Zonisamide for Weight Reduction in Obese Adults

A 1-Year Randomized Controlled Trial

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Background: Obese individuals who have failed to achieve adequate weight loss with lifestyle changes have limited nonsurgical therapeutic options. We evaluated the efficacy and tolerability of zonisamide, an antiepileptic drug, for enhancing weight loss in obese patients receiving diet and lifestyle guidance.

Methods: This was a 1-year, randomized, double-blind, placebo-controlled trial conducted from January 9, 2006, through September 20, 2011, at Duke University Medical Center. A total of 225 obese (mean [SD] body mass index, 37.6 [4.9]) participants included 134 women (59.6%) and 91 men (40.4%) without diabetes mellitus. (Body mass index is calculated as weight in kilograms divided by height in meters squared.) Interventions were daily dosing with placebo (n=74), 200 mg of zonisamide (n=76), or 400 mg of zonisamide (n=75), in addition to diet and lifestyle counseling by a dietitian for 1 year. Primary outcome was change in body weight at 1 year.

Results: Of the 225 randomized patients, 218 (96.9%) provided 1-year follow-up assessments. Change in body weight was –4.0 kg (95% CI, –5.8 to –2.3 kg; least squares mean, –3.7%) for placebo, –4.4 kg (–6.1 to –2.6 kg; –3.9%; $P=.79$ vs placebo) for 200 mg of zonisamide, and –7.3 kg (–9.0 to –5.6 kg; –6.8%; $P=.009$ vs placebo) for 400 mg of zonisamide. In the categorical analysis, 23 (31.1%) assigned to placebo, 26 (34.2%; $P=.72$) assigned to 200 mg of zonisamide, and 41 (54.7%; $P=.007$) assigned to 400 mg of zonisamide achieved 5% or greater weight loss; for 10% or greater weight loss, the corresponding numbers were 6 (8.1%), 17 (22.4%; $P=.02$), and 24 (32.0%; $P<.001$). Gastrointestinal, nervous system, and psychiatric adverse events occurred at a higher incidence with zonisamide than with placebo.

Conclusion: Zonisamide at the daily dose of 400 mg moderately enhanced weight loss achieved with diet and lifestyle counseling but had a high incidence of adverse events.

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Diet and exercise are often recommended as first-line treatment for obese patients, but long-term results are not impressive.[1,2] Although intensive lifestyle interventions of the type tested in the Diabetes Prevention Program[3] and Look AHEAD[4] trials have demonstrated approximately 6% to 8% weight loss in a year, these interventions are difficult to implement in primary care settings and third-party payers rarely reimburse.[5] Orlistat and lorcaserin hydrochloride, the only monotherapy drugs currently approved for long-term management of obesity, achieve an approximately 3-kg weight loss relative to placebo after 1 year.[6,7] Thus, for obese patients who do not achieve adequate benefit from lifestyle therapies, there is a dire need for additional nonsurgical therapeutic options. Zonisamide is an antiepileptic drug that demonstrated weight loss efficacy in obese adults (–5.9 vs –0.9 kg) in a 16-week trial with further weight loss in the additional 16-week extension phase.[8] In that trial, the daily zonisamide dose was titrated to 400 mg for all patients by week 7 and to 600 mg for patients not losing at least 5% weight. A subsequent review of

See Editor's Note at end of article

the data revealed that patients with inadequate weight loss at 400 mg had no appreciable additional weight loss at 600 mg. However, because the dose was increased to 400 mg regardless of the degree of weight loss, it was not known whether a lower dose would have been just

as effective in a longer duration. Furthermore, placebo treatment led to weight loss of only 0.9 kg, suggesting that the lifestyle intervention in that trial was not very effective. This trial was designed to answer 2 questions: (1) Does addition of 400 mg of zonisamide daily augment weight loss achievable with a fair quality lifestyle intervention that could be administered in a primary care setting? and (2) Is a lower dose (200 mg) of zonisamide used daily also efficacious? This report describes a long-term randomized controlled trial testing the efficacy and tolerability of 2 zonisamide doses (200 and 400 mg) in obese adults, who were also receiving diet and lifestyle counseling.

METHODS

STUDY DESIGN AND RANDOMIZATION

This was a randomized, double-blind, parallel-group, 3-arm trial conducted from January 9, 2006, through September 20, 2011, at Duke University Medical Center, Durham, North Carolina. Eligible patients were randomly assigned in a 1:1:1 ratio to receive once-daily treatment with placebo, 200 mg of zonisamide, or 400 mg of zonisamide for 1 year. In addition, all patients received diet and lifestyle counseling.

Randomization, facilitated by a pseudo-number generator, with a permuted block size of 9 and stratification for sex, was implemented by the medical center's Investigational Drug Service. Study drugs were dispensed by the Investigational Drug Service as identically appearing capsules, and investigators and patients remained masked to treatment assignment until all patient visits and data entry were completed.

PATIENTS

All patients gave written informed consent. Duke University's institutional review board approved the protocol. Eligible patients were 18 to 65 years old with a body mass index ranging from 30 to 50 (calculated as weight in kilograms divided by height in meters squared). Key exclusion criteria were diabetes mellitus, serious or unstable medical illness, renal calculi history, current major depression, alcohol or drug abuse, score of 11 or higher on the depression subscale of the Hospital Anxiety and Depression Scale (HADS),[9] psychosis or bipolar disorder or severe personality disorders, suicidality, antipsychotics or mood stabilizers, other psychotropic medications if taken for less than 3 months, and taking zonisamide or other antiepileptic drugs (see eMethods for details; http://www.archinternmed.com). Patients were recruited via local area advertisements, hospital website listings, and physician referrals. Patients were given a small stipend for travel expenses (maximum of $180 for 1 year).

STUDY DRUGS

Zonisamide and placebo capsules were prepared in accordance with Good Manufacturing Practice guidelines in the Duke Compounding Facility with the active pharmaceutical ingredient (Sochinaz SA, distributed by Bachem Americas) plus dextrose as an inactive ingredient. Identical-looking placebo capsules contained dextrose.

Each capsule contained 100 mg of zonisamide or placebo, with patients and study staff masked to the contents. Dose was gradually titrated upward as follows: 1 capsule for 15 days, 2 capsules during days 16 to 30, 3 capsules during days 31 to 45, and 4 capsules from day 46 onward. The entire dose was taken at night. Masked dose reduction was allowed, and dose increase could be withheld. Patients had the option to discontinue use of the drug and remain in the study, receiving only diet and lifestyle counseling. Adherence was assessed by comparing the number of capsules dispensed and returned.

DIET AND LIFESTYLE INTERVENTION

The study aimed to achieve at least 3% weight loss for all participants. Hence, all patients received diet and lifestyle counseling to promote weight loss. This counseling included an individualized diet plan to reduce daily energy intake by 500 kcal from the energy requirements calculated using the Mifflin-St Jeor resting metabolic rate equation.[10] Diet compositions were consistent with US Department of Agriculture guidelines, and patients were advised to consume 50% of their calories from carbohydrates, 20% from protein, and 30% from fat. Complex carbohydrates, whole grains, dietary fiber, and lean proteins were emphasized, and participants were also taught to minimize consumption of saturated and trans fats. Patients were asked to record and monitor their daily caloric intake with a food diary, and at monthly study visits, they met with a registered dietitian for 30 minutes to discuss their progress and any perceived challenges and receive individualized counseling and educational materials. Topics discussed included goal setting, planning healthy meals, understanding food labels, supermarket shopping, snacking and dining out, and basic guidance to increase aerobic exercise and strength training. All patients in the study were encouraged to exercise, and although a specific exercise program was not prescribed, the dietitian discussed strategies for increasing physical activity, such as walking at lunch breaks, wearing a pedometer to track steps, and setting weekly physical activity goals. Other areas covered were decision making, managing social situations, barriers to healthy eating, coping strategies, and relapse prevention.

VISITS AND ASSESSMENTS

After randomization and drug dispensing, visits occurred twice in the first month and at monthly intervals thereafter. Assessments included body weight, blood pressure, heart rate, waist circumference, clinical and laboratory evaluations, concomitant medications, treatment adherence, adverse events, HADS depression subscale, and a suicidal ideation question.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome, prespecified in the protocol, was absolute change in body weight in kilograms. Secondary outcomes included proportions of patients achieving 5% and 10% weight loss and changes in waist circumference, blood pressure, lipid levels, and other relevant blood test results. Safety outcomes included frequency of adverse events and HADS depression score change.

STATISTICAL ANALYSIS

Power analysis, based on the assumption that relative to placebo, the 400-mg and 200-mg zonisamide groups would lose 3% and 1.5%, respectively, indicated that 75 patients per treatment group, with primary end point data available for 65 patients at 1 year would provide more than 92% power to detect differences vs placebo at a $P \leq .05$ significance level (2-tailed).

Primary analysis was conducted on the intent-to-treat sample of all randomized patients. The primary end point was weight loss at 1 year (month 12 weight minus baseline weight in ki-

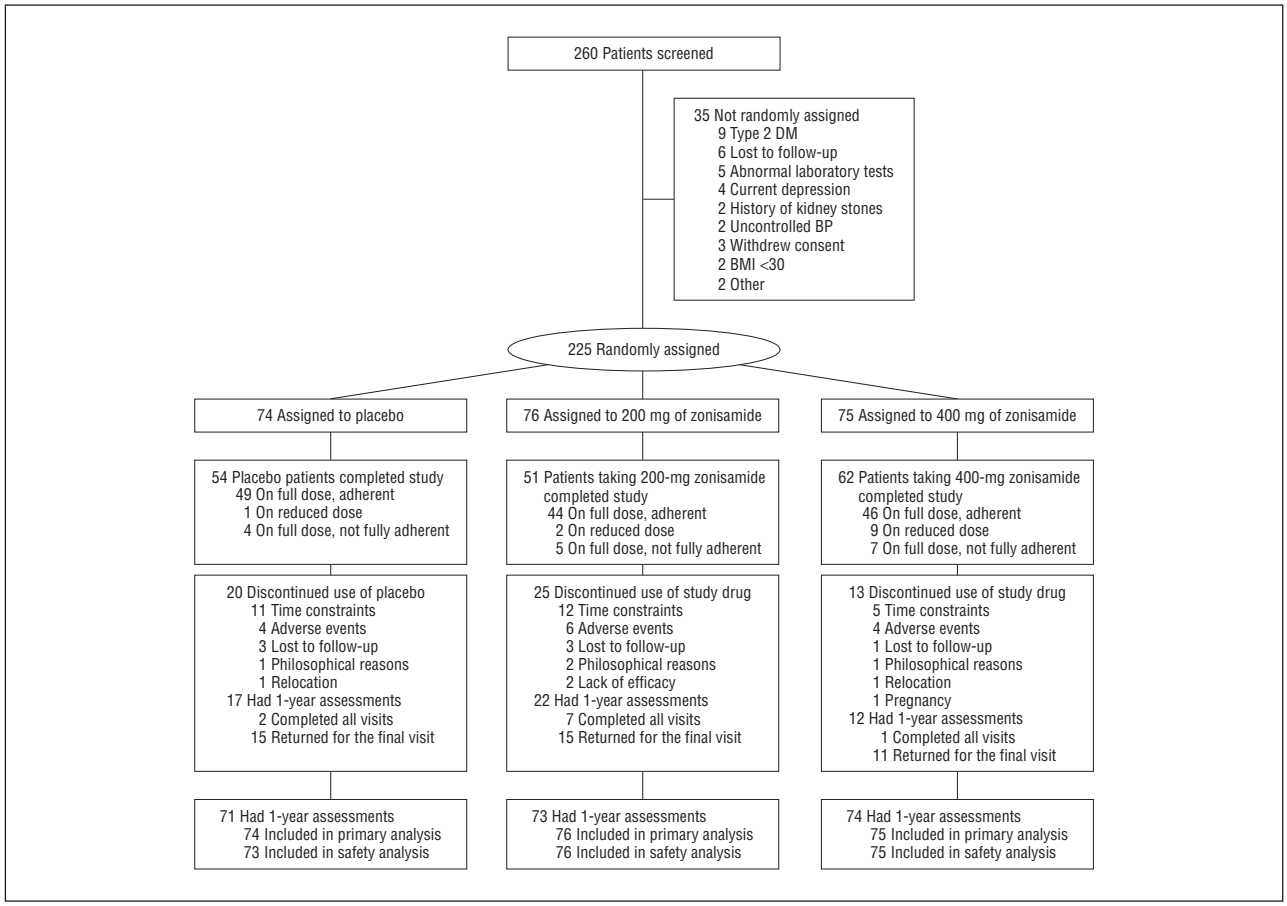


Figure 1. Flow of patient screening, randomization, and disposition. One patient became pregnant and discontinued drug use at month 5. She was followed up to the end of the study, but actual data for months 6 through 12 were replaced by imputed values. BMI indicates body mass index; BP, blood pressure; and DM, diabetes mellitus.

lograms). Using analysis of covariance, the resulting difference score was regressed on a 3-level proxy variable (1, placebo; 2, 200 mg; and 3, 400 mg) denoting randomization status to control for differences in initial body weight. Baseline weight and sex were included as covariates. Efficacy, testing the overall difference among the groups, was evaluated using a 2 *df* test. On the basis of a significant omnibus test, pairwise contrasts between treatments were subsequently tested using closed (stepdown) testing, with $P \leq .05$ indicating significance.

Missing data are a potential source of bias.[11] Many past imputation strategies, including last observation carried forward (LOCF) and completer analysis, often provide biased results[12] and are no longer favored relative to full likelihood-based and multiple imputation procedures, both of which are less subject to bias and inconsistencies under satisfying assumptions.[13] For this study, missing data for the primary analysis were augmented using multiple imputations in a 2-step process. On the basis of available weight data from all randomized patients, an initial imputation based on a Markov Chain Monte Carlo algorithm was used to establish a monotone missing data pattern. Missing values in the monotone data set were subsequently imputed multiple times (5 imputations) in a second step using regression procedures as described by Rubin and Schenker.[14] The primary month 12 outcome measure was calculated using the imputed data sets and analyzed using analysis of covariance regressions as described; data from the 5 analyses were subsequently combined into single estimates and tested as described by Schafer.[15] Two secondary sensitivity analyses were performed: an imputation using traditional LOCF procedures to replace the missing month 12 data point and a completers-based approach restricted to full-dose adherent patients (n=139). The latter 2 analyses facilitate comparisons with earlier published studies.

For responder analyses, 2 dichotomous outcome measures were calculated identifying patients with 5% or greater and 10% or greater weight loss. The latter measures were modeled with logistic regressions that included the 3-level group proxy and a baseline weight covariate, with omnibus testing preceding pairwise tests as before.

Analyses of secondary outcomes were based on intent-to-treat analyses of covariance. Difference scores from baseline to end point (month 12) for each measure were regressed on the 3-level proxy denoting group while controlling for the baseline value of the same measure. Contrasts were subsequently estimated in models, which had a significant overall treatment effect.

RESULTS

PATIENTS

Two hundred sixty patients signed consent forms, and 225 patients were randomly assigned to 3 treatment groups: 74 to placebo, 76 to 200 mg of zonisamide, and 75 to 400 mg of zonisamide. Of the 225 randomized patients, 218 (96.9%) provided 1-year follow-up assessments. Reasons for not randomizing 35 screened patients and subsequent flow are depicted in **Figure 1**. Twenty patients discontinued use of placebo, 25 discon-

Table 1. Patient Characteristics by Treatment Group[a]

Characteristic	Placebo (n = 74)	Zonisamide, 200 mg (n = 76)	Zonisamide, 400 mg (n = 75)
Age, y	43.5 (10.3)	44.2 (10.1)	42.3 (10.0)
Women, No. (%)	44 (59.5)	45 (59.2)	45 (60.0)
Race, No. (%)			
White	49 (66.2)	48 (63.2)	45 (60.0)
Black	23 (31.1)	27 (35.5)	27 (36.0)
Other	2 (2.7)	1 (1.3)	3 (4.0)
Married, No. (%)	47 (63.5)	48 (63.2)	44 (58.7)
Obese for >10 y, No. (%)	45 (60.8)	50 (65.8)	47 (62.7)
Family history of obesity, No. (%)	55 (74.3)	49 (64.4)	41 (54.7)
Psychiatric history, No. (%)	18 (24.3)	17 (22.4)	23 (30.7)
Taking antidepressant, No. (%)	6 (8.1)	5 (6.6)	9 (12.0)
Weight, kg	110.7 (18 · 8)	111.4 (21.0)	109.0 (14.9)
Body mass index[b]	37.8 (5.2)	37.5 (5.1)	37.7 (4.4)
Waist circumference, cm	113.1 (13.3)	114.3 (15.7)	112.8 (11.7)
Blood pressure, mm Hg			
Systolic	120.6 (13.7)	124.2 (14.0)	119.9 (12.1)
Diastolic	78.8 (9.7)	81.2 (9.1)	80.4 (9.3)
Heart rate, per min	73.0 (10.4)	75.4 (11.1)	72.4 (10.2)
Total cholesterol, mg/dL	197.1 (32.8)	189.4 (31.9)	189.4 (28.1)
LDL-C, mg/dL	122.4 (31.8)	116.0 (30.1)	116.9 (29.6)
HDL-C, mg/dL	51.0 (12.4)	50.0 (13.4)	48.4 (11.9)
Triglycerides, mg/dL	125.8 (66.1)	124.7 (81.5)	117.7 (58.6)
Fasting glucose, mg/dL	93.9 (14.4)	95.0 (10.8)	93.6 (11.0)
Hemoglobin A_{1c}, %	5.6 (0.4)	5.6 (0.5)	5.6 (0.5)

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert total cholesterol, LDL-C, and HDL-C to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113; and fasting glucose to millimoles per liter, multiply by 0.0555.

[a]Unless otherwise stated, data are presented as mean (SD).

[b]Calculated as weight in kilograms divided by height in meters squared.

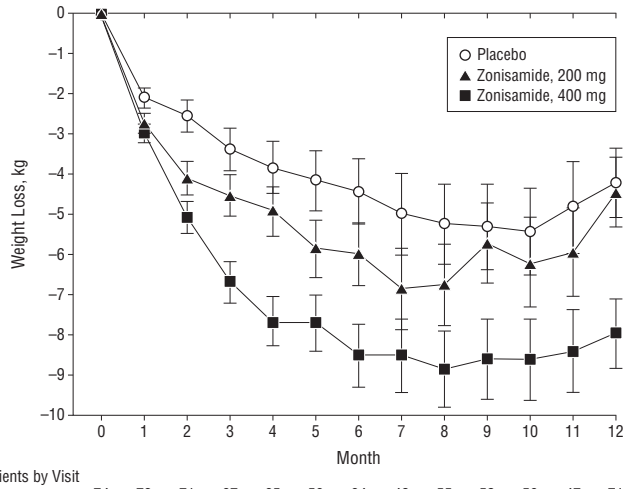
tinued use of 200 mg of zonisamide, and 13 discontinued use of 400 mg of zonisamide. However, some patients who discontinued use of the drug remained in the study and completed all visits, and 41 patients who discontinued use of the drug returned for their 1-year visit to complete final assessments. Thus, the primary end point assessment was available for 71 assigned to placebo, 73 assigned to 200 mg of zonisamide, and 74 assigned to 400 mg of zonisamide, leaving only 7 of 225 lost to follow-up.

Patient characteristics at baseline, listed in **Table 1**, were similar among the 3 groups. We enrolled 40.4% men and 36.9% ethnic minorities. Mean age and body mass index were 43 years and 37.6, respectively. Approximately 21.0% had depression history and 8.9% were taking antidepressants.

WEIGHT LOSS

Patients assigned to 400 mg of zonisamide lost more weight than those assigned to placebo, whereas the 200-mg dose was not superior to placebo (**Figure 2**). In the primary multiple imputation analysis, weight changes were –4.0 kg (95% CI, –5.8 to –2.3 kg; least squares mean, –3.7%) for placebo, –4.4 kg (–6.1 to –2.6 kg; –3.9%; $P = .79$) for 200 mg of zonisamide, and –7.3 kg (–9.0 to –5.6 kg; –6.8%; $P = .009$) for 400 mg of zonisamide. Last observation carried forward analysis revealed similar weight change (**Table 2**), and full-dose adherent patients had greater weight loss with similar between-group differences.

In the categorical multiple imputation analyses, 23 patients (31.1%) assigned to placebo achieved a 5% or greater weight loss compared with 26 (34.2%; $P = .72$ vs placebo) and 41 (54.7%; $P = .007$ vs placebo) assigned to 200 and 400 mg of zonisamide, respectively; for 10% or greater weight loss, the corresponding figures were 6 (8.1%), 17 (22.4%; $P = .02$), and 24 (32.0%; $P < .001$), respectively.



No. of Patients by Visit

Placebo	74	73	71	67	65	59	64	48	55	52	50	47	71
Zonisamide, 200 mg	76	76	70	71	71	65	71	49	52	58	47	50	72
Zonisamide, 400 mg	75	75	74	71	71	67	69	63	61	59	57	57	74

Figure 2. Least squares mean patterns of weight loss. Error bars indicate SE. For one patient who was pregnant at month 5, data collected between month 6 and month 12 are not included.

Table 2. Changes in Weight and Secondary Parameters[a]

Outcome Variable	Placebo (n = 74)	Zonisamide, 200 mg (n = 76)	*P* Value vs Placebo	Zonisamide, 400 mg (n = 75)	*P* Value vs Placebo
Weight change, kg					
MI analysis (n = 74, 76, 75)	−4.0 (−5.8 to −2.3)	−4.4 (−6.1 to −2.6)	.79	−7.3 (−9.0 to −5.6)	.009
LOCF analysis (n = 74, 76, 75)	−4.0 (−5.7 to −2.2)	−4.3 (−6.0 to −2.6)	.78	−7.4 (−9.1 to −5.7)	.006
Full-dose analysis (n = 49, 44, 46)	−5.1 (−7.4 to −2.8)	−6.0 (−8.4 to −3.5)	.62	−9.1 (−11.5 to −6.7)	.019
Weight change, %					
MI analysis	−3.7 (−5.3 to −2.1)	−3.9 (−5.4 to −2.3)	.88	−6.8 (−8.4 to −5.3)	.006
LOCF analysis	−3.7 (−5.2 to −2.1)	−3.8 (−5.3 to −2.2)	.87	−6.9 (−8.5 to −5.4)	.004
Full-dose analysis	−4.7 (−6.8 to −2.6)	−5.4 (−7.6 to −3.2)	.66	−8.7 (−10.8 to −6.5)	.009
Patients with >5% weight loss, No. (%)					
MI analysis	23 (31.1)	26 (34.2)	.72	41 (54.7)	.007
LOCF analysis	22 (29.7)	25 (32.9)	.66	41 (54.7)	.003
Full-dose analysis	21 (42.9)	17 (38.6)	.76	30 (65.2)	.03
Patients with >10% weight loss, No. (%)					
MI analysis	6 (8.1)	17 (22.4)	.02	24 (32.0)	<.001
LOCF analysis	5 (6.8)	17 (22.4)	.01	25 (33.3)	<.001
Full-dose analysis	5 (10.2)	13 (29.5)	.02	18 (39.1)	.002
Waist circumference, cm	−4.8 (−6.6 to −3.1)	−6.1 (−7.8 to −4.3)	.33	−8.5 (−10.2 to −6.8)	.003
Systolic BP, mm Hg	−0.6 (−2.9 to −1.7)	−4.4 (−6.7 to −2.1)	.03	−1.9 (−4.1 to 0.4)	.46
Diastolic BP, mm Hg	−1.5 (−3.2 to 0.1)	−3.6 (−5.3 to −2.0)	.08	−3.9 (−5.5 to −2.3)	.048
Heart rate, per min	−2.7 (−4.6 to −0.9)	−2.0 (−3.9 to −0.1)	.58	−2.4 (−4.2 to −0.5)	.76
Total cholesterol, mg/dL	−1.9 (−7.2 to 3.4)	4.1 (−1.0 to 9.2)	.11	−0.1 (−5.0 to 4.9)	.62
LDL-C, mg/dL	−2.0 (−6.7 to 2.7)	1.7 (−2.8 to 6.3)	.26	−0.3 (−4.7 to 4.1)	.60
HDL-C, mg/dL	2.5 (0.7 to 4.3)	1.5 (−0.3 to 3.2)	.44	3.4 (1.7 to 5.1)	.49
Triglycerides, mg/dL	−11.3 (−22.6 to 0.0)	0.7 (−10.1 to 11.5)	.13	−11.7 (−22.2 to −1.1)	.96
Fasting glucose, mg/dL	−2.6 (−5.1 to 0.0)	−1.4 (−3.9 to 1.2)	.51	−3.5 (−5.9 to −1.0)	.63
Hemoglobin A_{1c}, %	−0.01 (−0.07 to 0.05)	−0.05 (−0.12 to 0.01)	.38	−0.13 (−0.19 to −0.07)	.007
ALT, mg/dL	−0.8 (−3.5 to 2.0)	−0.3 (−3.0 to 2.4)	.79	−1.3 (−3.9 to 1.4)	.81
Creatinine, mg/dL	−0.03 (−0.06 to −0.01)	0.01 (−0.01 to 0.03)	.02	0.02 (0 to 0.04)	.003
Bicarbonate, mmol/L	0.04 (−0.6 to 0.06	−1.0 (−1.6 to −0.4)	.02	−0.5 (−1.1 to 0.1)	.21

Abbreviations: ALT, alanine aminotransferase; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LOCF, last observation carried forward; MI, multiple imputation.

SI conversion factors: To convert total cholesterol, LDL-C, and HDL-C to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; fasting glucose to millimoles per liter, multiply by 0.0555; ALT to microkatal per liter, multiply by 0.0167; creatinine to micromoles per liter, multiply by 88.4; and bicarbonate to milliequivalent per liter, muliply by 1.0.

[a] Data are presented as least squares mean (95% CI). Unless otherwise stated, analyses are for 218 patients who had 1-year assessments.

WEIGHT CHANGES FOR PATIENTS WHO DROPPED OUT AND RETURNED

Table 3 lists the weight changes for the 41 patients (15 assigned to placebo, 15 assigned to 200 mg of zonisamide, and 11 assigned to 400 mg of zonisamide) who dropped out but returned at 1 year. Weight gain was observed in all treatment groups, most notably for the 400-mg zonisamide group. Mean (SD) weight changes were 1.4% (3.1%) for patients assigned placebo, 0.7% (3.5%) for those assigned 200 mg of zonisamide (*P* vs placebo = .35), and 4.9% (3.4%) for those assigned 400 mg of zonisamide (*P* vs placebo = .008).

SECONDARY OUTCOMES

Waist circumference decreased in all treatment groups; there was a greater decrease with 400 mg of zonisamide than with placebo. Changes in blood pressure, heart rate, fasting glucose level, and lipid levels were favorable with all treatments without significant between-group differences. Although 400 mg of zonisamide led to a statistically significant (*P* = .007) greater reduction in glycated hemoglobin, the change was not clinically significant. No significant changes occurred in hepatic enzymes and serum bicarbonate levels.

ADVERSE EVENTS

This trial was not powered to detect differences in adverse events. Given the relatively small sample, we combined adverse events of similar nature into broader categories (eg, terms such as *sadness*, *crying*, *depression*, and *depressed mood* were combined as *depression related*). As indicated in **Table 4**, altered taste, constipation, diarrhea, dry mouth, headache, fatigue, nausea/vomiting, somnolence, language/speech problems, impaired attention/concentration, memory problems, and anxiety-related and depression-related adverse events were more frequent with one or both of the zonisamide doses. The HADS depression scores were less than 3 (within normal) at all time points in all treatment groups. No patients developed major depressive disorder, and none had suicidal ideation or panic attacks. Most neuropsychiatric adverse events were mild in severity, and all events resolved quickly on dose reduction or drug use discontinuation.

Fourteen patients discontinued use of the study drug because of adverse events: 4 taking placebo (1 patient each

Table 3. Weight Changes for Patients Who Withdrew Early and Returned for the 1-Year Visit

Patient No.	Treatment, mg[a]	Dropout Month	Weight Change at Dropout, kg (%)	Weight Change From Dropout Time to Return at 1 Year, kg (%)
1	Placebo	8	–8.8 (–7.6)	3.4 (3.2)
2	Placebo	4	–0.5 (–0.3)	–9.2 (–6.0)
3	Placebo	9	–5.7 (–5.5)	2.9 (3.0)
4	Placebo	8	2.8 (3.1)	4.9 (5.2)
5	Placebo	4	0.2 (0.1)	–0.5 (–0.3)
6	Placebo	1	0.8 (0.6)	–4.6 (–3.2)
7	Placebo	7	–8.4 (–5.8)	5.4 (4.0)
8	Placebo	8	–4.1 (–3.2)	4.4 (3.6)
9	Placebo	4	–1.0 (0.7)	2.6 (1.9)
10	Placebo	4	–2.8 (–2.5)	5.3 (4.8)
11	Placebo	8	–9.2 (–6.8)	2.4 (1.9)
12	Placebo	6	–9.0 (–7.5)	3.4 (3.1)
13	Placebo	6	0.3 (0.2)	0.2 (0.1)
14	Placebo	2	–1.2 (–1.2)	0.3 (0.3)
15	Placebo	1	–4.1 (–3.3)	–0.5 (–0.4)
16	200	5	0.7 (0.6)	–4.8 (–4.6)
17	200	9	6.4 (5.0)	–4.3 (–3.2)
18	200	7	–2.6 (–2.6)	–0.4 (–0.4)
19	200	6	3.0 (2.7)	5.0 (4.4)
20	200	8	–7.3 (–7.0)	–4.1 (–4.2)
21	200	4	3.3 (2.8)	4.5 (3.8)
22	200	9	–2.6 (–2.3)	–2.1 (–1.9)
23	200	9	–6.2 (–6.7)	–0.8 (–0.9)
24	200	9	–4.4 (–4.4)	5.6 (5.8)
25	200	7	–0.7 (–0.8)	2.3 (2.8)
26	200	6	–1.0 (–1.1)	2.1 (2.4)
27	200	3	–0.5 (–0.4)	8.0 (6.3)
28	200	4	1.5 (1.4)	–1.5 (–1.4)
29	200	6	3.3 (2.2)	0.2 (0.1)
30	200	6	–5.2 (–3.1)	1.3 (0.8)
31	400	6	–14.1 (–11.7)	7.3 (6.9)
32	400	5	–2.1 (–1.8)	1.9 (1.7)
33	400	7	–12.5 (–12.2)	10.2 (11.3)
34	400	7	–3.5 (–3.9)	3.8 (4.5)
35	400	2	–2.1 (–1.9)	2.3 (2.1)
36	400	9	3.8 (3.6)	–0.2 (–0.2)
37	400	2	–1.8 (–1.5)	2.0 (1.7)
38	400	4	–28.4 (–21.9)	6.4 (6.3)
39	400	9	–15.1 (–13.7)	4.4 (4.6)
40	400	9	–28.5 (–24.4)	7.5 (8.5)
41	400	5	–11.5 (–10.6)	5.8 (6.0)

[a]The numbers 200 and 400 refer to zonisamide doses.

for mental slowing, memory impairment, tactile hallucinations, and stomach ache), 6 taking 200 mg of zonisamide (2 patients for headache and 1 patient each for memory impairment, muscle weakness, irritability, and depressed mood), and 4 taking 400 mg of zonisamide (1 patient each for headache, somnolence, memory impairment, and depressed mood). Drug use (400 mg) was stopped for 1 patient who became pregnant; she gave birth to a healthy, full-term newborn. Twelve patients completed the study with a reduced dose (1 assigned to placebo, 2 assigned to 200 mg of zonisamide, and 9 assigned to 400 mg of zonisamide).

COMMENT

To our knowledge, this is the first randomized controlled trial examining the long-term efficacy of zonisamide for weight reduction. Zonisamide at a daily dose of 400 mg led to a 3.3-kg greater weight loss than diet and lifestyle intervention alone. Zonisamide at a daily dose of 200 mg was not efficacious.

A unique feature of this trial is the high retention rate. Of 48 patients who dropped out, 41 returned at the 1-year time point, leaving only 7 of 225 randomized patients lost to follow-up. Not surprisingly, multiple imputation and LOCF imputation procedures revealed almost identical results because few data were missing. Historically, dropout rates have generally been in the range of 30% to 50% in pharmaceutical weight loss trials, including recent long-term trials.[16-19] Interestingly, in the Contrave Obesity Research–Behavior Modification (COR-BMOD) trial that tested the addition of naltrexone and bupropion or placebo to intensive behavior modification, 42% withdrew early in the behavior modification (plus placebo) group and 12% cited an adverse event for discontinuation.[20] Simons-Morton et al[21] criticized obe-

Table 4. Adverse Events

Adverse Event[a]	No. (%) of Patients		
	Placebo (n = 74)	Zonisamide, 200 mg (n = 76)	Zonisamide, 400 mg (n = 75)
Altered taste	0	4 (5.3)	4 (5.3)
Dry mouth	3 (4.1)	5 (6.6)	1 (1.3)
Nausea/vomiting	4 (5.3)	4 (5.3)	10 (13.3)
Constipation	2 (2.7)	2 (2.6)	5 (6.7)
Diarrhea	1 (1.4)	2 (2.6)	4 (5.3)
Anxiety related	2 (2.7)	5 (6.6)	7 (9.3)
Depression related	3 (4.1)	3 (3.9)	5 (6.7)
Impaired attention/ concentration	1 (1.4)	1 (1.3)	4 (5.3)
Impaired memory	1 (1.4)	5 (6.6)	8 (10.7)
Language/speech problems	1 (1.4)	3 (3.9)	6 (8.0)
Headache	5 (6.8)	8 (10.5)	14 (18.7)
Fatigue	2 (2.7)	4 (5.3)	7 (9.3)
Somnolence	3 (4.1)	9 (11.8)	6 (8.0)
Insomnia	1 (1.4)	4 (5.3)	1 (1.3)
Infections	10 (13.5)	8 (10.5)	15 (20.0)
Musculoskeletal problems	9 (12.2)	11 (14.5)	8 (10.7)

[a] Adverse events reported by at least 5% patients in any of the treatment groups are listed.

sity trials with the argument that high attrition introduces a bias, and randomization does not serve its purpose when data from patients who have not adhered to treatment are not analyzed. A counterargument is that physicians are interested in treatment effects among patients who adhere to it and not the effect of being assigned to a treatment.

Various statistical models are used in obesity randomized controlled trials to make up missing data, the most common being LOCF. The Food and Drug Administration, in its guidance to industry,[22] recommends LOCF, which implicitly assumes that patients who withdraw early from a trial would have maintained the same weight at study exit as at the time of withdrawal. Other statistical imputation procedures make less restrictive assumptions for the individual patient or the assigned group based on patterns of weight change before dropout. Although some imputation procedures are superior to others, it is important to recognize that all imputation approaches make assumptions, some of which are inherently untestable (eg, that data are missing at random).[15]

Observations of weight change among the 41 patients in this trial, who dropped out early but returned for final assessment at 1 year, demonstrate that most obese patients gain weight or regain their lost weight after they drop out of a clinical trial, calling into question the results from trials with high dropout rates and the validity of commonly used imputation procedures in obesity randomized controlled trials. As indicated in Table 3, many patients who lost substantial weight before they dropped out regained considerable weight by the 1-year visit. The 11 dropouts in the 400-mg zonisamide group gained almost 5% weight on the average when they returned at 1 year.

There were no extraordinary efforts in this trial that could explain the high retention. There were no extended screening visits to ensure patients were serious about participation. Patients were educated about time and commitment required for participation and that they needed to make changes to their diet and lifestyle without which drug therapy would not help. They were counseled to have realistic expectations about what could be achieved in a year. Few patients were excluded during screening. They were told that if they withdrew early, they would be requested to return for a 1-year visit to complete final assessments, which would be valuable for the study's success. There was no coercion, and the stipend offered was minimal.

Historically, most obesity randomized controlled trials enrolled primarily white women. This trial enrolled a fair number of men (40.4%) and ethnic minorities (36.9%).

A notable limitation of this trial is that most patients did not have significant weight-related comorbidities. At baseline, patients had normal blood pressure, lipid levels, and glycemic measures. Reduction in risks associated with obesity is most demonstrable when patients with risk factors are enrolled. This is a consideration for future investigation.

In a preliminary trial by Gadde et al,[8] zonisamide achieved a 5-kg greater weight loss than placebo (5.9 vs 0.9 kg) in 16 weeks. The current randomized controlled trial examined whether zonisamide could enhance long-term weight loss achievable with a good quality diet and lifestyle intervention that is implementable in a primary care clinical setting. In contrast to the previous trial, the placebo group in the current randomized controlled trial achieved an impressive 4-kg weight loss. Our lifestyle intervention was not as intensive as the ones administered in the Diabetes Prevention Program,[3] Look AHEAD,[4] and COR-BMOD[20] trials and could be easily incorporated into primary care practices.

Although 400 mg of zonisamide demonstrated moderate efficacy of a magnitude similar to orlistat[6] and lorcaserin,[7] neuropsychiatric adverse events (mood changes and memory problems) occurred at a higher frequency relative to placebo. Hence, for treatment of obesity, the drug's benefit-to-risk ratio needs thoughtful and cautious assessment. The results of our trial must be considered in the context of our follow-up procedures, which were markedly different from those of typical weight loss trials.

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Medical Journal Editors Form for Disclosure of Potential Conflicts of Interest. Dr Gadde reported receiving grants from Bristol Myers Squibb, Forest Laboratories, National Institute of Diabetes and Digestive and Kidney Diseases, Pfizer, and Vivus in the past 36 months. He has been awarded several patents in the name of his institution for use of zonisamide as monotherapy and in combination with other drugs for treatment of obesity, as well as weight gain associated with psychotropic drugs; these patents have been licensed to Orexigen Therapeutics by his institution. Consequent to the licensing agreement, Dr Gadde owns equity in Orexigen, which is developing zonisamide and bupropion combination therapy for obesity, based on his patents. However, to the best of Dr Gadde's knowledge, no commercial entity has announced plans to develop zonisamide monotherapy for obesity or other applications claimed in his patents. Dr Allison has had financial interests with Arena Pharmaceuticals, EnteroMedics, Frontiers Foundation, Federal Trade Commission, Jason Pharmaceuticals, Kraft Foods, Mead Johnson Nutrition, Mead Johnson & Company, Medifast, Orexigen Therapeutics, Sage Publications, University of Arizona, University of Wisconsin, Vivus, Wolters Kluwer Pharma Solutions, and Paul, Weiss, Rifkind, Wharton & Garrison LLP. Dr Bray reported that he has been a consultant to Abbott Laboratories and Takeda Global Research Institute; is an advisor to Medifast, Herbalife, and Global Direction in Medicine; and has received royalties for the *Handbook of Obesity*.

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