ORIGINAL ARTICLE

A Randomized, Double-blind, Placebo-Controlled Study of Sibutramine in the Treatment of Binge-Eating Disorder

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Background: Although antidepressants are the pharmacological agents most often studied in the treatment of binge-eating disorder (BED), preliminary evidence from an open trial suggests that the antiobesity agent sibutramine hydrochloride may be effective. The objective of this study was to evaluate the efficacy and tolerability of sibutramine in obese patients with BED.

Methods: After a 2-week run-in period, 60 obese outpatients (body mass index [calculated as weight in kilograms divided by the square of height in meters] 30-45), who met *DSM-IV* criteria for BED were randomly assigned to receive sibutramine hydrochloride (n=30), 15 mg/d, or placebo (n=30) in a 12-week double-blind study at 2 centers. The primary outcome measure was binge frequency, expressed as the number of days with binge-eating episodes during the past week. Secondary outcome measures included Binge Eating Scale, Beck Depression Inventory scores, weight, and treatment responder status (remission and response). For each efficacy outcome, an intent-to-treat analysis was performed using random regression methods.

Results: There was a significant reduction in the number of days with binge episodes in the sibutramine group compared with the placebo group ($t_{203}=2.14$; $P=.03$); this was associated with an important and significant weight loss (–7.4 kg) compared with a small weight gain in the placebo group (1.4 kg) ($t_{147}=4.88$; $P<.001$). Sibutramine was also associated with a significantly greater rate of reduction in Binge Eating Scale ($t_{202}=3.64$; $P<.001$) and Beck Depression Inventory ($t_{201}=3.72$; $P<.001$) scores. Dry mouth ($P=.01$) and constipation ($P<.001$) were more common adverse reactions with sibutramine than placebo.

Conclusions: Sibutramine is effective and well tolerated in the treatment of obese patients with BED. Its effects address 3 main domains of the BED syndrome, ie, binge eating, weight, and related depressive symptoms.

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BINGE-EATING disorder (BED) is a newly recognized diagnostic entity characterized by episodes of uncontrolled consumption of large amounts of food (binge eating) that are not followed by the inappropriate compensatory behaviors that characterize bulimia nervosa.[1] Provisional diagnostic criteria for BED were included in Appendix B of the *DSM-IV*.[2] Although BED is not limited to obese individuals, it is a common diagnosis in this group, especially among patients seeking treatment for obesity.[3] Another important aspect of this syndrome is that patients with BED have higher than expected rates of comorbid psychiatric conditions, especially depression.[4,5] Thus, major goals of treatment include cessation of binge eating, weight loss, and reduction of the associated psychopathology.[6]

Pharmacological interventions may be an important part of a multidisciplinary approach to treat obese patients with BED.[7] Selective serotonin reuptake inhibitors,[8-11] the most studied group of agents, have been shown to significantly reduce binge-eating frequency in placebo-controlled studies. However, there is a possible lack of clinically important weight loss with these drugs. An increasing interest in new approaches such as other classes of antidepressants, anticonvulsants, and antiobesity agents in the treatment of BED has been observed.[12] Venlafaxine hydrochloride, a serotonin and norepinephrine reuptake inhibitor, has been reported to be effective in BED in an open study.[13] The anticonvulsant topiramate has been shown effective in reducing binge eating and weight in open studies[14,15] and in a placebo-controlled trial.[16] The first report of the use of an antiobesity agent to treat BED was published in 1996 by Stunkard et al,[17] who showed that *d*-fenfluramine hydrochloride (now with-

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drawn from the market) was more effective than placebo in the treatment of BED.

Sibutramine hydrochloride is a serotonin and norepinephrine reuptake inhibitor and represents a new class of agents approved by the US Food and Drug Administration for the treatment of obesity. Its efficacy in inducing initial weight loss and subsequent weight maintenance is well proved in short- and long-term clinical trials.[18-21] Sibutramine induces weight loss by affecting the physiological process of satiety and stimulating thermogenesis.[18] Unlike fenfluramine and *d*-fenfluramine, it does not induce serotonin release and has not been implicated in the development of valvular heart disease. Sibutramine is one of the few established and well-proved agents for the treatment of obesity available and is considered effective and safe in patients who require pharmacotherapy as part of the multimodal approach to weight loss.[18]

The results of an open trial[22] with 10 obese patients with BED suggested that sibutramine might be an effective and safe treatment for obese binge eaters. Sibutramine hydrochloride, 15 mg/d, was administered for 12 weeks. The 7 patients who completed the trial showed a complete remission of binge-eating episodes associated with body weight reduction. On the basis of this preliminary evidence, we conducted the present randomized placebo-controlled trial to evaluate the efficacy and tolerability of sibutramine in obese patients with BED.

METHODS

SUBJECTS

Male and female outpatients aged 18 to 60 years, with a body mass index (calculated as weight in kilograms divided by the square of height in meters) of 30 to 45 and who met *DSM-IV* criteria for BED and an additional binge-eating severity criterion[23] of at least a moderate level of binge-eating behavior (Binge Eating Scale [BES][24] score, >17), were recruited through media advertisements. Participation of women was contingent on use of a medically accepted form of contraception.

Exclusion criteria included pregnancy, lactation, bulimia nervosa (present or past diagnosis), psychosis, mania, organic dementia or alcohol or other drug abuse, suicide risk, diabetes mellitus, supine diastolic arterial pressure of greater than 110 mm Hg, unstable medical illness or clinically significant abnormal laboratory results, concomitant or previous use of sibutramine or other investigational drugs, concurrent use (on a regular basis, within 3 months of study entry) of antidepressants, antypsychotics, lithium carbonate, cyproheptadine hydrochloride, bromocriptine mesylate, ergotamine tartrate and related drugs, atropine, thyroid hormones, systemic steroids (except for menopause hormone therapy), antiobesity agents, drugs that interfere with gastrointestinal tract movements as antidiarrhea and antinausea drugs, anticoagulants, digitalis, anti-Parkinson drugs that interfere with amine activity, any kind of psychotherapy within 3 months of entry to the study, history of gastrointestinal tract surgery with the aim of losing weight, and smoking cessation within the past 3 months or intention to quit during the study period.

Sample size was determined on the basis of mean reduction in binge-eating rates with placebo from 2 published pharmacological trials[10,17] and the reduction with sibutramine from a pilot open-label trial,[22] with an expected difference of 40%, $\alpha = 5\%$, and $\beta = 20\%$. Potential participants (n = 750) underwent screening by telephone. The 233 who seemed to be qualified underwent evaluation by the staff groups of the 2 collaborative centers. All participants signed a written informed consent document before any study procedure was administered. Seventy-nine patients were enrolled from October 1, 2000, through July 31, 2001.

STUDY DESIGN

This randomized, double-blind, parallel study comparing a fixed dose of sibutramine with placebo was conducted at the following 2 sites: (1) the Obesity and Eating Disorders Group from the Institute of Psychiatry, Federal University of Rio de Janeiro, and the Institute of Diabetes and Endocrinology of Rio de Janeiro, Rio de Janeiro, Brazil, and (2) the Eating Disorders Program from the Federal University of São Paulo, São Paulo, Brazil. The study protocol was approved by ethics committees from both collaborative centers.

After completing the screening evaluations, patients received single-blind placebo capsules at breakfast in a 2-week run-in phase. Patients who maintained binge episodes on 2 or more days during the past week and a BES score of greater than 17 were randomized in a 1:1 ratio to 12 weeks of double-blind treatment. All randomization procedures were performed by Abbott Laboratórios do Brasil Ltda, São Paulo, at an independent facility. Patients were randomized in clusters of 10 subjects through a computer-generated randomization table to receive active drug or placebo. To ensure concealment of the randomization assignment, medication was provided in coded containers with a 20-day (baseline and week 2) or 40-day (weeks 4 and 8) supply of identical-appearing 15-mg capsules of sibutramine hydrochloride or placebo.

ASSESSMENT

Before inclusion, patients underwent a comprehensive clinical and psychiatric assessment by trained study technicians (endocrinologists and mental health specialists) at both centers, including a medical history, a physical examination, and a structured diagnostic interview. The Structured Clinical Interview for *DSM-IV*–Patient Version[25] was used for the diagnosis of BED and associated psychiatric conditions.

Study visits took place at baseline and at weeks 2, 4, 8, and 12. Hematologic and biochemical tests and electrocardiography were performed at baseline and at the end of the study. At every visit, patients were asked about binge frequency, medication dosage, medication compliance (ensured by means of capsule count), and adverse events.

The primary outcome measure was binge frequency, measured by binge days during the past week. A binge day was defined as a day on which the patient had at least 1 binge-eating episode. A binge day was used as our primary efficacy measure because it is a reliable method to assess binge frequency,[26] considered more accurate than the number of binge episodes.[27] As secondary outcome measures, we analyzed self-report evaluations of eating and depressive symptoms and weight change. We also categorized responder status during the course of the study, on the basis of percentage of decrease in binge days from baseline, as remission if there was a cessation of binging and response if there was a 50% reduction in binge frequency. Safety and tolerability were also assessed.

For screening purposes and during the study, a binge-eating episode was defined according to *DSM-IV*[2] criteria plus the additional criterion of consumption of at least 1500 kcal. In the screening phase, patients were taught this definition and were instructed to use it in their recall of binges throughout the study. At study visits they were asked to recall binge episodes for each day during the past week, their duration, the

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feelings and circumstances associated with the episode, the sense of lack of control over eating, and the estimated amount of food consumed during each episode. Study technicians masked to the study medication made the assessment of whether the behavior qualified as an objective binge-eating episode. Once the presence of an objective binge-eating episode was characterized, binge days were counted and registered. Technicians from both centers were trained before the beginning of the study to standardize binge assessment. Food diaries, a therapeutic intervention frequently used in cognitive behavioral therapy for eating disorders, were not used to assess binge frequency to avoid the effect of another intervention.[28] Nutritional counseling was also not used because it could interfere in binge frequency.[29] Patients were told they could be receiving a medication to control binge eating, and although they could lose weight, further weight loss strategies were not recommended during the study.

The severity of binge-eating behavior was also assessed dimensionally with the BES.[24,30] The BES is a 16-item questionnaire that identifies different levels of binge-eating severity. A BES cutoff score of at least 17 indicates a degree of severity that is at least moderate.[23] We used the Beck Depression Inventory (BDI)[31] to evaluate the depressive symptoms.

STATISTICAL ANALYSES

Baseline characteristics between groups were compared using a 2-tailed, unpaired *t* test or the χ^2 test.

We examined the temporal change of response to treatment by performing repeated random regression analyses,[32,33] using SAS software, version 8.0.[34] For the continuous variables of binge frequency, BES and BDI scores, and weight, we compared the rate of change in the sibutramine group with that in the placebo group for each dependent measure (SAS PROC MIXED), including terms for treatment, time (0, 2, 4, 8, and 12 weeks), center, treatment × time interaction, and treatment × center interaction. Since the treatment × center interaction was not significant ($P \geq .51$ in all analyses), it was dropped from the models, but centers were kept in.

First, we conducted a time-trend analysis. The term of interest was the treatment × time interaction, which estimates the rate of change. Time was treated as a continuous variable expressed as logarithm (weeks + 1).[9] We also conducted a point-by-point analysis through random effects analysis (SAS PROC MIXED) as used by Arnold et al[11] to estimate change from baseline with time as a categorical variable. This analysis estimated the difference between groups in the change from baseline to weeks 2, 4, 8, and 12.

Binge frequency was logarithm transformed to normalize the variable distribution. We tested the covariance structure of the models (autoregressive, unstructured, and compound symmetry) by the likelihood ratio test, and the unstructured covariance matrix appeared to be most adequate for these data.

Analyses of responder status (remission and response) during the course of treatment were performed using random regression methods as proposed by Leon.[35] Given the dichotomous nature of remission and response, we used logistic regression through PROC GENMOD in SAS (logit link function and binomial error distribution). The estimated odds ratio of responder status was modeled comparing the treatment group with the placebo group during the course of the trial, assuming an exchangeable (compound symmetry) covariance structure. The modeling process for these response categories was similar to those for the mean analyses.

Mean changes and categorical analyses were intent to treat, including dropouts at all time points. Changes in blood pressure and heart rate from baseline to the end of the study were compared using a 2-sided paired *t* test. Correlation coefficients between changes in binge frequency, weight, and BDI scores were calculated using Spearman rank correlation.

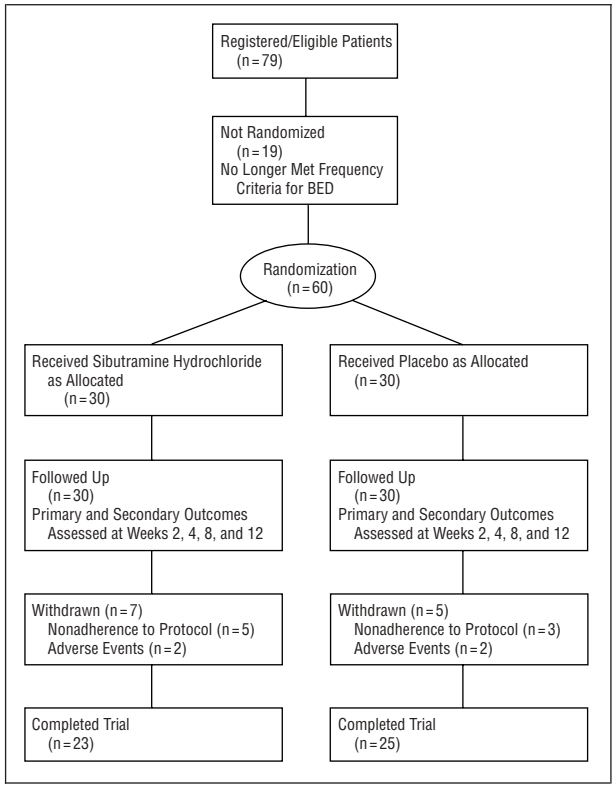

Figure 1. Progress of 79 patients during the trial. BED indicates binge-eating disorder.

RESULTS

PATIENT CHARACTERISTICS

Of the 79 enrolled patients, 19 were not included in the double-blind phase of the trial because they presented with less than 2 binge days during the last week after the placebo run-in phase. Any patient was excluded in this phase on the basis of BES severity criteria.. Thirty patients were randomly assigned to receive sibutramine and 30 to receive placebo. Twelve randomized patients (20%) withdrew before the end of the study, 7 in the sibutramine and 5 in the placebo group ($\chi^2 = 0.41$; $P = .75$) (**Figure 1**).

There were no significant differences between the sibutramine and the placebo groups on baseline demographic and clinical characteristics (**Table 1**).

BINGE-EATING OUTCOME

Random regression analyses revealed that the reduction in binge-eating frequency associated with sibutramine was sharper from baseline to week 2 and that the decrease was maintained throughout the study (**Figure 2**). During the course of treatment, the drug × time interaction was statistically significant ($t_{203} = 2.14$; $P = .03$) (**Table 2**). Compared with placebo, the response to sibutramine attained statistical significance by week 2 of treatment ($t_{57} = 3.32$; $P = .002$) and was still significant at week 12

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Table 1. Demographic and Clinical Characteristics of 60 Obese Patients With BED

	Study Groups*		
	Sibutramine Hydrochloride (n = 30)	Placebo (n = 30)	*P* Value
Age, mean (SD), y	35.2 (9.0)	36.6 (10.2)	.58*
No. (%) female	26 (87)	27 (90)	.50†
No. (%) white	22 (73)	26 (87)	.33†
History of major depression, No.	11 (37)	9 (30)	.62†
No. of binge days/week, mean (SD)	4.1 (1.8)	3.9 (1.8)	.62*
BES score, mean (SD)	29.2 (7.2)	29.1 (5.9)	.94*
BDI score, mean (SD)	17.3 (9.7)	18.6 (9.1)	.59*
Weight, mean (SD), kg	102.8 (13.2)	98.7 (12.9)	.23*

Abbreviations: BDI, Beck Depression Inventory; BED, binge-eating disorder; BES, Binge Eating Scale.
*By 2-tailed *t* test.
†By χ^2 test.

(t_{57}=2.07; P=.04). The change from baseline in binge days with sibutramine was 66% vs 41% in the placebo group.

Dimensional assessment of binge-eating behavior by means of the BES confirmed the binge frequency analyses. Random regression analyses revealed that during the course of treatment, the drug × time interaction was statistically significant (t_{57}=3.64; P<.001) (Table 2). Response to sibutramine attained statistical significance by week 4 of treatment (t_{57}=2.05; P=.04) and was still significant at week 12 (t_{57}=2.85; P=.006).

WEIGHT OUTCOME

At week 12, the weight change was −7.4 kg in the sibutramine group and +1.4 kg in the placebo group. Random regression analyses revealed that during the course of treatment, the drug × time interaction was statistically significant (t_{147}=4.88; P<.001). Response to sibutramine compared with placebo attained statistical significance by week 4 of treatment (t_{57}=2.45; P=.02) (Table 2).

DEPRESSION OUTCOME

The reduction of the associated depressive symptoms with sibutramine compared with placebo was progressive throughout the 12 weeks of the study (Figure 2), and during the course of treatment, the drug × time interaction was statistically significant (t_{201}=3.72; P<.001) (Table 2). Response to sibutramine only attained statistical significance at week 12 (t_{57}=3.16; P=.002). The change from baseline in BDI scores was greater with sibutramine (43%) compared with placebo (4%).

Sibutramine treatment was associated with a higher responder status than placebo during the course of the study. In terms of treatment effect, we observed a significant difference favoring sibutramine (**Figure 3**). The estimated odds of remission and response during the course of treatment with sibutramine was significantly greater than that observed for placebo (remission, P=.02; response, P=.005). A statistically significant time effect (remission, P=.005; response, P=.001), reflecting a progressive change in responder status with time in both treatment groups, was observed during the trial. However, the treatment × time interaction was not significant (remission, P=.40; response, P=.29), indicating that the effect of sibutramine on responder status did not increase with the duration of the treatment. Completer rates indicated that 12 (52%) of 23 sibutramine-treated patients and 8 (32%) of the 25 placebo-treated patients attained remission at week 12. In addition, 18 (78%) of 23 sibutramine-treated patients and 13 (52%) of 25 placebo-treated patients showed a 50% reduction in binge frequency (response) in the last visit.

Further analysis revealed that reductions in binge frequency and weight loss were significantly correlated in patients who completed the study (r_s=0.31; P=.01). The correlation between decrease in binge frequency and depressive symptoms expressed by BDI scores approached statistical significance (r_s=0.29; P=.05).

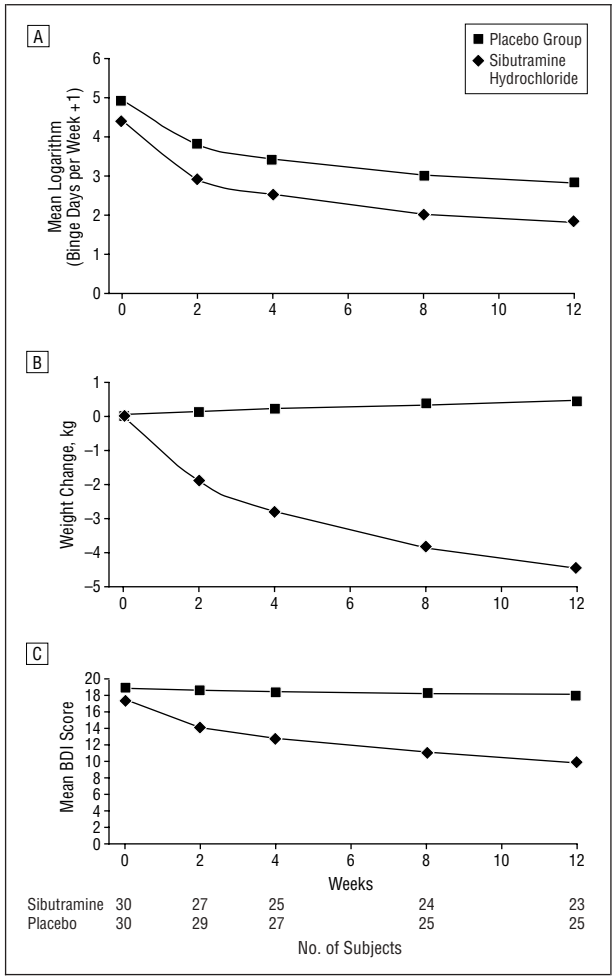

Figure 2. Results of random regression analyses comparing the effects of a 12-week treatment with sibutramine hydrochloride and placebo. Statistical tests relied on random regression analyses that do not correspond directly to the real values of each outcome measure. A, Mean binge days per week (t_{203}=2.14; P=.03). B, Weight change (t_{147}=4.88; P<.001). Estimates were smaller than real values because estimates were adjusted for weight at baseline. C, Mean scores on the Beck Depression Inventory (BDI) (t_{201}=3.72; P<.001).

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Table 2. Outcomes Measures by Time Point and Treatment*

	Study Group					
	Week 0		Week 2		Week 4	
	Sibutramine Hydrochloride	Placebo	Sibutramine	Placebo	Sibutramine	Placebo
DBE	4.1 ± 1.8	3.9 ± 1.8	1.7 ± 1.9	3.3 ± 2.2	1.7 ± 1.6	3.0 ± 2.1
BES score	29.2 ± 7.2	29.1 ± 5.9	26.8 ± 9.3	27.6 ± 6.5	23.6 ± 11.4	26.1 ± 8.8
Weight, kg	102.8 ± 13.2	98.7 ± 12.9	98.7 ± 11.0	99.2 ± 13.4	96.9 ± 10.8	99.7 ± 12.5
BDI score	17.3 ± 9.6	18.7 ± 7.9	14.6 ± 7.9	19.4 ± 11.2	13.1 ± 8.6	18.4 ± 10.4

	Study Group				Effect of Sibutramine†			
	Week 8		Week 12					
	Sibutramine	Placebo	Sibutramine	Placebo	Treatment × Time Interaction‡	SE	t_{df}	*P* Value
DBE	1.8 ± 2.2	2.5 ± 2.1	1.4 ± 2.0	2.3 ± 2.2	−0.135	0.063	2.14_{203}	.03
BES score	21.0 ± 12.6	26.4 ± 9.5	19.7 ± 12.4	24.4 ± 8.9	−0.201	0.055	3.64_{202}	<.001
Weight, kg	96.0 ± 11.4	99.9 ± 13.3	95.4 ± 12.3	100.1 ± 13.6	−1.983	0.406	4.88_{147}	<.001
BDI score	12.9 ± 8.5	18.3 ± 10.8	9.9 ± 7.6	17.9 ± 10.6	−2.558	0.687	3.72_{201}	<.001

Abbreviations: BDI, Beck Depression Inventory; BES, Binge Eating Scale; DBE, days per week of binge eating.
*Data are expressed as mean ± SD.
†Statistics relied on random regression analyses, which do not correspond directly to the means and fixed time points presented herein.
‡Represents the difference in rate of change between the sibutramine and placebo groups based on random regression analyses that included all subjects at all time points, including patients who dropped out before the end of the study.

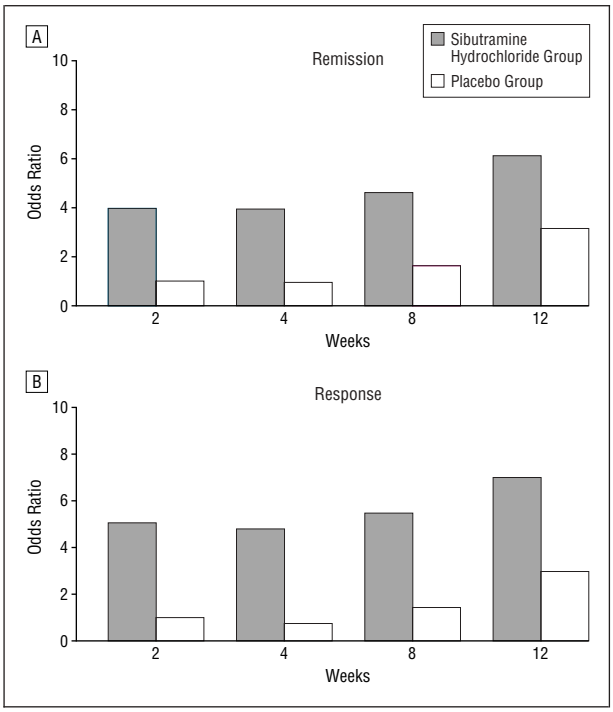

Figure 3. Estimated odds of remission and response during the course of the study based on random regression analysis. The categories of responder status were based on the percentage of decrease in binge days from baseline. Remission indicates cessation of binge eating; response, 50% reduction in binge frequency. A, Remission (treatment effect, *P*=.02; time effect, *P*=.005; and treatment × time interaction, *P*=.40). B, Response (treatment effect, *P*=.005; time effect, *P*=.001; treatment × time interaction, *P*=.29).

Table 3. Incidence of Adverse Events Reported During the Study

	Study Groups, No. of Patients		
Adverse Event	Sibutramine Hydrochloride	Placebo	Total
Dry mouth*	22	3	**25**
Headache*	6	14	**20**
Nausea	10	9	**19**
Insomnia	9	9	**18**
Constipation†	7	0	**7**
Sudoresis	6	1	**7**
Lumbar pain	3	6	**9**
Depressive mood	3	4	**7**
Flu syndrome	3	3	**6**
Malaise	1	4	**5**
Others	38	35	**73**
Total	**108**	**88**	**196**

*$P<.01$.
†$P<.001$.

TOLERABILITY AND SAFETY

Twelve patients withdrew from the study, including 4 in week 2, 4 in week 4, 3 in week 8, and 1 in week 12 (Figure 1). Four patients dropped out of the trial because of an adverse event, including 2 in the sibutramine group (insomnia and appendicitis) and 2 in the placebo group (nausea and headache). The patient in the sibutramine group had to be hospitalized to treat the appendicitis and was therefore withdrawn from the study. This serious adverse event was considered not related to the study medication.

Sibutramine was well tolerated, as shown by adverse events reported at any time during treatment (**Table 3**). There were no significant differences between groups in total incidence of adverse events, except for dry mouth and constipation in the sibutramine group and headache in the placebo group. There were no eletrocardiographic or laboratory abnormalities dur-

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ing the course of the trial. Treatment with sibutramine was not associated with a clinically or statistically significant change in systolic (week 12 vs week 0, 129.8 vs 129.3 mm Hg, respectively [t_{26}=0.81; P=.42]) or diastolic (week 12 vs week 0, 85.8 vs 84.6 mm Hg, respectively [t_{26}=0.36; P=.72]) blood pressure. As expected, there was a minor but significant increase of heart rate (mean±SD, week 12 vs week 0, 87.1±10.9 vs 79.8±8.7 beats/min [t_{26}=2.49; P=.007]).

COMMENT

To our knowledge, this is the first randomized, double-blind, placebo-controlled trial of an antiobesity agent approved at present by the US Food and Drug Administration for the treatment of BED. The results confirm our preliminary data[22] and suggest that sibutramine is an effective and safe short-term treatment for obese patients with BED. Sibutramine was more effective than placebo in primary and secondary outcome measures. The improvement in eating-related psychopathology was associated with a significant reduction in body weight and the concurrent decline in BDI. Although sibutramine was associated with a higher level of responder status during the course of the study compared with placebo, the treatment × time interaction was not statistically significant. Adverse effects related to sibutramine, such as dry mouth and constipation, were mild.

In terms of binge-eating reduction and overall response, our findings are consistent with those from other randomized placebo-controlled studies with pharmacological agents in BED or similar conditions.[9,10,17,28,36] McCann and Agras[28] in a study of 23 patients with nonpurging bulimia nervosa (as defined by *DSM-III-R*) found desipramine hydrochloride to be significantly superior to placebo in reducing binge-eating frequency (63% reduction vs 5.7% increase) with no significant weight loss. The efficacy of fluvoxamine maleate was examined in a randomized controlled trial in obese patients with BED.[9] After 9 weeks, the authors found a significant reduction of binge frequency with fluvoxamine compared with placebo, with a significant although mild effect on body weight. McElroy et al[10] reported similar results with sertraline hydrochloride in a 6-week trial. In their study, there was a significant reduction in binge frequency with sertraline compared with placebo (85% vs 46.5%) and a significant weight loss (−5.4 kg). In a double-blind placebo-controlled trial, 61 obese patients with BED were treated for 14 weeks with topiramate.[16] Topiramate treatment was associated with a significantly greater reduction, in relation to placebo, in the number of binge days per week and eating-related psychopathological symptoms and with an important weight loss. The antiobesity agent *d*-fenfluramine, currently withdrawn from the market, was found to produce a short-term binge-eating suppression.[28] Unexpectedly, the high level of binge-eating remission reported (80%) was not associated with weight loss, despite the known antiobesity effects of this drug. Furthermore, as reported in other trials,[10,17,28] we also found a high placebo response in binge-eating frequency.

Like many other agents, sibutramine treatment was associated with a significant reduction in binge eating, weight, and associated depressive symptoms. In our trial, the reduction in binge frequency with sibutramine was remarkable from the second week onward, followed by a plateau effect. Otherwise, the pronounced initial effect on weight was followed by progressive and continuous weight loss during the whole study period. This amount of weight loss observed with sibutramine has not been documented in studies of other drugs, except for topiramate.[15,16]

Psychological interventions are currently considered the first-choice treatment for BED.[1] However, in controlled studies,[37-39] cognitive behavior therapy and interpersonal therapy reduced binge-eating frequency with no relevant effects on body weight. Some authors[40] proposed that to stop gaining weight or to achieve a mild weight loss should be considered a desirable outcome in BED. They suggested that controlling binge eating with psychological interventions such as cognitive behavior therapy would prevent future weight gain. On the other hand, considering that most patients with BED are obese and often present with obesity-related comorbid conditions, it is also very important to promote a relevant weight loss. Therefore, an ideal intervention for this condition should address binge eating and obesity.[6]

In the obese population presenting with BED included in our trial, the safety profile of sibutramine was quite similar to what was observed in the more general obese population included in previous studies with this agent.[21] In the drug-treated group, dry mouth and constipation were the more often reported adverse events, in accordance to the known pharmacological profile of the drug.[19] Despite data from placebo-controlled trials that have shown that sibutramine elevates blood pressure and heart rate,[21] we did not find major changes in blood pressure. There was a discrete rise in heart rate. Nevertheless, considering that obese patients in clinical practice may have associated cardiovascular heart diseases, clinical judgment is required when treatment is considered for such patients. Increases in blood pressure and heart rate are possible adverse effects that require regular monitoring. In addition, in regard to the safety of the drug, reports of serious adverse events, including death, have been associated with the use of sibutramine.[41] Sibutramine has recently been the subject of a comprehensive review by the European Agency for the Evaluation of Medicinal Products. This review was undertaken at the request of the Italian regulatory agency, after the receipt of a number of serious adverse events. However, in a recent communication, the European Agency for the Evaluation of Medicinal Products[41] considered that the risk-benefit profile of sibutramine remained favorable for its use in the treatment of obesity.

Although sibutramine lacks amphetaminelike abuse liability,[42,43] prescribing an antiobesity agent to an obese patient with a psychiatric condition involves an exhaustive psychiatric screening evaluation. Patients with BED seen in clinical settings usually have associated comorbid psychiatric disorders.[4,5] We have to be aware of the risk for substance-induced mental syndromes in predisposed patients.[44,45] There is a potential risk for interaction between other psychotropic medications such as monoamine oxidase inhibitors and selective serotonin reuptake inhibitors.[46]

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This study has several limitations. We have excluded individuals with many forms of clinical and psychiatric comorbidity. Because obese binge eaters usually have a number of associated comorbid conditions, our exclusion criteria may have affected the generalization of our findings. Furthermore, to avoid the use of any sort of food diaries, we decided to use a recall method. Although this strategy was already used in other trials of BED,[26,27] it may be less accurate than self-monitoring methods. Our binge frequency outcome measure was based on binge days during the past week before the study visit, considering that it may reflect binge frequency during a longer period.[47] This procedure also may have rendered some imprecision about the counting of binge days. In addition, 3 months of treatment may be too short a time for a study with obese patients. It would be advisable to observe what happens with weight and behavioral outcomes in a much longer period and after discontinuation of medication therapy.

CONCLUSIONS

We found sibutramine to be effective in reducing binge eating, body weight, and associated depressive symptoms in this short-term study in obese patients with BED. These preliminary findings suggest that sibutramine is a promising agent to be used in obese patients with BED and need to be further replicated.

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