

Treatment of Bulimia Nervosa With Topiramate in a Randomized, Double-Blind, Placebo-Controlled Trial, Part 1: Improvement in Binge and Purge Measures

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Background: This randomized, double-blind, placebo-controlled trial was designed to assess the efficacy and safety of topiramate in bulimia nervosa.

Method: Patients with DSM-IV bulimia nervosa were randomly assigned in equal proportions to receive topiramate (N = 35) or placebo (N = 34) for 10 weeks (between April 1999 and Dec. 2000). Topiramate treatment was started at 25 mg/day and titrated by 25 to 50 mg/week to a maximum of 400 mg/day. The primary efficacy measure was mean weekly number of binge and/or purge days. Related outcome measures included mean weekly number of binge days and binge frequency, as well as mean weekly number of purge days and purge frequency.

Results: Sixty-four outpatients (33 placebo, 31 topiramate) were included in the intent-to-treat analysis. The median topiramate dose was 100 mg/day (range, 25–400 mg/day). Mean \pm SD baseline number of weekly binge and/or purge days was 5.0 ± 1.6 for topiramate patients and 5.1 ± 1.5 for placebo patients. The primary efficacy measure, mean weekly number of binge and/or purge days, decreased 44.8% from baseline with topiramate versus 10.7% with placebo ($p = .004$). The mean weekly number of binge days decreased 48.2% with topiramate versus 17.7% with placebo ($p = .015$), and mean binge frequency decreased 49.2% with topiramate versus 28.0% with placebo ($p = .071$). The mean weekly number of purge days decreased 43.4% with topiramate versus 16.6% with placebo ($p = .016$), and mean purge frequency decreased 49.8% with topiramate versus 21.6% with placebo ($p = .016$). Three patients (2 placebo, 1 topiramate) discontinued from the trial due to adverse events.

Conclusion: Topiramate was associated with significant improvements in both binge and purge symptoms in this study population and represents a potential treatment for bulimia nervosa.

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Bulimia nervosa is a chronic disorder involving repeated episodes of uncontrolled binge eating, followed by inappropriate compensatory behaviors such as self-induced purging, fasting, inappropriate use of diuretics or laxatives, and excessive exercise. The incidence of bulimia nervosa peaks during adolescence and young adulthood,¹ and the disorder may affect up to 5% of adolescent females in the United States.²

Eating disorders during adolescence have been correlated with poor health outcomes in early adulthood. In a recent study, 62% of adolescents with eating disorders had 2 or more chronic physical health problems during early adulthood, including cardiovascular conditions such as hypertension, fatigue, and migraine headaches, as compared with 22% of those without psychiatric disorders and 32% of those with psychiatric disorders other than eating disorders.³ Furthermore, those who employed self-induced vomiting as a compensatory method of weight gain prevention were more likely to endure adverse health outcomes such as respiratory illnesses, chronic pain, or migraine headaches in early adulthood as compared with those who used fasting, frequent exercise, or dieting.

Treatment options for bulimia nervosa encompass both nonpharmacologic and pharmacologic approaches.

Numerous studies have examined the utility of drugs such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) in the treatment of bulimia, and many of these trials found the study drug superior to placebo.^{4,5} Mean reductions in binge or purge frequency associated with antidepressant treatment are typically 45% to 65%,⁶ but the utility of some TCAs is limited by side effects such as weight gain, anticholinergic effects, drowsiness, and arrhythmias.⁷ Furthermore, relapse rates with TCAs can be as high as 30%.⁸

Topiramate, a broad-spectrum antiepileptic drug currently approved as adjunctive therapy in various forms of seizure disorders, has shown potential efficacy in the treatment of eating disorders. In patients with bipolar disorder, treatment with topiramate was associated with appetite suppression and weight loss.⁹ Topiramate has also demonstrated efficacy in pilot and controlled studies for the treatment of binge-eating disorder^{10,11} and bulimia nervosa.^{12,13} Several biochemical effects of topiramate have been described, including inhibition of voltage-gated sodium and L-type calcium channels, enhancement of GABA_A receptor-mediated chloride flux, and inhibition of glutamate-mediated excitation at α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainate receptor subtypes.¹⁴ Moreover, animal studies have shown that microinjection of glutamate, *N*-methyl-D-aspartate, kainate, or AMPA into the lateral hypothalamus of rats elicits a dose-dependent increase in food intake,¹⁵ suggesting that alterations in glutamate-mediated signal transduction have the potential to modulate eating disorder behaviors.¹⁶

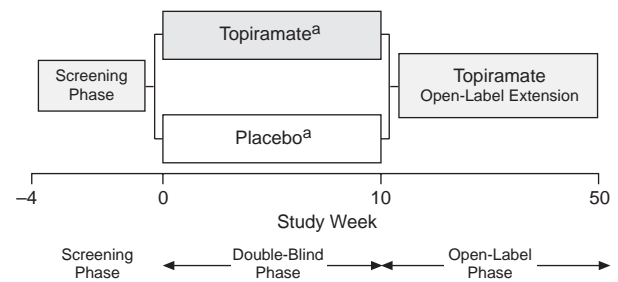
On the basis of these observations, the current study was undertaken to assess the efficacy and safety of topiramate for the treatment of bulimia nervosa in an outpatient setting. Secondary analyses of the effect of topiramate on psychological symptoms will appear in a subsequent report.¹⁷

METHOD

Study Design

This 10-week, randomized, double-blind, placebo-controlled trial assessed the efficacy of topiramate in patients with bulimia nervosa. The overall design of the study is depicted in Figure 1. Subjects were recruited from the community through newspaper and radio advertisements in the Boise and Salt Lake City areas and seen for treatment at either Mountain West Clinical Trials in Boise, Idaho, or the University of Utah Health Sciences Center in Salt Lake City, Utah, between April 1999 and December 2000. Study procedures were reviewed and approved by the institutional review boards of the respective institutions. Patients were informed about study procedures and possible side effects of treatment before being asked to sign an informed consent form. Eligible patients under-

Figure 1. Study Design: Treatment of Bulimia Patients With Topiramate or Placebo



^aStarting dose was 25 mg/day, with titration by 25 to 50 mg/week to 400 mg/day, complete or near-complete efficacy, or maximum tolerated dose.

went a 2- to 4-week screening and washout period during which baseline values for bingeing and purging behaviors were established. Patients who met the entrance criteria were randomly assigned to receive topiramate or placebo in a 1:1 ratio. Study medication was provided as 25-mg or 100-mg tablets of topiramate or matching placebo. All study medication was identical in appearance. Topiramate treatment was started at 25 mg/day for the first week, and patients were then titrated by 25 to 50 mg/week until the maximum tolerated dose, complete or near-complete efficacy, or the maximum daily dose of 400 mg was achieved. Once this level was achieved, patients continued at that dose through week 10. Patients were allowed 1 reduction in dose during the titration period if they experienced side effects. Patients were seen weekly for 10 weeks and then tapered from study medication and offered the option to continue into a 40-week open-label extension. Patients recorded binge and purge episodes (i.e., vomiting, laxative or diuretic use, and days of fasting), as well as the time and quantity of medication taken, in a daily diary to assist in accurate reporting.

At each visit, subjects were assessed using the Bulimic Intensity Scale and Carbohydrate Craving Scale, visual analog measurements that range from 0 (none) to 10 (maximal) and have been used in previous studies,¹⁸ but are not yet clinically validated. In addition, investigators rated their impression of the patients' severity of bulimia (using the Clinical Global Impressions-Severity of Illness scale [CGI-S]) and response to treatment (using the Clinical Global Impressions-Improvement scale [CGI-I]).¹⁹ An electrocardiogram (ECG) was performed at screening and week 11, vital signs were recorded weekly, and laboratory testing (hematology, blood chemistry, and urinalysis) was performed at screening and at weeks 2, 6, and 11.

Inclusion/Exclusion Criteria

Patients 16 to 50 years old were included in the study if they met the DSM-IV criteria for bulimia nervosa for at least 6 months.²⁰ The DSM-IV criteria are as follows:

1. Recurrent episodes of binge eating characterized by both of the following:
 - (a) eating an amount of food in a discrete period of time that is definitely larger than most people would eat during a similar period of time and under similar circumstances
 - (b) a sense of lack of control over eating during the episode.
2. Recurrent inappropriate compensatory behavior to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise.
3. Self-evaluation is unduly influenced by body shape and weight.
4. The disturbance does not occur exclusively during episodes of anorexia nervosa.

Patients were excluded from the study if they had a recent history of clinically significant suicidality, substance abuse, bipolar disorder I or II, major depressive disorder, anxiety disorder, or any personality disorder that could have interfered with assessments. Patients with a history of nephrolithiasis were excluded, as were female patients who were pregnant or lactating. Patients were not permitted to have taken psychoactive medications within 2 weeks prior to the study other than occasional use of short-acting sedatives for sleep. Patients with a diagnosis of anorexia nervosa, a body mass index ≤ 17.5 kg/m², or a serum potassium level of < 3.0 mmol/L were also excluded. Patients were not permitted to initiate psychotherapy during the study, but were allowed to be randomized if psychotherapy had been started 3 months prior to the study.

Efficacy Measures

The primary efficacy measure was the mean weekly number of days in which a patient binged, purged, or both binged and purged (referred to in this article as "binge and/or purge days"). Secondary measures included mean weekly number of binge days, mean weekly binge frequency, mean weekly number of purge days, mean weekly purge frequency, and scores on the Bulimic Intensity Scale, Carbohydrate Craving Scale, CGI-S, and CGI-I. Safety was assessed by ECG, vital signs, physical examinations, clinical laboratory tests, and evaluation of adverse events.

Statistical Analyses

The planned sample size was 60 patients. Based on the results of previous clinical studies of bulimia,²¹ a sample size of 60 patients (30 per group) would have an 80% power to detect a mean difference of 5.9 episodes per week, assuming that the standard deviation is 8 episodes per week using a 2-group t test with a 5% significance level.

Table 1. Baseline Clinical and Demographic Data in Bulimia Patients Receiving Topiramate or Placebo^a

Characteristic	Topiramate (N = 34)	Placebo (N = 34)
Age, y	29.0 \pm 9.7	29.6 \pm 8.1
Gender, N		
Female	33	34
Male	1	0
	(ITT, N = 31)	(ITT, N = 33)
Body weight, kg	61.3 \pm 10.3	65.9 \pm 14.2
Binge and/or purge days per week	5.0 \pm 1.6	5.1 \pm 1.5
Binge days per week	4.8 \pm 1.7	4.7 \pm 1.7
Binge episodes per week	10.8 \pm 10.4	11.3 \pm 10.7
Purge days per week	4.8 \pm 1.9	4.8 \pm 1.6
Purge episodes per week	13.3 \pm 13.5 ^b	12.4 \pm 13.0
CGI-S score	4.9 \pm 0.7	4.6 \pm 0.7
Bulimic Intensity Scale score	7.1 \pm 1.6	7.4 \pm 1.8
Carbohydrate Craving Scale score	7.0 \pm 2.6	7.3 \pm 2.4

^aData shown as mean \pm SD unless otherwise noted.

^bOne patient reporting 708 episodes of purging per week was excluded from this calculation, but not from any other analyses.

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, ITT = intent-to-treat.

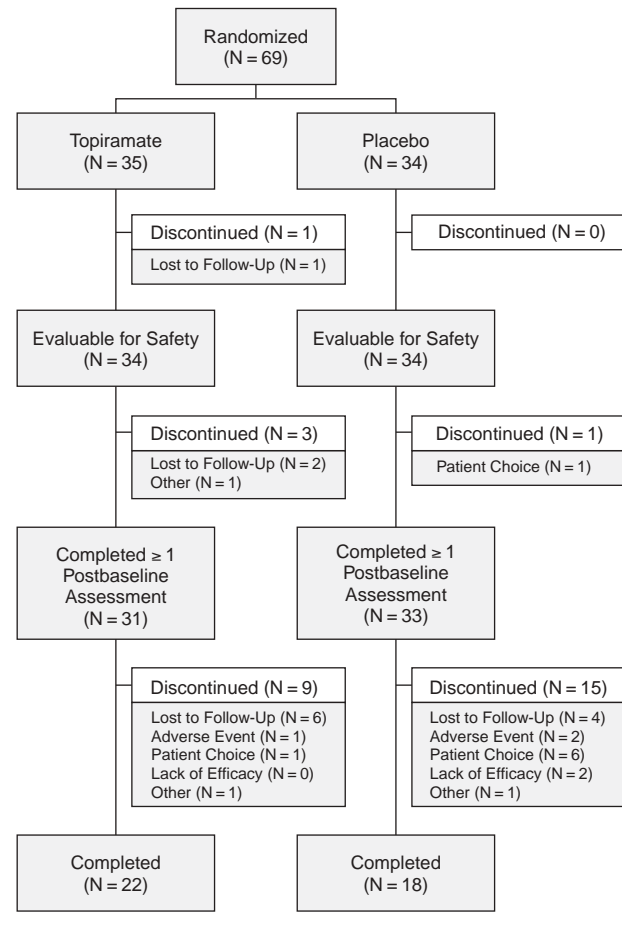
Efficacy analyses were conducted on the intent-to-treat population, which included all randomized patients who received at least 1 dose of study medication and had at least 1 postbaseline efficacy measure. Patients who had taken at least 1 dose of study medication were considered evaluable for safety. The primary statistical analysis was a comparison of the mean percentage change from baseline for each treatment group in the intent-to-treat population, performed using a Wilcoxon rank sum test. Measures of bulimic behavior included in this analysis were binge and/or purge days, mean weekly number of binge days, mean weekly binge frequency, mean weekly number of purge days, and mean weekly purge frequency. All other secondary variables were analyzed according to mean change from baseline to the last visit using analysis of covariance.

Response to treatment was also analyzed categorically in terms of the reduction in bingeing and/or purging for both days and episodes.^{22,23} Response categories were defined based on the percentage decrease from baseline: remission = cessation of binges or purges, marked response = 75% to 99% decrease, moderate response = 50% to 74% decrease, and no response = less than 50% decrease. Analysis was based on the Cochran-Mantel-Haenszel test, stratified by site.

RESULTS

The treatment groups were similar with respect to demographic and clinical characteristics (Table 1). In the intent-to-treat population, 64 subjects (100.0%) reported self-induced vomiting at baseline. In addition, 13 subjects (20.3%) reported taking laxatives, 5 (7.8%) reported taking diuretics, and 11 (17.2%) reported fasting. The treatment groups were equally balanced with respect to the various purging methods utilized at baseline. Two

Figure 2. Patient Disposition for Bulimia Patients Treated With Topiramate or Placebo

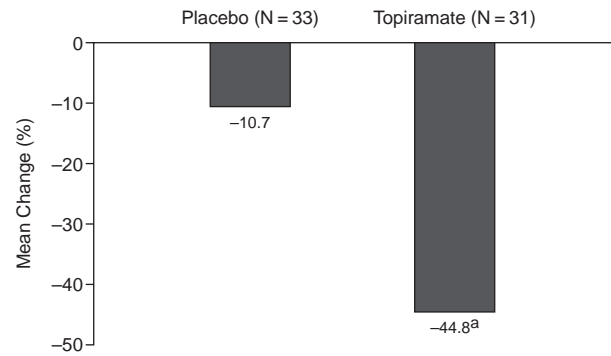


patients in the topiramate group and 1 in the placebo group were randomized into the study without interruption of their long-term psychotherapy.

Patient Disposition

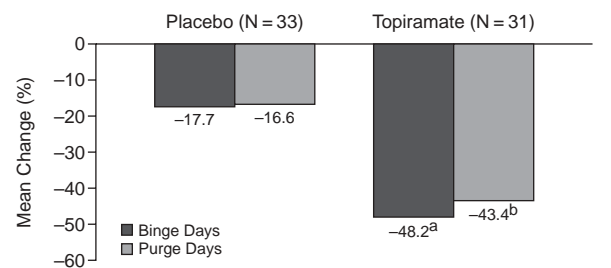
Figure 2 depicts patient disposition during the study. Sixty-nine patients were randomized and assigned to either topiramate (N = 35) or placebo (N = 34). Sixty-eight of these patients (N = 34 topiramate, N = 34 placebo) received at least 1 dose of study medication and were considered evaluable for safety; 64 subjects (N = 31 topiramate, N = 33 placebo) returned for at least 1 post-baseline visit and were included in the intent-to-treat population. Of the 68 patients in the safety population, 28 discontinued treatment (N = 12 topiramate, N = 16 placebo). Discontinued patients were lost to follow-up (N = 8 topiramate, N = 4 placebo) or withdrew due to adverse events (N = 1 topiramate, N = 2 placebo), patient choice (N = 1 topiramate, N = 7 placebo), lack of efficacy (N = 0 topiramate, N = 2 placebo), or other reasons (N = 2 topiramate, N = 1 placebo). A post hoc analysis

Figure 3. Change in Weekly Number of Binge and/or Purge Days Among Bulimia Patients Treated With Topiramate or Placebo



^ap = .004, Wilcoxon rank sum test.

Figure 4. Change in Weekly Number of Binge Days and Purge Days Among Bulimia Patients Treated With Topiramate or Placebo



^ap = .015 vs. placebo; Wilcoxon rank sum test.

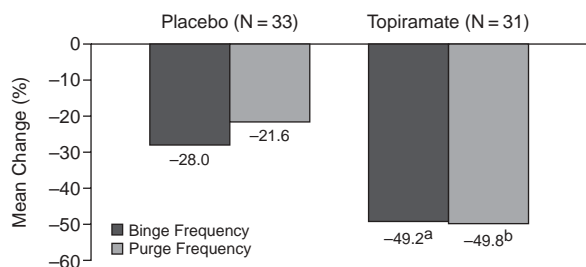
^bp = .016 vs. placebo; Wilcoxon rank sum test.

indicated that there was no statistically significant difference in the number of patients who discontinued treatment for any reason (all reasons combined) (p > .05). Of the specific reasons for discontinuation, a statistically significant difference between groups was observed only in the number of patients who discontinued due to patient choice (N = 7 placebo, N = 1 topiramate; p = .028).

Efficacy Data

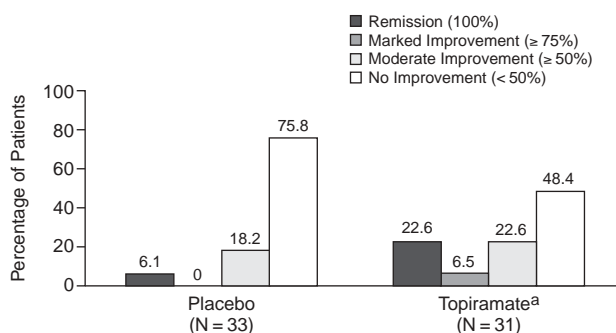
The primary analysis revealed that topiramate was associated with a greater percent reduction in mean weekly number of binge and/or purge days (Figure 3). Patients treated with topiramate exhibited a 44.8% reduction in mean weekly number of binge and/or purge days, while those treated with placebo exhibited a 10.7% reduction (p = .004). Topiramate was associated with a 48.2% reduction in mean weekly number of binge days (Figure 4) and a 49.2% reduction in mean weekly binge frequency (Figure 5), which were significantly greater than the reductions in the placebo group for binge days (17.7%, p = .015), but not binge frequency (28.0%, p = .071).

Figure 5. Change in Binge Frequency and Purge Frequency Among Bulimia Patients Treated With Topiramate or Placebo



^ap = .071 vs. placebo; Wilcoxon rank sum test.
^bp = .016 vs. placebo; Wilcoxon rank sum test.

Figure 6. Responder Analysis for Binge and/or Purge Days in Bulimia Patients Treated With Topiramate or Placebo



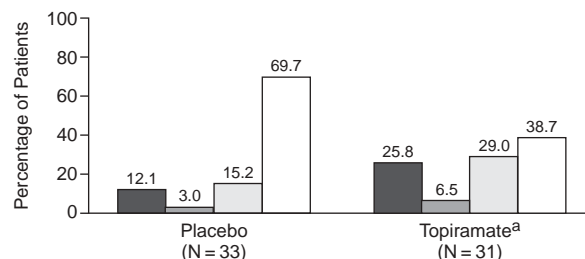
^ap = .012 based on Cochran-Mantel-Haenszel test stratified by site.

Topiramate was associated with a 43.4% reduction in mean weekly purge days (Figure 4) and a 49.8% reduction in mean weekly purge frequency (see Figure 5), which were significantly greater than the reductions in the placebo group for purge days (16.6%, $p = .016$) and purge frequency (21.6%, $p = .016$).

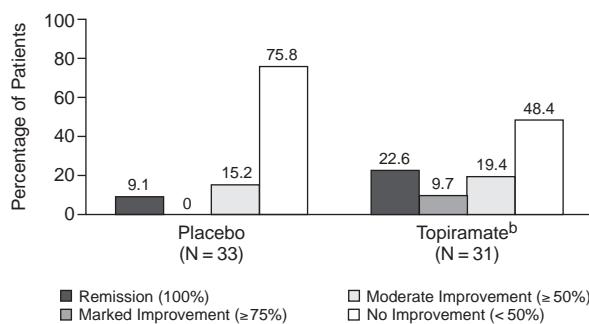
The percentage of patients who achieved at least moderate improvement ($\geq 50\%$ reduction) in the number of binge and/or purge days was greater for the group treated with topiramate (51.6%, 16/31) than for the group treated with placebo (24.2%, 8/33; $p = .012$) (Figure 6). The percentage of patients who experienced marked improvement or complete remission of binge and/or purge days was larger for the group treated with topiramate (29.0%, 9/31) than for the group treated with placebo (6.1%, 2/33; $p = .021$). Proportionately more patients treated with topiramate experienced remission of binge and/or purge days (22.6%, 7/31) than did patients treated with placebo (6.1%, 2/33; $p = .078$), although this difference did not reach statistical significance. This treatment effect was seen across all bingeing and purging behaviors; the percentage of patients who achieved at least moderate improvement ($\geq 50\%$ reduction) in the number

Figure 7. Responder Analysis for Binge Days (A) and Purge Days (B) in Bulimia Patients Treated With Topiramate or Placebo

A. Binge Days



B. Purge Days



^ap = .032 based on Cochran-Mantel-Haenszel test stratified by site.
^bp = .021 based on Cochran-Mantel-Haenszel test stratified by site.

of days on which they binged was greater for the group treated with topiramate (61.3%, 19/31) than for the group treated with placebo (30.3%, 10/33; $p = .032$) (Figure 7). Similarly, the percentage of patients who achieved at least moderate improvement ($\geq 50\%$ reduction) in the number of days on which they purged was greater for the group treated with topiramate (51.6%, 16/31) than for the group treated with placebo (24.2%, 8/33; $p = .021$). Significant decrease for this responder analysis was seen for purge frequency ($p = .013$), but decrease in binge frequency was only numerically favorable ($p = .085$).

The mean final reductions in scores on the Bulimic Intensity Scale (37% for topiramate vs. 14% for placebo, $p = .007$) and Carbohydrate Craving Scale (43% for topiramate vs. 16% for placebo, $p = .011$) were significantly greater for patients treated with topiramate than with placebo. The final mean \pm SD scores on both the CGI-S (3.7 ± 1.4 vs. 4.3 ± 1.1 , $p = .002$) and CGI-I (2.8 ± 1.3 vs. 3.6 ± 1.0 , $p = .004$) also significantly favored patients taking active treatment. Mean body weight for topiramate-treated patients decreased by 1.8 kg (4.0 lb), while in the placebo group, mean weight increased by 0.2 kg (0.4 lb) ($p = .004$). The median topiramate dose was 100 mg/day (range, 25–400 mg/day).

Table 2. Incidence of Treatment-Emergent Adverse Events ($\geq 10\%$ of Patients) in Bulimia Patients Treated With Topiramate or Placebo

WHO Preferred Term	Topiramate (N = 34)		Placebo (N = 34)	
	N	%	N	%
Fatigue	11	32	8	24
Influenza-like symptoms	10	29	6	18
Paresthesia	8	24	2	6
Hypoesthesia	7	21	1	3
Nausea	6	18	3	9
Constipation	5	15	2	6
Difficulty with concentration/attention	5	15	2	6
Headache	4	12	5	15
Nervousness	4	12	2	6

Abbreviation: WHO = World Health Organization.

Safety Data

Adverse events reported by 10% or more of study patients are presented in Table 2. The most common treatment-emergent adverse events in the topiramate group included fatigue (N = 11 topiramate, N = 8 placebo), flu-like symptoms (N = 10 topiramate, N = 6 placebo), and paresthesia (N = 8 topiramate, N = 2 placebo). Adverse events were generally mild or moderate in nature and resolved with time or dose reduction. Furthermore, these events did not typically lead to patient withdrawal from the study. The patient treated with topiramate who withdrew due to an adverse event did so due to nausea, while those treated with placebo did so due to facial rash and irritability. No serious adverse medical events were observed among the topiramate-treated patients. There were no changes in ECG, vital signs, physical examination findings, or clinical laboratory values suggestive of drug-related toxicity.

DISCUSSION

Topiramate treatment was both effective and safe for the treatment of bulimia nervosa in this patient population. Treatment with topiramate was associated with a significantly greater percent reduction in the weekly number of days on which patients either binged or purged compared with treatment with placebo. In addition, topiramate was associated with a greater percentage of patients who experienced at least a 50% improvement in binge or purge behaviors. Visual analog scales of bulimic intensity and carbohydrate craving as assessed by the patient demonstrated improvement in parallel during topiramate treatment. Moreover, the investigators favorably rated clinical improvement across the study duration. While the current report is limited to the 10-week double-blind phase of treatment, open-label extension data may help confirm that these results project to longer treatment periods.

Attrition rates due to adverse events and overall side effect profile for patients treated with topiramate indicate

that treatment was well tolerated. Two placebo patients and 1 topiramate patient withdrew due to adverse events. Compliance with topiramate in patients with this eating disorder could reflect in part the lack of weight gain associated with this medication. The weight loss characteristic of the drug might be a beneficial feature among this patient population; however, this feature, along with a higher incidence of certain side effects such as paresthesia, could have contributed to a functional unblinding in some patients.

Current treatment options for bulimia nervosa include nonpharmacologic options such as cognitive-behavioral therapy and interpersonal psychotherapy, as well as pharmacologic options such as the TCAs desipramine and imipramine and SSRIs such as fluoxetine. While psychotherapy is a valuable tool for treating bulimia nervosa, not all patients achieve significant reductions in bulimic behaviors.²⁴ Treatment with antidepressants is typically associated with reductions in binge frequency of approximately 45% to 65%.^{7,20,25,26} In a larger controlled study of fluoxetine, the proportions of responders who exhibited at least a 50% reduction in binge frequency and purge frequency were 63% and 57%, respectively, on treatment with 60 mg/day of fluoxetine.²¹ In the acute treatment phase of a longer study, only 18% of bulimia patients treated with fluoxetine achieved remission of purging symptoms.²⁷ Additionally, the relapse rates for bulimic patients on antidepressant therapy can be 33%, even when they exhibit initial responsiveness to drug therapy and remain on treatment for up to 1 year.^{26,27} Clearly, additional treatment options are necessary.

In pilot studies, topiramate has exhibited efficacy in the treatment of binge-eating disorder^{10,28} and bulimia.²⁹ In a case series of 13 female patients, Shapira and colleagues¹⁰ found that topiramate treatment was associated with at least a 50% reduction in binge frequency for 9/13 patients (69%), which was maintained for a mean duration of 18 months. Additionally, a recent randomized, double-blind, placebo-controlled study of topiramate in binge-eating disorder found that topiramate was associated with a 93% decrease in binge days (vs. 46% with placebo).¹¹ Of those patients who completed the 14-week study, 13/16 (81%) experienced a remission of bingeing. Taken together with the efficacy shown in these trials, topiramate's efficacy in the current trial for reduction of binge symptoms in patients with bulimia further supports its role in treating disordered eating behavior. The results of this study suggest that these effects may also extend to purging behaviors, which are often more difficult to treat and are the cause of significant physiologic damage.

The mechanism of action (or combination of actions) through which topiramate alleviates the behaviors associated with bulimia nervosa is not clear, although recent work has established novel potential biochemical actions of topiramate, including blockade of voltage-

dependent sodium and calcium channels, enhancement of γ -aminobutyric acid (GABA) activity at a nonbenzodiazepine site on GABA_A receptors, and blockade of AMPA/kainate glutamate receptors.¹⁴ Animal studies have shown that injection of glutamate and glutamate agonists into the lateral hypothalamus causes a dose-dependent increase in food intake.^{15,16} Thus, alterations in glutamatergic neurotransmission may have important implications in eating disorder pathogenesis. Glutamate-mediated increases in food intake are inhibited by pretreatment with AMPA/kainate receptor antagonists, which is one of topiramate's proposed pharmacologic sites of action.³⁰ Preliminary observations suggest that topiramate may be beneficial in psychiatric conditions comorbid with eating disorders, such as posttraumatic stress disorder.³¹ It is unlikely that the effects observed in this population are secondary to improvements in comorbid conditions, as patients with other major psychiatric illnesses were excluded from the study.

Therapy with topiramate exhibited a beneficial effect on several aspects of behaviors associated with bulimia nervosa in this patient population, including both bingeing and purging behaviors. Additional trials may help better define the role of topiramate either as monotherapy or in combination with other treatment modalities.

Drug names: desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), topiramate (Topamax).

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