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# Long-term Weight Loss With Sibutramine

## A Randomized Controlled Trial

Alfred Wirth, MD

Jutta Krause

**T**ODAY, OBESITY HAS REACHED ENDEMIC proportions<sup>1</sup> and the widespread lack of clinical success<sup>2</sup> calls for effective treatment of this chronic disorder. Therapeutic intervention prevents the serious and cost-intensive sequelae of this condition.<sup>3</sup> The reluctance of the medical profession to treat obesity<sup>4</sup> is fortunately no longer justified because short-term weight reduction achieved by interventions, such as dieting, exercise, and behavior modification programs, can lead to long-term weight loss through the use of effective medicines.<sup>5-8</sup> These drugs are designed to be used as an adjunct to non-medical therapy.<sup>9-11</sup> Obesity can be seen as the underlying condition predisposing persons to cardiovascular risk factors. Thus, symptomatic treatment of these risk factors can now be replaced by a causal therapy that addresses obesity itself. The main objective of this pharmacotherapeutic approach is to achieve long-term weight loss,<sup>12</sup> and there is evidence that even moderate weight loss of 5% to 10% results in reduced morbidity<sup>13</sup> and mortality.<sup>14</sup>

Sibutramine hydrochloride enhances satiety, primarily by blocking the reuptake of 2 neurotransmitters, noradrenaline and serotonin. It is also postulated that sibutramine increases the metabolic rate by enhancing peripheral noradrenaline function via  $\beta$ 3-adrenoceptors leading to an increase in energy expenditure.<sup>15</sup> So far, approximately 8000 patients have taken sibutramine in clinical studies. Its effectiveness in reducing weight and achieving weight maintenance already has been shown in sev-

**Context** Treatment of obesity requires long-term therapy, which can be hampered by difficulties in achieving patient compliance. The effectiveness of sibutramine hydrochloride in treating obesity has been shown in randomized controlled trials.

**Objective** To compare the effectiveness of 2 distinct sibutramine regimens with each other and with placebo for weight reduction among obese persons.

**Design** Randomized, double-blind, parallel-group placebo-controlled trial from April 1997 to September 1998.

**Setting** One hundred eight private practices and 3 outpatient departments of university hospitals in Germany.

**Patients** A total of 1102 obese adults (body mass index, 30-40 kg/m<sup>2</sup>) entered the 4-week open-label run-in period with 15 mg/d of sibutramine, 1001 of whom had weight loss of at least 2% or 2 kg were randomized into the 44-week randomized treatment period.

**Interventions** Patients were randomly assigned to receive 15 mg/d of sibutramine continuously throughout weeks 1-48 (n = 405); 15 mg/d of sibutramine intermittently during weeks 1-12, 19-30, and 37-48, with placebo during all other weeks (n = 395); or placebo for weeks 5-48 (n = 201).

**Main Outcome Measure** Weight loss during the randomized treatment period, compared among all 3 groups.

**Results** Mean weight loss in the intention-to-treat population during the 44-week randomized treatment period was 3.8 kg (4.0%) in patients receiving continuous therapy (95% confidence interval [CI], -4.42 to -3.20 kg) and was 3.3 kg (3.5%) in patients receiving intermittent therapy (95% CI, -3.96 to -2.66 kg), vs a mean weight gain of 0.2 kg (0.2%) (95% CI, -0.60 to 0.94 kg) in patients receiving placebo. Therapeutic equivalence of the 2 active treatments could be shown. Although there was a greater weight loss in the continuous than in the intermittent group, this difference was nonsignificant ( $P = .28$ ) and the 95% CIs were within the pre-defined range of therapeutic equivalence— $0 \pm 1.5$  kg (-1.37 to 0.28 for the intent-to-treat population). Overall weight loss during the 48-week period was 7.9 kg and 7.8 kg in the continuous and intermittent groups, respectively, but was 3.8 kg in the sibutramine run-in placebo group. Waist circumference reduction, triglyceride levels, and high-density lipoprotein cholesterol concentrations were also positively influenced by sibutramine treatment. Systolic and diastolic blood pressures were stable across all 3 groups. Overall, adverse events occurred at similar frequencies across all treatment groups, but the proportion was lowest in the group receiving intermittent therapy.

**Conclusions** Sibutramine, administered for 48 weeks to a typically obese population, results in clinically relevant weight loss compared with placebo. Regarding effectiveness, continuous and intermittent sibutramine therapies are equivalent and the safety profiles for both treatments are comparable.

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eral randomized, double-blind studies.<sup>16,17</sup> The aim of this randomized study was to show equivalent weight reduction in an obese population using 2 thera-

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peutic approaches: a continuous and intermittent therapy with sibutramine and the superiority of both therapies over placebo. To our knowledge, this study is the first in which such a randomized approach has been adopted in the treatment of obesity.

## METHODS

### Patients

This 48-week multicenter study had a double-blind, placebo-controlled, randomized parallel-group design. Obese (body mass index [BMI; calculated as weight in kilograms divided by the square of height in meters]) (30-40 kg/m<sup>2</sup>) men and women aged between 18 and 65 years and with at least 1 unsuccessful attempt to lose weight by dietary measures in the past were recruited from 108 private practices and 3 hospital outpatient departments in Germany. The study was conducted from April 1997 to September 1998. The study was approved by the ethics committee and conducted in accordance with the German Medicines Act, the Declaration of Helsinki, and the European guidelines for Good Clinical Practice. Accordingly, only patients who had given their written informed consent to participate in the study were included. Patients with serious cardiovascular or metabolic diseases as defined in the study protocol were excluded from participation. In addition, patients with a history of drug or alcohol abuse, in need of antidepressant agents, monoamine oxidase inhibitors,  $\beta$ -blockers, or of any drugs influencing body weight were not allowed to participate. To enter the study, women of childbearing age either had to have had hysterectomies or had to be using a safe and medically accepted contraceptive method, such as oral contraceptives or an intrauterine device.

### Design

The total treatment period for each patient was 48 weeks, comprising a run-in open-label period of 4 weeks and a double-blind treatment period of 44 weeks. During the 4-week run-in period, each patient was treated with 15

mg of sibutramine, administered orally, once daily. This dosage was chosen based on earlier trials in which 5 to 30 mg/d of sibutramine produced a dose-related weight loss, and treatment with 15 mg/d of sibutramine led to favorable results.<sup>18-21</sup> Patients with a weight loss of at least 2% and/or 2 kg or more (responders) during this period were randomized to 1 of 3 treatment groups—continuous or intermittent therapy or placebo. All patients took 1 capsule daily for the subsequent 44 weeks. Thus, patients in continuous therapy received 15 mg of sibutramine throughout the entire study period, and those in intermittent therapy received 15 mg of sibutramine during weeks 1 through 12, 19 through 30, and 37 through 48 and then received placebo during the other weeks. The intermittent pattern was developed based on the observation that while patients are undergoing long-term treatment, the weight reduction slows down after the first 3 months.<sup>22</sup> Earlier studies also had shown that after cessation of sibutramine treatment, the increase in weight compared with placebo was slower than expected, especially during weeks 4 to 6 after the end of treatment.<sup>23,24</sup>

Allocation to the 3 treatment groups used computer-generated, balanced permuted blocks with a block size of 5 at a ratio of 2:2:1. Neither the patient nor the investigator was aware of the assigned treatment; patient codes were stored with their physicians and treatment codes with the statistical department of Knoll Deutschland GmbH. Therapy was administered in the form of capsules that, irrespective of treatment, were identical in form and color.

The study was conducted using the everyday routines prevailing in the private practices or hospitals in Germany, that is, physicians advised their patients and provided them with booklets concerning dietary recommendations; formal dietary or behavior modification programs were not applied. Thus, in addition to evaluating effectiveness, this study assessed the effectiveness of treatment. Written monitoring conventions

as well as the monitoring visits (approximately every 6 weeks) served to standardize the study throughout all study sites.

### Study Protocol

Assessments were made at each of 10 visits; the first was scheduled on visit 1 (day 0, baseline) at the start of the 4-week run-in phase of the study, visit 2 at the end of week 4, visit 3 at the end of week 8, visit 4 at the end of week 12, and the subsequent 6 visits every 6 weeks until the end of the 48-week study period. At each visit, weight (primary outcome) was assessed together with secondary measures, such as BMI, waist circumference, as well as vital signs (blood pressure and heart rate), using standard methods.<sup>25</sup> Fasting serum concentrations of triglycerides, cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured at baseline (visit 1), after the 4-week run-in period (visit 2), and at the end of weeks 12 (visit 4), 30 (visit 7), and 48 (visit 10). Safety laboratory tests based on standard hematological and clinical chemistry parameters were performed. A certified central laboratory in Freiburg, Germany, performed these tests.

The patients' demographic data, their medical history, and any concomitant diseases were recorded at baseline. Physical examinations also were performed at baseline and on visits 4, 7, and 10. The investigator checked compliance by counting the number of capsules returned on each visit. Patients were also asked about their intake of the medication, for example, if they took the capsules every day at about the same time of the day. Concomitant medication and adverse events were documented, and the investigators used their judgement to assess the causal relationship between an adverse event and the study therapy. Serious adverse events (following common definition, ie, those adverse events that required hospitalization, were life-threatening, or resulted in a persistent or significant disability or death) had to be reported immediately.

At the end of the study, patients and investigators globally assessed the effectiveness and tolerability of the type of therapy received using a 5-point scale (very good, good, moderate, poor, or none).

### Statistical Analysis

Sample size estimation for the 2 active drug treatment groups was based on the following assumptions: two 1-sided *t* tests with an equivalence range of  $\pm 1.5$  kg were performed. Standard deviation of weight loss was assumed to be 5.5 kg. With  $\alpha = .05$  and a power of 80%, 231 patients per treatment group were needed to complete the study. Assuming that 25% of the patients screened would be excluded from treatment after the 4-week run-in period, combined with an assumed dropout rate from the study of 20%, 400 patients per treatment group had to be screened.

As the effectiveness of sibutramine had already been demonstrated in previous studies,<sup>16,17</sup> 2 therapeutic regimens were compared in this study. Results are given for the intention-to-treat (ITT) population for the primary parameter. In addition, results are given for the protocol population (PP; those who completed all 48 weeks) because according to the study protocol the analysis of effectiveness was based on this population. Two-sided 95% confidence intervals (CIs) were calculated and compared with the pre-defined equivalence range of  $\pm 1.5$  kg to establish therapeutic equivalence. The CIs were based on an analysis of covariance (ANCOVA) model, including center, sex, treatment as fixed effects, and the body weight at baseline and the baseline body weight by sex interaction as covariates, thus being adjusted for effects included in the model (SAS software, version 8.1, SAS institute, Cary, NC).

Analysis of safety and tolerability was based on the ITT population. Moreover, subgroups were created for statistical analysis and were evaluated qualitatively with respect to effectiveness and safety. For the ITT population, last observation carried forward was applied for

the primary study parameter, weight loss measured in kilograms, between the last measurement and the measurement at visit 2 of body weight, whereas only the observed values were evaluated for the PP population.

All adverse events experienced by each patient throughout the 48-week therapeutic period were recorded. The severity, relationship to therapy, and body system of each adverse event was assessed using Hoechst Adverse Reaction Terminology System tables (Hoechst AG, Med Abteilung, Frankfurt, Germany). Adverse events occurring in the initial 4-week run-in period and treatment-emergent signs and symptoms were included in the randomized analysis of treatment groups

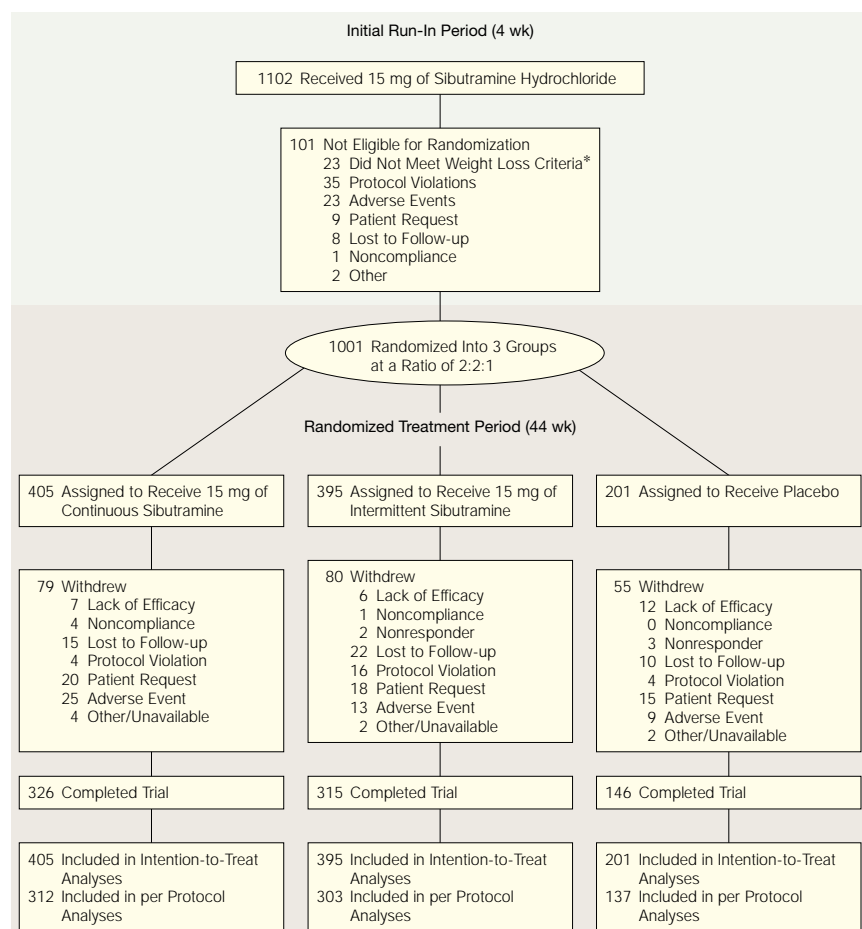
if they were present during the double-blind treatment period and their severity increased.

## RESULTS

### Enrollment

Patients (n=1001 in 101 centers) completing the initial run-in period were randomized to 3 different treatment groups in a ratio of 2:2:1 (FIGURE 1). The ITT population comprised 405 and 395 patients receiving continuous and intermittent treatment with sibutramine, 15 mg, once-daily, respectively, and 201 patients given placebo for the 44-week treatment period. In all, 214 patients (21.4%) did not complete the study. The proportions of withdrawals from active treatments were simi-

**Figure 1.** Trial Profile



\*Weight loss of at least 2% or 2 kg following the 4-week run-in period.

**Table 1.** Characteristics of the Intent-to-Treat Population at Randomization (Week 4)

Characteristic	Continuous Therapy (n = 405)	Intermittent Therapy (n = 395)	Placebo (n = 201)
Sex, No (%)			
Male	103 (25.4)	84 (21.3)	46 (22.9)
Female	302 (74.6)	311 (78.7)	155 (77.1)
Age, mean (SD), y	43.1 (11.2)	42.6 (12.0)	44.0 (11.1)
Anthropometry, mean (SD)			
Weight, kg	98.6 (14.3)	98.2 (15.1)	98.2 (14.7)
Height, cm	168.0 (8.7)	167.1 (8.7)	167.0 (9.1)
Body mass index, kg/m <sup>2</sup>	34.7 (3.4)	34.9 (3.4)	35.0 (3.4)
Waist circumference, cm	106.6 (11.3)	106.6 (12.7)	106.6 (12.0)
Alcohol consumption, No. (%) <sup>*</sup>	183 (45.2)	167 (42.3)	86 (42.8)
Smokers, No. (%)	149 (36.8)	132 (33.4)	63 (31.3)
Obesity in family history, No. (%)	288 (71.1)	283 (71.6)	156 (77.6)

<sup>\*</sup>Defined as occasional or daily consumption and is based on the number of drinks consumed.

lar (20%,  $P = .77$ ). The proportions withdrawing from placebo (27%) were significantly higher than from active treatments (continuous vs placebo,  $P = .01$  and intermittent vs placebo,  $P = .03$ ).

Reasons for dropping out of the study are summarized in Figure 1 and show that in the placebo group 12 patients (6.0%) withdrew from the study due to a lack of effectiveness, according to the opinion of the patient or physician, compared with only 7 patients (1.7%) and 6 patients (1.5%) in continuous and intermittent therapy, respectively.

In addition to the 214 dropouts, there were 14, 12, and 9 protocol violators who did not drop out of the study from the continuous, intermittent, and placebo groups, respectively, who were not included in the PP population, which thus included 752 patients.

All but 2 patients were white Europeans. Demographic, anthropometric, and baseline characteristics were similar in the treatment groups after randomization (TABLE 1).

### Weight Loss

FIGURE 2A shows the weight change for all 1001 patients of the ITT population. In the initial 4-week run-in phase in which all patients received 15 mg of sibutramine, weight loss was similar in the 3 treatment groups: patients lost a mean 4.1 kg (4.2%), 4.5 kg (4.6%), and 4.0 (4.1%) of body weight with subsequent treatment with continuous, intermittent, and placebo, respectively.

During the 44-week randomized treatment period, mean weight loss for the ITT population was 3.8 kg (4.0%) for patients receiving continuous therapy (95% CI,  $-4.42$  to  $-3.20$ ) and 3.3 kg (3.5%) for patients receiving intermittent therapy (95% CI,  $-3.96$  to  $-2.66$ ), and a mean weight gain of 0.2 kg (0.2%; 95% CI,  $-0.60$  to  $0.94$ ) for patients receiving placebo. Weight loss was statistically significantly different in patients receiving either continuous or intermittent therapy compared with those receiving placebo ( $P < .001$ ). In all 3 groups, women tended to lose more weight than men (continuous therapy:  $-2.9$  kg in men vs  $-4.1$  kg in women,  $P = .08$ ; intermittent therapy:  $-1.5$  kg in men vs  $-3.8$  kg in women,  $P = .004$ ; placebo: 1.2 kg in men vs  $-0.1$  kg in women,  $P = .14$ ) throughout the 48-week study period (Figure 2B and 2C).

The result of the ANCOVA showed a center effect ( $P < .001$ ). In an additional ANCOVA model, including a center by treatment interaction, this interaction was not significant and therefore not included for the calculation of CIs.

Overall weight loss during the 48-week period for the continuous and intermittent groups was 7.9 kg and 7.8 kg, respectively, but 3.8 kg in the placebo group.

The percentage of patients losing 5% and 10% of baseline weight (measured at visit 1) was evaluated. This percentage acknowledges that not all the reduction in body weight seen in the active treatment groups could be fully ascribed to the effect of sibutramine, just

as some of the weight loss in the placebo group was also due to the effect of sibutramine during the 4-week run-in period. In the active treatment groups, 65% of continuous and 63% of intermittent patients experienced a 5% weight loss response, and 32% and 33% of these patients had a 10% weight loss response. These weight loss responses in the active sibutramine treatment groups were significantly greater than the placebo group, which for 5% and 10% reduction, 35% and 13% of patients responded ( $P < .001$  both for 5% and 10% responders). Both sibutramine groups were comparable ( $P = .22$  for 5% and  $P = .39$  for 10% responders).

Although there was a greater weight loss in the continuous than in the intermittent group, this difference was small, not significant ( $P = .28$ ), and the 95% CIs were within the predefined range of therapeutic equivalence— $0 \pm 1.5$  kg ( $-1.33$  to  $0.42$  for the PP population, which was the primary study population as defined in the study protocol, and  $-1.37$  to  $0.28$  for the ITT population), which demonstrates the therapeutic equivalence of the 2 active treatments.

Similar reductions in the active treatment groups also were observed for waist measurements during the 48-week study period. Patients receiving continuous treatment had an 7.8-cm decrease in waist circumference (95% CI,  $-8.58$  to  $-7.10$ ) vs 8.2 cm (95% CI,  $-8.91$  to  $-7.42$ ) in patients receiving intermittent treatment and 4.1 cm (95% CI,  $-5.15$  to  $-3.15$ ) in the placebo group. The majority of patients and investigators assessed the effectiveness of treatment as good to very good; the percentage of patients and investigators from the continuous (55.8% and 55.3%, respectively) and intermittent (46.6% and 47.8%) therapies were considerably higher than those from placebo (30.9% and 31.4%).

### Cardiovascular Risk Factors

FIGURE 3 shows the difference between the mean plasma lipid levels and lipoprotein cardiovascular risk factors in the 3 treatment groups (including the

ITT group and the last observation carried forward) from baseline week 0 to week 48.

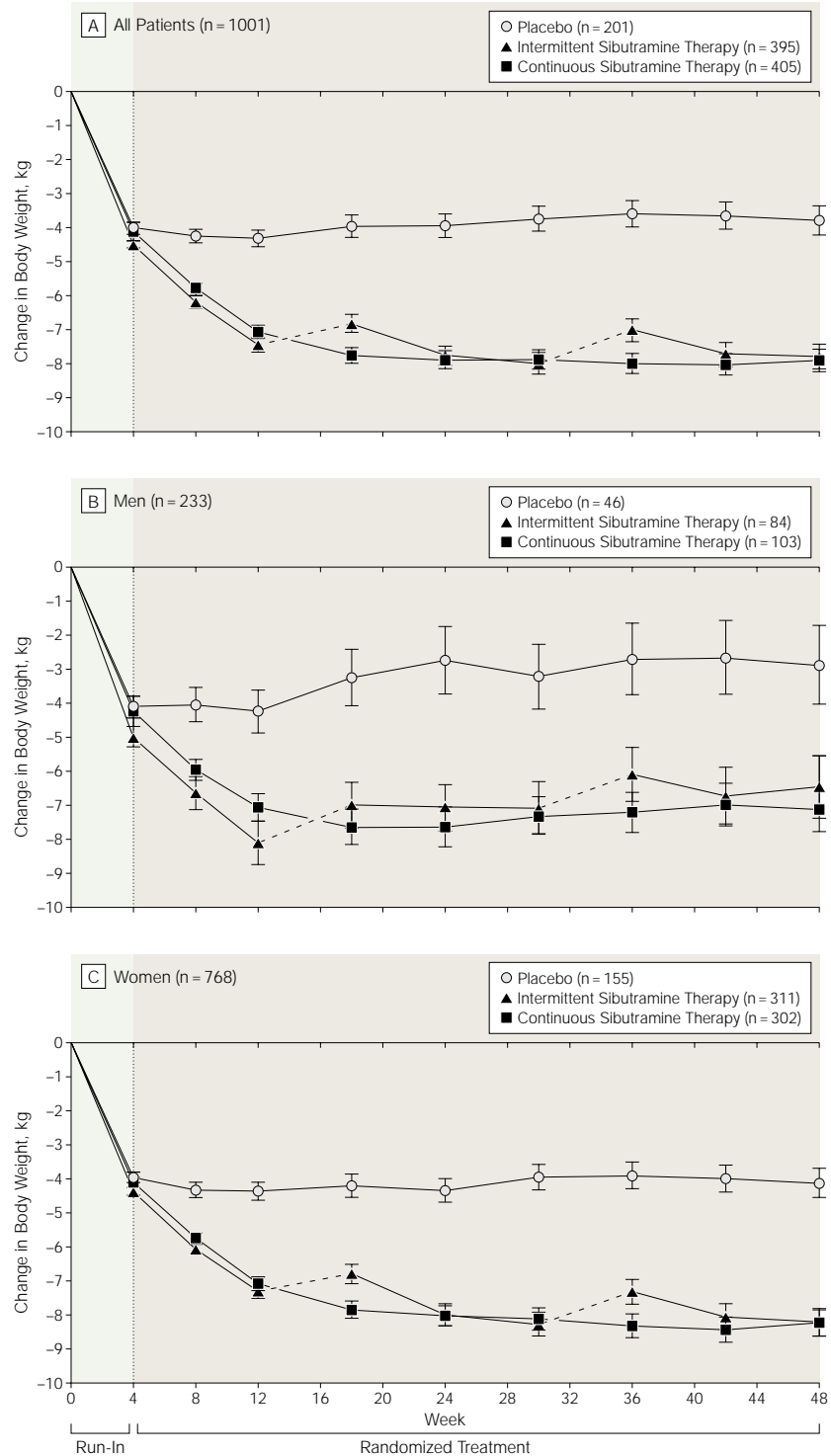
Total cholesterol values were comparable between the 3 groups and there was negligible change between visits 1 and 10. Mean HDL-cholesterol values increased in all 3 groups between visits 1 and 10 (continuous treatment group 15.3%; intermittent treatment group 10.0%, and placebo group 7.1%). There were similar decreases in LDL-cholesterol values in both the continuous and placebo groups and a substantial decline in triglyceride levels for both active treatment groups relative to the placebo group. For each of the treatment groups, the mean LDL/HDL ratio was relatively stable across the 48-week study period. For visits 1 and 10 respectively, the mean HDL/LDL declined from 2.9 to 2.5 in the continuous treatment group, from 2.8 and 2.5 in the intermittent treatment group, and from 2.9 and 2.6 in the placebo group.

No changes in blood pressure were observed during the study period in any of the treatment groups (FIGURE 4). The overall ANCOVA for the change from randomization to last visit yielded  $P = .53$  for the systolic blood pressure and  $P = .40$  for the diastolic blood pressure. Subgroup analyses revealed that there was a slight reduction in blood pressure values for 5% and 10% of responders. In contrast, patients with less weight loss (>2% but <5%) exhibited a very weak to a slight increase in blood pressure values, which were of no clinical relevance.

### Adverse Events

Since patients had already received drug treatment in the initial 4-week run-in phase, adverse events during this period and during the randomized treatment period were analyzed separately (TABLE 2). During the run-in period, 274 patients (25%) experienced adverse events. These adverse events were in keeping with the usual adverse event profile for sibutramine<sup>26</sup>; dry mouth was most frequent ( $n = 70$ ; 6.4%), followed by constipation ( $n = 37$ ; 3.4%), in-

**Figure 2.** Mean (SE) Change in Body Weight During the Study Period for All Patients, for Men, and for Women



The mean (SE) changes for the intent-to-treat population are shown for the 4-week run-in period with 15 mg of sibutramine hydrochloride (week 0-4) and the randomized treatment period. The broken line in the intermittent therapy curves denote the two 6-week placebo periods.

creased sweating ( $n=24$ ; 2.2%), and headache ( $n=22$ ; 2.0%). A total of 154 patients (14%) were classified as having drug-related adverse events. There were 23 withdrawals (2.1%) due to adverse events during the initial run-in period and only 2 patients (0.2%) had serious adverse events, neither considered

to be drug-related (one patient experienced edema and pain in the lower left leg and another patient had renal colic and ureterolithiasis).

In the randomized 44-week treatment period, 737 of 1001 (73.6%) patients experienced adverse events (TABLE 3). The percentage of patients

experiencing adverse events was similar in all groups ( $P=.52$  for overall comparison). Only 4.7% of patients ( $n=47$ ) withdrew from the study due to adverse events. The proportion of withdrawals due to adverse events was 3.3% in the group receiving intermittent therapy ( $n=13$ ) vs 6.2% for those receiving continuous therapy ( $n=25$ ) and 4.5% given placebo ( $n=9$ ), although these proportions were not significantly different from each other ( $P=.16$ ; Fisher exact test). But the difference in withdrawals between continuous and intermittent therapy approached significance ( $P=.07$ ; Fisher exact test) in favor of the intermittent therapy.

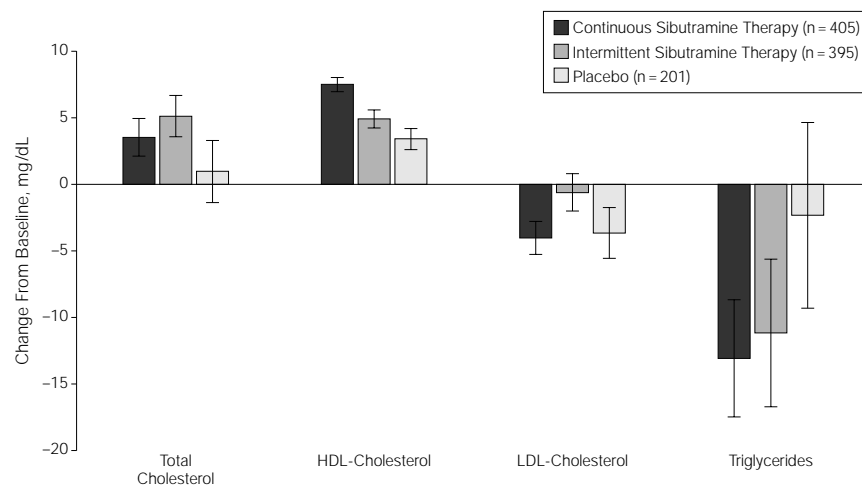
Compared with the initial run-in period, the incidence of adverse events typically induced by sibutramine during the randomized 44-week treatment period was low; for instance, the total incidence of dry mouth was only 1.3% ( $n=13$ ) and constipation, 4.1% ( $n=41$ ). The number of patients experiencing drug-related adverse events was 67 (17%) with continuous treatment, 55 (14%) with intermittent therapy, and 23 (11%) with placebo.

Serious adverse events were reported for 52 patients (5.2%) in the 44-week, randomized treatment period; in the group receiving continuous therapy, 30 patients (7.4%) experienced serious adverse events vs 10 (2.5%) and 12 (6.0%) in the groups receiving intermittent treatment and placebo, respectively, the difference between the continuous and intermittent groups was significant ( $P=.002$ ).

Throughout the study, there were no clinically significant changes in any of the hematological and biochemical laboratory parameters. There were no differences between the groups regarding any changes in laboratory values outside the normal range between baseline week 0, week 4, and the last recorded measurement (data available from author).

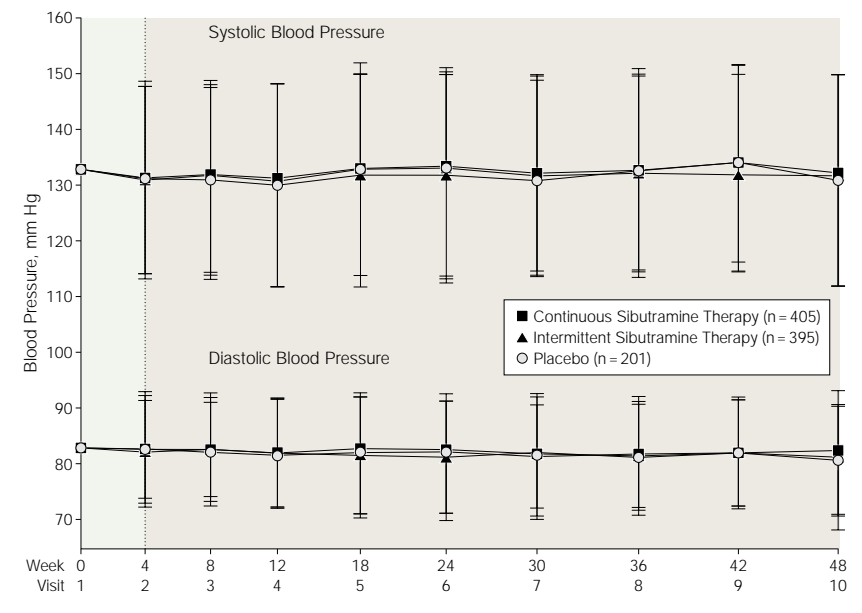
The vast majority of patients and investigators assessed the safety of treatment as good to very good, this percentage being comparable between the

**Figure 3.** Difference in Mean (SE) Plasma Lipid Levels Between Placebo, Continuous, and Intermittent Therapies With 15 mg of Sibutramine Hydrochloride



HDL indicates high-density lipoprotein; LDL, low-density lipoprotein. To convert mg/dL to mmol/L, multiply by 0.0259.

**Figure 4.** Mean (SD) Systolic and Diastolic Blood Pressures in the Overall Intent-to Treat Population Receiving Placebo, Continuous, or Intermittent Therapies With 15 mg of Sibutramine Hydrochloride



3 treatment groups (data available from author).

## COMMENT

This randomized study showed that patients receiving continuous and intermittent therapy with sibutramine lost significantly more weight than patients receiving placebo after an initial 4-week run-in period with sibutramine. This result is consistent with those obtained in previous studies demonstrating that sibutramine therapy results in long-term weight loss.<sup>21,27,28</sup> Mean weight loss in the initial run-in phase was approximately 4.2 kg, thus confirming the expectations for the effectiveness of sibutramine during short-term treatment.<sup>19</sup> In the randomized 44-week treatment phase, patients receiving continuous therapy lost a further 3.8 kg vs 3.3 kg in patients receiving intermittent therapy and a weight gain of 0.2 kg in patients receiving placebo. In view of the fact that patients in the placebo group also had received sibutramine in the initial run-in phase, the net overall effect of sibutramine in the 2 active groups cannot be calculated accurately, but can be estimated to be greater than 3.8 kg or 3.5 kg, respectively, but both less than 7.9 kg. Some of the weight loss in the first 4 weeks may have been due to regression to the mean and those patients included in the trial had to have had at least a 2 kg or 2% weight loss, but the weight reductions observed in the present trial clearly reached the levels expected by an effective treatment with sibutramine,<sup>9</sup> for both short-term and long-term treatment.

As even a moderate weight loss of approximately 5% provides unquestionable benefits for obese patients, the number of patients achieving such a weight loss reflects the possible advantage of a treatment with sibutramine: more than 60% of the patients in the 2 active treatment groups lost 5% or more of their weight, compared with only 35% in the placebo group.

The results from the continuous therapy group confirm those of other long-term studies that show rates of

weight loss reached their maximum during the first 3 months of treatment.<sup>16</sup> Thereafter, weight loss continued but at a slower rate and was maintained up to month 12. This rate reduction possibly indicates that while taking sibutramine an equilibrium between energy intake and energy expenditure at a lower level is reached after a particular length of time. One possible explanation for the weight gain during placebo periods is that food intake increases and the metabolic rate slows down, increasing again when sibutramine therapy is restarted. This induces a concomitant decrease in food intake thereby reinforcing the weight reducing effect of sibutramine.

Weight gain after cessation of sibutramine treatment in the intermittent group was expected because obesity as a chronic disease is not cured by any pharmacological agent. With respect to long-term weight loss over 48 weeks, the continuous and intermittent treatments were demonstrated to be equivalent despite the fact that patients receiving intermittent therapy had minor mean weight gains of 0.6 and 1.0 kg, respectively, in the two 6-week placebo periods of this treatment arm. However, this minor weight gain was compensated by the greater mean

weight loss in the subsequent two 12-week periods (−1.2 kg and −0.8 kg, respectively) compared with that lost by patients receiving continuous treatment for the same periods (−0.1 kg and 0.1 kg, respectively).

Changes in waist circumference follow those changes in body weight. The 2 active treatment groups were equivalent with respect to the reduction in waist circumference and both drug groups were superior to placebo. These results confirm those from previous studies that sibutramine also caused a statistically and clinically significant de-

**Table 2.** Frequency of Adverse Events During the Initial 4-Week Run-In Period in the Different Body Systems (Total Incidence  $\geq 1\%$ )

Adverse Event*	15 mg of Sibutramine Hydrochloride Over 4 Weeks, No. (%) (N = 1102)
Dry mouth	70 (6.4)
Constipation	37 (3.4)
Sweating increased	24 (2.2)
Headache	22 (2.0)
Insomnia	21 (2.0)
Back pain	14 (1.3)
Bronchitis	13 (1.2)
Dizziness	11 (1.0)
<b>Total of patients with adverse events</b>	<b>274 (25)</b>
<b>Total No. of adverse events</b>	<b>467</b>

\*One patient could have had more than 1 adverse event.

**Table 3.** Frequency of Adverse Events in the Randomized 44-Week Treatment Period (Total Incidence  $\geq 5\%$ )\*

Adverse Event	Continuous Therapy (n = 405)	Intermittent Therapy (n = 395)	Placebo (n = 201)	Total (n = 1001)
Bronchitis	67 (16.5)	56 (14.2)	30 (14.9)	153 (15.3)
Back pain	50 (12.4)	58 (14.7)	28 (13.9)	136 (13.6)
Flu syndrome	49 (12.1)	30 (7.6)	21 (10.5)	100 (10)
Pharyngitis	34 (8.4)	29 (7.3)	16 (8.0)	79 (7.9)
Gastroenteritis	24 (5.9)	25 (6.3)	14 (7.0)	63 (6.3)
Infection	26 (6.4)	22 (5.6)	14 (7.0)	62 (6.2)
Sinusitis	28 (6.9)	23 (5.8)	11 (5.5)	62 (6.2)
Pain in extremity	27 (6.7)	25 (6.3)	8 (4.0)	60 (6.0)
Headache	27 (6.7)	16 (4.1)	12 (6.0)	55 (5.5)
Eczema	24 (5.9)	16 (4.1)	13 (6.5)	53 (5.3)
Gastritis	23 (5.7)	20 (5.1)	8 (4.0)	51 (5.1)
Upper respiratory tract infection	19 (4.7)	14 (3.5)	11 (5.5)	44 (4.4)
<b>Total of patients with adverse events†</b>	<b>303 (74.8)</b>	<b>283 (71.7)</b>	<b>151 (75.1)</b>	<b>737 (73.6)</b>
<b>Total No. of adverse events</b>	<b>1111</b>	<b>996</b>	<b>468</b>	<b>2575</b>

\*All values are expressed as No. (%) unless otherwise indicated.

†One patient could have had more than 1 adverse event.

crease in waist circumference.<sup>29,30</sup> Computerized tomography scans showed that the percentage decrease in intra-abdominal fat was nearly twice that in subcutaneous fat.<sup>29</sup> These factors contribute to the reduction in cardiovascular risk factors present in patients with abdominal adiposity.

The dropout rate of 21.4% was within the range anticipated when the study was designed (ie, 25%). Premature study termination always presents a problem, especially in studies designed to last approximately 1 year. The close monitoring as well as the time tables provided to the patients might have helped to ensure patient compliance, which is reflected not only by the excellent patient compliance based on the use of the capsules but also by the relatively small number of dropouts, especially in the placebo group. That the number of dropouts in the placebo group nevertheless exceeded the corresponding number in the 2 active treatment groups is another indication of the favorable effectiveness profile of sibutramine.

A positive feature of sibutramine treatment is that the small number of patients who do not respond to sibutramine treatment (in this trial 23 patients [nonresponders]) can be easily identified. Earlier trials has shown that patients who do not lose at least 2% or 2 kg (responders) during the first weeks also do not benefit from long-term treatment.<sup>31</sup> Unnecessary long-term treatment of nonresponders can be avoided, thus increasing the benefit/risk ratio of sibutramine.

Possible bias of the results was limited by the design of a multicenter trial. The data are based on an obese study population characteristic for the situation in Germany, as patients were recruited predominantly from a variety of private practices, which mirrors the actual situation more closely than would a recruitment in university hospitals. That the study population reflects a very realistic situation is furthermore confirmed by the number of obese patients with hypertension (46%, following the definition of systolic blood

pressure values  $\geq 140$  mm Hg or diastolic blood pressure values  $\geq 90$  mm Hg at visit 1), because both the Prospective Cardiovascular Munster study and the Nurses Health study showed that about every second obese patient has hypertension.<sup>3,32,33</sup> Based on this parameter, the setting mirrors the actual situation more closely than the population included in the Sibutramine Trial of Obesity Reduction and Maintenance trial, in which only about 8% of the patients were reported to have hypertension.<sup>28</sup>

The decline and increase in triglyceride and HDL-cholesterol levels observed in this study are not drug-specific effects but are commonly observed following weight loss.<sup>34</sup> It has been shown that a decrease in triglyceride levels and an increase in HDL-cholesterol may reduce the risk of cardiovascular disease.<sup>35</sup> This therapeutic effect demonstrates the benefits of drug therapy by improving lipid metabolism disorders that are frequently present in patients with obesity constituting an atherogenic risk factor.<sup>32</sup>

Weight loss is usually associated with a decrease in blood pressure. In this study, mean blood pressure in the total patient population did not change. This stability may be because treatment with sibutramine gives rise to 2 opposing effects: weight loss results in a decrease of blood pressure and this decrease is offset by the sympathomimetic effect of sibutramine causing an increase in blood pressure. Generally, these effects caused by sibutramine neutralize each other.<sup>36</sup>

The frequency of adverse events observed across all groups was comparable with a slightly better adverse event profile, especially for serious events, from the group receiving intermittent therapy. Typical drug-related adverse events include dry mouth, constipation, increased sweating, and headache, which all decreased with prolonged exposure to sibutramine.

The equivalent effectiveness profile but slightly better safety profile of intermittent sibutramine therapy compared with continuous therapy sug-

gest that long-term treatment with this drug regimen may be beneficial to patients with obesity. This approach may possibly contribute to improved patient compliance.

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Dr Wirth, as principal investigator, had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analyses (as certified by S. Hantel, PhD, statistician from ECRON, Frankfurt, Germany).

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