Acamprosate in the Treatment of Binge Eating Disorder: A Placebo-Controlled Trial

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ABSTRACT

Objective: To assess preliminarily the effectiveness of acamprosate in binge eating disorder (BED).

Method: In this 10-week, randomized, placebo-controlled, flexible dose trial, 40 outpatients with BED received acamprosate ($N = 20$) or placebo ($N = 20$). The primary outcome measure was binge eating episode frequency.

Results: While acamprosate was not associated with a significantly greater rate of reduction in binge eating episode frequency or any other measure in the primary longitudinal analysis, in the endpoint analysis it was associated with statistically significant improvements in binge day frequency and measures of obsessive-compulsiveness of binge eating, food craving, and quality of life. Among completers, weight and BMI decreased slightly in the acamprosate group but increased in the placebo group.

Discussion: Although acamprosate did not separate from placebo on any outcome variable in the longitudinal analysis, results of the endpoint and completer analyses suggest the drug may have some utility in BED. © 2010 by Wiley Periodicals, Inc.

Keywords: acamprosate; binge eating disorder; obesity; glutamate

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Introduction

Binge eating disorder (BED), characterized by recurrent binge-eating episodes without inappropriate compensatory weight loss behaviors,[1] is an important public health problem. Its lifetime prevalence in the United States general population is estimated to be 3% and it is associated with psychiatric comorbidity, obesity, impaired quality of life, and disability.[2–4]

The treatment of BED remains a challenge.[5] Cognitive behavioral and interpersonal therapies and selective serotonin-reuptake inhibitor (SSRI) antidepressants are effective for reducing binge eating, but usually are not associated with clinically significant weight loss.[6–8] Sibutramine, topiramate, zonisamide, atomoxetine, and orlistat are effective for decreasing both binge eating and body weight, but are associated with problematic side effects and relatively high

discontinuation rates.[9–17] Moreover, a substantial number of patients do not respond adequately to these psychological or pharmacological treatments. Novel treatments are therefore needed for BED.

Several lines of evidence suggested that acamprosate—a glutamate receptor modulator approved for maintenance of abstinence in patients with alcohol dependence in many countries[18,19]—might be a useful treatment for BED. First, eating disorders, including BED, may be related to addictive disorders.[20–23] Persons with BED from the general population have elevated rates of substance use disorders.[3] The binge eating of BED is characterized by craving for food and loss of control over eating that are similar to the craving for alcohol and drugs and loss of control over the use of these substances that are seen in persons with addictions. Indeed, eating disorders with binge eating have been conceptualized as forms of food addiction.[21]

Second, increasing research indicates that the glutamate system plays an important role in the regulation of food intake[24,25] as well as the abuse of alcohol and illicit drugs,[26,27] and that compounds that diminish glutamate system function may reduce binge eating.[11,12] Acamprosate, which antagonizes the glutamate *N*-methyl-D-aspartate (NMDA) receptor, has been reported to reduce food craving and weight gain in patients with alcoholism.[28] Topiramate antagonizes the glutamate kainate receptor and is efficacious in alcohol dependence[29,30] and bulimia nervosa,[30,31] as well as BED.[11,12] Treatment with both the NMDA antagonist memantine and the mGluR5 antagonist MTEP has been shown to reduce consumption of highly palatable food in a baboon model of binge eating disorder.[32] Memantine has been shown to reduce binge eating in open-label trials in patients with BED,[33,34] and acamprosate, in addition to antagonizing NMDA receptors, may also decrease mGluR5 function.[35]

Third, it has been hypothesized that binge eating and addiction may share a common pathophysiology, that highly palatable food and drugs of abuse compete for the same brain reward circuitry, and that there may be a class of drugs that reduce craving, ultimately by modulating neurotransmission in the systems that comprise this circuitry.[36] This class of "anticraving" drugs has been hypothesized to include acamprosate, along with topiramate, naltrexone, and bupropion. Since binge eating is often characterized by craving, it might be further hypothesized that anticraving medications (beyond topiramate) would be efficacious in eating disorders with binge eating, including BED. Preliminary data suggest naltrexone, which is indicated for alcohol and opioid dependence, may be effective for bulimia nervosa and BED when administered at supratherapeutic doses (e.g., 200–400 mg days^{-1}),[37,38] whereas bupropion, which is indicated for smoking cessation, has been shown superior to placebo in one randomized trial in bulimia nervosa.[39] Thus, the "anticraving" properties of acamprosate in substance use disorders suggest it might have antibingeing properties in BED.

Finally, acamprosate is well tolerated. Compared with the antidepressants, antiepileptics, and antiobesity agents used in BED, acamprosate is associated with substantially lower rates of sexual dysfunction, cognitive impairment, hypertension, and severe diarrhea, respectively.

These observations led us to hypothesize that the binge eating symptoms of BED would respond to the anticraving agent acamprosate. To test this hypothesis, we conducted a single-center, randomized, parallel-group, placebo-controlled, flexible-dose study to assess the efficacy and tolerability of acamprosate during a 10-week course of treatment in 40 outpatients with BED. We also evaluated the treatment effects of acamprosate on food craving, various metabolic measures, including weight, and quality of life, in this patient group.

Method

Patients

Study participants were outpatients at the Lindner Center of HOPE, Mason, Ohio who were recruited by radio and newspaper advertisements requesting volunteers for a medication study for binge eating. Patients were enrolled into the study if they met the following inclusion criteria: (1) were male or female from 18 through 65 years of age; (2) met DSM-IV-TR criteria for BED; (3) weighed ≥85% of the midpoint of ideal body weight for height (according to the metropolitan height/weight tables); (4) and had ≥3 binge eating episodes and ≥2 binge days in the week before receiving study medication (confirmed with prospective diaries while the patient received single-blind placebo run in; see outcome measures).

Patients were excluded from participation in the study if they met any of the following criteria: (1) had concurrent anorexia nervosa or bulimia nervosa (by DSM-IV-TR criteria); (2) had a substance use disorder (by DSM-IV-TR criteria) within 6 months of study entry (except nicotine abuse or dependence); (3) had a lifetime history of a psychotic disorder, a bipolar disorder, or dementia or other cognitive disorder (by DSM-IV-TR criteria); (4) had a personality disorder that could interfere with diagnostic assessment, treatment, or compliance; (5) displayed clinically significant suicidality or homicidality; (6) had

received cognitive behavioral 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) required treatment with any drug that might adversely interact or obscure the action of acamprosate; (10) had clinically significant laboratory or electrocardiogram abnormalities; (11) had received monoamine oxidase inhibitors, tricyclic antidepressants, lithium, antipsychotics, or fluoxetine within 4 weeks prior to randomization; (12) had received other psychoactive medication (other than hypnotics, e.g., zolpidem or zaleplon, as needed for insomnia) within 1 week of study medication initiation; (13) had received investigational medications or depot antipsychotics within 3 months prior to randomization; or (14) had previously been treated with acamprosate. Women 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 June, 2007 through August, 2009.

Study Design

This was a 10-week, outpatient, randomized, double-blind, parallel-group, flexible-dose study conducted at the Lindner Center of HOPE, Mason, Ohio. The trial consisted of three phases: a 1- to 2-week screening period which included a 1-week single-blind placebo run in during which patients had to display ≥3 binge episodes and ≥2 binge days to be randomized; a 10-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, 6, 8, and 10 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)[40] to establish BED and comorbid axis I diagnoses; the eating disorder examination-questionnaire[41] to confirm the diagnosis of BED; a physical examination; vital signs; height and weight; an electrocardiogram; fasting routine leptin and ghrelin blood chemical and hematological tests; 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 tablets taken on a daily basis (see outcome measures). 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 acamprosate 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 tablet count; adverse events; use of nonstudy medications; vital signs; and weight.

All study medication was in tablets (333 mg of acamprosate or placebo) supplied in numbered containers and dispensed to patients according to a predetermined randomization schedule (see below). Study medication was begun at 1,998 mg daily given as 666 mg three times per day for the first 2 weeks. After the second week of treatment, study medication could be increased, as tolerated, to a maximum of 2,997 mg daily to optimize response. Study medication could be reduced to a minimum of 999 mg daily because of bothersome side effects at any time during the 10-week treatment period. Patients took all their daily study medication in three divided doses.

Patients were randomized to receive acamprosate or placebo in a 1:1 ratio according to computer-generated coding. Randomization was balanced by use of permuted blocks. Allocation concealment was achieved by having the research pharmacy perform the randomization, package the study medication, and maintain the integrity of the blinded information throughout the trial.

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 or nurse investigator working with that particular patient). Secondary outcome measures were weekly frequency of binge days (days when the patient had one or more binges); weight (kg); body mass index (BMI, calculated by dividing body weight in kg by height in m^2); and scores on the Clinical Global Impression-Severity (CGI-Severity) and Improvement Scales (CGI-Improvement),[42] Yale-Brown Obsessive-Compulsive Scale modified for Binge Eating (YBOCS-BE),[43] Food Craving Inventory scale (FCI),[44] Three Factor Eating Questionnaire (TFEQ),[45] Montgomery Asberg Depression Rating Scale (MADRS),[46] and the medical Outcomes Study 12-item Short-Form Health

Survey (SF-12).[47] Weight was obtained with the patient in light clothing without shoes on the same scale zeroed at each measurement. The YBOCS-BE is a modified version of the Yale-Brown Obsessive-Compulsive Scale[43] used in previous pharmacotherapy studies of BED[11,12,14,15] (and available from the authors on request) that measures obsessiveness of binge eating thoughts and compulsiveness of binge eating behaviors. The FCI is a self-report measure of 28 specific food cravings which has been validated in obese patients with BED.[44,48] The TFEQ (also called the Eating Inventory) is a self-report questionnaire that measures three dimensions of eating pathology: cognitive restraint in eating (cognitive restraint); disinhibition of control over eating (disinhibition); and perceived hunger (hunger).[45] The SF-12 is a general health survey used as a quality of life measure that has physical and mental health subscales.[47] As done in many previous BED pharmacotherapy studies, response categories were tabulated based on percentage decrease in frequency of binges from baseline (the week before treatment initiation) to endpoint (the final week of treatment). These 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, time to recovery was assessed, defined as the first four consecutive weeks during which the patient had no binge eating episodes.

The following safety measures were assessed: adverse events, clinical laboratory data, physical examination findings, and vital signs. Reportable adverse events were new symptoms or illnesses that occurred during the treatment phase and those that increased in severity compared with baseline.

Statistical Methods

The baseline characteristics of each group were compared by using chi-square or Fisher's exact test for categorical variables and independent-samples t tests for continuous variables. SAS software (version 9.1, Cary, NC) was used to calculate the longitudinal data analysis and Stata SE (version 10.1, College Station, TX) was used to conduct all other analyses. All statistical tests and confidence intervals were two-sided. Alpha was .05, two-tailed.

The primary efficacy analysis was a longitudinal analysis comparing the rate of change of binge frequency during the treatment period between groups. The same analysis was applied to the secondary outcomes measured at each study visit including: binge day frequency, weight, BMI, CGI-severity score, and YBOCS-BE scale scores. The difference in rate of change was estimated by random regression methods, as described in Fitzmaurice et al.[49] and Gibbons et al.[50] and as used in other pharmacotherapy studies of BED.[11,12,14,15,51–55] 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/week] + 1) and log ([binge days/week +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. The best fitting correlation structure, as determined by the lowest AIC value, was chosen for each independent variable and included unstructured, first-order antedependence and first-order autoregressive. The longitudinal analyses included all available observations from all patients.

Several secondary analyses were performed. Using the last observation carried forward (LOCF), baseline-to-endpoint change scores 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. An extension of the WIlcoxon rank-sum test ("nptrend" in Stata) was used to analyze categorical response to treatment (as defined above) for the intent-to-treat and completer groups. Time to recovery (defined as the first four consecutive binge-free weeks after baseline) was analyzed with a log-rank test of survival function for the intent-to-treat population.

For laboratory measures, including weight, the mean difference between endpoint and baseline measures was computed for each treatment group and then compared using the t test.

Results

Of 63 individuals screened, 23 were not enrolled because they did not meet entry criteria ($N = 22$) or chose not to participate ($N = 1$). Forty patients met entry criteria and were randomized to acamprosate ($N = 20$) or placebo ($N = 20$) (sample used for safety analysis). Thirty four (85%) patients were women, 35 (87.5%) were Caucasian, 4 (10%) were African-American, and 1 (2.5%) was Hispanic. Depressive disorders were the most common cooccurring psychiatric disorders, occurring in 9 (22.5%) patients as past lifetime diagnoses. There were no significant differences between the treatment groups in demographic or clinical variables at baseline (**Table 1**).

Thirty-nine patients (19 receiving acamprosate and 20 receiving placebo) had at least one postran-

TABLE 1. Baseline characteristics of participants with binge eating disorder randomly assigned to 10 weeks of double-blind treatment with acamprosate or placebo

	Acamprosate (*n* = 20)	Placebo (*n* = 20)	*p* value[a]
Demographic Characteristics			
Female *N* (%)	16 (80.0)	18 (90.0)	.66
Caucasian race *N* (%)	18 (90.0)	17 (85.0)	.61
Age mean (SD)	46.2 (12.2)	45.8 (9.1)	.91
Diagnostic Characteristics			
EDE mean (SD)	140.1 (26.6)	150.6 (37.7)	.38
Depressive disorder diagnosis *N* (%)			
Current	0	0	N/A
Lifetime	5 (25.0)	4 (20.0)	1.00
Primary Outcome Variable			
Binge frequency (per week) mean (SD)	4.5 (2.1)	4.5 (2.2)	.96
Secondary Outcome Variables			
Binge day frequency (per week) mean (SD)	4.1 (1.7)	3.8 (1.2)	.47
Body mass index mean (SD)	39.8 (7.5)	39.2 (8.4)	.83
Weight (kg) mean (SD)	116.5 (27.3)	107.7 (23.7)	.28
CGI severity mean (SD)	4.9 (0.8)	4.8 (0.9)	.71
CGI improvement mean (SD)	.40 (1.23)	1.0 (1.78)	.22
YBOCS-BE total score mean (SD)	19.6 (2.8)	19.9 (4.7)	.81
YBOSC-BE obsession subscale mean (SD)	9.9 (1.8)	10.0 (2.7)	.94
YBOSC-BE compulsion subscale mean (SD)	9.7 (1.7)	10.0 (2.3)	.70
FCI mean (SD)	82.4 (16.3)	79.4 (18.0)	.58
MADRS mean (SD)	1.8 (2.0)	1.2 (1.4)	.30
SF-12 physical health score mean (SD)	42.6 (10.1)	46.0 (10.0)	.31
SF-12 mental health score mean (SD)	48.7 (9.8)	49.3 (9.2)	.85
TFEQ total score mean (SD)	32.2 (4.2)	32.7 (5.8)	.76
TFEQ cognitive restraint subscale mean (SD)	7.3 (4.0)	8.2 (3.6)	.49
TFEQ disinhibition subscale mean (SD)	14.2 (1.6)	13.5 (2.1)	.21
TFEQ hunger subscale mean (SD)	10.7 (2.6)	11.1 (2.7)	.63

Notes: CGI, Clinical Global Impression scale; EDE, Eating Disorder Examination; FCI, Food Craving Inventory; MADRS, Montgomery Asberg Depression Rating Scale; SD, standard deviation; SF-12, 12-Item Short-Form Health Survey; TFEQ, Three Factor Eating Questionaire; YBOCS, Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating.

[a] Chi-square, Fishers Exact Test or *t* tests were used to determine statistical differences between the acamprosate and placebo groups.

domization efficacy measure (intent to treat [ITT] population), and 24 (62%) patients completed the 10-weeks of treatment with study medication. Significantly more patients in the acamprosate group (*N* = 15 [79%]) than in the placebo group (*N* = 9 [45%]) completed all 10 weeks of treatment (Fisher exact *p* = .05). Three patients withdrew from the study because of adverse events (acamprosate: *N* = 2; placebo: *N* = 1); four because of lack of efficacy (all placebo); and two because of scheduling difficulties (acamprosate: *N* = 1; placebo: *N* = 1); six were lost to follow-up (acamprosate: *N* = 1; placebo: *N* = 5).

The primary efficacy analysis using random regression showed that patients receiving acamprosate and those receiving placebo had the same rate of reduction in binge episodes per week (**Table 2**, **Fig**. 1). In addition, there were no statistically significant differences in the rate of change in binge day frequency, weight, BMI, or scores on the CGI-Severity or YBOCS-BE scales between the treatment groups (**Table 2**).

In the secondary analysis of baseline-to-endpoint change scores using LOCF, acamprosate was associated with statistically significant decreases in binge days per week, and scores on the YBOCS-BE

total and obsessions scales, FCI, and SF-12 Mental Health scale compared with placebo (**Table 2**). The associated standardized effect sizes were moderate to large (Cohen's *d* = .65, .74, .74, .77, and .96, respectively). There were no statistically significant differences between groups in the changes in binge episode frequency, weight, BMI, or scores on the CGI scales; YBOCS-BE compulsions scale; TFEQ total, hunger or cognitive restraint scales; MADRS; or SF-12 physical health scale. However, the associated standardized effect sizes were moderate for binge frequency (.54), CGI-Severity score (.55), YBOCS-BE compulsions subscale score (.59), TFEQ cognitive restraint score (.44), TFEQ disinhibition score (.42), and MADRS score (.47).

In the categorical response analyses, levels of response did not differ between acamprosate-treated or placebo-treated patients in either the ITT or completer groups (**Table 3**). Acamprosate was not associated with a significantly shortened time to recovery of binge eating in the intent-to-treat group ($\chi^2 = 2.20$, *p* = .14).

Patients receiving acamprosate experienced a mean (SD) weight loss of .33 (3.09) kg from baseline to endpoint, whereas those receiving placebo experienced a mean (SD) weight gain of 1.16 (3.0) kg

TABLE 2. Outcome measures before and after 10 weeks of treatment with acamprosate versus placebo and analysis of change in outcome

| | Mean (SD) | | | | | | Estimated Difference Between Groups at 10 Weeks | | | | | |
| | Baseline (N = 39) | | Last Observation[a] (N = 39) | | Week 10[b] (N = 24) | | Longitudinal Analysis | | | Endpoint Analysis[a] | | |
Outcome Measure	Placebo (N = 20)	Acamp (N = 19)	Placebo (N = 20)	Acamp (N = 19)	Placebo (N = 9)	Acamp (N = 15)	Estimate [95% CI]	p Value	d	Estimate [95% CI]	p Value	d
Binges/wk	4.5 (2.2)	4.5 (2.1)	2.8 (2.5)	1.9 (2.4)	2.7 (3.1)	1.6 (2.0)	−0.30 [−.40, .01]	.61	.21	−0.98 [−.18, 2.13]	.09	.54
Binge days/wk	3.8 (1.2)	4.2 (1.7)	2.6 (2.1)	1.8 (2.2)	2.2 (2.4)	1.6 (2.0)	−0.06 [−.42, .50]	.23	.51	−1.14 [−2.22, −.05]	.04	.62
Weight (kg)	107.7 (23.7)	116.0 (27.9)	108.9 (24.3)	116.3 (27.6)	123.9 (17.9)	114.8 (24.7)	−.86 [−3.05, 1.33]	.44	.25	−0.83 [−1.15, 2.81]	.40	.27
BMI, (kg m^{-2})	39.2 (8.4)	39.7 (7.7)	39.7 (8.9)	39.7 (7.4)	45.6 (4.0)	38.9 (6.2)	−.41 [−1.21, .40]	.32	.32	−0.34 [−.40, 1.08]	.35	.31
CGI-S score	4.8 (.9)	4.8 (.8)	3.5 (1.4)	2.7 (1.7)	3.1 (2.0)	2.6 (1.5)	−.62 [−1.77, .53]	.29	.35	−0.81 [−.12, 1.74]	.09	.55
CGI-I score	1.0 (1.8)	0.4 (1.3)	2.6 (1.1)	2.1 (1.1)	2.1 (1.1)	2.0 (1.1)				0.03 [−1.24, 1.17]	.96	.02
YBOCS-BE												
Total	19.9 (4.7)	19.6 (2.9)	15.4 (6.3)	10.6 (7.1)	13.3 (7.6)	10.8 (6.6)	−2.44 [−7.40, 2.51]	.33	.31	−4.5 [−8.23, −.77]	.02	.74
Obsessions	10.0 (2.7)	9.9 (1.9)	7.9 (3.0)	5.3 (3.6)	7.0 (3.2)	5.4 (3.5)	−.20 [−1.87, 1.47]	.81	.08	−2.53 [−4.63, −.43]	.02	.74
Compulsions	10.0 (2.3)	9.7 (1.8)	7.6 (3.6)	5.3 (3.6)	6.3 (4.7)	5.4 (3.4)	−.65 [−3.42, 2.12]	.65	.15	−1.97 [−.11, 4.05]	.06	.59
FCI score[c]	79.4 (18.0)	82.2 (16.7)	69.7 (22.7)	59.5 (15.6)	65.1 (27.9)	59.1 (16.7)				−12.93 [2.75, 23.12]	.01	.77
TFEQ[c]												
Total	32.7 (5.8)	32.2 (4.3)	31.5 (6.4)	28.9 (5.5)	28.6 (4.9)	29.2 (5.6)				−2.07 [−1.54, 5.68]	.25	.37
Cognitive restraint	8.2 (3.6)	6.9 (3.6)	8.5 (5.2)	8.7 (5.0)	7.0 (5.3)	9.3 (5.4)				1.49 [−3.66, .69]	.17	.44
Disinhibition	13.5 (2.1)	14.3 (1.6)	12.3 (3.6)	11.2 (3.9)	11.8 (4.2)	10.9 (3.9)				−2.01 [−.29, 4.30]	.08	.55
Hunger	11.1 (2.7)	11.0 (2.3)	10.7 (3.1)	9.1 (3.6)	9.8 (4.1)	9.1 (3.7)				−1.55 [−.81, 3.91]	.19	.42
MADRS score[c]	1.2 (1.4)	1.9 (2.1)	1.8 (1.9)	1.4 (2.5)	1.7 (2.1)	1.5 (2.7)				−0.95 [−.36, 2.25]	.15	.47
SF-12 Physical health score[c]	46.0 (10.0)	42.6 (10.1)	48.2 (8.8)	45.7 (9.4)	44.9 (5.8)	46.7 (7.6)				0.84 [−3.97, 2.29]	.59	.18
SF-12 Mental Health score[c]	49.3 (9.2)	48.7 (9.8)	46.9 (11.9)	53.1 (9.1)	48.8 (12.3)	53.1 (9.7)				7.42 [2.91, 11.93]	<.00	.96

Notes: BMI, body mass index (weight in kilograms divided by height in m^2); CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; CI, confidence interval; FCI, Food Craving Inventory Scale; MADRS, Montgomery-Asberg Depression Rating Scale; SF-12, 12-Item Short-Form Health Survey; TFEQ, Three-Factor Eating Questionnaire; YBOCS-BE, Yale–Brown Obsessive-Compulsive Scale Modified for Binge Eating.

[a] Last Observation Endpoint was defined using last observation carried forward.
[b] Week 10 Endpoint was available for only those participants that completed the study.
[c] Measured at weeks 0,1,3,6 8, and 10 only.

FIGURE 1. Mean weekly binge episodes over 10 weeks with random assignment to acamprosate or placebo.
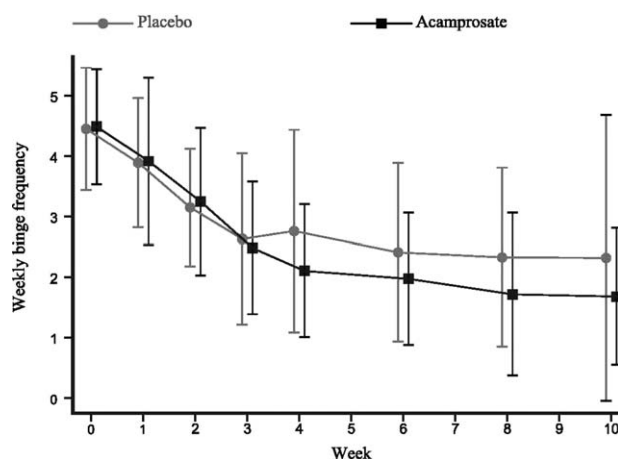
FIGURE 2. Mean weight change over 10 weeks with random assignment to acamprosate or placebo.
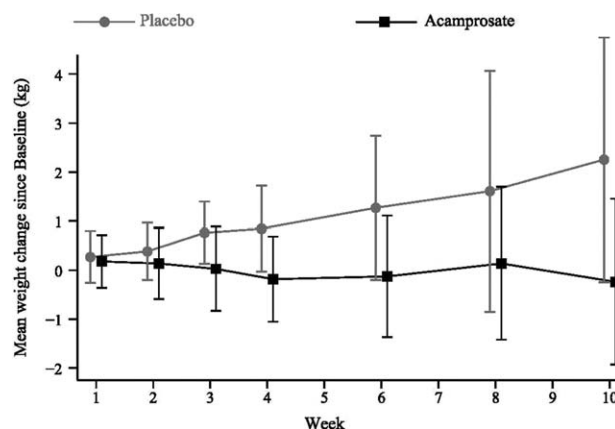
TABLE 3. Response to treatment among participants with binge eating disorder randomly assigned to 10 weeks of double-blind treatment with acamprosate or placebo

	Intent-to-Treat Group[a]		Patients who Completed 10 Weeks of Treatment[b]	
Response[c]	Placebo (*n* = 20) *N* (%)	Acamprosate (*n* = 19) *N* (%)	Placebo (*n* = 9) *N* (%)	Acamprosate (*n* = 15) *N* (%)
None	10 (50)	6 (32)	4 (44)	4 (27)
Moderate	4 (20)	4 (21)	1 (11)	4 (27)
Marked	2 (10)	3 (16)	0 (0)	3 (20)
Remission	4 (20)	6 (32)	4 (44)	4 (27)

[a] Participants had at least one post-randomization efficacy measure; there were no statistically significant differences between groups.
[b] There were no statistically significant differences between groups.
[c] Categories defined by the percentage decrease in binge frequency from baseline: remission = cession of binges; marked = 75–99% reduction; moderat = 50–74% reduction; none = less than a 50% reduction.

(see **Fig**. **2**). Among patients who completed the 10 weeks of treatment, the corresponding changes in weight were −0.19 (3.05) kg and 2.68 (3.25) kg and this difference was statistically significant (p = .04). The difference in BMI for patients that completed the study was also statistically significant (acamprosate −.06 (1.07) and placebo 1.05 (1.32), p = .04).

There were no significant differences between patients receiving acamprosate and those given placebo in mean change from baseline to final visit for the fasting measurements of insulin (3.7 and 2.0 μIU/ml), glucose (0 and 0 mg/dl), triglycerides (9.8 and 10.4 mg/dl), LDL cholesterol (0.1 and 0.4 mg/dl), and total cholesterol (1.3 and 1.0 mg/dl).

The mean (SD) daily dose of acamprosate at endpoint evaluation was 2597 (605) mg. The mean (SD) daily dose for the 15 patients who completed the 10-week trial was 2795 (559) mg.

Adverse events occurring in at least two patients receiving acamprosate are listed in **Table 4**. Diarrhea was significantly more common with acam-

prosate than with placebo (55% vs. 26%, p = .05). Of the two patients who discontinued acamprosate due to adverse events, one reported chest pain and the second reported diarrhea, cramping, and flatulence. The adverse event causing discontinuation in the placebo-treated patient was depressive symptoms. No patient experienced a serious adverse event during the study. There were no changes in physical examination findings, vital signs, or clinical laboratory values suggesting drug-related toxicity.

Discussion

In the primary longitudinal analysis of this 10-week, randomized trial in patients with BED, acamprosate was not significantly superior to placebo in rate of reduction of binge frequency, binge day frequency, body weight, BMI, obsessive-compulsive features of binge eating symptoms, or overall severity of illness. Acamprosate was not associated with a significantly higher level of categorical response

TABLE 4. Adverse events reported by ≥2 participants with binge eating disorder receiving treatment with acamprosate

Adverse event	Acamprosate (N = 20)		Placebo (N = 20)	
	N	%	N	%
Diarrhea[a]	11	55	5	26
Flatulence	7	35	2	11
URI	4	20	1	5
Flu syndrome	3	15	0	0
Headache	3	15	2	11
Edema	2	10	0	0
Fatigue	2	10	0	0
Insomnia	2	10	1	5
Nausea	2	10	2	11
Urination frequency	2	10	0	0
Vivid dreams	2	10	1	5

[a] Diarrhea ($p = 0.05$) occurred more frequently in the acamprosate group than the placebo group.

in either the endpoint or completer analyses, or with a shortened time to recovery of binge eating. However, significantly more acamprosate-treated patients than placebo-treated patients completed the trial. In addition, the secondary analysis, change from baseline to endpoint using LOCF, yielded several positive findings, with acamprosate being associated with significant decreases in binge day frequency, obsessive-compulsive features of binge eating symptoms, and food craving, and improved quality of life. There were also clinically significant trends for improvement in binge frequency, overall severity of illness, and disinhibited eating. In a completers' analysis, the mean weight loss in the group receiving acamprosate was 0.19 kg, as compared with a mean 2.68 kg weight gain in the group receiving placebo. There was no significant change in MADRS scores, but mean MADRS scores were low at baseline.

Taken together, these findings provide preliminary evidence that acamprosate may have some utility in BED. The potential improvement observed with acamprosate in this study appears dissimilar to results reported in studies of other pharmacotherapies in patients with BED. Although an isolated finding, the significantly higher completion rate seen with acamprosate than with placebo contrasts with that observed in studies with antiepileptic, antiobesity, and antidepressant agents, in which drug and placebo discontinuation rates are generally similar.[8–14,16] In the endpoint analysis, acamprosate's effects appeared somewhat stronger for improving overall quality of life (SF-12 Mental health scale effect size = .96), food craving (FCI score effect size = .77), and obsessive-compulsive features of binge eating (YBOCS-BE obsession subscale effect size = .74, YBOCS-BE total score effect size = .74) than for improving binge eating (binge frequency effect size = .54 and binge days effect size = .65) and other aspects of eating psychopathology (TFEQ disinhibition effect size = .55, TFEQ cognitive restraint effect size = .44, and TFEQ hunger effect size = .42). Compared with antiepileptic and antiobesity agents that have produced weight loss, acamprosate seemed to stabilize weight and prevent weight gain. Although preliminary, these findings suggest acamprosate might exert beneficial effects in BED by improving quality of life, reducing food craving, and stabilizing weight.

Since the glutamate system is involved in the regulation of feeding behavior and acamprosate is a glutamate modulator, one possible mechanism by which acamprosate might exert beneficial effects in BED is by reducing food craving through its effects on this system. Decreased food craving may lead to decreased binge eating or other forms of overeating, which might reduce energy intake and, secondarily, prevent further weight gain. In fact we found evidence in our study to support this relationship. Participants that experienced a 25% or greater reduction in food craving had on average 1.5 fewer binge days ($p < .01$). Additionally, participants in the acamprosate group with a 25% or greater reduction in food craving had 2.13 fewer binge days compared to 1.47 fewer binge days in the placebo group ($p < .00$). Alternatively, another possible mechanism is that acamprosate might prevent weight gain via its gastrointestinal side effects.

Our findings add to the literature suggesting that there may be a relationship between binge eating and food craving. Not all food cravers binge eat, but those that do are more likely to be heavier and meet criteria for bulimia nervosa.[56] Reactivity to food cues has been shown to be associated with binge eating and BMI, and to be possibly influenced by genetic factors,[57] while sweet craving has been shown to precede binges in obese women with and without BED.[58] In women with eating disorders, food cravings are more strongly correlated with loss of control eating than dietary restraint tendencies.[59] Our findings further suggest that degree of food craving in individuals with BED may be clinically relevant.

Several limitations of this study should be considered. First, the small sample size may have compromised the ability of the study to detect clinically important treatment effects. In particular, this study had low power to detect clinically important differences of moderate size. Second, the attrition rate was high, with 38% of patients withdrawing before study completion, rendering the results heavily dependent on assumptions regarding missing data.

A third limitation is that because the study group was primarily female and Caucasian, and the duration of treatment was short (10 weeks), the results may not generalize to males or non-Caucasians with BED, or to longer treatment periods. A fourth limitation is that because persons with psychotic disorders, bipolar disorders, substance use disorders, severe personality disorders, and unstable medical disorders were excluded, the results may not generalize to BED when it cooccurs with these conditions.

In summary, in a 10-week trial in outpatients with BED, acamprosate was superior to placebo in reducing binge day frequency, improving obsessive-compulsive symptoms related to BED, and preventing weight gain on secondary endpoint and completers analyses, but not on the primary longitudinal analysis. It was also associated with significant improvements in food craving and quality of life scores, and a higher completion rate than placebo. Controlled trials of acamprosate in larger groups of patients with BED, especially those with high levels of food craving, may be warranted.

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