In the originally published article, Figures 1 and 2 on page 1901 were incorrectly shown with lines connecting week 16 to endpoint.

Zonisamide in the Treatment of Binge Eating Disorder With Obesity: A Randomized Controlled Trial

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Objective: Binge eating disorder (BED) is associated with obesity. Zonisamide is a novel antiepileptic drug associated with weight loss. The purpose of this study was to evaluate zonisamide in the treatment of BED associated with obesity.

Method: In this 16-week, single-center, randomized, double-blind, placebo-controlled, flexible-dose (100–600 mg/day) trial, 60 outpatients with DSM-IV-TR BED received zonisamide (N = 30) or placebo (N = 30). The primary outcome measure was weekly frequency of binge eating episodes. The primary analysis of efficacy was a longitudinal analysis of the intent-to-treat sample, with treatment-by-time interaction as the effect measure. Patients were enrolled from September 5, 2003, through October 1, 2004.

Results: Compared with placebo, zonisamide was associated with a significantly greater rate of reduction in binge eating episode frequency ($p = .021$), body weight ($p < .001$), BMI ($p = .001$), and scores on the Clinical Global Impressions-Severity scale ($p < .001$), Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating ($p < .001$), and Three Factor Eating Questionnaire disinhibition scales ($p < .001$). Plasma ghrelin concentrations increased with zonisamide but decreased with placebo ($p = .001$). The mean (SD) zonisamide daily dose at endpoint evaluation was 436 (159) mg/day. Twelve patients (N = 8 receiving zonisamide, N = 4 receiving placebo) discontinued because of adverse events. The most common reasons for discontinuing zonisamide were accidental injury with bone fracture (N = 2), psychological complaints (N = 2), and cognitive complaints (N = 2).

Conclusion: Zonisamide was efficacious, but not well tolerated, in the short-term treatment of BED associated with obesity.

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Binge eating disorder (BED) is characterized by recurrent and distressing episodes of binge eating without the inappropriate compensatory weight loss behaviors of bulimia nervosa or anorexia nervosa.[1,2] Mounting evidence indicates that BED is an important public health problem. Its prevalence in the U.S. general population is estimated to be 1% to 2%,[3,4] and it is associated with psychopathology,[5,6] obesity, and other types of medical comorbidity,[4,7–10] impaired quality of life,[11] and disability.[4]

BED's association with obesity appears to be particularly strong. There is an elevated prevalence of BED in persons presenting for weight management and bariatric surgery,[2,8,12,13] and, conversely, an elevated prevalence of obesity, especially severe obesity (a body mass index [BMI] ≥ 40 mg/kg^2), among individuals with BED.[4,14] Familial factors underlying BED, which likely include genetic factors, may contribute to the development of severe obesity.[14] Moreover, abnormalities in the appetite control system, including melanocortin-4 receptor gene (*MC4R*) variants, altered gastric capacity, and dysregulation of the orexigenic hormone ghrelin, may be involved in BED associated with obesity.[15–17]

No treatments are currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of BED. Treatment objectives for BED include reduction of binge eating, weight loss or prevention of further

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weight gain, and management of comorbid psychopathology and medical conditions.[2,18–24] The National Institute for Clinical Excellence (NICE) guidelines[25] from Britain recommend the use of cognitive-behavioral and interpersonal therapies and selective serotonin reuptake inhibitor (SSRI) antidepressants. All of these treatments have limitations. Both cognitive-behavioral therapy and interpersonal therapy often result in reduced binge eating and associated psychopathology but usually are not associated with statistically significant weight loss.[18,19,22–24] By contrast, although several SSRIs were associated with statistically significant reductions in binge eating and weight in placebo-controlled, short-term monotherapy trials,[20,21,26–29] fluoxetine was ineffective for binge eating and weight loss in 2 controlled studies that compared it with cognitive-behavior therapy.[22,23] Three treatments have been shown in controlled trials to significantly reduce both binge eating and body weight: orlistat with cognitive-behavior therapy,[30] sibutramine,[31,32] and topiramate.[33,34] All 3 medications, however, are associated with side effects that may be problematic for some patients. These include gastrointestinal complaints for orlistat, increased blood pressure and pulse for sibutramine, and neurologic effects for topiramate.[35,36] Novel treatments that reduce both binge eating and weight are therefore needed for BED, especially when it is associated with obesity.

Several lines of evidence suggested to us that zonisamide—a structurally and pharmacologically novel antiepileptic drug—might be a useful treatment for BED.[37] First, zonisamide was associated with anorexia and weight loss in clinical trials in epilepsy patients[38–40] and has been shown to be superior to placebo in inducing weight loss in 1 study in patients with obesity without psychopathology.[41] Second, zonisamide has effects on several neurotransmitter systems involved in regulating eating behavior.[42,43] These include the serotonin, dopamine, and glutamate systems.[38,41,44–47] Third, a range of antidepressants has been reported to reduce binge eating in BED and the related condition bulimia nervosa,[20,21,48] and preliminary observations suggest zonisamide may have therapeutic thymoleptic properties, including antidepressant effects in bipolar disorder.[49,50]

These observations led us to conduct an open-label trial[37] of zonisamide in 15 patients with BED, which suggested that the drug was effective in reducing binge frequency, obsessive-compulsive symptoms related to binge eating, illness severity, and body weight in this patient population. The objective of the present study was to replicate the earlier open-label study in a larger controlled trial. We therefore conducted a single-center, randomized, parallel-group, placebo-controlled, flexible-dose study to assess the efficacy and safety of zonisamide during a 16-week course of treatment in 60 outpatients with BED associated with obesity. We also compared the effects of treatment with zonisamide and treatment with placebo on fasting plasma leptin and ghrelin concentrations and various metabolic measures in this patient group.

METHOD

Patients

Study participants were outpatients at the University of Cincinnati Medical Center who were recruited by radio and newspaper advertisements requesting volunteers for a study of a medication for binge eating and obesity. Patients were enrolled into the study if they met the following inclusion criteria: were male or female between 18 and 62 years; met DSM-IV-TR criteria for BED[1]; were obese, defined as having a BMI ≥ 30 kg/m^2 (reference 51); and had ≥ 2 days with binge eating episodes (binge days) in the week before receiving study medication, which were confirmed with prospective diaries (see Outcome Measures).

Patients were excluded from study participation if they met any of the following criteria: (1) had concurrent anorexia nervosa or bulimia nervosa (per DSM-IV-TR criteria); (2) had a substance use disorder (per DSM-IV-TR criteria) within 6 months of study entry; (3) had a lifetime history of a psychotic disorder, a bipolar disorder, or dementia or other cognitive disorder (per DSM-IV-TR criteria); (4) had a personality disorder that could interfere with diagnostic assessment, treatment, or compliance (the presence of which was determined clinically during the screening process); (5) displayed clinically significant suicidality or homicidality; (6) had received cognitive-behavioral therapy or interpersonal psychotherapy or behavioral weight management for BED within 3 months of study entry; (7) had a clinically unstable medical illness; (8) had a history of seizures, including childhood febrile seizures; (9) had a history of nephrolithiasis; (10) had clinically significant laboratory or electrocardiogram abnormalities; (11) received psychoactive medication (other than hypnotics, e.g., zolpidem or zaleplon, as needed for insomnia) within 2 weeks of study medication initiation; or (12) had previously been treated with zonisamide. Female patients were excluded if they were pregnant, lactating, or, if fertile, not practicing a form of medically accepted contraception.

The Institutional Review Board at the University of Cincinnati Medical Center approved the study protocol, and the study was conducted in compliance with the Declaration of Helsinki. All patients signed approved written informed consent forms after the study procedures had been fully explained and before any study procedures were performed. Patients were enrolled from September 5, 2003, through October 1, 2004.

Study Design

This was a 16-week, outpatient, randomized, double-blind, parallel-group, flexible-dose study conducted at the University of Cincinnati Medical Center. The trial consisted of 3 phases: a 1- to 2-week screening period, a

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16-week double-blind treatment period, and a 1-week treatment discontinuation period. Patients were evaluated at least twice during the screening period; after 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, and 16 weeks during the treatment period; and 1 week after study medication discontinuation.

The screening evaluation included an interview for demographic and clinical information and medical, psychiatric, and family histories; the Structured Clinical Interview for DSM-IV-TR (SCID)[52] to establish BED and comorbid Axis I diagnoses; a physical examination; vital signs; height and weight; electrocardiogram; fasting routine blood chemical and hematological tests and plasma leptin and ghrelin concentrations; and urinalysis. At this evaluation and each of the following visits, patients were given take-home diaries in which to record any binges and, once study medication was initiated, the number of capsules taken on a daily basis. At the last visit of the screening period (the baseline assessment), patients were evaluated to see if they continued to meet entry criteria. Patients continuing to meet these criteria were enrolled in the treatment period and randomly assigned in a 1:1 ratio to therapy with zonisamide or placebo. At each visit following the baseline visit, patients were assessed for number of binges experienced since the last visit, other outcome measures, medication dose, medication compliance ascertained by capsule count, adverse events, use of non-study medications, vital signs, and weight.

All study medication was in identical 100-mg capsules supplied in numbered containers and dispensed to patients according to a predetermined randomization schedule. Study medication was encapsulated and randomized by the hospital research pharmacy. Zonisamide was begun at 100 mg/day for the first 7 days. The dosage could then be increased, as tolerated, by 100 mg/day every 7 days to a maximum of 600 mg/day. For the last 4 weeks of the treatment period (weeks 13–16), study medication dose was not changed unless a medical reason (e.g., adverse event) necessitated such a change. Study medication could be reduced to a minimum of 100 mg daily because of bothersome side effects at any time during the 16-week treatment period. Patients took all their daily dose of study medication in the evening. However, if patients preferred, they could take half of the daily dose in the morning.

Outcome Measures

The primary outcome measure was the weekly frequency of binge eating episodes (binge frequency), defined as the mean number of binges per week in the interval between visits (total number of binges in the interval divided by number of days in the interval, and then multiplied by 7). Binges were defined using DSM-IV-TR criteria[1] and assessed via clinical interview and review of patient take-home diaries, upon which patients recorded binges, duration of binges, and food consumed during binges (so that binges could be confirmed by the research assistant and physician investigator working with that particular patient). Secondary outcome measures were weekly frequency of binge days (days when the patient had 1 or more binges); weight (kg); body mass index (BMI, calculated by dividing body weight in kg by height in m^2); Clinical Global Impressions-Severity scale (CGI-S) and -Improvement scale (CGI-I)[53] scores; Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (YBOCS-BE)[54] scores; Three Factor Eating Questionnaire (TFEQ)[55] scores; and Hamilton Rating Scale for Depression (HAM-D)[56] total scores. The patient's weight was obtained on the same scale zeroed at each measurement with the patient in light clothing and without shoes. The YBOCS-BE is a modified version of the Yale-Brown Obsessive Compulsive Scale[54] used in previous pharmacotherapy studies of BED[26–29,33,34,36,37] (and available from the authors on request) that measures obsessiveness of binge eating thoughts and compulsiveness of binge eating behaviors. The TFEQ (also called the Eating Inventory) is a self-report questionnaire that measures 3 dimensions of eating behavior thought to be dysregulated in eating disorders and obesity: cognitive restraint in eating (cognitive restraint), susceptibility to periodic disinhibition of control over eating (disinhibition), and perceived hunger (hunger).[55] Also, as done in many previous pharmacotherapy studies in BED, we tabulated response categories based on percentage decrease in frequency of binges from baseline (the week before treatment initiation) to endpoint (the final week of treatment). Response categories were defined as follows: remission = cessation of binges; marked = 75%–99% decrease; moderate = 50%–74% decrease; and none = less than 50% decrease. In addition, we assessed time to recovery, defined as the first 4 consecutive weeks during which the patient had no binge eating episodes.

By using commercial radioimmunoassay kits (Linco, Inc., St. Louis, Mo.), leptin and ghrelin concentrations were measured on fasting plasma samples obtained from the screening and week 16 visits (or the last treatment visit if the patient terminated the trial prematurely). The assays were performed according to the manufacturer's recommended protocol, and results of standards and controls were within the range of expected values.

The following safety measures were assessed: adverse events, clinical laboratory data, physical examination findings, and vital signs. Adverse events were obtained through spontaneous patient reporting and by open-ended inquiring by investigators. Reportable adverse events were new symptoms or illnesses that occurred during the treatment phase as well as those that increased in severity compared with baseline.

Statistical Methods

The baseline characteristics of each group were compared by using Fisher exact test for categorical variables and independent-samples t tests for continuous variables.

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Table 1. Baseline Characteristics of Patients With Binge Eating Disorder Randomly Assigned to 16 Weeks of Double-Blind Treatment With Zonisamide or Placebo

	Treatment Group			
	Zonisamide N = 30		Placebo N = 30	
Characteristic	Mean	SD	Mean	SD
Age, y	44.8	9.3	43.0	10.7
Binges/wk	4.7	1.4	4.4	2.0
Binge days/wk	3.9	1.1	3.9	1.3
Duration of BED, y	19.0	13.8	17.9	12.9
Assessment scores				
CGI-S	4.7	0.5	4.5	0.7
HAM-D	4.4	4.4	4.9	5.5
YBOCS-BE	19.1	4.0	18.6	4.8
Obsessions	9.2	2.7	8.9	3.4
Compulsions	9.9	2.1	9.8	2.4
Weight, kg	118.0	30.7	112.8	24.3
Body mass index, kg/m^2	42.7	9.5	40.6	7.6
Leptin, ng/mL[a]	29.1	9.7	27.1	7.8
Ghrelin, ng/L[a]	995.7	216.0	934.7	212.0
	N	%	N	%
Female	27	90.0	26	86.7
White	23	76.6	20	66.7
Lifetime comorbid diagnosis				
Depressive disorder[b]	19	63.3	16	53.3
Anxiety disorder	9	30.0	7	23.3
Substance use disorder	5	16.7	3	10.0

[a]Measure obtained in 29 patients in each group.
[b]N = 5 patients in each group had a current depressive disorder diagnosis.
Abbreviations: BED = binge eating disorder, CGI-S = Clinical Global Impressions-Severity Scale, HAM-D = Hamilton Rating Scale for Depression, YBOCS-BE = Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating.

The primary analysis of efficacy was a longitudinal analysis comparing the rate of change of binge frequency during the treatment period between groups. The same analysis was applied to binge day frequency, weight, BMI, and scores on the CGI-S, YBOCS-BE, TFEQ, and HAM-D scales. The difference in rate of change was estimated by random regression methods, as described in Fitzmaurice et al.[57] and Gibbons et al.[58] and as used in 7 previous pharmacotherapy studies of BED.[26–29,31,33,34] We used a model for the mean of the outcome variable that included terms for treatment, time, and treatment-by-time interaction. Time was modeled as a continuous variable, expressed as the square root of days since randomization (baseline). For the analyses of binge frequency and binge day frequency, we used the logarithmic transformations log ([binges/wk] + 1) and log ([binge days/wk + 1]), respectively, to normalize the data and stabilize the variance. To simultaneously account for individual differences in initial level of the outcome, rate of change over time, and serial autocorrelation (i.e., the tendency for correlation among observations to decrease as a function of the amount of time between them), we used the SAS procedure MIXED (SAS Institute, Inc., Cary, North Carolina), with random intercept and slope terms, and a first-order antedependence structure for the residual correlation matrix. The longitudinal analyses were intent-to-treat, using all available observations from all time points from all patients who completed a baseline evaluation.

Several secondary analyses were also performed. Change scores from baseline to endpoint, using the last observation carried forward (LOCF), were computed for each measure (on the logarithmic scale for the binging measures) and independent-samples t tests were used to compare these changes between the treatment groups. Categorical response to treatment (as defined above) was also analyzed for the intent-to-treat and completer groups, using the Cochran-Armitage exact trend test for 2-by-k ordered tables in SAS (PROC FREQ). Time to recovery (defined as the first 4 consecutive binge-free weeks after baseline) was analyzed with a Cox proportional hazards model for the intent-to-treat population.

For laboratory measures, including weight, leptin, and ghrelin, we computed the mean difference between endpoint and baseline measures and then compared the treatment groups using the t test. We calculated the correlation between percentage change in binge frequency and change in weight using rank-transformed data (Spearman rank correlation).

All statistical tests and confidence intervals were 2-sided, $\alpha = .05$.

RESULTS

Overall, 83 patients were screened; 23 patients were not enrolled because they chose not to participate (N = 12) or did not meet entry criteria (N = 11), and 60 patients who met entry criteria were randomly assigned to zonisamide (N = 30) or placebo (N = 30). Fifty-three patients were women, 43 were white, and 17 were African-American. Depressive disorders were the most common co-occurring psychiatric disorders, occurring in 35 (58.3%) patients as lifetime diagnoses and currently in 10 (16.7%) patients. No patient had a prior history of bulimia nervosa or anorexia nervosa. At baseline, there were no significant differences between the treatment groups in demographic or clinical variables (Table 1).

Fifty-seven patients (28 receiving zonisamide and 29 receiving placebo) had at least 1 post-randomization efficacy measure. Eighteen patients (60%) in the zonisamide group and 12 patients (40%) in the placebo group did not complete all 16 weeks of treatment (Fisher exact p = .20). Twelve patients withdrew from the study for the following reasons: adverse events (zonisamide, N = 8; placebo, N = 4), lack of efficacy (zonisamide, N = 1), and difficulties with protocol adherence (zonisamide, N = 9; placebo, N = 8). The latter specifically included those patients in the zonisamide group that withdrew because they had work obligations (N = 1), were lost to follow-up (N = 4), and chose to withdraw (N = 4) and

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Figure 1. Mean Binge Frequency Over 16 Weeks of Treatment in Patients With Binge Eating Disorder Randomly Assigned to Zonisamide or Placebo

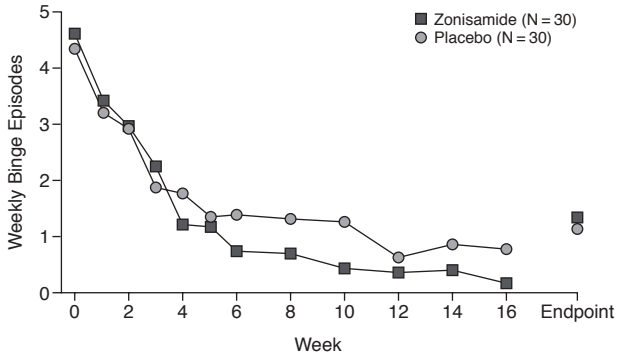

Figure 2. Weight Loss in Patients With Binge Eating Disorder Randomly Assigned to 16 Weeks of Double-Blind Treatment With Zonisamide or Placebo

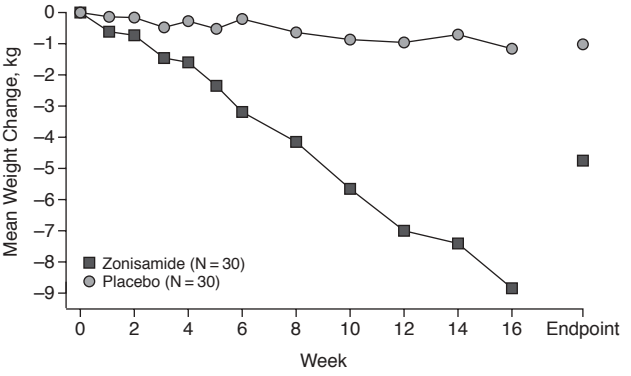

Table 2. Mean Model-Based Differences Between Zonisamide and Placebo Groups in Change From Baseline to Week 16 for Patients With Binge Eating Disorder (N = 60) Randomly Assigned to 16 Weeks of Double-Blind Treatment With Zonisamide or Placebo

	Longitudinal Analysis[a]				Endpoint Analysis[b]			
Outcome Measure	Estimate	95% CI	χ^2 (df = 1)	p	Estimate	95% CI	t (df = 55)	p
Binges/wk[c]	–0.315	–0.504 to –0.055	5.29	.021	0.002	–0.143 to 0.171	–0.03	.979
Binge days/wk[d]	–0.271	–0.476 to 0.016	3.03	.082	–0.040	–0.176 to 0.119	0.53	.596
CGI-S	–1.43	–2.12 to –0.75	17.01	< .001	–0.79	–1.57 to 0.00	–2.01	.049
HAM-D	–0.18	–2.79 to 2.42	0.02	.892	2.13	–0.78 to 5.04	1.47	.147
YBOCS-BE	–7.01	–10.45 to –3.57	16.02	< .001	–3.50	–7.15 to 0.15	–1.92	.060
Obsessions	–4.14	–6.14 to –2.24	18.29	< .001	–1.88	–4.08 to 0.32	–1.71	.093
Compulsions	–2.82	–4.82 to –0.82	7.71	.006	–1.62	–3.48 to 0.24	–1.74	.087
TFEQ[e]	–3.49	–8.09 to 1.12	2.26	.136	–6.19	–11.14 to –1.24	–2.55	.016
Cognitive restraint	2.74	–0.27 to 5.76	3.25	.074	1.32	–2.18 to 4.81	0.77	.448
Disinhibition	–4.44	–7.05 to –1.83	11.38	< .001	–4.26	–7.49 to –1.04	–2.69	.011
Hunger	–2.90	–5.95 to 0.14	3.59	.061	–3.24	–6.43 to –0.05	–2.07	.047
Weight, kg	–2.86	–4.57 to –1.14	10.72	< .001	–3.68	–5.91 to –1.45	–3.31	.002
Body mass index, kg/m^2	–1.02	–1.64 to –0.41	10.75	.001	–1.32	–2.07 to –0.56	–3.51	< .001

[a]Estimate is for mean (week 16 minus baseline) for zonisamide minus mean (week 16 minus baseline) for placebo. Test statistic is the treatment-by-time interaction term, which represents the difference in rate of score change between the zonisamide and placebo groups, with time modeled as square root of days since randomization. The estimate and its CI were obtained by multiplying the treatment-by-time interaction and its CI by 112 (112 days in 16 weeks) and squaring.
[b]Estimate is for mean (week 16 minus baseline) for zonisamide minus mean (week 16 minus baseline) for placebo. The estimate is the test statistic, which is the mean difference in change scores (endpoint minus baseline) between the zonisamide and placebo groups.
[c]Log transformation (log [binges/week] + 1) was used for analysis; values in table are expressed in the original scale.
[d]Log transformation (log [binge days/week] + 1) was used for analysis; values in table are expressed in the original scale.
[e]Measured at weeks 0, 4, 8, and 12 only.
Abbreviations: CGI-S = Clinical Global Impressions-Severity Scale, HAM-D = Hamilton Rating Scale for Depression, TFEQ = Three Factor Eating Questionnaire, YBOCS-BE = Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating.

those patients in the placebo group that withdrew because they were lost to follow-up (N = 2), began taking an exclusionary medication (N = 1), and had work obligations (N = 5). Patients who discontinued zonisamide did not differ significantly from those who completed the 16-week trial on any baseline variable (data not presented). The remaining 30 patients completed the 16 weeks of treatment (N = 12 receiving zonisamide and N = 18 receiving placebo).

The mean frequency of binges decreased over the study period in both treatment groups, but more so in the zonisamide group (Figure 1). Mean body weight dropped considerably over the study period in the zonisamide group, but not in the placebo group (Figure 2).

The primary efficacy analysis using random regression showed that patients receiving zonisamide had a significantly greater rate of reduction in binge episodes per week than patients receiving placebo (Table 2). Zonisamide was also associated with a significantly greater rate of improvement than placebo for the following variables: body weight; BMI; and scores on the CGI-S, YBOCS-BE, and TFEQ Disinhibition scales (Table 2). However, there was no difference between the treatment groups in the rate of change in reduction in binge days per week or in TFEQ

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Table 3. Response to Treatment Among Patients With Binge Eating Disorder Randomly Assigned to 16 Weeks of Double-Blind Treatment With Zonisamide or Placebo[a]

	Intent-to-Treat Group[c]		Completer Group[d]	
Response[b]	Placebo (N = 29)	Zonisamide (N = 28)	Placebo (N = 18)	Zonisamide (N = 12)
None	4 (14)	5 (18)	1 (6)	0 (0)
Moderate	7 (24)	4 (14)	5 (28)	1 (8)
Marked	5 (17)	4 (14)	4 (22)	0 (0)
Remission	13 (45)	15 (54)	8 (44)	11 (92)

[a]Values shown as N (%).
[b]Categories defined by the percentage decrease in binge frequency from baseline: remission = cessation of binges; marked = 75%–99% reduction; moderate = 50%–74% reduction; none = less than a 50% reduction.
[c]Patients had at least 1 post-randomization efficacy measure; nonsignificant difference between groups (p = .82, exact Cochran-Armitage trend test).
[d]Significant difference between groups (p = .025, exact Cochran-Armitage trend test).

Table 4. Adverse Events Reported by ≥ 2 Patients With Binge Eating Disorder Randomly Assigned to 16 Weeks of Double-Blind Treatment With Zonisamide or Placebo

	Treatment Group[a]			
	Zonisamide (N = 30)		Placebo (N = 30)	
Adverse Event	N	%	N	%
Dry mouth	13	43	10	33
Somnolence	12	40	7	23
Headache	11	37	9	30
Nausea	11	37	5	17
Nervousness	8	27	3	10
Flatulence	7	23	8	27
Taste perversion	7	23	2	7
Dyspepsia	6	20	1	3
Gastrointestinal virus	5	17	2	7
Thinking abnormality	5	17	3	10
Amnesia	5	17	3	10
Paresthesias	4	13	4	13
Dizziness	4	13	2	7
Insomnia	4	13	2	7
Back pain	4	13	1	3
Abdominal pain	3	10	3	10
Libido decrease	3	10	1	3
Urine frequency	3	10	4	13
Diarrhea	2	7	5	17
Constipation	2	7	5	17
Heart palpitations	2	7	5	17
Upper respiratory infection	2	7	3	10
Bone fracture[b]	2	7	0	0

[a]There were no significant differences between groups (all p > .10, Fisher exact test).
[b]Resulting from accidental injury.

scores for cognitive restraint or hunger. There was also no difference in the rate of change in HAM-D scores between the treatment groups (Table 2).

In the secondary analysis of baseline-to-endpoint change scores using LOCF, zonisamide was associated with significant decreases in weight, BMI, and scores on the CGI-S, the TFEQ total, and the TFEQ hunger and Disinhibition scales compared with placebo (Table 2). Marginally nonsignificant changes were obtained for the YBOCS-BE total score and the YBOCS-BE obsession and compulsion subscale scores. There was no significant difference between groups in the change in weekly binge episodes, weekly binge days, or scores on the TFEQ cognitive restraint or the HAM-D scales.

Regarding global responses, the mean final CGI-I at endpoint was rated "much improved" or "very much improved" in 21 (75%) of zonisamide-treated patients as compared with 17 (59%) of placebo-treated patients (Fisher exact p = .26). In the categorical response analyses, there were significantly higher levels of response for zonisamide-treated patients compared with placebo-treated patients in the completer group but not in the intent-to-treat group (Table 3). Remission of binge episodes was attained by 54% of zonisamide-treated patients at endpoint compared with 45% of placebo-treated patients (Fisher exact p = .43) in the intent-to-treat population, versus 92% and 44% (Fisher exact p = .018), respectively, in the completer population. Zonisamide was associated with a significantly shortened time to recovery of binge eating in the intent-to-treat group (hazard ratio for recovery = 2.76, $\chi^2 = 4.52$, p = .033).

Patients receiving zonisamide experienced a mean (SD) weight loss of 4.8 (5.1) kg from baseline to endpoint, whereas those receiving placebo experienced a mean (SD) weight loss of 1.0 (3.0) kg. Among patients who completed the 16 weeks of treatment, the corresponding weight losses were 8.9 (5.0) kg and 1.2 (3.8) kg. Weight loss since baseline was significantly correlated with percentage reduction in binge frequency at week 16 among patients receiving zonisamide (Spearman $\rho = 0.72$, $p < .001$) as well as in the overall sample (Spearman $\rho = 0.52$, $p < .001$).

There were no significant differences between patients receiving zonisamide and those given placebo in mean change from baseline to final visit for the fasting measurements of leptin (–5.1 and –1.1 ng/mL, respectively), insulin (15.7 and 8.4 μU/mL), glucose (0.4 and –1.1 mg/dL), triglycerides (–4.5 and –12.2 mg/dL), low-density lipoprotein cholesterol (7.2 and 2.9 mg/dL), and total cholesterol (8.5 and –5.4 mg/dL). Zonisamide, however, was associated with a significant change in plasma ghrelin concentration at the last visit compared with placebo in the intent-to-treat group (+98.6 vs. –156.8 ng/L, respectively; t = 4.0, df = 27, p = .001). Specifically, ghrelin level increased in the zonisamide group and decreased in the placebo group.

The mean (SD) daily dose of zonisamide at endpoint evaluation for all 28 patients was 436 (159) mg; the mean (SD) daily dose for the 12 patients who completed the 16-week trial was 558 (90) mg.

Adverse events occurring in at least 2 patients receiving zonisamide are listed in Table 4. Although adverse events appeared to be more common overall with zonisa-

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mide than with placebo, there was no statistically significant difference between treatment groups in the incidence of any particular adverse event. More patients discontinued zonisamide (26.7%) for adverse events than placebo (13.3%), but this difference in incidence also was not statistically significant (Fisher exact p = .33). Adverse events causing discontinuation among zonisamide-treated patients were accidental injury with bone fracture (N = 2), persistent cough (N = 1), depression (N = 1), paranoid ideation (N = 1), memory impairment (N = 1), word finding difficulties (N = 1), and somnolence with "feeling cold and a stiff neck" (N = 1). Urticaria (N = 1), dyspepsia (N = 1), gastrointestinal distress (N = 1), and renal stone (N = 1) were the adverse events causing discontinuation among placebo-treated patients.

Two patients were hospitalized for serious adverse events during the study; 1 patient had chest pain while receiving placebo and the other patient had an infected varicocele while receiving zonisamide. The chest pain was thought to be musculoskeletal in origin and resolved spontaneously; the infected varicocele responded to antibiotic treatment. Both patients continued taking study medication.

There were no changes in physical examination findings, vital signs, or clinical laboratory values suggestive of drug-related toxicity. There was no evidence of withdrawal symptoms in the 18 patients in whom zonisamide was discontinued.

DISCUSSION

In the primary longitudinal analysis of this randomized, double-blind trial in patients with BED and obesity, zonisamide was significantly superior to placebo in rate of reduction of binge frequency (but not binge day frequency), body weight, BMI, obsessive-compulsive features of binge eating symptoms, disinhibited eating, and overall severity of illness. A secondary analysis, change from baseline to endpoint using LOCF, yielded fewer positive findings, with significant decreases in body weight, BMI, disinhibited eating, and overall severity of illness, but no significant change in binge episode or binge day frequency or in obsessive-compulsive features of binge eating symptoms. Also, zonisamide was not associated with a higher level of categorical response in the endpoint analysis. However, it was associated with a significantly shortened time to recovery of binge eating, as well as a higher level of response, including remission, among patients completing the 16-week trial. In addition, the mean weight loss in the intent-to-treat group receiving zonisamide was 4.8 kg, as compared with 1.0 kg in the group receiving placebo. There was no significant change in HAM-D scores, but the mean HAM-D score was low at baseline. Taken together, these findings provide preliminary evidence for the efficacy of zonisamide in BED associated with obesity.

The differences between the longitudinal and endpoint analyses are attributable to differences in power, assumptions regarding missing data, and modeling assumptions, discussed in detail elsewhere.[57–59] In brief, compared with the endpoint analysis using LOCF, the longitudinal analysis has greater power because it uses all observations, rather than only those at baseline and endpoint. The greater power, in turn, accounts in part for the finding of more drug-placebo differences. The longitudinal analysis also has more plausible assumptions regarding missing data, in that it permits missingness to depend on observations prior to dropout (i.e., missing at random as opposed to missing completely at random). It makes the assumption that change is linear on the scale of time measurement and that missing data follow the same linear trajectory as previously observed data, rather than using only the final observation to estimate change, under the assumption that any missing observations after the final observation are the same as the final observation. The more realistic assumptions regarding the mechanisms for missing data and the modeling of missing data of the longitudinal analysis lessen the potential for bias relative to the endpoint analysis.

The reduction in binge frequency and overall improvement observed with zonisamide in this study appear comparable to the results reported in studies[18–34] of cognitive-behavioral therapy, interpersonal therapy, SSRIs, sibutramine, topiramate, and orlistat plus cognitive-behavioral therapy in patients with BED. The weight loss appears comparable to that seen for sibutramine, topiramate, and orlistat plus cognitive-behavioral therapy. Of note, zonisamide was associated with an increase in fasting ghrelin levels relative to placebo, consistent with previous reports that weight loss causes increases in circulating levels of this peptide.[60] However, leptin, which typically decreases with even small amounts of weight loss, did not differ between the 2 groups. Appropriately designed controlled comparison trials are required to accurately determine zonisamide's comparative efficacy and tolerability with other treatments of BED associated with obesity. Ideally, such trials would explore treatment effects on eating behavior, weight, and biological markers such as ghrelin and leptin.

The potential mechanism of action of zonisamide in BED is unknown. Mechanisms hypothesized to account for zonisamide's antiepileptic properties include antagonism of voltage-gated sodium and T-type calcium channels, reduction of glutamate transmission by blockade of potassium-evoked glutamate release and upregulation of excitatory amino acid carrier-1 (EAAC-1), modulation of central dopaminergic and serotonergic function, and carbonic anhydrase inhibition.[38,44–47,61] Enhancement of serotonin and dopamine transmission[42] and inhibition of glutamate transmission[43] have been shown to reduce feeding behavior. One type of mechanism by which

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zonisamide might reduce binge eating, therefore, is by decreasing appetite or enhancing satiety through some combination of its effects on the serotonin, dopamine, and glutamate systems. Decreased binge eating might lead to reduced energy intake and, secondarily, to weight loss. Alternatively, a second possible type of mechanism is that zonisamide might reduce binge eating via its side effects of dyspepsia, nausea, and taste perversion.[41] A third possible type of mechanism is that zonisamide may secondarily decrease binge eating through direct weight loss effects. For example, carbonic anhydrase inhibitors have been hypothesized to induce weight loss by inhibiting carbonic anhydrase–mediated de novo lipogenesis.[62]

In this study, zonisamide's effects on weight loss appeared to be more pronounced than its effects on binge eating. Although this finding may have been due to methodological limitations (changes in binge eating behavior may be more difficult to measure and differentiate from placebo than changes in weight for certain treatments[30]), another interpretation is that zonisamide may have other mechanisms of action in BED with obesity. Thus, zonisamide might decrease other forms of overeating beyond binge eating in patients with BED that might contribute to weight gain. Such forms of overeating have been identified in BED and have been variously labeled subjective overeating, grazing, emotional eating, and night eating.[63–66]

Several limitations of this study should be considered. First, perhaps most important, is that the attrition rate was high, with half of patients withdrawing before study completion. This feature renders the results heavily dependent on assumptions regarding missing data. While the longitudinal analysis, unlike the endpoint analysis, allows that the missingness can depend on observations obtained before withdrawal (e.g., a patient who is failing to improve may be more likely to withdraw), it is nevertheless vulnerable to missingness that depends on factors that are not measured prior to withdrawal (technically, missing not at random or nonignorable missingness). The 60% attrition rate with zonisamide in the study was much higher than the 10% attrition rate in Gadde and colleagues' 16-week study of zonisamide in obese adults,[41] but comparable to the 47% attrition rate in our earlier open-label trial of zonisamide in adults with BED (most, but not all, of whom were obese).[37] The 2 most common reasons for dropout with zonisamide in this study were difficulties with protocol adherence (30%) and adverse events (27%). In the Gadde et al. study, 1 patient (3%) dropped out for adverse events and 2 patients (7%) dropped out for protocol nonadherence (N = 1 for lost to follow-up and N = 1 for protocol violation). It is unknown if the different dropout rates in the 2 studies reflect chance variation, differences in dose titration (zonisamide could be increased at a slightly faster rate in our study, but the mean daily dose at last evaluation of 436 mg is comparable to the mean highest daily dose of 427 mg in the earlier study), other differences in study design (patients in the Gadde et al. study[41] received ancillary dietary counseling whereas patients in this study received no adjunctive treatment), or differences in patient populations (patients in the Gadde et al. study[41] were less severely obese and had no associated psychopathology).

Second, the accuracy of the self-report methods used to obtain binge eating data is uncertain.[61,67] However, patient diaries were used to enhance patient recall of binges, and randomization and double-blinding should have equalized any patient or investigator bias in the recording or rating of overeating episode as binges. Third, because the study group was small and primarily female and the duration of treatment was short (16 weeks), the results may not generalize to larger groups of persons with BED or to longer treatment periods. Fourth, individuals with several forms of psychopathology were excluded. Thus, the results may not generalize to BED when it co-occurs with these forms of psychopathology, such as substance use disorders, bipolar disorders, or severe personality disorders.

In summary, in a 16-week trial in outpatients with BED and obesity, zonisamide was found to be superior to placebo in reducing binge frequency, weight, and severity of illness. However, it was associated with only fair tolerability and a relatively high treatment discontinuation rate.

Drug names: fluoxetine (Prozac and others), orlistat (Xenical), sibutramine (Meridia), topiramate (Topamax and others), zaleplon (Sonata), zolpidem (Ambien), zonisamide (Zonagran and others).

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