Combination Therapy of Zonisamide and Bupropion for Weight Reduction in Obese Women: A Preliminary, Randomized, Open-Label Study

Kishore M. Gadde, M.D.; Gretchen M. Yonish, R.D.; Mariko S. Foust, R.D.; and H. Ryan Wagner II, Ph.D.

Objective: Zonisamide and bupropion have been investigated for weight reduction in obese adults. We conducted a preliminary study comparing the effect on body weight of the combination of these 2 drugs versus zonisamide monotherapy.

Method: This was a 12-week, randomized, open-label, parallel-group comparison of 2 active interventions conducted from October 2003 to June 2004. Eighteen obese women (mean [SE] body mass index of 36.8 [1.2] kg/m^2) were randomly assigned to receive the combination of zonisamide and bupropion (N = 9) or zonisamide alone (N = 9). All subjects were prescribed a balanced hypocaloric diet (500 kcal/day deficit) and compliance was monitored with self-rated food diaries. Zonisamide therapy was started at 100 mg/day, with a gradual increase to 400 mg/day over 4 weeks for both groups. In addition, the group assigned to combination therapy received bupropion, which was started at 100 mg/day, with an increase to 200 mg/day after 2 weeks. Zonisamide was administered at night and bupropion in the morning. Body weight in kilograms was the primary outcome measure.

Results: In an intent-to-treat analysis, carrying the last observation forward for all randomly assigned participants with at least 1 postbaseline assessment, the combination group lost more body weight than the zonisamide group (mean [SE] = 7.2 [1.2] kg [7.5%] vs. 2.9 [0.7] kg [3.1%]; F = 4.7, df = 4,56; p = .003) during the 12-week period. For the subset of 12 patients (combination, N = 7; zonisamide, N = 5) that completed the full 12-week treatment, the mean (SE) weight loss was 8.1 (1.4) kg (8.5%) for the combination group versus 3.0 (0.9) kg (3.3%) for the zonisamide group (F = 4.6, df = 4,40; p = .004). Six subjects in the combination group and 2 in the zonisamide group lost at least 5% of body weight.

Conclusion: In this short-term, open-label, preliminary trial, combination treatment of zonisamide and bupropion resulted in more weight loss than treatment with zonisamide alone.

(J Clin Psychiatry 2007;68:1226–1229)

Received July 15, 2006; accepted Nov. 27, 2006. From the Obesity Clinical Trials Program, Duke University Medical Center, Durham, N.C.

There was no external funding for this research.

Dr. Gadde has received research support from the National Institute of Diabetes and Digestive and Kidney Diseases, GlaxoSmithKline, Elan, Johnson & Johnson, Eli Lilly, and Vivus; has served as a consultant for Orexigen, GlaxoSmithKline, and Vivus; and owns stock in Orexigen Therapeutics. Duke University was awarded U.S. patent 7,109,198 for this combination therapy in September 2006 titled "Method for Treating Obesity" with Dr. Gadde as an inventor; Duke University has licensed this invention to Orexigen. Ms. Yonish, Ms. Foust, and Dr. Wagner report no additional financial affiliations or other relationships relevant to the subject of this article.

Corresponding author and reprints: Kishore M. Gadde, M.D., Box 3292, Duke University Medical Center, Durham, NC 27710 (e-mail: gadde001@mc.duke.edu).

Bupropion, marketed as an antidepressant and smoking cessation aid, has been demonstrated to promote weight loss in obese adults in 3 randomized controlled trials.[1–3] There is evidence from one randomized controlled trial that zonisamide, an antiepileptic drug, is superior to placebo in assisting obese individuals to lose weight.[4] Bupropion is known to enhance the activity of norepinephrine and dopamine, whereas zonisamide has similar effects on serotonin and dopamine.[1,4] We hypothesized that because all 3 major neurotransmitters that regulate appetite and energy homeostasis are targeted with the combination of zonisamide and bupropion, the combination therapy might lead to greater weight loss than either drug alone. Another reason for combining these drugs was the hope that certain known adverse effects of zonisamide, such as somnolence, psychomotor slowing, cognitive impairment, fatigue, and depression, could potentially be offset by the known side effects of bupropion, such as insomnia, activation, and psychomotor agitation, as well as its antidepressant effect. Further, zonisamide might potentially reduce the seizure risk associated with bupropion. Therefore, we conducted this preliminary investigation to examine the effect of the combination therapy on body weight compared with zonisamide monotherapy.

METHOD

Experimental Design

This was a 12-week, randomized, open-label, parallel-group comparison of zonisamide versus zonisamide plus

bupropion combination. The protocol was approved by the Duke University 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 of Durham, N.C. Nineteen women were screened, and 18 were randomly assigned from October 2003 to June 2004. All participants provided written informed consent.

Included were women aged 21 to 55 years, with a body mass index of 30 to 44 kg/m^2, mean (SE) = 36.8 (1.2) kg/m^2. Given the potential risk of unbalanced gender distribution across the 2 treatment groups creating difficulty in interpreting results in this small sample study, we decided to restrict participation to women only.

Exclusion criteria were obesity of a known endocrine origin, such as hypothyroidism or Cushing's syndrome; serious or unstable medical illness; history of seizure disorder or significant head trauma; history of bulimia or anorexia; history of renal calculi; diabetes mellitus; uncontrolled hypertension; untreated or uncontrolled thyroid disease; major psychiatric disorder or alcohol or substance abuse within the past year; weight loss of greater than 4 kg in the past 3 months; history of bariatric surgery; current or recent use of other weight-loss medications, herbs, or dietary supplements known to affect body weight or have the potential to compromise patient safety in combination with the study drugs; current participation in other weight-loss programs; known hypersensitivity to sulfonamides, zonisamide, or bupropion; women of childbearing potential not adhering to an acceptable form of contraception; pregnant or breast-feeding women; and individuals judged by the investigators to be inappropriate for reasons such as inability to follow instructions and study procedures.

Randomization and Study Drugs

Subjects were randomly assigned to 1 of the 2 study interventions via a computer-generated random-number table. There was no stratification by demographic characteristics. Subjects and investigators were not blind to the treatment assignment. The zonisamide group received zonisamide only, whereas the combination group received zonisamide plus bupropion.

All study subjects received zonisamide, which was started at 100 mg/day, and the dose was increased to 200 mg/day during the second week, 300 mg/day during the third week, and 400 mg/d from the fourth week onward. The entire daily dose of zonisamide was administered at bedtime. The subjects assigned to the combination group received bupropion in addition. Sustained-release bupropion was started at 100 mg/day, the dose was increased to 200 mg/day at the beginning of the third week, and this dose was continued until the final visit (week 12). The entire daily dose of bupropion was administered in the morning. Dose titration was flexible, based on tolerability. Medication compliance was overseen by comparing the number of capsules dispensed and returned.

Diet Counseling

Participants in both groups were instructed to follow a balanced diet that was calculated to reduce their energy intake by 2100 kJ/day (500 kcal/day deficit) from the maintenance level of caloric intake using the World Health Organization equations for basal metabolic rate with adjustment for activity level.[5] Study participants were asked to record their dietary intake in food diaries given to them. A registered dietician reviewed the food diaries and provided advice via 10-minute individual sessions every 4 weeks.

Measurements and Visits

Screening assessments (baseline visit) included review of medical history and physical examination. There was no run-in period. Subjects meeting eligibility criteria were started on the study drug(s) with follow-up visits taking place at weeks 2, 4, 8, and 12. During each visit, the following assessments were performed: blood pressure, heart rate, weight, adverse effects, and medication accountability. Body weight was measured on a calibrated electronic scale to the nearest 0.1 kg. Participants were weighed in a hospital gown and weighed twice for accuracy with the average of the 2 measurements recorded. Waist circumference was assessed at baseline and study exit. Adverse events were gathered via spontaneous reporting by participants as well as by open-ended questions. Reportable adverse effects were problems that emerged during the course of treatment or increased in severity relative to baseline.

Measures of Outcome

The primary study outcome of interest was change in body weight in kilograms from baseline to study exit using actual weight. In addition, we examined percent change in weight and the number of participants in each group who achieved at least 5% weight loss. Secondary outcome measures included waist circumference, heart rate, and blood pressure.

Statistical Analysis

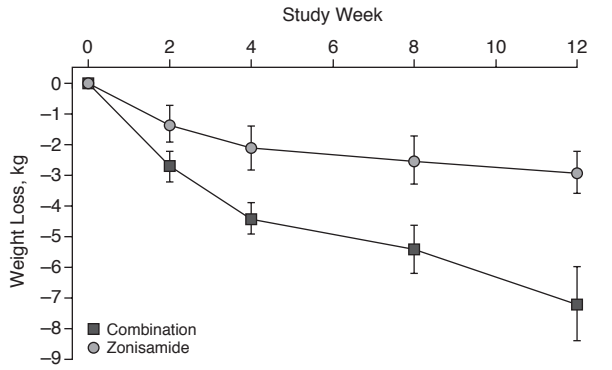
All randomly assigned subjects who had at least 1 post-randomization assessment were included in the primary analysis. Weight change over time was analyzed using 2-way repeated measures analysis of variance with the last-observation-carried-forward (LOCF) method of imputation for missing data. A repeated measures analysis of covariance adjusted for the demographic variables of age, race, and baseline weight was conducted to confirm the repeated measures analysis of variance results.

Table 1. Baseline Characteristics of the Subjects in a Study of Zonisamide Alone or in Combination With Bupropion for Obesity[a]

Characteristic	Zonisamide + Bupropion (N = 9)	Zonisamide Alone (N = 9)
Age, y	35.8 (3.5)	41.0 (2.8)
Race, N		
Black	6	3
White	3	6
Weight, kg	96.4 (5.0)	101.9 (7.1)
Body mass index, kg/m^2	36.3 (1.8)	37.3 (1.8)

[a]Age, weight, and body mass index are presented as group means (SE). There were no statistically significant differences between the groups with regard to baseline characteristics.

Figure 1. Pattern of Weight Change From Baseline to Week 12 in Obese Women Who Received Zonisamide Monotherapy or Zonisamide Plus Bupropion Combined Therapy[a]



[a]Data are from intent-to-treat last-observation-carried-forward analysis of 16 subjects (9 in the combination group, 7 in the zonisamide group) who had at least 1 postbaseline assessment.

Categorical outcomes were compared using Fisher exact test. For secondary analyses, data of subjects completing all visits were analyzed using 2-way repeated-measures analysis of variance or t tests as appropriate.

RESULTS

Characteristics and Disposition of Participants

Of the 19 individuals screened for participation, 1 subject decided not to participate. Eighteen subjects were randomly assigned in a 1:1 ratio to 1 of 2 treatments—9 to receive zonisamide monotherapy and 9 to receive the combination of zonisamide and bupropion. Six participants—4 in the zonisamide group and 2 in the combination group—withdrew early; thus, 12 subjects completed the full 12-week treatment. Reasons for early withdrawal were adverse effects (2 in the combination group), lost to follow-up (1, zonisamide), lack of efficacy (1, zonisamide), and consent withdrawn (2, zonisamide). Both early withdrawals in the combination group were related to neuropsychiatric adverse events. One subject reported irritability, headache, and difficulty with concentration, language, and speech. The second subject reported mild short-term memory impairment. In both cases, the adverse effects resolved a few days after discontinuing the study drugs.

The baseline characteristics of participants were essentially similar between treatment groups (Table 1) with no statistically significant differences.

For the intent-to-treat last-observation-carried-forward (ITT-LOCF) analysis, 16 patients were included. Excluded were 2 zonisamide subjects who had no postrandomization assessments; for these participants, reasons were "lost to follow-up" and "consent withdrawn (no longer a priority)."

Weight Loss

The curves for weight loss in kilograms over the 12-week duration for the zonisamide and combination groups are shown in Figure 1. For the ITT-LOCF sample, the mean (SE) body weight changed from 96.4 (5.0) kg at baseline to 89.2 (4.9) kg at week 12 for the combination group (N = 9), whereas for the zonisamide group (N = 7), the corresponding change was 100.2 (8.8) kg to 97.4 (9.0) kg (treatment × time interaction: $F = 4.7$, $df = 4,56$; $p = .003$); i.e., mean weight change for the combination group was –7.2 (1.2) kg (–7.5%) over the 12-week period versus –2.9 (0.7) kg (–3.1%) for zonisamide. Six subjects in the combination group and 2 in the zonisamide group lost at least 5% of body weight.

For the subset of patients completing the full 12-week treatment, the mean (SE) absolute weight for the combination group (N = 7) changed from 97.4 (6.5) kg at baseline to 89.2 (6.4) kg at week 12; for the zonisamide group (N = 5), the corresponding change was 97.9 (10.7) kg to 94.9 (10.9) kg (treatment × time interaction: $F = 4.6$, $df = 4,40$; $p = .004$). Thus, the 2 treatments differed significantly with regard to change in weight (–8.1 [1.4] kg [–8.5%] vs. –3.0 [0.9] kg [–3.3%]).

A repeated measures ANCOVA adjusted for the subject age, race, and baseline weight yielded significant time × treatment interaction for the LOCF ($F = 7.0$, $df = 1,46$; $p = .011$) and completer ($F = 7.1$, $df = 1,34$; $p = .011$) samples described above. To insure that the latter findings were not biased by patterns of missing data, the above model was reestimated after full-sample multiple imputation using SAS version 9.1, PROC MI and PROC MIANALYZE (SAS Institute, Cary, N.C.).[6] As indicated by the time × treatment interaction, weight loss over the study duration again was significantly greater for subjects randomized to combination treatment ($t = –2.60$; $p = .010$).

Secondary Measures

Waist circumference decreased significantly for the overall study sample ($p = .002$); however, there was no

significant difference between the groups. There were no significant changes in blood pressure or heart rate over time for the overall sample or between the groups.

Safety and Tolerability

The following adverse events were recorded (number of subjects): anxiety (1, combination group); dry mouth (1, combination; 1, zonisamide); memory problems (2, combination); difficulty with concentration (1, combination; 1, zonisamide); language and speech difficulty (1, combination); irritability (1, combination; 1, zonisamide); light-headedness (1, combination); drowsiness (1, zonisamide); fatigue (1, zonisamide); metallic taste (1, zonisamide); nausea (1, combination); constipation (1, combination); diarrhea (1, zonisamide).

DISCUSSION

To our knowledge, this is the first study examining the effect of combination therapy of zonisamide and bupropion on body weight in obese individuals. This preliminary study has several limitations and weaknesses, such as open-label administration of study treatments, small sample size, short duration, and no male subjects. Additionally, 2 comparison groups—bupropion monotherapy and placebo—were not included in the study design, thus limiting interpretation of the results.

Nevertheless, our data provide a preliminary suggestion that combined administration of zonisamide and bupropion might be associated with a more robust weight-loss effect than zonisamide monotherapy. Relative to the results reported in a previously published randomized controlled trial of zonisamide, weight loss achieved with zonisamide monotherapy in this study was of a smaller magnitude; higher rate of attrition in the zonisamide only group might have affected the mean weight loss in this group. Whereas our data do not suggest improved tolerability for the combination treatment, we must keep in mind that much larger samples are typically needed for assessment of safety and comparison of adverse effects. Future studies could consider using different doses of bupropion and zonisamide (e.g., higher dose of bupropion combined with a lower dose of zonisamide), slower dose titration of zonisamide, inclusion of bupropion monotherapy and placebo groups, larger samples, and trials of longer duration.

Drug names: bupropion (Wellbutrin, Zyban, and others), zonisamide (Zonegran and others).

REFERENCES

1. Gadde KM, Parker CB, Maner LG, et al. Bupropion for weight loss: an investigation of efficacy and tolerability in overweight and obese women. Obes Res 2001;9:544–551
2. Anderson JW, Greenway FL, Fujioka K, et al. Bupropion SR enhances weight loss: a 48-week double-blind, placebo-controlled trial. Obes Res 2002;10:633–641
3. Jain AK, Kaplan RA, Gadde KM, et al. Bupropion SR vs placebo for weight loss in obese patients with depressive symptoms. Obes Res 2002; 10:1049–1056
4. Gadde KM, Franciscy DM, Wagner HR II, et al. Zonisamide for weight reduction in obese adults: a randomized controlled trial. JAMA 2003; 289:1820–1825
5. World Health Organization. WHO Energy and Protein Requirements. Geneva, Switzerland: World Health Organization; 1985
6. Gadbury GL, Coffey CS, Allison DB. Modern statistical methods for handling missing repeated measurements in obesity trial data: beyond LOCF. Obes Rev 2003;4:175–184

