An Open-Label Trial of Sibutramine in Obese Patients With Binge-Eating Disorder

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Background: Binge-eating disorder was recently included in Appendix B of the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV). Binge-eating disorder is a common diagnosis among patients who seek treatment for obesity. There are scant data about the efficacy of the novel antiobesity agents for binge-eating disorder. The objective of this article is to present data from an open-label study of the efficacy and tolerability of sibutramine in a group of obese binge eaters.

Method: Ten obese patients with DSM-IV binge-eating disorder and no medical comorbidity were consecutively selected from individuals seeking treatment for obesity in our clinic. Treatment with sibutramine, 15 mg/day, was administered for 12 weeks. The number of days with binge episodes per week, the number of binge episodes per week, the Binge Eating Scale (BES), the Beck Depression Inventory, and body weight evaluation were employed for outcome assessment.

Results: Seven patients completed the trial. They showed a complete resolution of binge-eating disorder with no binge-eating episodes at the end of the treatment. The mean ± SD number of days with binge episodes per week changed significantly from 5.2 ± 1.8 at baseline to 0.8 ± 1.9 at the end of the study ($p < .001$), and the mean BES score fell from 31.2 ± 6.2 to 15.2 ± 8.2. There was a reduction of body weight (mean = 4.0 kg [8.9 lb]) from baseline to the end of the study. No serious adverse effects were observed.

Conclusion: Sibutramine might be an effective and well-tolerated agent in the treatment of binge-eating disorder in obese patients.

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Binge-eating disorder was recently included in Appendix B of the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV). Although there is no established treatment for binge-eating disorder, pharmacologic intervention may be an important part of a multidisciplinary approach to treating binge-eating behavior.[1] Selective serotonin reuptake inhibitors (SSRIs),[2] the most studied group of agents, have been shown to significantly reduce binge-eating frequency in placebo-controlled studies of obese patients with binge-eating disorder.[3,4] The first report of the use of an antiobesity agent to treat binge-eating disorder was published in 1996.[5] In a placebo-controlled trial, Stunkard et al.[5] reported that *d*-fenfluramine (recently withdrawn from the market) was more effective than placebo in the treatment of binge-eating disorder.

Sibutramine, a novel serotonin and norepinephrine reuptake inhibitor, represents a new class of U.S. Food and Drug Administration–approved agents for the treatment of obesity.[6] Despite the clinical impression that sibutramine treatment affects eating behavior, this drug has not yet been studied in patients with binge-eating disorder.[7] This is the first study to evaluate the efficacy and tolerability of sibutramine in obese patients with binge-eating disorder.

METHOD

Ten consecutive female outpatients who came to our group seeking treatment to lose weight were recruited. They fulfilled the following inclusion criteria: a body mass index above 30, a diagnosis of binge-eating disorder according to DSM-IV Appendix B criteria,[8] and at least a moderate severity level of binge-eating behavior as shown

by a Binge Eating Scale (BES)[9] score above 17. Exclusion criteria included pregnancy, lactation, bulimia nervosa, psychosis, mania or organic dementia, any kind of psychotherapy within 3 months of entry to the study, clinically unstable medical illness, clinically significant abnormal laboratory results, and use of psychiatric medication or antiobesity agents within 3 months of entry to the study. The study was approved by the Institute of Diabetes and Endocrinology of Rio de Janeiro Ethical Committee. All subjects provided informed consent after the study procedures were fully explained.

For the diagnosis of binge-eating disorder and other associated psychiatric conditions, the Structured Clinical Interview for DSM-IV, Patient Edition,[10] was used. The BES was used to assess the severity of the binge-eating behavior, and the Beck Depression Inventory (BDI)[11] was used to evaluate the associated depressive symptoms.

The patients were treated with sibutramine, 15 mg/day, administered before breakfast, over a period of 3 months (12 weeks). Clinical evaluations were performed by a psychiatrist (J.C.A. or L.F.F.) and an endocrinologist (L.C., M.C., or A.V.) at 2-week intervals during the first month of treatment and at the end of the second and third months. At each visit, patients were asked the number of days with binge-eating episodes per week (DBE) and the total number of binge-eating episodes per week (NBE) since the last visit. Other variables measured included BDI scores, weight, and adverse effects. Measurements of blood pressure and pulse were also recorded. Routine hematologic and biochemical tests were performed at baseline and at the end of the study.

The primary efficacy variable was binge frequency (DBE and NBE), and secondary efficacy outcome measures included self-report evaluations of eating and depressive symptoms (BES and BDI scores) and weight. The mean and standard deviation or the frequency (%) of the data was calculated. Statistical analysis utilized paired t tests to assess changes in scores from pretreatment to posttreatment. An intent-to-treat analysis was used, with the last available evaluation carried forward as endpoint.

RESULTS

All patients were women, with a mean ± SD age of 35.4 ± 8.9 years. Eight patients identified themselves as white and 2, as black. Comorbid DSM-IV Axis I disorders included current major depressive disorder (N = 3), past major depressive disorder (N = 1), generalized anxiety disorder (N = 2), dysthymia (N = 2), and social phobia (N = 1). The relationship between comorbidity and clinical outcome is presented in Table 1.

Table 1. Comorbidity and Clinical Outcome of Binge-Eating Disorder Patients Treated With Sibutramine[a]

Patient	Comorbid Diagnoses (DSM-IV)	No. of Days With Binge-Eating Episodes		BDI Score		Outcome
		Baseline	Final	Baseline	Final	
1	Dysthymia	7	0	43	11	Remission
2	Dysthymia, current MDD	7	2	41	23	Discontinued (visit 3)
3	...	3	0	15	16	Remission
4	...	5	0	16	17	Remission
5	GAD	2	0	23	16	Remission
6	Current MDD	5	0	37	1	Remission
7	...	7	0	11	8	Remission
8	Current MDD	7	6	25	34	Discontinued (visit 3)
9	Past MDD, social phobia	4	0	30	25	Discontinued (visit 5)
10	GAD	4	0	27	7	Remission

[a]Abbreviations: BDI = Beck Depression Inventory, GAD = generalized anxiety disorder, MDD = major depressive disorder.

Seven patients attended all 5 visits. One patient discontinued the drug due to personal reasons; she moved to a full-time job and could not come to the medical visits. Another patient interrupted the treatment after the third visit because of lack of efficacy. The third patient discontinued the medication before the last visit due to gastric discomfort. Seven patients showed a total remission of binge episodes (no more days with binge-eating episodes). The mean DBE at the beginning was 5.2 ± 1.8 and at the final visit was 0.8 ± 1.9. The DBE change was statistically significant ($t = 6.8$, $df = 6$, $p < .001$). The mean NBE at baseline was 8.2 ± 4.4 and at the last visit was 1.4 ± 3.5, a statistically significant reduction ($t = 3.8$, $df = 6$, $p < .05$). The BES scores fell from 31.2 ± 6.2 to 15.2 ± 8.2 at visit 5. The depressive symptoms evaluated by the BDI showed a clinical reduction from 25.7 ± 11.8 to 14.9 ± 9.3. There was a reduction of body weight (mean = 4.0 kg [8.9 lb]) from baseline to the end of the study.

Benign adverse reactions were reported during the trial. Four patients reported dry mouth, 3 had constipation, and 3 complained of nausea. Other adverse events reported during the study were insomnia (N = 2), headache (N = 2), palpitations (N = 1), hypersomnia (N = 1), nervousness (N = 1), and sweating (N = 1). There were no observed variations of blood pressure during the study. The mean blood pressure was 127.7/81.1 mm Hg at the beginning of the study and 127.1/80.0 mm Hg at visit 5. The great majority of adverse reactions were benign in nature and lasted for only a few weeks.

DISCUSSION

Our results suggest that sibutramine may be an effective agent in the treatment of obese patients with binge-

eating disorder. Seven of 10 patients showed a total remission of binge eating, and 3 patients dropped out (1 patient had no response). Most side effects were mild and transient. Dry mouth, nausea, and constipation were the most commonly reported side effects.

The binge-eating remission and overall response observed in this trial are consistent with the findings of previous studies with SSRIs, *d*-fenfluramine, and combined phentermine-fluoxetine and tricyclic antidepressants in binge-eating disorder.[3–5,12,13] Because all these agents interfere with serotonergic and/or noradrenergic pathways, one possible mechanism of binge-eating reduction related to sibutramine may be a direct central effect on eating behavior.

These patients also reported an improvement in associated depressive symptoms as shown by BDI score reduction (Table 1). Although we cannot establish whether this improvement is the result of a reduction in binge eating or a direct central effect, the fact that sibutramine was first studied as an antidepressant[14] favors the latter assumption. The patients experienced a body weight reduction with no nutritional counseling. Thus, this weight loss may be related to the remission of binge eating or to the direct or indirect effects of the drug on energy expenditure.

Our results must be interpreted with care. The possibility that the observed favorable response to sibutramine was, in fact, a placebo response cannot be excluded. It is well known that patients with binge-eating disorder have a very high placebo response.[15] For example, in the study by Stunkard et al.,[5] almost half of the patients who began a 4-week placebo washout phase had a substantial response. We also have to consider the possibility of a spontaneous remission or a response to nonspecific interventions, which is frequently seen in this syndrome. Moreover, the improvement of mood could be another possible explanation for the observed reduction in binge eating. Additionally, 3 months of treatment may be too short a period of time to observe the behavioral modifications and the weight reduction. We also need to observe the patients in a follow-up period, after medication discontinuation.

In summary, the results of this open-label study suggest that sibutramine may be an effective and safe treatment for obese patients with binge-eating disorder. Controlled studies with longer treatment periods are needed to confirm these preliminary observations.

Drug names: fluoxetine (Prozac and others), phentermine (Adipex-P and others), sibutramine (Meridia).

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