Double-Blind, Randomized, Placebo-Controlled Trial of Topiramate Plus Cognitive-Behavior Therapy in Binge-Eating Disorder

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Objective: To evaluate the efficacy and tolerability of adjunctive topiramate compared to placebo in reducing weight and binge eating in obese patients with binge-eating disorder (BED) receiving cognitive-behavior therapy (CBT).

Method: A double-blind, randomized, placebo-controlled trial of 21 weeks' duration was conducted at 4 university centers. Participants were 73 obese (body mass index ≥ 30 kg/m^2) outpatients with BED (DSM-IV criteria), both genders, and aged from 18 to 60 years. After a 2- to 5-week run-in period, selected participants were treated with group CBT (19 sessions) and topiramate (target daily dose, 200 mg) or placebo (September 2003–April 2005). The main outcome measure was weight change, and secondary outcome measures were binge frequencies, binge remission, Binge Eating Scale (BES) scores, and Beck Depression Inventory (BDI) scores.

Results: Repeated-measures random regression analysis revealed a greater rate of weight reduction associated with topiramate over the course of treatment ($p < .001$), with patients taking topiramate attaining a clinically significant weight loss (–6.8 kg) compared to patients taking placebo (–0.9 kg). Although rates of reduction of binge frequencies, BES scores, and BDI scores did not differ between groups during treatment, a greater number of patients of the topiramate plus CBT group (31/37) attained binge remission compared to patients taking placebo (22/36) during the trial ($p = .03$). No difference between groups was found in completion rates; 1 patient (topiramate group) withdrew for adverse effect. Paresthesia and taste perversion were more frequent with topiramate, and insomnia was more frequent with placebo ($p < .05$).

Conclusions: Topiramate added to CBT improved the efficacy of the later, increasing binge remission and weight loss in the short run. Topiramate was well tolerated, as shown by few adverse events during treatment.

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Binge-eating disorder (BED) is an eating disorder not elsewhere specified that is characterized by recurrent, uncontrollable, and distressing binge eating that is not associated with those compensatory behaviors seen in bulimia nervosa.[1] The estimated prevalence of BED in the general population ranges from 1.0% to 3.3%.[2–5] Although BED is not limited to obese individuals, it is a common diagnosis in this group[2,3,6,7] that seems to be more prevalent as the degree of obesity increases.[4,5,8,9]

Three main focuses in the treatment of obese subjects with BED are usually targeted: control of binge-eating behavior, improvement of psychological distress and associated psychiatric symptoms, and promotion of weight loss.[10,11] Cognitive-behavior therapy (CBT) used in the treatment of bulimia nervosa has been adapted and tested in BED with positive results.[12–14] CBT is regarded by some investigators as the best established intervention for BED.[15] In controlled trials, CBT showed considerable reduction of binge eating (reaching 94% decrease)[13] and variable recovery rates (28% to 79%).[13,14,16,17] Although CBT has also shown efficacy in improving associated psychopathology, impact on weight is usually

low and related to cessation of binge eating during the treatment.[14,16–18]

Many classes of drugs have been investigated in short-term controlled trials for the treatment of BED,[19,20] including antidepressants, antiobesity agents, and anticonvulsants. Although reduction of binge-eating behavior and weight loss were generally obtained, clinically significant weight losses were not the rule, with a few exceptions.[21–23]

Topiramate is a broad-spectrum neurotherapeutic agent approved for use in epilepsy and prophylaxis of migraine that has also been studied in many psychiatric conditions.[24] There is an increasing interest about the usefulness of topiramate in BED, considering its possible effect on eating behavior and weight and on impulsive and mood disorders, which are frequent comorbidities of BED.[23–25] Topiramate has shown weight loss properties in at least 6 placebo-controlled obesity trials.[26]

Although considered an interesting therapeutic strategy, combination of medication and psychotherapy have not been widely investigated in BED. Available clinical trials suggest that combining antidepressants and CBT does not systematically add to the effect of CBT in reducing binge eating,[17,27–29] but they can augment weight loss beyond the effects of psychotherapy[17,30] or antidepressants alone,[27] although usually modestly. One recent study[28] reported increased binge remission with fluoxetine plus CBT compared to medication alone, with no enhanced weight loss.

The aim of this trial is to investigate the efficacy and tolerability of adjunctive topiramate with CBT in obese patients with BED through improvement in binge eating, related psychopathology, and weight loss.

METHOD

Subjects

Study participants were 73 obese adults (aged from 18 to 60 years) of both genders, with a body mass index ([BMI]: weight[kg]/height[m^2]) ≥ 30 kg/m^2 who met DSM-IV-TR criteria[1] for BED. To ensure that patients had at least a moderate severity level of binge eating, only those with a score > 17 on the Binge Eating Scale (BES)[31,32] were accepted (inclusion criteria). Participants were patients spontaneously seeking treatment or subjects recruited through media advertisements.

Exclusion criteria were prior exposure or known contraindication for use of topiramate; exposure to any other experimental drug within 1 year prior to enrollment; pregnancy, lactation, or not using a medically accepted form of birth control; clinically significant or unstable psychiatric disorders (e.g., schizophrenia, major affective disorders, alcohol or drug abuse, or a high potential suicidal risk) or medical illnesses (e.g., seizures, renal impairment, glaucoma); history of nephrolithiasis; previous surgical procedures that cause weight loss; recent smoking cessation or intention to quit; and concurrent use (on a regular basis, within 3 months of study entry) of drugs such as antipsychotics, cyproheptadine, antiepileptics, systemic steroids (except for menopause hormone replacement therapy or contraception), antiobesity agents, antidiabetes agents, and those that interfere with gastrointestinal movements and other agents. Use of antidepressants, lithium, or thyroid hormones was allowed if doses were stable for at least 3 months. An additional exclusion criterion was enrollment in any kind of psychotherapy aiming at weight loss or eating disorders treatment within 3 months of entry to the study.

The protocol was approved by ethics committees in all 4 centers in Brazil: Federal Universities of São Paulo (São Paulo), Rio de Janeiro (Rio de Janeiro), and Bahia (Salvador) and the State University of São Paulo (São Paulo). Written informed consent was obtained from patients prior to performance of any study-related procedure. The study was conducted from September 2003 through April 2005.

Study Design

This was a 21-week multicenter, double-blind, parallel-group, randomized controlled trial comparing the efficacy and tolerability of an add-on treatment with 200 mg/day of topiramate versus placebo in obese patients with BED receiving group CBT. Randomly assigned patients were those who still met inclusion criteria for the study after a 2- to 5-week run-in phase in which they received placebo (single-blind).

During the run-in phase, laboratory assessments and electrocardiogram tests were performed. Patients were given a food diary and instructed to register their consumption during the final week of the run-in phase and throughout the study. Binge-eating behavior was also explained, and they were asked to highlight these episodes in the diary. Placebo responders were subjects who did not present at least 2 binge episodes during the final week of the run-in phase.

The sample size was determined based on the mean weight reduction from a topiramate randomized control trial,[23] considering an $\alpha = .05$ and power = 0.80, and the estimated sample size was 70 subjects. Randomization procedures were performed at an independent facility from the sites (Janssen-Cilag Farmacêutica, São Paulo, Brazil).

Patients were randomly assigned by clusters of 10 subjects through a computer-generated randomization table to either active drug or placebo in a 1:1 ratio basis. Seventy-three patients showed up at the first CBT session and received randomized medication (Figure 1). To ensure concealment of allocation, medication supplied by the manufacturer was provided in coded containers with identical-appearing capsules of 25 mg or 50 mg of topiramate or placebo.

Patients randomly assigned to the active medication received 25 mg of topiramate at bedtime for 14 days. The daily dose was then increased by 25-mg increments every 14 days, up to 150 mg, and, henceforth, by weekly increments of 25 mg until the target dose of 200 mg. At that point, patients who presented ≤ 5% reduction in baseline weight or < 50% reduction in the number of days with binge episodes were prescribed additional increments of 25 mg weekly until they reached the maximum dose of 300 mg daily. Dose reductions were allowed for patients who did not tolerate their current dose (minimum dose required = 25 mg daily).

Patients received 19 sessions of CBT (adapted Fairburn model for BED)[33,34] in groups of 10 patients treated consecutively in each center (2 CBT groups per center). Groups were led by a therapist and a cotherapist that were previously trained (in 2 pilot groups each) and were supervised during treatment by a specialist in CBT (M.D.). All sessions were videotaped and discussed with the supervisor every week to ensure adherence to the CBT manual.[33] CBT sessions lasted 90 minutes and were weekly until the 3 last sessions, which occurred every other week.

Patients' weight, food diary records, and homework were reviewed by therapists in each session for therapeutic purposes and to check adherence to the CBT. Adverse events and medications were registered in the diaries and also reported at every session. Nutritional counseling was not offered apart from the recommendations that were given during the CBT sessions. Subjects were withdrawn from the trial if they were absent for more than 4 sessions.

Diagnostic Assessment and Outcome Measures

Before inclusion, patients underwent a comprehensive clinical and psychiatric assessment by trained study technicians. BED diagnosis was confirmed by the *Structured Clinical Interview for DSM-IV Axis I Disorders*–Patient Edition (SCID I/P).[35] In terms of binge eating definition, to standardize the amount of food eaten during an episode, a minimum of 1000 calories (based on a manual for counting calories) per binge was also required for screening purposes and throughout the study. Evaluation of binge episodes was done at the study visits by trained dieticians and physicians blind to treatment condition.

For the diagnosis of obesity, subjects had their height and weight measured at baseline while wearing light clothes; those with a BMI ≥ 30 were considered eligible for the trial and required to wear light clothes to all study visits. In each center, calibrated balance beam scales and stadiometers were used for these measurements.

Initial evaluation also investigated associated psychiatric morbidities with the short structured diagnostic interview Mini-International Neuropsychiatric Interview (MINI Plus) (based on DSM-IV and ICD-10).[36] The Beck Depression Inventory (BDI),[37] a self-report questionnaire, was used to assess depressive symptoms at the screening stage and during the trial.

The primary efficacy measure was weight change. Secondary outcome measures included BMI, binge frequencies, BES scores, depressive symptoms (BDI scores), and treatment tolerability. The main measure of binge frequency was "binge day" frequency, which was based on the number of days per week in which patients had at least 1 binge-eating episode (DSM-IV-TR criteria). Assessment of binge frequency was done by means of food diary records considering the 7 days previous to each visit. The outcome *remission* was defined as cessation of binge eating during treatment, evaluated by the absence of binge episodes in the food diary records of the last week of the trial (week 21).

Tolerability was investigated through reported adverse events and dropouts, and reasons for leaving the study were analyzed.

All primary and secondary outcomes were measured at baseline and at 5 time points (weeks 3, 7, 13, 17, and 21) as were evaluation of safety (through physical examination and laboratory tests), medication dosage, and medication compliance (by means of drug count).

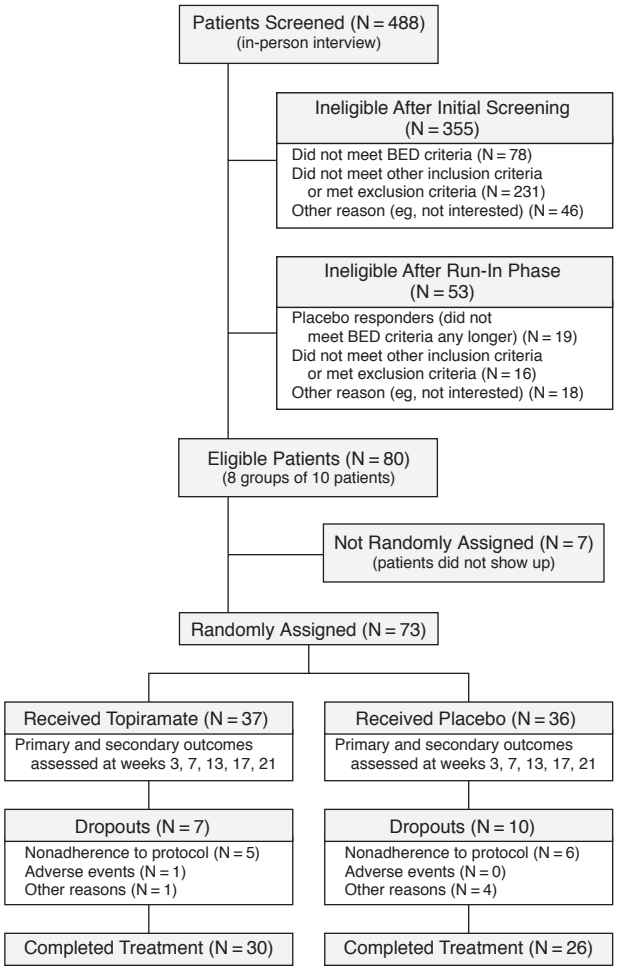
Statistics Analysis

Statistical analysis was performed blind to treatment allocation and under the main investigator's (A.M.C.) supervision. All statistical tests were interpreted at the 5% significance level (2-tailed). Baseline characteristics of groups were compared using Student t test for continuous variables and the χ^2 test for categorical variables.

The temporal change of response to treatment was examined through repeated-measures random regression analysis[38,39] using the SAS software,[40] version 8.0. Analyses were intention-to-treat, including dropouts at all time points (all randomly assigned subjects irrespective of their compliance to protocol). The main analysis of efficacy compared the rate of change in weight between groups during treatment (SAS PROC MIXED); the same analysis was performed for the other continuous variables: BMI, binge frequencies (binge days/wk and binge episodes/wk), BES, and BDI. Weight was log transformed as were binge episodes and binge days (log [binges + 1]). Analysis included terms for treatment, time (0, 3, 7, 13, 17, and 21 weeks), center, treatment-by-time interaction, and treatment-by-center interaction.

A time-trend analysis was conducted, with the term "treatment-by-time interaction" being considered the main measure of interest (effect), as it estimates the difference in the rate of change. Time was treated as a continuous linear variable. For binge frequency analysis, time was expressed as log (weeks + 1) because change was much sharper in the beginning of the follow-up. For weight but not for the other outcomes, treatment-by-center interaction was statistically significant (p = .03).

Figure 1. Progress of Obese Patients With BED During the Study



Abbreviation: BED = binge-eating disorder.

This interaction was due to 1 center with a greater baseline mean weight among those taking placebo compared to those taking topiramate, whereas the other centers had a nonsignificantly greater weight at baseline in the topiramate group compared to placebo. After adjustment for weight at baseline, treatment-by-center interaction disappeared (p = .33). BMI and weight analysis included baseline values. Additionally, the weight loss during follow-up was quite similar for all 4 centers. Centers were kept in the analysis. As groups differed at baseline on age and history of major depression, all analyses were age-adjusted, and BDI analysis was also adjusted for history of major depression.

The covariance structure of the models (autoregressive, unstructured, and compound symmetry) was tested by the likelihood ratio test, and the unstructured covariance matrix appeared to be most adequate for all these data.

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

Variable	Placebo (N = 36)	Topiramate (N = 37)	p Value
Age, mean (SD), y	35.4 (10.7)	41.1 (9.9)	.02[a]
Female, N (%)	34 (94.4)	36 (97.3)	.54[b]
Race, white, N (%)	19 (52.8)	23 (62.1)	.64[b]
History of major depression, N (%)	10 (27.8)	16 (43.2)	.06[b]
Binge days/wk, mean (SD)	3.4 (1.3)	4.2 (3.4)	.18[a]
Binge episodes/wk, mean (SD)	3.8 (1.5)	4.7 (3.3)	.13[a]
Binge Eating Scale score, mean (SD)	26.5 (7.4)	27.2 (6.5)	.67[a]
Beck Depression Inventory score, mean (SD)	15.9 (9.4)	16.8 (8.3)	.67[a]
Weight, mean (SD), kg	98.4 (10.9)	96.6 (16.7)	.23[a]
Body mass index, mean (SD), kg/m^2	37.4 (3.5)	37.4 (4.9)	.93[a]

[a]By 2-tailed t test.
[b]By χ^2 test.
Abbreviation: BED = binge-eating disorder.

Intention-to-treat analysis of the outcome "remission of binge eating" was conducted with the last-observation-carried-forward (LOCF) method, using the χ^2 test. Additional analyses of those who completed 21 weeks of treatment were also performed.

RESULTS

Randomization and Patient Characteristics

From 488 volunteers screened, 80 potential patients were selected to participate in the trial. Only 73 patients showed up for randomization on the first CBT session: 37 were assigned to topiramate and 36 to placebo. Figure 1 gives details on reasons for exclusions and dropouts during the selection phase and the trial.

Groups differed at baseline on age and history of major depression, with the topiramate group being older and reporting more depression (Table 1). Even though patients were allowed to maintain their previous antidepressant or mood stabilizer treatments if doses were kept stable, no patient included in the trial was taking either of these classes of medications.

Weight Change Outcome

Random regression analyses revealed that, over the course of treatment, the topiramate × time interaction was statistically significant for weight loss (χ^2 = 16.1, p < .001) (Table 2, Figure 2A). At the final visit, the weight change was –6.8 kg in the topiramate group versus –0.9 kg in the placebo group, and mean weights were 89.8 kg (SD = 13.4) and 97.5 kg (SD = 10.5), respectively. Patients taking topiramate reached a final BMI of 35 kg/m^2 (SD = 3.5), and those taking placebo reached a final BMI of 36.7 kg/m^2 (SD = 4.7).

Among patients who completed treatment (N = 56), a statistically significant difference (p = .04) in mean

Table 2. Effect of Topiramate on Outcome Measures

Outcome Measure	Treatment-by-Time Interaction[a]	SE	p Value[b]
Weight, kg	–0.10	0.03	< .001
Body mass index, kg/m^2	–0.04	0.01	.0002
Binge days/wk	–0.02	0.02	.27
Binge episodes/wk	–0.03	0.03	.18
Binge Eating Scale	–0.40	0.54	.46
Beck Depression Inventory	0.66	0.52	.20

[a]Represents the difference in rate of change between the topiramate and placebo groups based on random regression analysis that included all randomly assigned subjects at all time points (including patients that dropped out before the end of the study).
[b]By χ^2 test.

percentage of weight loss was observed between groups: 6.8% (SD = 5.2) for the topiramate group (N = 30) versus 4.1% (SD = 4.3) for the placebo group (N = 26). At the end of the trial, a greater percentage of patients that took topiramate (33.3% or 11/30) attained a weight loss > 10% (a clinically significant weight loss) compared to those that took placebo (11.5% or 3/26) ($\chi^2 = 3.71$, p = .05) (Figure 2B).

Binge Eating Outcome

Binge-eating behavior (binge frequencies and BES scores) improved significantly (p < .001) from baseline in both groups.

During treatment, random regression analysis found no statistically significant difference for the rate of change of binge days/wk (Figure 2C), binge episodes/wk, or BES scores between treatments (Table 2). The mean frequency of binge days/wk was reduced from 4.2 (SD = 3.4) to 0.0 (SD = 0.2) in patients taking topiramate and from 3.4 (SD = 1.3) to 0.3 (SD = 0.6) in those taking placebo, and binge episodes/wk decreased from 4.7 (SD = 3.3) to 0.0 (SD = 0.2) for the topiramate group and from 3.8 (SD = 1.5) to 0.3 (SD = 0.8) for the placebo group. Dimensional evaluation of binge-eating behavior showed that mean BES scores decreased from 27.2 (SD = 7.4) to 7.5 (SD = 7.1) for the topiramate group and from 26.5 (SD = 7.4) to 8.6 (SD = 5.7) for the placebo group.

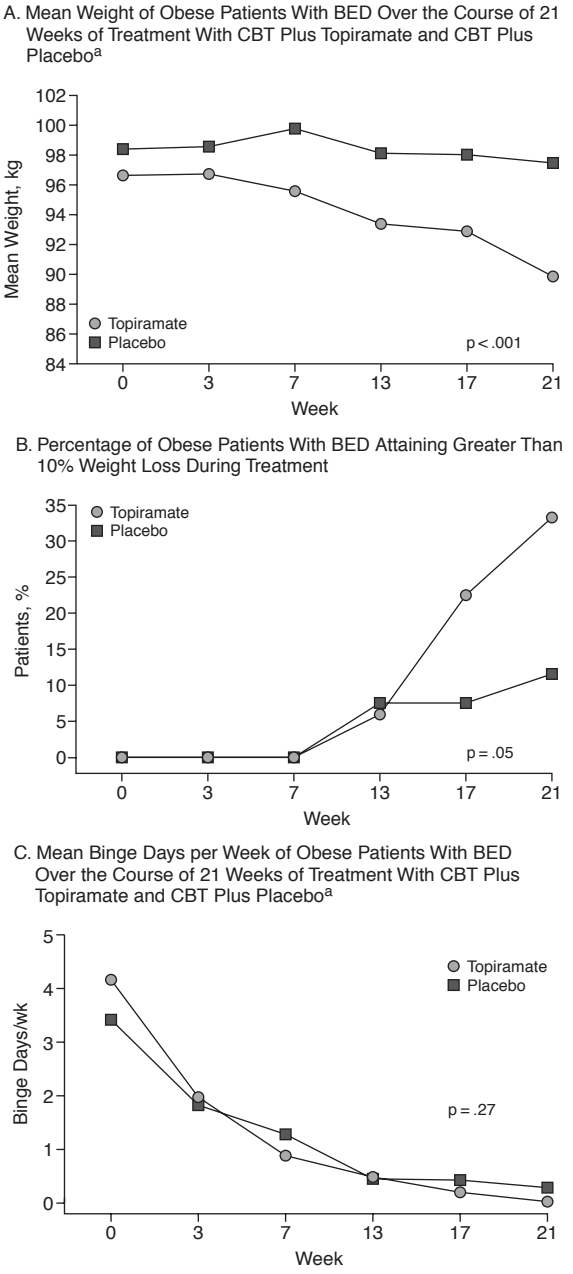
Secondary analysis of completers (N = 53) revealed that there was a slightly greater percentage of reduction of binge days/wk among those taking topiramate (99.5% [SD = 2.6], N = 29) compared to those taking placebo (92.9% [SD = 17.7], N = 24, p = .08).

A greater rate of remission of binge eating in the intention-to-treat group was found for patients taking topiramate, 83.8% (31/37), compared to 61.1% (22/36) for those taking placebo ($\chi^2 = 4.71$, p = .03); among completers, rates were 96.5% (28/29) and 83.3% (20/24), respectively ($\chi^2 = 2.68$, p = .1).

Depression Outcome

Depressive symptoms were significantly reduced (p < .001) from baseline in both treatment groups without attaining a statistically significant difference (p = .20) (Table 2). Mean BDI scores decreased from 16.8 (SD = 8.3) to 10.9 (SD = 7.0) in the topiramate group and from 15.9 (SD = 9.4) to 9.2 (SD = 6.9) in the placebo group.

Figure 2. Results of the Effects of CBT Plus Topiramate or Placebo in Obese Patients With BED



[a]p Values for time-by-time based on random regression analysis.
Abbreviations: BED = binge-eating disorder, CBT = cognitive-behavior therapy.

Completion Rates, Tolerability, and Safety

Fifty-six patients (76.7%) completed the trial; 7 patients (18.9%) of the topiramate group and 10 patients

Table 3. Adverse Events Reported by ≥ 10% of Obese Patients With BED Taking Topiramate or Placebo

	Topiramate (N = 37)		Placebo (N = 36)	
Adverse Event	N	%	N	%
Paresthesia	18	48.6*	4	11.1
Headache	19	51.3	19	52.8
Dyspepsia	3	8.1	5	13.9
Dizziness	11	29.7	7	19.4
Somnolence	8	21.6	10	27.8
Nervousness	4	10.8	7	19.4
Back pain	4	10.8	8	22.2
Nausea	8	21.6	3	8.3
Taste perversion	9	24.3*	0	0
Confusion	5	13.5	4	11.1
Diarrhea	2	5.4	7	19.4
Tooth pain	6	16.2	2	5.6
Constipation	5	13.5	2	5.6
Gases	1	2.7	4	11.1
Insomnia	1	2.7	6	16.7*
Edema	3	8.1	4	11.1
Dysuria	5	13.5*	0	0
Malaise	5	13.5	4	11.1
Eye pain	6	16.2	2	5.6
Leg pain	4	10.8*	0	0

*$p < .05$.
Abbreviation: BED = binge-eating disorder.

(27.8%) of the placebo group withdrew before the end of the study, a difference that did not reach statistical significance ($\chi^2 = 0.80$, $p = .37$). The reasons for discontinuation of treatment per group are described in Figure 1. The final mean daily dose of topiramate used (completers' analysis) was 205.8 mg (SD = 35.8) (range, 100–300 mg) and of placebo used was 208.6 mg (SD = 46.3) (range, 100–300 mg). There was only 1 dropout, in the topiramate group, that was due to adverse event: the patient took wrong doses of the medication and reported worsening of paresthesia, confusion, and feeling unable to control doses afterwards. Overall, topiramate was well tolerated, as shown by relatively few adverse events reported during treatment (Table 3). The adverse events that were more commonly reported by patients receiving topiramate (N = 37) compared to those receiving placebo (N = 36) ($p < .05$) were paresthesia, taste perversion, dysuria, and leg pain; insomnia occurred more often among those taking placebo compared to topiramate patients. No serious adverse events were reported during the trial as well as no significant changes in physical examination or laboratory tests. A test of integrity revealed that investigators correctly guessed the patient group in approximately 44% of the whole sample and in 35% of patients taking topiramate.

DISCUSSION

To the best of our knowledge, this is the first study that has assessed the combination of topiramate and psychotherapy in BED. This trial has shown that treatment with topiramate, when combined with CBT, produced a marked reduction in binge eating, as shown by 83.8% of the patients presenting binge remission and a significant decrease of BES scores (compared to baseline); it improved the associated depressive symptomatology (reduction of BDI scores) and promoted considerable weight loss. In this trial, patients treated with topiramate plus CBT, when compared to placebo plus CBT, presented a higher mean weight loss (–6.8 kg vs. –0.9 kg, respectively), a difference that was not only statistically ($p < .001$) but also clinically significant, as shown by the greater number of patients in the topiramate group that lost more than 10% of their baseline weight ($p = .05$). Additionally, the combination of topiramate and CBT was considered safe and well tolerated, evidenced by the high completion rate (81%) in this group, with no serious adverse events reported and only 1 withdrawal due to side effects.

Combining pharmacologic agents with psychological and/or nutritional interventions is a strategy frequently used and expected to improve the efficacy of each single approach.[41] Considering that CBT, one of the most extensively studied interventions for BED,[42] showed no significant impact in weight parameters most of the time[14,19,28,29] and that patients with BED tend to experience weight gain over time,[43] some authors have argued that weight stabilization is probably a more realistic goal in the treatment of this condition.[10,14] Although reasonable, this view is controversial, since obesity is associated with several medical problems and increased mortality. Thus, weight losses of at least 5% of body weight are generally pursued for its clinical impact in improving health and reducing risks.[44] The rationale for this study was in line with this view, and results suggest that the addition of topiramate can enhance the benefits of CBT by promoting a clinically significant weight reduction and greater remission of binge eating in the short run.

Many classes of medications have been studied in BED, but, besides topiramate, only sibutramine[21,45] and sertraline[22] produced clinically significant weight reductions in short-term trials along with greater rates of reduction of binge frequencies. In a 6-week trial[22] (N = 34), patients who took sertraline had a mean weight loss of 5.6 kg compared to 2.4 kg in the placebo group. Sibutramine was tested against placebo in 2 randomized controlled trials[21,45] of 12 weeks' duration. In the larger one (N = 60), sibutramine 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). These findings were confirmed in the smaller trial[45] (N = 20).

Most of the antidepressant trials in BED, however, were not able to show clear benefits of these medications in weight loss when added to psychotherapy[27–29] or when used as monotherapy.[46] The 2 more recent combination trials[28,29] used a 4-cell design and compared CBT plus fluoxetine, CBT plus placebo, and fluoxetine and placebo.

The first[28] enrolled 108 obese BED patients for 16 weeks and found CBT, but not fluoxetine, to demonstrate efficacy for the behavioral and psychological features of BED, with no effect on obesity; the authors reported a greater weight loss in patients of the CBT groups who remitted binge eating but not in those of the medication only groups. The second trial[29] included 116 patients during 20 weeks, all also treated with group behavioral weight control treatment (besides CBT and medication); all groups improved in binge eating and in both general and eating-related psychopathology, but they showed little weight loss; patients in the CBT groups attained more binge abstinence (cessation of binge eating), and abstainers lost more weight than nonabstainers. Two combination trials[17,27] with 108 patients each described some more positive results: the first one[17] found that adding desipramine enhanced the weight loss beyond the weight reduction achieved by CBT plus weight-loss treatment at the 12-month follow-up. The second study[27] reported a trend towards a greater weight reduction during treatment with fluoxetine and CBT or fluvoxamine and CBT compared to CBT only, but this improvement was partially lost at the 12-month follow-up.

In this trial, we could not find a statistically significant difference in the rate of reduction of binge frequencies among groups over the course of treatment. However, a higher percentage (~84%) of patients who received topiramate plus CBT (intention-to-treat analysis) achieved binge remission at the last week of trial compared to those treated with placebo plus CBT (61.1%). Among completers, the rate reached 96.5% of patients that took topiramate. This finding must be highlighted since cessation of binge eating seems to be an important goal in the treatment of BED due to its association with greater weight reduction and possible better prognostic value.[14,17,18,28,29]

Depressive symptoms and mood disorders are commonly associated with BED,[47] and binge eating has even been considered a marker of psychopathology among obese patients.[48] Although patients who took part in this trial presented light and not-medicated depressive symptoms, these symptoms were significantly reduced from baseline during treatment, but no difference was evident between groups.

Topiramate was well tolerated, as shown by the few adverse events reported during treatment and by the fact that most patients were able to take the target dose (mean dose used was ~206 mg). Initial trials[23,49] testing topiramate have reported a high discontinuation rate and higher incidence of adverse events. In the more recent and larger trial,[25] however, tolerability was better with a median dose of 300 mg/day. The good tolerability profile seen in this study might be explained by the slow drug titration, the low target dose, and the combination with CBT, which provided support to management of adverse events.

This study presents some important limitations: the sample size was relatively small, hence, the power to detect smaller interactions of CBT plus topiramate might have been compromised; generalization of these findings is limited as the exclusion criteria used were broad (one criterion precluded obese subjects with medical problems, which represent a great proportion of obese patients, from participating; in addition, patients with serious psychiatric comorbidities, who usually take psychotropic drugs that might lead to weight gain[44] were not included); and, as in other trials, most participants were women. On the other hand, the study was multicenter and thus was able to comprehend the huge cultural diversity present in a continental country like Brazil, and, in comparison to other trials, it included more nonwhite subjects (~43%). Finally, this was also a short-term trial (21 weeks), as are most trials in BED. Since BED has an intermittent course,[12,43] with relapses and remissions, a short-term trial may not be able to detect maintenance of response in the long run. It has been demonstrated that CBT provides consistent changes in cognitive and behavioral aspects of BED, benefits that seem to be kept for longer periods.[14,27] Therefore, sustained binge remission and weight loss with CBT plus topiramate are targets that need to be addressed in longer trials for a better definition of the role of this approach in the treatment of obese patients with BED.

CONCLUSIONS

This study showed the efficacy of adjunctive topiramate with CBT in obese patients with BED, with a good tolerability profile. Topiramate plus CBT produced significant binge remission and weight reduction, when compared to placebo, besides the marked improvement in related psychopathology.

Drug names: desipramine (Norpramin and others), fluoxetine (Prozac and others), sertraline (Zoloft and others), sibutramine (Meridia), topiramate (Topamax and others).

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