behavioral approach appears to be the most effective treatment,<sup>12-14</sup> but most studies have reported mean weight losses of only 1 to 4 kg. Participants typically remained obese at the end of therapy.

Weight-loss medications, including sibutramine and orlistat, facilitate weight control in adults<sup>15-22</sup> and potentially could be used with obese adolescents. No weight-loss agents are currently Food and Drug Administration approved for children younger than 16 years. We agree with Dietz<sup>8</sup> that weight-loss medications should be used only on an experimental basis with adolescents and solely "as an adjunct to behavior modification, family therapy, increased activity . . ." and that ". . . the

See also pp 1813 and 1851.

**Context** Adolescent obesity is becoming a national public health problem. Weight-loss medications including sibutramine facilitate weight control in adults and could be used with obese adolescents in combination with behavior therapy (BT).

**Objective** To examine whether increased weight loss in obese adolescents is induced when sibutramine is added to a family-based, behavioral weight control program.

**Design, Setting, and Participants** Randomized, double-blind, placebo-controlled trial consisting of 82 adolescents aged 13 to 17 years with a body mass index (BMI) of 32 to 44 conducted from March 1999 to August 2002 at a university-based clinic for 6 months, followed by open-label treatment during months 7 to 12.

**Interventions** For the first 6 months, participants received either BT and sibutramine or BT and placebo. From months 7 to 12, all participants received sibutramine in open-label treatment.

**Main Outcome Measures** Percentage change in BMI; systolic and diastolic blood pressure and pulse; and hunger.

**Results** In intention-to-treat analysis at month 6, participants in the BT and sibutramine group lost a mean (SD) of 7.8 kg (6.3 kg) and had an 8.5% (6.8%) reduction in BMI, which was significantly more than weight loss of 3.2 kg (6.1 kg) and reduction in BMI of 4.0% (5.4%) in the BT and placebo group. Significantly greater reductions in hunger ( $P=.002$ ) also were reported by participants who received BT and sibutramine. From months 7 to 12, adolescents initially treated with sibutramine gained 0.8 kg (10.5 kg) with continued use of the medication, whereas those who switched from placebo to sibutramine lost an additional 1.3 kg (5.4 kg). Medication dose was reduced ( $n=23$ ) or discontinued ( $n=10$ ) to manage increases in blood pressure, pulse rate, or other symptoms.

**Conclusions** The addition of sibutramine to a comprehensive behavioral program induced significantly more weight loss than did BT and placebo. Until more extensive safety and efficacy data are available, medications for weight loss should be used only on an experimental basis in adolescents and children.

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initial studies of these agents should be blinded and placebo controlled.” The aim of the present study was to increase weight loss in obese adolescents by combining a comprehensive behavioral program with pharmacotherapy. This study is to our knowledge the first randomized, placebo-controlled trial of sibutramine in the treatment of obese youth.

**METHODS**

**Study Design**

A randomized, double-blind, placebo-controlled trial was conducted for 6 months (phase 1), after which all participants received sibutramine in an open-label extension for an additional 6 months (phase 2) (FIGURE 1). We hypothesized that participants who received behavior therapy (BT) and sibutramine would lose significantly

more weight during phase 1 than those who received BT and placebo. Participants, parents, and all study personnel were blinded to treatment condition during phase 1. Only the research pharmacist was aware of treatment status. This study was approved by the institutional review boards of the University of Pennsylvania and The Children’s Hospital of Philadelphia and was conducted from March 1999 to August 2002 at the Weight and Eating Disorders Program at the University of Pennsylvania School of Medicine, Philadelphia.

**Participants**

Candidates were boys and postmenarcheal girls aged 13 to 17 years who had a body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) of 32 to 44.

Contraindications to participation included cardiovascular disease (including arrhythmias); type 1 or 2 diabetes mellitus; major psychiatric disorders; pregnancy; use of a weight-loss medication or a weight loss of 5 kg or more in the prior 6 months; use of medications promoting weight gain (eg, oral steroids); use of medications contraindicated with use of sibutramine<sup>23</sup>; or cigarette smoking. Adolescents, accompanied by a parent or guardian, completed a behavioral assessment, conducted by a staff psychologist or psychiatrist. Written informed consent was obtained from the parent and assent from the adolescent. The adolescent’s primary care physician performed a history and physical examination to exclude the noted contraindications.

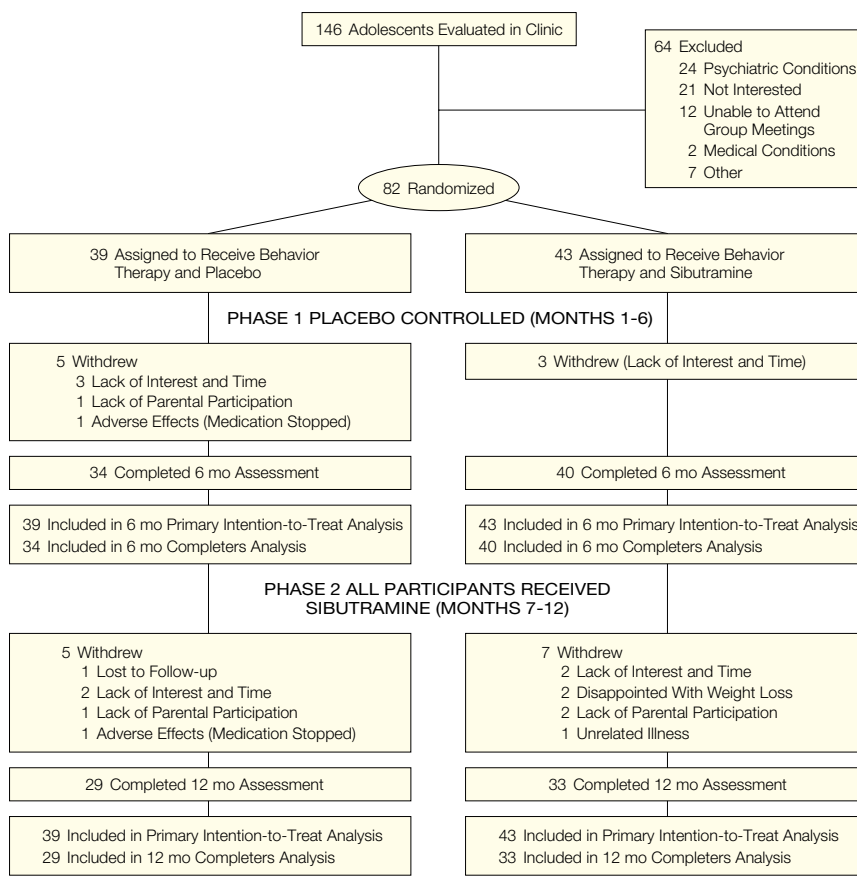
**Interventions**

**Behavioral Protocol.** Adolescents in both treatment conditions received the same comprehensive family-based behavioral weight-loss program delivered following detailed treatment manuals.<sup>24-26</sup> In phase 1, participants attended 13 weekly group sessions followed up by 6 biweekly group sessions. In phase 2, group sessions were held biweekly from months 7 to 9 and monthly from months 10 to 12. Parents met separately in group sessions held on the same schedule as the adolescents’ meetings. Groups were led by dietitians, psychologists, or psychiatrists.

Adolescents in both treatment groups were instructed to consume a 1200 to 1500 kcal/d diet of conventional foods, with approximately 30% from fat, 15% from protein, and the remainder from carbohydrate. They were prescribed an eventual goal of walking or engaging in similar aerobic activity for 120 minutes per week or more. Participants kept daily eating and activity logs that they submitted at each session. The content of the parents’ sessions paralleled that of their children’s sessions. Parents praised their adolescents for adhering to the diet and activity program.

**Medication Protocol.** During phase 1, all participants received placebo

**Figure 1.** Flow of Participants Throughout the Trial



(single blind) the first week. At week 2, they received either placebo or 5 mg/d of sibutramine. In medication-treated participants, sibutramine was increased to 10 mg/d at week 3 and to 15 mg/d at week 7. Knoll Pharmaceutical Co and Abbott Laboratories manufactured and provided both the placebo and sibutramine for the study. Placebo capsules looked exactly like sibutramine capsules and were dispersed in the same way.

Increases in blood pressure (BP) and pulse have been reported previously in adults who received sibutramine.<sup>15,23</sup> Thus, in the present study, participants whose systolic or diastolic BP increased from baseline by 10 mm Hg or more (or who had increases in pulse rate of  $\geq 15\%$ ) for 2 or more consecutive visits had their medication dose reduced in 5-mg decrements until acceptable BP and pulse rate values were obtained. Sibutramine was discontinued in participants in whom dose reductions did not reverse the 10-mm Hg or more increase or in whom systolic or diastolic BP increased 20 mm Hg or more at any single visit. During phase 2, all participants were treated with sibutramine following the same dose titration schedule used in phase 1.

### Dependent Measures

Weight was measured at each treatment visit and at the major assessments (ie, baseline and months 3, 6, 9, and 12). Height and waist circumference were measured at the major assessments following standard techniques.<sup>27</sup>

Adherence to the lifestyle program was assessed by the number of days of food records completed during phase 1. Medication adherence during this same period was evaluated by pill counts. Hunger was evaluated at the major assessments by the Eating Inventory (range, 0-14).<sup>28</sup> Maternal level of education was assessed on a 6-point scale ranging from some high school to doctoral degree (some high school = 1, high school graduate = 2, some college = 3, college graduate = 4, master's degree = 5, and doctoral degree = 6).

Lipids, lipoproteins, serum glucose, and insulin levels were measured at the major assessments following an overnight fast (Quest Diagnosis Incorporated, Horsham, Pa). An electrocardiogram was also obtained at these times. Systolic and diastolic BP, as well as pulse rate, were measured at the major assessments (and biweekly for the first 8 months and then monthly) with a Dinamap monitor (XL Model 9300, Johnson & Johnson, New Brunswick, NJ). Assessments were obtained after the adolescent stayed still for at least 5 minutes. Three readings were taken at 1-minute intervals; the second and third measures were averaged. Adverse events were assessed and recorded at each medical visit.

### Data Analysis

The present study was powered to detect a 4.0% difference in baseline BMI between the 2 treatment groups. The study was powered using the effect size statistic  $d$  by Cohen,<sup>29</sup> defined as the difference between the 2 treatment groups divided by the pooled SD. The pooled SD was estimated to be 5%. Given a 4.0% difference in percentage change in BMI and an SD of 5%, this corresponds to a large effect size (Cohen  $d = .80$ ).<sup>29</sup> Assuming a 2-tail analysis,  $\alpha = .05$  and an SD of 5%, 93% power was obtained to detect a percentage BMI reduction as small as 4% between the 2 treatment groups.<sup>29</sup>

Changes in degree of obesity were evaluated by changes in weight, BMI, and BMI  $z$  scores,<sup>30</sup> as well as by percentage change in initial BMI. This latter measure controls for changes in height over time, as well as for differences among participants in baseline BMI. Differences between treatment conditions in changes on these measures from baseline to month 6 (phase 1) and from months 7 to 12 (phase 2) were examined using a  $2 \times 3$  (condition  $\times$  time) repeated measures analysis of variance. An intention-to-treat analysis was used in which missing data were replaced by the participant's baseline body weight (ie, a baseline-carried-forward analysis). A completers analysis (with weight data

for completers at 6 and 12 months) and a mixed-model analysis also were performed. The family-wise error term for each analysis was set at .05, and all data were analyzed using SAS version 8.0 (SAS Institute, Cary, NC).  $P \leq .05$  was considered statistically significant. Results of all analyses yielded the same statistical conclusions. Only the results of the intention-to-treat analysis for percentage change in BMI are presented.

Secondary outcome measures, including BP, pulse, and hunger, also were analyzed using repeated measures analysis of variance. For each variable, the family-wise error term was set at .05. All secondary analyses were conducted using treatment completers. This was done, in part, to minimize potential masking of changes in BP or pulse that might occur with an intention-to-treat analysis, which would replace missing BP or pulse values with baseline values; vital signs have been shown to increase while taking sibutramine.

## RESULTS

### Participants

Characteristics of the 82 patients who were randomized to treatment are shown in TABLE 1 and Figure 1. There were no significant differences between treatment groups on any of the baseline measures or in attrition from therapy.

### Weight Change and Percentage Reduction in BMI

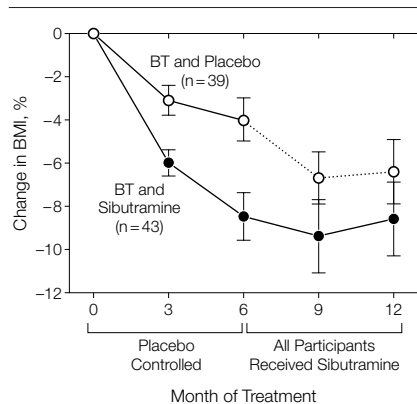
At month 6 during phase 1 (placebo controlled), participants in the BT and sibutramine group lost a mean (SD) of 7.8 kg (6.3 kg) equal to an 8.5% (6.8%) reduction in initial BMI (FIGURE 2 and TABLE 2). In contrast, adolescents treated with BT and placebo lost 3.2 kg (6.1 kg) equal to a significantly smaller 4.0% (5.4%) reduction in BMI (effect size, 0.73; 95% confidence interval [CI], 0.28-1.18;  $P = .001$ ). More than twice as many adolescents in the BT and sibutramine group reduced their initial BMI by 10% ( $P = .02$ ) and 15% ( $P = .02$ ) compared with those treated by BT and placebo (TABLE 3). In Table 2, statistically significant differences between

**Table 1.** Baseline Characteristics for Participants Assigned to Behavior Therapy (BT) and Placebo or Sibutramine\*

Characteristic	Total Sample (N = 82)	BT and Placebo (n = 39)	BT and Sibutramine (n = 43)
Age, mean (SD), y	14.1 (1.2)	14.1 (1.2)	14.1 (1.3)
Weight, mean (SD), kg	103.6 (15.4)	105.3 (16.2)	102.0 (14.7)
Height, mean (SD), cm	165.4 (8.0)	166.2 (8.4)	164.6 (7.7)
BMI, mean (SD)	37.8 (3.8)	38.0 (3.6)	37.5 (4.0)
BMI z score, mean (SD)	2.4 (0.2)	2.5 (0.2)	2.4 (0.2)
Waist circumference, mean (SD), cm	110.8 (10.0)	111.5 (10.2)	110.3 (9.9)
Sex, female, No. (%)	55 (67.1)	24 (61.5)	31 (72.1)
Race, No. (%)			
White	45 (54.9)	24 (61.5)	21 (48.8)
Black	34 (41.5)	13 (33.3)	21 (48.8)
Other	3 (3.6)	2 (5.2)	1 (2.3)
Hunger score, mean (SD)	4.9 (3.3)	5.5 (3.4)	4.5 (3.1)
Maternal BMI, mean (SD)	32.7 (9.6)	34.4 (11.3)	31.2 (7.4)
Maternal level of education, mean (SD)	3.1 (1.1)	3.3 (1.2)	2.9 (1.0)

Abbreviations: BMI, body mass index calculated as weight in kilograms divided by the square of height in meters.

\*Other race included 1 Hispanic and 2 were more than 1 race. Hunger scores ranged from 0 to 14. Maternal level of education is defined in "Methods."

**Figure 2.** Mean Percentage Change in Initial Body Mass Index (BMI) by Month of Treatment for Adolescents Treated With Behavior Therapy Combined With Sibutramine or Placebo (Intention-to-Treat Analysis)


BT indicates behavior therapy; BMI, body mass index calculated as weight in kilograms divided by the square of height in meters. Error bars indicate SEM. Dotted line indicates that BT and placebo group received sibutramine during months 7 to 12. At month 3 and 6, the BT and sibutramine group difference was significant ( $P = .001$  for both).

groups also were observed in changes in waist circumference and BMI z score.

In phase 2 (open-label sibutramine treatment), participants who were originally treated with placebo and were switched to sibutramine from months 7 to 12 lost an additional 1.3 kg (5.4 kg) during this period, reducing their

baseline BMI by an additional 2.4% (5.0%). In contrast, participants originally treated with sibutramine who continued medication gained 0.8 kg (10.5 kg) during months 7 to 12 equal to a 0.2% (5.4%) reduction in initial BMI (BMI decreased even with weight gain because of increases in height). The difference in percentage reduction in BMI between groups (months 7-12) approached significance (effect size,  $-0.22$ ; 95% CI,  $-0.66$  to  $0.21$ ;  $P = .057$ ).

From baseline to month 12, participants treated throughout the study with BT and sibutramine lost a total of 7.0 kg (9.3 kg) equal to an 8.6% (9.9%) reduction in initial BMI. Those participants in the BT and placebo group who were switched at month 7 to sibutramine lost a total of 4.5 kg (8.8 kg) equal to a 6.4% (8.3%) reduction in initial BMI. The difference between groups at month 12 was not significant (Figure 2). Weight loss was not related at any time to participants' baseline characteristics, including maternal BMI or education.

#### Adherence, Hunger, and Weight Loss

During the first 6 months, participants in the BT and sibutramine group monitored their food intake for a mean (SD) of 58.9 days (44.9 days) compared with 61.3 days (38.2 days) for

those in the BT and placebo group. The effects of treatment condition (placebo vs sibutramine) and self-monitoring on percentage reduction in BMI at month 6 were examined using stepwise linear regression. Number of food records completed during this period accounted for 17.7% of the variance ( $R^2 = 0.177$ ) in the percentage change in BMI. Treatment group accounted for an additional 12.9% ( $R^2 = 0.129$ ), bringing the total variance explained to 30.6% ( $R^2 = 0.306$ ,  $P < .001$ ). FIGURE 3 presents weight change data according to treatment condition and the frequency of participants' self-monitoring.

Participants treated with BT and sibutramine used (determined by pill count) 79.1% (21.7%) of the total number of pills they were prescribed during the first 6 months compared with 78.3% (15.9%) for adolescents in the BT and placebo group. In the BT and sibutramine group, the total dose of medication taken correlated significantly with percentage reduction in initial BMI at month 6 ( $r = 0.44$ ,  $P = .003$ ). Participants in this group compared with those treated with placebo reported significantly greater reductions in hunger at month 3 (effect size,  $0.39$ ; 95% CI,  $-0.07$  to  $0.86$ ;  $P < .001$ ) and month 6 (effect size,  $0.43$ ; 95% CI,  $-0.06$  to  $0.86$ ;  $P = .002$ ). Mean (SD) changes were  $-2.1$  (3.3) vs  $-0.3$  (3.2) and  $-2.1$  (3.3) vs  $-0.71$  (3.7) at the 2 periods, respectively. No significant differences in hunger were observed at month 12.

#### Serum Chemistries

There were no differences between groups during phases 1 or 2 in changes in lipids, triglycerides, serum insulin, serum glucose, or homeostasis model of insulin sensitivity (HOMA).<sup>31</sup> Collapsing across conditions, however, at month 12 there was a significant increase in high-density lipoprotein cholesterol ( $P = .001$ ) and significant reductions in serum insulin ( $P < .001$ ) and HOMA ( $P < .001$ ) (TABLE 4). At this time, there were significant correlations between percentage change in BMI and percentage reduction in total cholesterol

**Table 2.** Changes in Degree of Obesity at Month 6 for Adolescents Treated With Behavior Therapy and Placebo or Sibutramine (Intention-to-Treat Analysis)

Variable	Median (Range) Change		Mean (SD) Change		P Value*	Mean Difference (95% CI)
	BT and Placebo (n = 39)	BT and Sibutramine (n = 43)	BT and Placebo (n = 39)	BT and Sibutramine (n = 43)		
Weight, kg	-1.2 (-19.2 to 5.5)	-6.9 (-23.8 to 1.2)	-3.2 (6.1)	-7.8 (6.3)	.001	4.6 (2.0-7.4)
Change in initial BMI, %	-2.8 (-18.7 to 4.7)	-8.0 (-24.4 to 1.1)	-4.0 (5.4)	-8.5 (6.8)	.001	4.5 (1.8-7.2)
Change in BMI z score	-0.1 (-0.6 to 0.1)	-0.2 (-0.9 to 0.0)	-0.1 (0.1)	-0.2 (0.2)	.003	0.1 (0.04-0.2)
Waist circumference, cm†	-2.0 (-19.6 to 8.0)	-6.7 (-25.2 to 1.8)	-2.8 (5.6)	-8.2 (6.9)	<.001	5.4 (2.5-8.2)

Abbreviations: BMI, body mass index calculated as weight in kilograms divided by the square of height in meters; BT, behavior therapy; CI, confidence interval.

\*Between-group comparisons.

†BT and placebo, n = 37; BT and sibutramine, n = 41.

( $r=0.30$ ,  $P=.02$ ), low-density lipoprotein cholesterol ( $r=0.33$ ,  $P=.01$ ), insulin ( $r=0.30$ ,  $P=.02$ ), glucose ( $r=0.30$ ,  $P=.02$ ), triglycerides ( $r=0.36$ ,  $P=.005$ ), and HOMA ( $r=0.34$ ,  $P=.01$ ). Percentage reduction in BMI also correlated with percentage increase in high-density lipoprotein cholesterol ( $r=-0.32$ ,  $P=.01$ ).

**BP and Pulse Rate**

In TABLE 5, mean (SD) systolic BP decreased 3.6 mm Hg (8.6 mm Hg) at month 3 in the BT and placebo participants compared with a significant increase of 1.8 mm Hg (10.7 mm Hg) in adolescents treated with sibutramine (effect size, 0.55; 95% CI, 0.10-1.00;  $P=.02$ ). Values for these 2 groups at month 6 were -4.0 mm Hg (8.9 mm Hg) and 0.4 mm Hg (9.0 mm Hg), respectively. The difference between groups approached significance (effect size, 0.45; 95% CI, -0.02 to 0.92;  $P=.06$ ). There were no other significant differences between groups at any period in changes in systolic or diastolic BP. Table 5 also shows that pulse rate increased significantly (5-6/min) at months 3 and 6 in participants who received BT and sibutramine compared with BT and placebo. Similarly, during months 7 to 12, pulse rate increased by 7.6/min (12.7/min) in participants who were switched from placebo to sibutramine.

During phase 1, medication dose was reduced or discontinued in 19 of 43 participants in the BT and sibutramine condition in response to elevations in BP, pulse rate, or both. Thus, the values reported in Table 5 reflect deliberate efforts to minimize increases. To estimate the effects of sibutramine with BP and pulse, in the absence of such in-

**Table 3.** Number of Adolescents Achieving at Least 5%, 10%, and 15% Reductions in Initial Body Mass Index at Month 6 (Intention-to-Treat Analysis)\*

Reduction in Initial BMI, %	No. (%)		$\chi^2$	P Value	Odds Ratio (95% CI)
	BT and Placebo (n = 39)	BT and Sibutramine (n = 43)			
≥5	14 (36)	27 (63)	5.92	.02	3.0 (1.2-7.4)
≥10	6 (15)	17 (40)	5.91	.02	3.6 (1.2-10.4)
≥15	1 (3)	8 (19)	5.39	.02	8.7 (1.0-73.0)

Abbreviations: BMI, body mass index calculated as weight in kilograms divided by the square of height in meters; BT, behavior therapy; CI, confidence interval.

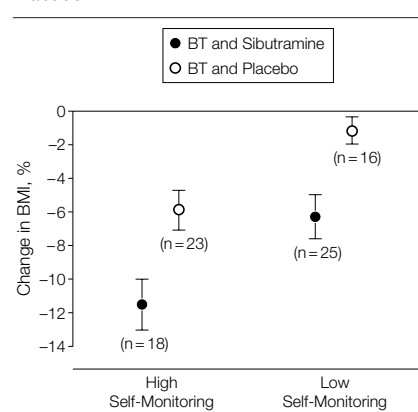
\*Data are cumulative, such that the percentage of participants who lost 5% or more includes those who lost 10% or more and 15% or more.

tervention, baseline values for the subset of 19 participants were compared with their values at the time dose reduction was triggered. In these 19 adolescents, systolic BP increased from a baseline of 112.3 mm Hg (13.8 mm Hg) to 122.3 mm Hg (14.4 mm Hg) and diastolic BP rose from 55.6 mm Hg (5.1 mm Hg) to 64.2 mm Hg (8.3 mm Hg) ( $P<.001$  for both). Pulse rate increased from 77.5/min (11.5/min) to 91.8/min (12.7/min) ( $P<.001$ ).

**Adverse Events**

When adverse events (TABLE 6) characterized as elevations in BP and pulse rate, BP alone, or pulse rate alone are combined, differences approach significance ( $P=.06$ ). One participant had ventricular premature complexes (VPCs) after 6 months of treatment with sibutramine. The participant was asymptomatic and had no other significant changes on electrocardiographic examination. The participant continued to have VPCs in the 6 months following discontinuation of sibutramine, following a course similar to that of benign VPCs that may be observed during adolescence. A second adolescent was observed to have VPCs at month 9, 3 weeks

**Figure 3.** Self-monitoring and Percentage Change in Initial Body Mass Index at Month 6 for Participants Treated With Behavior Therapy Combined With Sibutramine or Placebo



BT indicates behavior therapy. Error bars indicate SE. Mean percentage change in initial body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) is presented according to treatment condition and a median split analysis of participants' monitoring of food intake (ie, high [ $>48$  days of completed food records at 6 months] vs low [ $\leq 48$  days of completed food records at 6 months]). Participants achieving the best results (11.5% decrease) received sibutramine and were classified as high self-monitors. Those participants receiving sibutramine who were low self-monitors decreased BMI by 6.3% comparable with high self-monitors receiving placebo (5.9%). A decrease of only 1.2% was observed for low self-monitors receiving placebo. These findings suggest that sibutramine and regular self-monitoring of food intake had separate and additive effects.

following discontinuation of medication because of elevations of BP and pulse rate; by month 12, there was no evidence of VPCs.

Ventricular premature complexes and extrasystoles have been reported in sibutramine postmarketing surveillance.<sup>23</sup> During the full 12-month study, sibutramine was reduced to 10 mg in 16 participants, to 5 mg in 7 additional adolescents, and discontinued in 10 participants (6 because of increased BP and/or pulse rate, 2 for ecchymoses, 1 for VPCs, and 1 because of rash of unclear etiology). Reductions were made primarily to manage elevations in BP and pulse rate.

**COMMENT**

The addition of sibutramine with a comprehensive behavioral program induced significantly more weight loss in

obese adolescents than traditional behavioral treatment (with placebo). Participants who received both BT and pharmacotherapy during the first 6 months decreased their initial BMI more than those who received BT and placebo, and reported significantly greater reductions in hunger. Results of this controlled trial of sibutramine in adolescents suggest there may be benefits of combining behavioral and pharmacological therapies.<sup>32,33</sup>

The potential benefits of weight-loss medication were further suggested in the open-label phase. The BMI decreased an additional 2.4% (during months 7-12) in participants who were switched from placebo to sibutramine, and adolescents originally treated with medication maintained their weight loss at month 12 with continued use of sibutramine. Additional pla-

cebo-controlled trials are needed to determine if sibutramine and orlistat facilitate the maintenance of weight loss in obese adolescents, as has been shown in adults.<sup>20,34</sup> Because data are not available beyond month 12 in the present study, changes in weight (eg, weight regain) following discontinuation of medication are unknown.

Weight loss continued through month 6 in the BT and sibutramine group and then plateaued. Weight loss tends to plateau in obese adults after 6 months of treatment with BT or pharmacotherapy.<sup>35</sup> We can only speculate that counterregulatory biological mechanisms, reduced total energy expenditure, or behavioral fatigue may limit weight reduction following about a 10% weight loss.<sup>36,37</sup>

There was a 6.4% decrease in initial BMI at month 12 for participants who started taking placebo and then switched to sibutramine at month 6. This compares with an 8.5% reduction for those participants who started taking sibutramine at month 6. The smaller weight loss in the former group when switched to sibutramine may have been attributable to the reduced number of behavior modification sessions provided during the second 6 months. Further research is needed to evaluate the optimal timing and duration of pharmacological treatment when combined with BT.

Similar to studies of adults,<sup>15,23</sup> we observed sibutramine-related increases in pulse rate of 5 to 8/min. Moreover, during the first 6 months of treatment, 19 of 43 adolescents experienced signifi-

**Table 4.** Changes in Serum Chemistries From Baseline Values for Participants Treated With Behavior Therapy and Placebo or Sibutramine (Completers Analysis)\*

	Baseline (n = 74)	Change From Baseline, % (SD)			
		Month 6 (n = 74)†	P Value	Month 12 (n = 62)‡	P Value
Lipid values, mg/dL					
Triglycerides	101.7 (51.2)	-9.3 (36.2)	.03	-9.0 (36.0)	.05
Total cholesterol	165.5 (30.0)	-3.2 (9.8)	.01	-2.3 (12.1)	.14
HDL cholesterol	45.4 (8.9)	2.3 (13.8)	.16	7.6 (17.7)	.001
LDL cholesterol	99.8 (26.1)	-2.5 (14.9)	.16	-4.6 (18.3)	.05
Insulin, µU/mL	27.0 (13.9)	-12.8 (44.6)	.02	-20.2 (42.7)	<.001
Serum glucose, mg/dL	90.3 (8.8)	-1.9 (10.8)	.13	-2.6 (10.5)	.06
HOMA	6.1 (3.3)	-14.8 (47.4)	.01	-22.8 (43.2)	<.001

Abbreviations: HDL, high-density lipoprotein; HOMA, homeostasis model assessment of insulin sensitivity; LDL, low-density lipoprotein.

SI conversion factors: To convert insulin to pmol/L, multiply by 6.945; serum glucose to mmol/L, multiply by 0.0555; total, HDL, and LDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.

\*Results from the entire cohort are collapsed across conditions because no significant between-group differences were found.

†At baseline and month 6, n = 74 except for LDL cholesterol and serum glucose (n = 73) and HOMA (n = 72).

‡At month 12, n = 62 except for LDL cholesterol (n = 61), serum glucose (n = 59), HOMA (n = 52), and insulin (n = 60).

**Table 5.** Systolic and Diastolic Blood Pressure and Pulse Rate at 3 Periods for Participants Treated With Behavior Therapy and Placebo or Sibutramine (Completers Analysis)\*

	Systolic Blood Pressure, Mean (SD), mm Hg			Diastolic Blood Pressure, Mean (SD), mm Hg			Pulse Rate, Mean (SD), Beats/min		
	BT and Placebo	BT and Sibutramine	P Value†	BT and Placebo	BT and Sibutramine	P Value†	BT and Placebo	BT and Sibutramine	P Value†
Baseline	114.3 (11.3)	113.0 (11.0)		55.9 (5.8)	56.8 (5.4)		83.2 (10.1)	79.4 (10.5)	
Month 3	110.7 (13.4)	114.8 (11.3)	.02	55.7 (7.1)	58.4 (8.0)	.23	81.6 (10.3)	85.6 (10.6)	<.001
Month 6	110.3 (10.4)	112.9 (10.9)	.06	55.3 (6.2)	58.6 (6.7)	.11	81.2 (11.6)	84.8 (12.5)	.007
Month 12	112.1 (13.8)	110.5 (10.9)	.23	56.8 (6.2)	58.7 (6.0)	.33	87.8 (11.3)	82.7 (11.4)	<.001

Abbreviation: BT, behavior therapy.

\*At baseline and month 3, n = 36 for BT and placebo and n = 42 for BT and sibutramine. At months 6 and 12, n = 33 and n = 27, respectively, for BT and placebo and n = 39 and n = 34, respectively, for BT and sibutramine. During months 7 to 12, BT and placebo group received sibutramine.

†Represents the difference between treatment conditions between baseline and month 3, baseline and month 6, and months 6 to 12.

cant elevations in BP and pulse rate that required reductions in the dose of sibutramine. During the entire study, 5 participants had marked and sustained increases in BP ( $\geq 10$  mm Hg) that required discontinuation of the medication. These cases underscore the need to closely monitor vital signs in patients prescribed sibutramine. Our dose-reduction strategy prevented mean systolic and diastolic BP from rising significantly during the year. However, larger and longer studies are needed of BP and pulse rate in adolescents treated with sibutramine.

The Committee for Proprietary Medicinal Products<sup>38</sup> in Europe recently investigated concerns about the cardiovascular safety of sibutramine. The committee noted increases in BP and pulse rate in some patients and also concluded that current recommendations for identifying contraindications to treatment and for close monitoring of BP and pulse rate adequately addressed safety concerns. With these precautions, the committee determined that the benefit/risk balance of sibutramine was favorable for obese adults and recommended reduction or discontinuation of dose in response to significant elevations in BP and pulse rate.

The rapid increase in the prevalence of type 2 diabetes mellitus in children and adolescents is likely related to the increase in the prevalence of obesity.<sup>39</sup> The high mean baseline insulin and HOMA levels for the participants in this study are consistent with significant insulin resistance, suggesting that the adolescents in our study are at increased risk of developing type 2 diabetes mellitus. However, with mean decreases in BMI of less than 10%, participants' insulin and HOMA levels decreased 20% and 23% at month 12, respectively. Decreases in these values suggest the positive effects of weight loss in adolescents at risk for type 2 diabetes mellitus. Moreover, the 8% increase in high-density lipoprotein cholesterol suggests the benefits of weight loss and increased physical activity in decreasing the risk of cardiovascular disease.<sup>40</sup> Further investigations, how-

**Table 6.** Adverse Events in Participants Treated With Behavior Therapy and Placebo or Sibutramine

	No. (%)	
	BT and Placebo (n = 39)	BT and Sibutramine (n = 43)
<b>Adverse Events During Phase 1 (Months 1-6)</b>		
Elevated blood pressure and pulse rate*	0	3 (7.0)
Elevated blood pressure only	0	1 (2.3)
Elevated pulse rate only	0	1 (2.3)
Atrial premature beats	1 (2.6)	0
Tonsillectomy	2 (5.1)	0
Knee surgery	0	1 (2.3)
<b>Adverse Events During Phase 2 (Months 7-12)†</b>		
Elevated blood pressure and pulse rate	1 (2.6)	0
Elevated blood pressure only	0	0
Elevated pulse rate only	1 (2.6)	0
Ventricular premature beats	1 (2.6)	1 (2.3)
Cholelithiasis/cholecystectomy	0	1 (2.3)
Ecchymoses	2 (5.1)	0
Rash, viral	0	1 (2.3)

Abbreviation: BT, behavior therapy.

\*Difference in rates approaches significance ( $P = .06$ ) when adverse events regarding blood pressure and pulse rate, blood pressure only, or pulse rate only are combined.

†BT and placebo group received sibutramine during months 7 to 12.

ever, are needed to confirm these findings that were observed during the open-label phase of our study.

This study revealed an apparent interplay between medication and behavior. The medication was associated with significant reductions in hunger that likely facilitated adherence to a low-calorie diet (thus, producing more weight loss).<sup>18</sup> On the other hand, as reported in adults,<sup>41</sup> adherence to self-monitoring optimized response to treatment with medication. Adolescents who adhered closely to the behavioral program, measured by the number of days they completed their food records, and who were treated with sibutramine achieved the greatest decrease in BMI during the first 6 months. The behavioral and pharmacological treatments appeared to have additive effects that maximized weight loss.<sup>32,33</sup>

Data were not collected concerning whether participants could guess if they were taking sibutramine or placebo. It is possible that those who thought they received the drug (ie, who experienced adverse effects) worked harder in the behavioral program to achieve weight reduction. The adherence mea-

sure (ie, number of completed food records), however, did not reveal differences between participants who received placebo or sibutramine.

Results of this placebo-controlled trial showed that the addition of sibutramine with BT significantly increased weight loss in obese adolescents compared with traditional BT alone (with placebo). These findings suggest that weight loss medication may be of benefit to adolescents. Sibutramine, however, must be carefully monitored in adolescents, as in adults, to control increases in BP and pulse rate. Moreover, larger and longer studies are needed to assess the benefits and costs of pharmacological treatment in obese adolescents. Until more extensive safety and efficacy data are available, we agree with Dietz<sup>8</sup> that weight-loss medications should be used only on an experimental basis for adolescents.

**Author Contributions:** Dr Terhakovec and Ms Cronquist had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

**Study concept and design:** Berkowitz, Wadden.

**Acquisition of data:** Berkowitz, Terhakovec, Cronquist.

**Analysis and interpretation of data:** Berkowitz, Wadden, Terhakovec.

*Drafting of the manuscript:* Berkowitz, Wadden, Tershakovec, Cronquist.

*Critical revision of the manuscript for important intellectual content:* Berkowitz, Wadden, Tershakovec.

*Statistical expertise:* Wadden.

*Obtained funding:* Berkowitz, Wadden.

*Administrative, technical, or material support:* Cronquist.

*Study supervision:* Berkowitz, Wadden, Tershakovec, Cronquist.

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