Long-term Weight Loss With Sibutramine: A Randomized Controlled Trial

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Jutta Krause

Today, obesity has reached epidemic proportions and the widespread lack of clinical success calls for effective treatment of this chronic disorder. Therapeutic intervention prevents the serious and cost-intensive sequelae of this condition. The reluctance of the medical profession to treat obesity 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. These drugs are designed to be used as an adjunct to nonmedical therapy. 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, and there is evidence that even moderate weight loss of 5% to 10% results in reduced morbidity and mortality.

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 B3-adrenoceptors leading to an increase in energy expenditure. 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 several randomized, double-blind studies. The aim of this randomized study was to show equivalent weight reduction in an obese population using 2 thera-

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(Reprinted) JAMA. 2001;286:1331-1339 www.jama.com

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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/m²) men and women aged between 18 and 65 years and with at least 1 un成功的 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, monooamine oxidase inhibitors, β-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. 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. 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.

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. 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, i.e., 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 ± 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,\(^{16,37} \) 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 predefined equivalence range of ± 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 randomised 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-

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**Figure 1. Trial Profile**

<table>
<thead>
<tr>
<th>Initial Run-In Period (4 wk)</th>
<th>Randomized Treatment Period (44 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1102 Received 15 mg of Sibutramine Hydrochloride</td>
<td>1001 Randomized into 3 Groups at a Ratio of 2:2:1</td>
</tr>
<tr>
<td>101 Not Eligible for Randomization</td>
<td>405 Assigned to Receive 15 mg of Continuous Sibutramine</td>
</tr>
<tr>
<td>23 Did Not Meet Weight Loss Criteria*</td>
<td>395 Assigned to Receive 15 mg of Intermittent Sibutramine</td>
</tr>
<tr>
<td>35 Protocol Violations</td>
<td>201 Assigned to Receive Placebo</td>
</tr>
<tr>
<td>9 Patient Request</td>
<td>79 Withdraw</td>
</tr>
<tr>
<td>8 Lost to Follow-up</td>
<td>6 Lack of Efficacy</td>
</tr>
<tr>
<td>1 Noncompliance</td>
<td>4 Noncompliance</td>
</tr>
<tr>
<td>2 Other</td>
<td>15 Lost to Follow-up</td>
</tr>
<tr>
<td>28 Adverse Event</td>
<td>20 Protocol Violation</td>
</tr>
<tr>
<td>4 Other/Unavailable</td>
<td>25 Patient Request</td>
</tr>
<tr>
<td>2 Other/Unavailable</td>
<td>13 Adverse Event</td>
</tr>
<tr>
<td>2 Other/Unavailable</td>
<td>2 Other/Unavailable</td>
</tr>
<tr>
<td>326 Completed Trial</td>
<td>315 Completed Trial</td>
</tr>
<tr>
<td>146 Completed Trial</td>
<td>405 Included in Intention-to-Treat Analyses</td>
</tr>
<tr>
<td>312 Included in per Protocol Analyses</td>
<td>395 Included in Intention-to-Treat Analyses</td>
</tr>
<tr>
<td>303 Included in per Protocol Analyses</td>
<td>201 Included in Intention-to-Treat Analyses</td>
</tr>
<tr>
<td>137 Included in per Protocol Analyses</td>
<td></td>
</tr>
</tbody>
</table>

*Weight loss of at least 2 % or 2 kg following the 4-week run-in period.
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### Table 1. Characteristics of the Intent-to-Treat Population at Randomization (Week 4)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Continuous Therapy (n = 405)</th>
<th>Intermittent Therapy (n = 399)</th>
<th>Placebo (n = 201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>103 (25.4)</td>
<td>84 (21.3)</td>
<td>46 (22.9)</td>
</tr>
<tr>
<td>Female</td>
<td>302 (74.6)</td>
<td>311 (78.7)</td>
<td>155 (77.1)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>43.1 (11.2)</td>
<td>42.6 (12.0)</td>
<td>44.0 (11.1)</td>
</tr>
<tr>
<td>Anthropometry, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>98.6 (14.3)</td>
<td>98.2 (15.1)</td>
<td>98.2 (14.7)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168.0 (8.7)</td>
<td>167.1 (8.7)</td>
<td>167.0 (9.1)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>34.7 (3.4)</td>
<td>34.9 (3.4)</td>
<td>35.0 (3.4)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>106.6 (11.3)</td>
<td>106.6 (12.7)</td>
<td>106.6 (12.0)</td>
</tr>
<tr>
<td>Alcohol consumption, No. (%)</td>
<td>183 (45.2)</td>
<td>167 (42.3)</td>
<td>86 (42.8)</td>
</tr>
<tr>
<td>Smokers, No. (%)</td>
<td>149 (36.8)</td>
<td>132 (33.4)</td>
<td>63 (31.3)</td>
</tr>
<tr>
<td>Obesity in family history, No. (%)</td>
<td>288 (71.1)</td>
<td>283 (71.6)</td>
<td>156 (77.6)</td>
</tr>
</tbody>
</table>

*Defined as occasional or daily consumption and is based on the number of drinks consumed.*

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 ± 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 a 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 therapy 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: dry mouth was most frequent (\( n = 70; 6.4\% \)), followed by constipation (\( n = 37; 3.4\% \)), in-
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
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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. 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. In the random-effectiveness of sibutramine during confirming the expectations for the phase was approximately 4.2 kg, thus

Mean weight loss in the initial run-in period with sibutramine was approximately 4.2 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, 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. 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

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Continuous Therapy (n = 405)</th>
<th>Intermittent Therapy (n = 395)</th>
<th>Placebo (n = 201)</th>
<th>Total (n = 1001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>19 (4.7)</td>
<td>14 (3.5)</td>
<td>14 (7.0)</td>
<td>47 (4.7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>23 (5.7)</td>
<td>20 (5.1)</td>
<td>13 (6.5)</td>
<td>56 (5.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>24 (6.0)</td>
<td>22 (5.6)</td>
<td>15 (7.5)</td>
<td>61 (6.1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>25 (6.2)</td>
<td>24 (6.1)</td>
<td>17 (8.5)</td>
<td>66 (6.6)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>34 (8.5)</td>
<td>32 (8.1)</td>
<td>18 (9.0)</td>
<td>84 (8.4)</td>
</tr>
<tr>
<td>Gastrointestinal tract infection</td>
<td>26 (6.4)</td>
<td>25 (6.3)</td>
<td>14 (7.0)</td>
<td>65 (6.5)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>23 (5.7)</td>
<td>20 (5.1)</td>
<td>11 (5.5)</td>
<td>54 (5.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>27 (6.7)</td>
<td>26 (6.6)</td>
<td>12 (6.0)</td>
<td>65 (6.5)</td>
</tr>
<tr>
<td>Eczema</td>
<td>24 (5.9)</td>
<td>25 (6.3)</td>
<td>13 (6.5)</td>
<td>62 (6.2)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>23 (5.7)</td>
<td>20 (5.1)</td>
<td>8 (4.0)</td>
<td>51 (5.1)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>30 (7.4)</td>
<td>28 (7.1)</td>
<td>15 (7.5)</td>
<td>73 (7.3)</td>
</tr>
<tr>
<td>Total patients with adverse events†</td>
<td>303 (74.8)</td>
<td>283 (71.7)</td>
<td>151 (75.1)</td>
<td>737 (73.6)</td>
</tr>
<tr>
<td>Total No. of adverse events</td>
<td>1111</td>
<td>996</td>
<td>468</td>
<td>2575</td>
</tr>
</tbody>
</table>

*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 ≥5%)*

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

*All values are expressed as No. (%) unless otherwise indicated.
†One patient could have had more than 1 adverse event.

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crease in waist circumference. Computed tomography scans showed that the percentage decrease in intra-abdominal fat was nearly twice that in subcutaneous fat. 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 have shown that the percentage decrease in intra-abdominal fat was nearly twice that in subcutaneous fat. This approach may possibly contribute to improved patient compliance.

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. It has been shown that a decrease in triglyceride levels and an increase in HDL-cholesterol may reduce the risk of cardiovascular disease. 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.

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.

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 suggests 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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Author Contributions: Study concept and design: Wirth. Acquisition of data: Krause. Drafting of the manuscript: Wirth. Critical revision of the manuscript for important intellectual content: Krause. Administrative, technical, or material support: Krause. Study supervision: Krause.

Financial Disclosure: As principal investigator for this study, Dr Wirth received financial support from Knoll Deutschland GmbH for personal expenditures and technical costs (related to design of the study, contact with investigators, co-organizing and attending meetings, manuscript preparation, travel costs, and participation in congresses), but does not have any stock ownership or options, grants, or patients with the company. Ms Krause was originally the project manager for this study for Knoll Deutschland GmbH and is employed by the company.

Dr Wirth, as principal investigator, had full access to all 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).

Role of the Sponsor: The study design was developed by Dr Wirth in close cooperation with Knoll Deutschland GmbH. Ms Krause, coauthor of this article, originally was the project manager at Knoll Deutschland GmbH for this clinical trial. Study medication was provided by Knoll Deutschland GmbH following the Good Manufacturing Practice Guidelines. Also, the randomization list was provided by Knoll Deutschland GmbH. Monitoring, data collection, and data analysis were performed by a contract research organization (Quintiles Transnational, Mannheim, Germany). Quintiles Transnational also provided assistance in the preparation of the original version of the manuscript. Another contract research organization (ECRON) performed the additional analyses necessary to provide the revised version of the manuscript. Dr Wirth takes responsibility for the content of the article. Dr Boos, presently the project manager from Knoll Deutschland GmbH, was informed about the status concerning publication. Neither his approval nor that of any other person of Knoll Deutschland GmbH was required for publication of the data in this article.

Funding/Support: This study was supported by a research grant from Knoll Deutschland GmbH, Ludwigshafen, Germany.

Acknowledgment: We thank Barbara Glocker, PhD, (ECRON), Georg Comes (Quintiles), and Stefan Hantel, PhD, (ECRON) for the provision of statistical tables. German Multicenter Investigators: C. Adler (Traben-Trarbach), H. Anderten (Hildesheim), H. Anger (Bielefeld), K. Balck (Meine), M. Baum (Kaiserslautern), S. Baumbach (Apolda), J. Berger (Herbertshofen), M. Bergmann (Bruttig-Fankel), K. Birk (Neu-Isenburg), S. Bluhm (Salzgitter), G. Bröck (Trier), U. Burkhardt (Herrenberg), R. Dakieler (Ginsheim), W. Daut (Kallstadt), C. Delank (Hamburg), M. Detendorf (Bochum), J. Dick (Wallenfanger), G. Dienhart-Schneider (Beckingen), E. Döpping (Gebsheide), S. Dutler (Biberbach), G. Ebert (Hagenbach), H. M. Faenster (Duisberg), W. Folger (Amorbach), A. Franke (Erfurt), E. Friedrich (Jena), J. Fuchs (Hannover), R. Fuchs.
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