

Use of Sibutramine, an Inhibitor of the Reuptake of Serotonin and Noradrenaline, in the Treatment of Binge Eating Disorder: A Placebo- Controlled Study

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ABSTRACT

Binge-eating disorder, which is characterized by repeated episodes of uncontrolled eating, is common in obese patients and is often accompanied by comorbid psychiatric disorders, especially depression. In previous studies, selective serotonin reuptake inhibitors have demonstrated efficacy in reducing the frequency of binge eating and addressing comorbid psychiatric disorders, but they have not shown the ability to promote weight loss. Sibutramine, a new serotonin and norepinephrine reuptake inhibitor, has been shown in short- and long-term studies to be effective in promoting and maintaining weight loss in obese patients who have binge-eating disorder. In this randomized, double-blind, placebo-controlled study, the efficacy, safety, and tolerability of sibutramine were evaluated in the treatment of binge-eating disorder in obese patients. Twenty patients were

randomly assigned in equal numbers to receive either sibutramine 10 mg/day or placebo for 12 weeks. Assessments were made at baseline and every 2 weeks throughout the study. Binge frequency, defined as the number of days during the previous week that included binge-eating episodes, was the primary outcome measure. By the end of the study, the binge frequency among patients given sibutramine was significantly lower than that among those given placebo. The main adverse events in the sibutramine group were dry mouth and constipation. The findings suggest sibutramine is an effective medication in the treatment of binge-eating disorders and is well tolerated. In addition, it addresses the 3 main goals in the treatment of binge-eating disorder: reducing the frequency of binge eating, promoting and maintaining weight loss, and treating the comorbid psychiatric conditions.

Keywords: | binge-eating disorder; sibutramine; obesity

INTRODUCTION

Until the late 1970s, anorexia nervosa was the only eating disorder defined by specific diagnostic criteria.¹⁻³ In the 1980s, the *Diagnostic and Manual of Mental Disorders*, 3rd edition (DSM-III) included the diagnostic criteria for bulimia nervosa.¹⁻³ By 1994, however, a significant number of cases of eating disorder had been described that did not meet the DSM-IV diagnostic criteria of either anorexia nervosa or bulimia nervosa.¹⁻³ Diagnosed as nonspecific eating disorders, these conditions did in fact share specific psychopathologic characteristics not addressed in established criteria.^{4,6} In all such cases, the patients held distorted beliefs regarding food and diet and body weight and shape and demonstrated ritualized behavior in their eating habits.

Among these patients were those who frequently demonstrated the same binge-eating pattern observed in patients with bulimia nervosa but, unlike that group, did not engage in inappropriate compensatory behavior, such as fasting, purging, or excessive exercise, after an episode of excessive eating.^{4,6} This particular disorder, now referred to as binge-eating disorder, has in recent years aroused increasing interest, particularly as it is closely related to obesity.^{4,6}

In 1959, Albert Stunkard was the first to identify this disorder. In his studies of subgroups of obese patients who presented with binge eating as the characteristic symptom, he recognized binge eating as a compulsive attack during which a patient eats food in great quantity without control.^{7,8} Today, the term binge-eating disorder is used to indicate both the symptom of binge eating and the symptomatology that distinguishes the disorder from bulimia nervosa.⁹⁻¹¹

In the general population, binge-eating disorder is quite rare. Its reported prevalence ranges from 0.7% to 4.6%. The disorder is quite common in patients undergoing treatment for obesity, however.⁹⁻¹¹ In fact, approximately two thirds of patients with binge-eating disorder have above-average weight, and among obese patients, the prevalence of binge-eating disorder tends to increase in proportion to the severity of the weight disorder. Recent statistics on binge-eating disorder show a prevalence of 16% among patients who follow nonmedical weight-loss programs, 30% among those who undergo specialized outpatient treatments, and 70% among hospitalized obese patients.⁹⁻¹¹

The prevalence among men and women is similar, but among those who follow a specialized diet, the prevalence is greater among women. The disorder is frequently diagnosed in adults between 30 and 40 years of age, and most of these have a history of an eating disorder beginning, on average, between the age of 15 and 20 years. Obese patients with binge-eating disorder also tend to have a life-long history of obesity and early struggles with low-calorie diets.⁹⁻¹¹ In addition, patients suffering from binge-eating disorder are more likely than the general population to have a lifetime history of mental disorders, such as depression and dysthymia (in more than 60% of the cases), anxiety disorders, and alcohol and drug dependence.⁹⁻¹¹ They are also susceptible to the same conditions and sequelae linked to obesity, such as diabetes mellitus, arterial hypertension, cardiovascular disease, and neoplasia. Again, the risk and severity of these conditions correlate with the seriousness of the obesity.

Therapy

The treatment of binge-eating disorder in most patients is particularly difficult because therapy must address both the eating disorder and obesity simultaneously.¹²⁻¹⁹ Currently, no standard protocol has been established for the pharmacologic treatment of binge-eating disorder. The major studies conducted thus far have focused on the use of antidepressants, both tricyclic agents (especially desipramine and imipramine) and selective serotonin reuptake inhibitors,¹²⁻¹⁹ which have demonstrated only short-term efficacy in reducing the frequency of binge episodes and minimal efficacy in reducing weight.

Recently, the antiobesity medication sibutramine has been used to treat binge-eating disorder.²⁰⁻²³ Sibutramine is a tertiary amine originally developed as a potential antidepressant, but it has also demonstrated the ability to induce weight loss.²⁰⁻²³ It inhibits the reuptake of the neurotransmitters serotonin (5-HT) and noradrenaline by the nerve cells of the brain.²⁰⁻²⁷ Its activity is evidenced mainly through 2 metabolic processes (the supplementation of the physiologic process of satiation and the stimulation of thermogenesis) that induce weight loss by affecting both the hunger impulse and energy consumption. These processes increase the activity of the sympathetic effectors in the thermogenically active brown adipose tissue.²⁵⁻²⁷ Sibutramine is usually effective and well tolerated at concentrated doses between 5 and 15 mg/day. The most frequent adverse effects are cephalalgia, nausea, insomnia, dry mouth, constipation, tachycardia, and arterial hypertension.²⁸⁻³⁰

The purpose of this study is to substantiate the effectiveness and tolerability of sibutramine in patients suffering from binge-eating disorder.

METHOD

The study included 20 female patients, aged between 24 and 36 years old, who suffered from binge-eating disorder, defined according to the DSM-IV criteria. Ten of these patients were randomly assigned to receive sibutramine 10 mg/kg/day for 12 weeks and the other 10 were given placebo. During the study, the participants were instructed to maintain daily diaries in which they recorded their food choices, bulimic seizures, weight, and any compensatory behaviors and their clinical status was monitored at twice weekly outpatient visits.

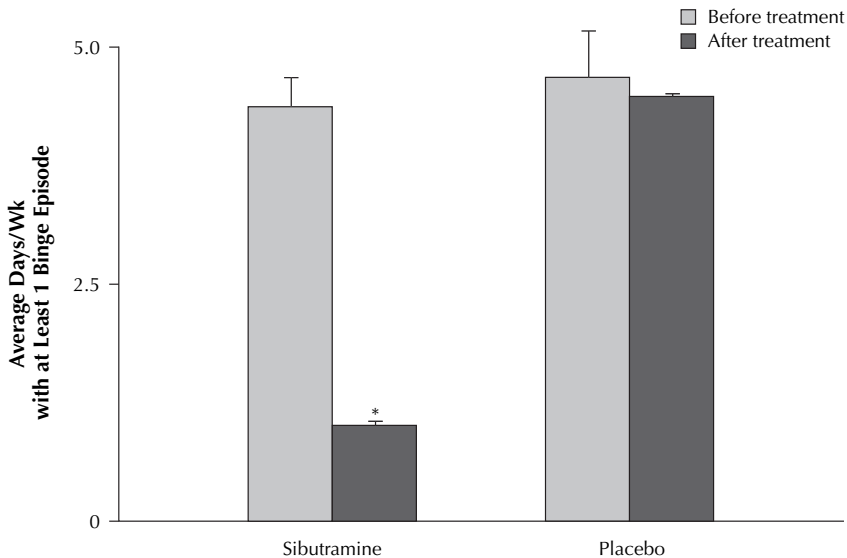
The primary outcome measure was the binge frequency, defined as the average number of days per week during which at least 1 binge-eating episode occurred. In addition, the patients' Body Esteem Scale (BES) scores and consistency of weight control throughout the study were assessed.

RESULTS

All patients in the 2 groups completed the trial. Among the women given sibutramine, the average (\pm SD) binge frequency was reduced from 4.4 (1.0) days/week to 1.0 (1.0) day/week by the end of the study ($P < .001$). Among those given placebo, however, the binge frequency did not change significantly (from 4.7 [1.3] days/week to 4.4 [0.5] days/week) (Fig 1). The average (\pm SD) BES score among patients given sibutramine was reduced significantly from 28.4 (3.6) to 17.4 (3.5) ($P < .001$), whereas the score among patients given placebo did not change significantly (dropping from 29.4 [3.6] to 28.7 [2.3]) (Fig 2). The average (\pm SD) weight reduction among women given sibutramine was 4.48 (2.1) kg, whereas among those given placebo, it was 0.59 (.05) kg (Fig 3).

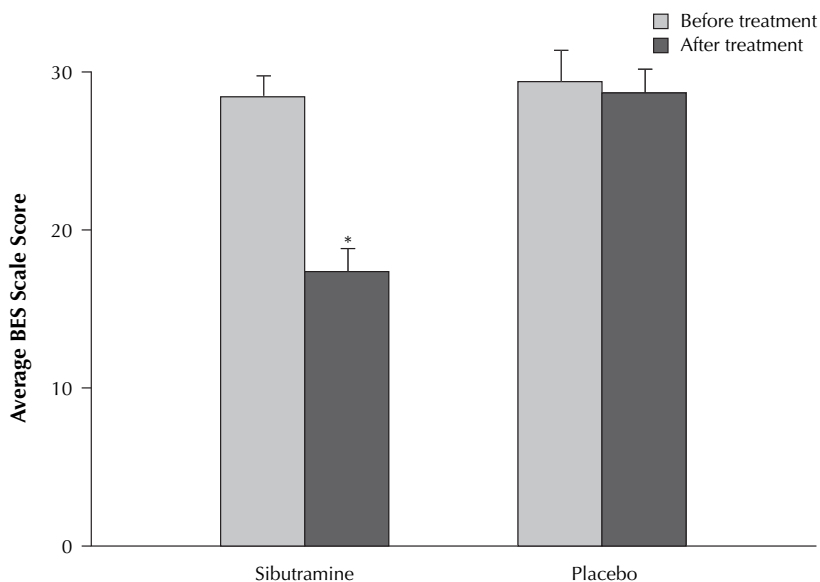
No significant adverse reactions occurred among patients given sibutramine. Among those who demonstrated an adverse event, 40% had dry mouth, 20% had constipation, and 10% had tachycardia, insomnia, cephalalgia, or nausea. Among patients given placebo who had an adverse reaction, 50% demonstrated anxiety, 20% sedation, and 10% cephalgia, insomnia, or constipation.

Fig 1. Mean (\pm SD) binge frequency reduction with sibutramine (10 mg/kg/day) and placebo after 12 weeks.



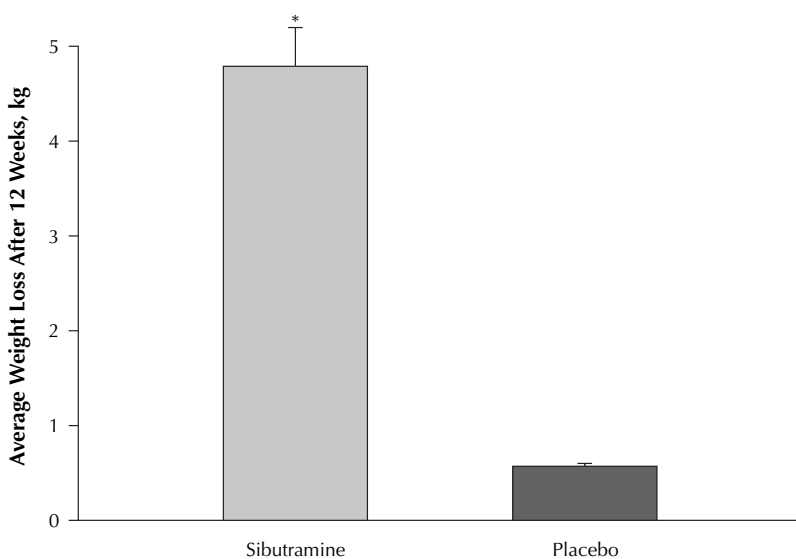
* $P < .001$ vs placebo

Fig 2. Mean (\pm SD) BES score reduction with sibutramine (10 mg/kg/day) and placebo after 12 weeks.



* $P < .001$ vs placebo

Fig 3. Mean (\pm SD) weight reduction with sibutramine (10 mg/kg/day) and placebo after 12 weeks.



* $P < .001$ vs placebo

CONCLUSIONS

In this study, sibutramine was efficacious and well tolerated in controlling both binge-eating disorder and obesity. The importance of weight control cannot be overlooked in the treatment of binge-eating disorder. Even when overweight is the only ostensible consequence of the disorder, it must be addressed as aggressively as the gorging impulse, since a patient's self-image and the prevention of obesity-related sequelae are critical in maintaining the long term the benefits gained from therapy. This integrated approach to the treatment of binge-eating disorder is the distinctive advantage of sibutramine, which, owing to its unique mechanism of action, addresses the 3 main goals in the treatment of binge-eating disorder: reducing the frequency of binge eating, promoting and maintaining weight loss, and treating the comorbid psychiatric conditions.

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