

Zonisamide for Weight Loss in Obese Adults A Randomized Controlled Trial

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THE PREVALENCE OF OBESITY HAS increased dramatically in the past decade in the United States and many other developed countries.^{1,2} Because obesity is associated with a significantly increased risk for type 2 diabetes, coronary heart disease, hypertension, numerous other major illnesses, and overall mortality from all causes,^{3,4} weight reduction is critical for the obese patient.^{5,6} There is good evidence that pharmacotherapy can enhance weight loss when combined with interventions aimed at changing lifestyle,⁷ although pharmacological therapies currently approved by the US Food and Drug Administration fail to provide adequate benefit for many obese patients because of adverse effects, contraindications, or lack of positive response.⁷ Hence, there is impetus for developing new treatments for the management of obesity.

Zonisamide is a marketed antiepileptic drug. In short-term clinical trials of zonisamide in epileptic patients concomitantly receiving other antiepileptic agents, weight loss was an adverse effect.⁸ Whereas the anticonvulsant activity of zonisamide is believed to be related to its sodium and calcium channel (T-type) blocking activity,⁸ this drug is also known to exert dose-dependent biphasic dopaminergic⁹ and serotonergic¹⁰ activity. With this background, we hypothesized that zonisamide would be therapeutic for obese patients seeking to lose weight.

Context Zonisamide is a marketed antiepileptic drug that has serotonergic and dopaminergic activity in addition to blockade of sodium and calcium channels. Weight loss was an adverse effect associated with zonisamide treatment in epilepsy clinical trials.

Objective To evaluate the efficacy of zonisamide for weight loss in obese adults.

Design and Setting Sixteen-week randomized, double-blind, placebo-controlled trial with an optional single-blind extension of the same treatment for another 16 weeks, conducted at Duke University Medical Center from March 2001 to March 2002.

Participants Fifty-five (92%) women and 5 (8%) men (mean [SE] body mass index, 36.3 [0.5]; mean age, 37.0 (1.0) years).

Interventions Patients were randomly assigned to receive zonisamide (n=30) or placebo (n=30). All participants were prescribed a balanced hypocaloric diet (500 kcal/d deficit) and compliance was monitored with self-rated food diaries. Zonisamide therapy was started at 100 mg/d orally, with gradual increase to 400 mg/d and further increase to 600 mg/d for patients losing less than 5% of body weight at the end of 12 weeks. Placebo dosing was identical.

Main Outcome Measure Change in body weight.

Results Of the 60 randomized patients, 51 completed the 16-week acute phase. In an intent-to-treat analysis using the available data for all randomized participants with the last observation carried forward, the zonisamide group lost more body weight than the placebo group (mean [SE], 5.9 [0.8] kg [6.0% loss] vs 0.9 [0.4] kg [1.0% loss]; $t=5.5$; $P<.001$) during the 16-week period. A longitudinal mixed-model regression for weight change controlling for age, race, sex, body mass index, and percent body fat estimated that zonisamide treatment over the 16-week study duration was associated with significantly greater weight loss than was placebo ($t=6.4$; $P<.001$). Seventeen (57%) of 30 in the zonisamide group and 3 (10%) of 30 in the placebo group lost at least 5% of body weight ($P<.001$) by week 16. Of the 37 participants who entered the extension phase, 36 completed week 32. The zonisamide group (n=19) had a mean weight loss of 9.2 kg (1.7 kg) (9.4% loss) at week 32 compared with 1.5 kg (0.7 kg) (1.8% loss) for the placebo group (n=17) ($t=4.0$; $P<.001$). Zonisamide was tolerated well, with few adverse effects.

Conclusion In this short-term, preliminary trial, zonisamide and hypocaloric diet resulted in more weight loss than placebo and hypocaloric diet in the treatment of obesity.

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METHODS

This study was conducted at Duke University Medical Center, Durham, NC, from March 2001 to March 2002. The protocol was approved by the medical center's institutional review board before the trial began.

Study Participants

Study participants were selected from the clinic patient population and those

responding to advertisement fliers posted in the local area, and were enrolled between March 2001 and July 2001. Sixty-eight individuals were screened for participation and 60 were

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randomized. All participants provided written informed consent.

Included were men or women aged 21 to 50 years, with mean (SE) body mass index (BMI) of 36.3 (0.5). The minimum BMI range for inclusion, as specified in the protocol, was 30 to 44. Exclusion criteria were obesity of a known endocrine origin, such as hypothyroidism or Cushing syndrome; serious/unstable medical or psychiatric illness; current major psychiatric disorder; current drug or alcohol abuse; history of or current kidney disease or renal calculi; significant liver disease; uncontrolled hypertension; current diabetes mellitus; untreated or uncontrolled thyroid disease; weight loss or gain greater than 4 kg in past 3 months; history of obesity surgery; current or recent use of weight loss medications, herbs, or supplements; current or recent use of drugs, herbs, or dietary supplements known to significantly affect body weight; concomitant medications that significantly affect cytochrome P₄₅₀ 3A4 hepatic microsomal enzymes; hypersensitivity to sulfonamides; women of childbearing age not adhering to an acceptable form of contraception; pregnant or breastfeeding women; and individuals judged to be unable to follow instructions and study procedures.

Study Design

The study had 2 phases. The first was a 16-week, randomized, double-blind, parallel-group comparison of zonisamide and placebo. At the end of this phase, participants wishing to continue received the same treatment in a single-blinded fashion for an additional 16-week extension phase.

Randomization, Medication Dosing, and Dispensing

Study participants were randomized in a 1:1 ratio to receive zonisamide (Elan Biopharmaceuticals, Dublin, Ireland) or placebo capsules. The research pharmacy dispensed the study medication under blinded conditions through computer-based randomization. The randomization was generated using a random-number table with a block size of

10. There was no stratification by sex or other demographic variables. The study investigators were blinded to the “blocking” method used by the pharmacy. Treatment assignment codes were not available to the investigators until all patients completed the acute phase, the data had been entered, and the database for this phase was locked, precluding any subsequent changes to the data.

The study medication was dispensed in identically designed capsules—each capsule containing either 100 mg of zonisamide or placebo. The dose escalation was as follows: 1 capsule (zonisamide, 100 mg or placebo) daily for the first 2 weeks; 2 capsules (zonisamide, 200 mg or placebo) daily during weeks 3 and 4; 3 capsules (zonisamide, 300 mg or placebo) daily during weeks 5 and 6; and 4 capsules (zonisamide, 400 mg or placebo) daily from week 7 onward. At week 12, the dose could be increased further to 6 capsules (zonisamide 600 mg or placebo) daily for participants who had not lost at least 5% of their initial body weight. The entire daily dose was administered in the evening. If a patient preferred not to take all 6 capsules at one time, taking half of the daily dose in the morning was an option. Based on tolerability, dose escalation could be withheld or decreased. Medication compliance was overseen by recording the number of tablets returned and comparing this number with the number of capsules dispensed at each visit.

Diet and Lifestyle Counseling

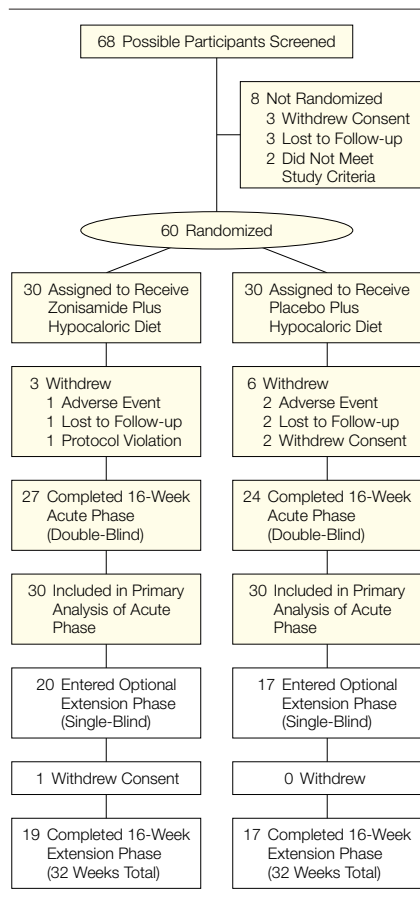
Patients in both groups were instructed to follow an individual diet that was calculated to reduce their daily energy intake by 500 kcal/d from the amount needed to maintain weight using the World Health Organization recommendations. The prescribed diet, based on eating a variety of foods from the US Department of Agriculture Food Guide Pyramid, emphasized decreasing portions, eating more fruits and vegetables, and drinking eight 8-oz glasses of water each day. Increased physical activity was also encouraged for participants in both groups. All study partici-

pants were asked to record their dietary intake and portion sizes in provided food diaries. A registered dietitian reviewed food diaries and provided counseling to all participants, who were encouraged to make healthy changes in their diets and physical activity.

Visits and Measurements

Patients were examined at weeks 0, 2, 4, 8, 12, and 16 in the acute phase, and every 4 weeks in the extension phase. During each visit, the following assessments were performed: blood pressure, heart rate, weight, dietary compliance, medication accountability and tolerability, and adverse effects. Body weight was measured on a calibrated electronic scale to the nearest 0.1 kg. The participants were always weighed in a hospital gown and weighed twice for accuracy. A registered dietitian reviewed food diaries and assessed dietary compliance. Adverse effects were gathered via spontaneous reporting by patients as well as open-ended inquiries by the clinicians. Reportable adverse effects were new symptoms or illnesses that emerged during treatment or those that had an increase in severity compared with baseline.

Study participants also completed the Impact of Weight on Quality of Life (IWQOL) questionnaire¹¹ at baseline, week 8, and week 16. The IWQOL is a self-report measure with 74 items that assess the perceived effect of weight on quality of life in the following domains (subscales): health, social/interpersonal life, work, mobility, self-esteem, sexual life, activities of daily living, and eating (comfort with food). Improvement with treatment is reflected by decreasing scores on all the subscales with the exception of the eating (comfort with food) subscale, which tends to move in the opposite direction. Body composition (fat and lean masses) and bone mineral density (BMD) were determined at baseline and week 32 by dual-energy x-ray absorptiometry (DXA). All DXA measurements were obtained using the same equipment and techniques. Participants were instructed to fast for 8 hours and not to drink water or other beverages

Figure 1. Flow of Participants Through the Study

ages for at least 4 hours prior to DXA measurement.

End Points and Measures of Outcome

The primary study end point was change in absolute body weight in kilograms from baseline to final assessment. In addition, we examined percent change in weight and the number of participants in each group who achieved weight losses of 5% or greater and 10% or greater. Secondary outcome measures included heart rate, blood pressure, frequency of adverse effects, fasting electrolytes and lipids, waist measurement, IWQOL score, body composition, and BMD.

Statistical Analysis

All randomized patients were included in the primary analysis. Weight

change during the study was assessed in terms of actual weight change over the 6 study intervals using multivariable regression methods, and as a dichotomous outcome of response, ie, 5% and 10% weight loss at week 16, and 10% weight loss at week 32. The proxy variables denoting response status were tested across treatment conditions using the Fisher exact test. Three multivariable regression analyses were conducted. In the first, body weights were regressed as above with missing observations carried forward from the last recorded weight, based on an intent-to-treat (ITT) approach. For the second set of analyses, body weight at each time point was modeled using a random-effects growth-curve model. Heuristically, the model fits a regression line for each patient using available data points, thus maximizing use of actual data. The final model was restricted to the subset of respondents with no missing data (completers). All models included covariates for age, sex, race, and baseline measures of percent body fat and BMI as well as proxy variables denoting treatment condition, time, and a term for the interaction of treatment \times time. In some instances, differences between the baseline and final measures were tested with the *t* test.

Secondary analyses were conducted for various clinical and laboratory measures (see "End Points and Measures of Outcome" section). When appropriate, analyses were based on 2-way repeated-measures analysis of variance that included time, treatment, and their interaction (time \times treatment). In each case, the interest was to determine if patients in the zonisamide group were differentially affected relative to controls as operationally determined by testing the significance of the estimated interaction term. For analysis of the IWQOL subscales, repeated measurements were taken at baseline, week 8, and week 16. In some instances, differences between the baseline and final measures were tested with the *t* test.

Bivariate change in body mass from baseline to week 32 by treatment condition was tested using the *t* test. As a

null hypothesis postulating equality of variances between the 2 conditions was rejected, differences were tested using the Satterwaite method for unequal variances. Data also are presented as percent change although statistical testing was conducted using actual units. The association between change in body weight and change in fat mass was tested using ordinary least-squares regression. Change in body weight from baseline to week 32 was regressed on change in fat mass, treatment condition, and an interaction term crossing the 2 main effect variables.

The frequencies of occurrence of individual adverse effects were tested across drug conditions using the Fisher exact test. All analyses were carried out using SAS v8.0 (SAS Institute Inc, Cary, NC); $P = .05$ was used to determine statistical significance.

RESULTS

Patient Characteristics and Disposition

Of the 68 individuals screened for participation, 8 were ineligible (FIGURE 1). The 60 remaining patients were randomized, with 30 receiving zonisamide and 30 receiving placebo; all patients also adhered to a hypocaloric diet. Nine patients—3 in the zonisamide group and 6 in the placebo group—dropped out prematurely; thus, 51 of 60 completed the first 16 weeks.

The baseline characteristics of participants were similar between the treatment groups, except that all 5 men in the study were randomized to zonisamide ($P = .08$) and baseline BMI was slightly lower ($P = .07$) in the zonisamide group (TABLE).

16-Week Treatment Phase

The prescribed mean (SE) highest daily dose of zonisamide was 427 (29) mg, corresponding to 4.27 capsules, whereas the placebo group received 500 mg, corresponding to 5.00 capsules.

Weight Loss. The curves for weight loss in kilograms over the 16-week duration for the zonisamide and placebo groups are shown in FIGURE 2. In the last observation carried forward

(LOCF) analyses for the ITT population, the mean (SE) absolute weight for the zonisamide group changed from 98.2 (2.5) kg at baseline to 92.3 (2.5) kg at week 16, whereas for the placebo group, the corresponding change was 97.8 (2.6) kg to 96.9 (2.8) kg; ie, the zonisamide group lost 5.9 (0.8) kg (6.0%) during the initial 16-week period vs 0.9 (0.4) kg (1.0%) for placebo patients ($t=5.5$; $P<.001$).

For the subset of patients completing the initial 16-week phase as randomized, the mean (SE) absolute weight for the zonisamide group changed from 97.2 (2.4) kg at baseline to 90.8 (2.3) kg at week 16; for the placebo group, the corresponding change was 97.6 (2.7) kg to 96.5 (2.9) kg. Thus, the difference between treatment groups in the achieved weight loss over time remained significant (6.4 [0.8] kg [6.6%] vs 1.1 [0.4] kg [1.3%]; $t=5.4$; $P<.001$).

Results from the longitudinal regression analyses supported differential weight loss for zonisamide-treated patients. Regardless of imputation procedure, the time \times treatment interaction differed significantly from zero in all models. For the LOCF-imputed ITT model, the estimated regression coefficient associated with the interaction term predicted weight loss in excess of 0.29 kg/wk over the 16-week study period ($t=6.4$; $P<.001$); complementary values for the other 2 models were 0.33 kg/wk using the growth-curve model ($t=10.5$; $P<.001$), and 0.31 kg/wk as estimated from the model only on data for patients completing the protocol as randomized ($t=6.1$; $P<.001$).

In the LOCF population, 17 of 30 patients (57%) in the zonisamide group and 3 of 30 patients (10%) in the placebo group achieved a weight loss of 5% or greater at week 16 ($P<.001$). Of the 17 responders in the zonisamide group, 7 attained a weight loss of 10% or more; none of the patients in the placebo group achieved 10% weight loss ($P=.005$).

Other Efficacy Measures. The following subscales of the IWQOL scale improved more significantly in the zonisamide group over the placebo

group at week 16: health ($F_{2,98}=4.6$; $P<.01$), work ($F_{2,98}=4.5$; $P<.01$), mobility ($F_{2,98}=3.9$; $P<.02$), and activities of daily living ($F_{2,98}=4.9$; $P<.01$). Mean (SE) waist circumference decreased more with zonisamide therapy over the 16 weeks (103.5 [1.6] cm to 97.2 [1.8] cm vs 103.2 [1.9] cm to 100.5 [2.0] cm; interaction of treatment \times time: $F_{2,98}=7.8$; $P<.001$). Heart rate decreased by an average of approximately 2/min in the overall sample ($P<.001$), although there was no difference between the groups. Systolic and diastolic blood pressure readings did not change over time. There were no clinically significant changes in levels of lipids or fasting blood glucose with either treatment.

Safety Measures. Patients assigned to zonisamide reported, on average, 2.1 adverse effects over the study period compared with 1.6 for those assigned to placebo ($t=1.6$; $P=.12$). Of the individual adverse effects, 10 patients in the zonisamide group and 1 in the placebo group reported fatigue ($P<.006$ by Fisher exact test); no other adverse effects were reported differentially between the groups. Mean (SE) serum creatinine concentration increased from 0.79 (0.03) mg/dL (69.8 [2.6] $\mu\text{mol/L}$) at baseline to 0.92 (0.03) mg/dL (81.3 [2.6] $\mu\text{mol/L}$) with zonisamide treatment while the change for placebo was 0.76 (0.02) mg/dL (67.2 [1.8] $\mu\text{mol/L}$) to 0.79 (0.02) mg/dL (69.8 [1.8] $\mu\text{mol/L}$) ($t=3.9$; $P<.001$).

Extension Phase

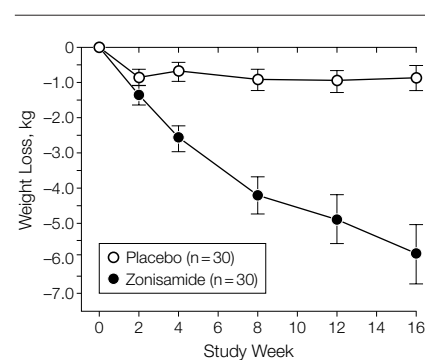
There were no significant group differences with regard to baseline characteristics of the extension phase participants with the exception of a slightly lower mean BMI in the zonisamide group (34.9 vs 37.3; $P<.05$). Moreover, the characteristics of those who participated in the extension phase were essentially the same as those of the 60 participants who originally entered the study. Of the 37 patients (20 zonisamide, 17 placebo) who entered the extension phase, 36 completed week 32. One patient in the zonisamide group withdrew prematurely, citing time con-

Table. Baseline Characteristics of the Participants

Characteristic	Zonisamide Group (n = 30)	Placebo Group (n = 30)
Age, mean (SE), y	37.5 (1.3)	36.4 (1.6)
Sex, No. (%)		
Men	5 (16.7)	0
Women	25 (83.3)	30 (100)
Race, No. (%)		
Black	12 (40.0)	17 (56.7)
White	18 (60.0)	13 (43.3)
Weight, mean (SE), kg	98.2 (2.5)	97.8 (2.6)
Body mass index, mean (SE)*	35.4 (0.7)	37.2 (0.8)
Body fat, mean (SE), %	40.8 (0.9)	42.6 (0.8)

*Defined as weight in kilograms divided by the square of height in meters (kg/m^2). Baseline body mass index differed slightly between groups ($P=.07$).

Figure 2. Pattern of Weight Change From Baseline to Week 16 in Obese Patients Who Received Zonisamide or Placebo



Data from the last observation carried forward, intent-to-treat analysis. Error bars indicate SE.

straints. Ten of 19 zonisamide patients and none of the placebo patients lost at least 10% weight at week 32 ($P<.001$). Mean (SE) weight changed over the 32 weeks for patients in the zonisamide group from 96.9 (3.0) kg to 87.6 (3.0) kg, whereas the change for the patients in the placebo group was from 96.4 (3.0) kg to 94.9 (3.4) kg; ie, zonisamide therapy led to a weight loss of 9.2 (1.7) kg (9.4%) at week 32 compared with 1.5 (0.7) kg (1.8%) with placebo therapy ($t=4.0$; $P<.001$).

The following subscales of the IWQOL scale improved more significantly in the zonisamide group vs the placebo group at week 32: health

($F_{3,102}=5.0$; $P<.003$), work ($F_{3,102}=4.5$; $P<.005$), mobility ($F_{3,102}=5.3$; $P<.002$), and activities of daily living ($F_{3,102}=6.4$; $P<.001$).

Mean (SE) waist circumference decreased more in the zonisamide group over the 32 weeks (103.5 [2.0] cm to 93.6 [2.2] cm vs 103.8 [2.4] cm to 100.5 [2.5] cm in the placebo group; ie, a reduction of 9.8 (1.7) cm for patients treated with zonisamide vs 3.3 (0.6) cm for patients receiving placebo ($F_{3,102}=8.4$; $P<.001$).

Mean (SE) systolic blood pressure decreased in both treatment groups although the decrease was significantly greater in the zonisamide group (129.1 [2.5] mm Hg to 122.3 [1.8] mm Hg vs 128.2 [1.8] mm Hg to 126.8 [1.8] mm Hg; interaction of treatment \times time: $F_{9,306}=2.7$; $P<.005$). Diastolic blood pressure decreased with zonisamide treatment, but not with placebo (82.5 [1.8] mm Hg to 79.7 [1.2] mm Hg vs 82.5 [1.8] mm Hg to 82.2 [1.1] mm Hg; interaction of treatment with time: $F_{9,306}=2.0$; $P<.04$). Neither treatment was associated with a significant change in heart rate. There were no clinically significant changes in lipid levels with either treatment.

Mean (SE) fat mass for patients receiving placebo increased by 0.5% (1.5%) over the course of 32 weeks. In contrast, patients treated with zonisamide had a decrease in fat mass of 11.7% (3.2%). Satterwaite *t* test of this difference was significant ($t=3.7$; $P<.001$). A multivariable analysis regressing weight change on fat mass change, treatment, and an interaction term crossing the latter 2 variables yielded a significant interaction term indicating that weight loss for patients treated with zonisamide was significantly associated with a decrease in fat mass ($t=2.2$; $P<.04$). Lumbar spine BMD did not change over time in either group. Total BMD showed a small but statistically significant ($P<.02$) increase in the overall sample although there was no difference between the groups. As in the acute phase, fatigue was the only adverse event that was reported more frequently by patients treated with zonisamide than by con-

trols (7 vs 0; $P<.009$). Mean (SE) serum creatinine concentration increased from 0.78 (0.03) mg/dL (69.0 [2.6] μ mol/L) at baseline to 0.92 (0.03) mg/dL (81.3 [2.6] μ mol/L) with zonisamide treatment while the change for placebo was 0.75 (0.02) mg/dL (66.3 [1.8] μ mol/L) to 0.77 (0.02) mg/dL (68.1 [1.8] μ mol/L) ($F_{2,68}=11.0$; $P<.001$).

COMMENT

This randomized study demonstrated that zonisamide therapy combined with a hypocaloric diet produced significantly greater weight loss than dietary intervention alone in a population of obese. During the first 16 weeks, when the treatment was administered in a double-blind fashion, the superior weight loss efficacy of zonisamide over placebo was demonstrated in all the various analyses undertaken. The difference in the weight loss efficacy between the active treatment and placebo was evident by 4 weeks and increased as the study progressed.

The extension phase (second 16 weeks) of the trial demonstrated that patients receiving zonisamide therapy continued to lose weight, whereas the group that received dietary intervention and placebo lost less weight. Given the low-key adjunctive dietary and lifestyle intervention provided in this study, a mean weight loss of 9.2 kg (9.4%) at 32 weeks may be regarded as a clinically meaningful finding.

In addition to weight loss, zonisamide therapy led to improvement of some risk factors associated with obesity. Waist circumference decreased more significantly with zonisamide therapy compared with placebo, which was likely related to a greater degree of weight loss rather than being an independent effect. In addition, a reduction in systolic blood pressure was noted with zonisamide therapy although the study participants were not hypertensive at baseline. Zonisamide therapy was associated with a significant improvement of quality of life as noted by decreased scores on the following IWQOL measures: mobility, general health, occupational functioning, and activities of daily

living. Because there is some evidence¹² that weight loss leads to reduction of BMD, we examined this before and after 32 weeks of treatment. No significant loss of BMD was observed for participants in our study.

Zonisamide was tolerated well in this study. Premature withdrawals were much less frequent than expected in obesity trials of similar duration. Only 1 patient withdrew from the zonisamide group citing an adverse effect. Overall, fatigue was the only adverse effect that occurred at a significantly higher frequency for zonisamide treatment than for placebo. Our data collection relied on spontaneous reporting and open-ended inquiries that may have yielded a lower frequency of adverse effects than could be elicited with structured questionnaires. Although not observed frequently in this study, the following adverse effects occurred frequently with zonisamide therapy in epilepsy trials: dizziness, cognitive impairment, and somnolence.^{8,13} Because zonisamide is a sulfonamide, there is a potential for hypersensitivity reactions. Although rare, kidney stones and serious hematologic events have been reported with zonisamide therapy in patients with epilepsy. Consistent with data from epilepsy trials, we noted an increase in serum creatinine concentration with zonisamide therapy, but not with placebo. Whereas the increase in the first 16 weeks (approximately 16%) was significant, there was no further increase in the extension phase; no value exceeded the upper limit of normal range, and there were no clinical events associated with the increase.

To our knowledge, the present study is the first clinical trial to specifically assess the therapeutic potential of zonisamide as a weight loss tool in the management of clinically defined obesity. Whereas zonisamide was associated with a small degree of weight loss as an adverse effect in the treatment of patients with epilepsy, this was investigated as the desired effect in this study, and the observed weight loss was significant and clinically meaningful.

The pharmacological properties of zonisamide that contributed to its anorectic effect have not been precisely delineated. Whereas the antiepileptic properties of zonisamide are believed to be related to its blocking effects on sodium and T-type calcium channels,⁸ its effects on brain serotonin (5-HT)¹⁰ and dopamine⁹ systems may explain, at least partly, its weight loss efficacy in the present study. Serotonin has been implicated in modulation of satiety; nevertheless, some, but not all, drugs that enhance serotonergic tone via different mechanisms have been found to be valuable tools in the management of obesity.¹⁴ There is evidence that zonisamide stimulates serotonin turnover in the striatum and hippocampus in therapeutic doses, whereas very high doses have the opposite effect.¹⁰

Although the precise mechanisms involving a zonisamide-induced increase in extracellular serotonin levels are not known, 2 mechanisms have been suggested: an increase in ion-dependent serotonin release,^{15,16} and increased synthesis of serotonin.¹⁷ Dopamine is thought to mediate many

pleasurable behaviors including food intake.¹⁸ Dopamine D₂-receptor agonists inhibit feeding,¹⁹ and obese individuals have reduced density of striatal D₂ receptors.²⁰ Zonisamide, in therapeutic doses, enhances dopamine synthesis with a resultant increase in levels of intracellular dopamine and metabolites; although some degree of monoamine oxidase type B enzyme inhibition may be caused by zonisamide, this is not a major finding during chronic administration of this drug. It has also been suggested that zonisamide stimulates D₂ receptors.⁹

Nevertheless, other drugs (eg, carbamazepine) having a few similar effects on monoamine systems have not been known to be associated with significant weight loss. A relatively weak property of zonisamide is inhibition of carbonic anhydrase activity.¹³ In this context, it may be of interest that carbonic anhydrase inhibitors have been reported to alter taste, thereby causing an anorectic effect.²¹⁻²³ Numerous peptides acting in the brain as well as in the periphery have been strongly implicated in modulating appetite and feeding signals,²⁴ and the effects, if any,

of zonisamide on these substrates are not known. Although we have speculated about the possible mechanisms for zonisamide-induced weight loss, the precise mechanism is not known.

In conclusion, the results of this short-term study provide preliminary evidence that zonisamide, in conjunction with diet, can be more effective than diet alone for obese patients seeking to lose weight.

Author Contributions: Dr Gadde, as principal investigator of this study, had full access to all of the data in this study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: Gadde, Franciscy, Krishnan.

Acquisition of data: Gadde, Franciscy.

Analysis and interpretation of data; statistical expertise: Gadde, Wagner.

Drafting of the manuscript; critical revision of the manuscript for important intellectual content: Gadde, Franciscy, Wagner, Krishnan.

Obtained funding: Gadde.

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