Treatment of Bulimia Nervosa With Topiramate in a Randomized, Double-Blind, Placebo-Controlled Trial, Part 2: Improvement in Psychiatric Measures

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Background: We conducted a 10-week, randomized, double-blind, placebo-controlled trial to examine the efficacy of topiramate in the treatment of bulimia nervosa. Primary efficacy analyses showed that topiramate treatment significantly reduced days on which patients binged and/or purged. This article describes further analyses investigating topiramate's effect on psychological symptoms associated with disordered eating.

Method: Patients with DSM-IV bulimia nervosa were randomly assigned to receive topiramate (N = 35) or placebo (N = 34) for 10 weeks. Topiramate treatment was started at 25 mg/day and titrated by 25 to 50 mg/week to a maximum of 400 mg/day. Secondary psychiatric endpoints, including the Eating Disorder Inventory (EDI), Eating Attitudes Test (EAT), Hamilton Rating Scale for Anxiety (HAM-A), Hamilton Rating Scale for Depression (HAM-D), and Patient Global Improvement (PGI) were assessed for change from baseline in the topiramate versus placebo group.

Results: Thirty-one patients receiving topiramate and 33 receiving placebo were included in the intent-to-treat analysis. Percent change from baseline on the EDI indicated significantly greater improvement in the topiramate group compared with the placebo group for subscales measuring bulimia/uncontrollable overeating ($p = .005$), body dissatisfaction ($p = .007$), and drive for thinness ($p = .002$). The EAT showed significant improvement in the topiramate group compared with the placebo group for the bulimia/food preoccupation ($p = .019$) and dieting ($p = .031$) subscales and the total score ($p = .022$). For the topiramate group, the reduction in mean HAM-A score was significantly greater ($p = .046$) than that in the placebo group, while reduction in HAM-D scores was greater in the topiramate group compared with the placebo group but did not reach statistical significance ($p = .069$). Significantly more patients treated with topiramate compared with placebo reported improvement on the PGI ($p = .004$).

Conclusion: Topiramate treatment improves multiple behavioral dimensions of bulimia nervosa. Binge and purge behaviors are reduced, and treatment is associated with improvements in self-esteem, eating attitudes, anxiety, and body image. These results support topiramate as a viable therapeutic option for the treatment of bulimia nervosa. Additional, longer-term multicenter trials are indicated.

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Bulimia nervosa, a disabling eating disorder involving repeated episodes of uncontrolled binge eating followed by inappropriate compensatory behaviors, is also associated with incessant obsession over food and body weight, a distorted body image, low self-esteem, high anxiety, and depression.[1–5] Bulimic patients are forced to struggle with the psychological impact of this illness on a daily basis, and the binge and purge/compensatory behaviors help provide temporary relief of their emotional pain.[6] Treatment that could have a long-lasting beneficial effect on bulimia's associated psychological factors would help ameliorate the daily distress of the bulimic patient as well as mitigate the behaviors of bingeing and purging.

In recent years, the treatment of bulimia has evolved into a comprehensive, multimodal approach including the use of both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors,[7] as well as nonpharmacologic modalities such as cognitive-behavioral and interpersonal therapies.[8,9] Several recent studies have examined the ability of fluoxetine to reduce bingeing and purging behaviors associated with bulimia nervosa.[10–12] One of these studies, an 8-week, double-blind trial of fluoxetine,[12] utilized the Eating Disorder Inventory (EDI) and Eating Attitudes Test (EAT) to assess patients'

subjective responses. At the higher dose of fluoxetine tested (60 mg/day), the investigators found significant changes in median scores from baseline to endpoint for several subscales of the EDI, including bulimia/uncontrollable overeating, body dissatisfaction, drive for thinness, and ineffectiveness, but not for the perfectionism, interpersonal distrust, or interoceptive awareness subscales. Median changes on each of the subscales of the EAT also indicated significant reductions.

Clinical studies have also supported the use of antidepressants such as desipramine[13] and fluvoxamine[14] in the treatment of bulimia nervosa, but have not often addressed underlying psychological factors. A study of *d*-fenfluramine found it to be statistically no better than placebo in 43 bulimia patients who also received psychotherapy.[15] Despite moderate success with medication, bulimia continues to be a chronic, relapsing illness. The effectiveness of medication, particularly the TCAs, has been limited by side effects (weight gain, drowsiness, and arrhythmias).[16,17]

Topiramate, a broad-spectrum antiepileptic drug currently approved as adjunctive therapy in various forms of seizure disorders, has been shown to have efficacy in the treatment of binge-eating disorder in a case series and a recent randomized clinical trial[18,19] and has also shown efficacy in the management of patients with bulimia nervosa in case studies.[20–22] We now report secondary outcome measurements from a randomized, placebo-controlled trial[23] of topiramate in patients with bulimia nervosa, including the examination of pathologic eating attitudes and behaviors. Results of primary efficacy analyses and additional details of methodology appear in a previous report.[23]

METHOD

Study Design

Patients were enrolled and treated as outpatients either at the University of Utah Health Sciences Center in Salt Lake City or at Mountain West Clinical Trials in Boise, Idaho. Study procedures were reviewed and approved by the respective institutional review boards for each site. After receiving a full explanation of the study procedures and possible side effects, patients signed an informed consent statement. Eligible patients underwent a 2- to 4-week screening and washout phase 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 according to a 1:1 ratio. Study medication was provided as 25-mg or 100-mg tablets of topiramate and matching placebo. All study medication was identical in appearance. Topiramate 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, whichever dose was lowest. 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. After 10 weeks, patients were tapered from study medication and offered the option to continue into a 40-week open-label treatment phase. Patients recorded binge and purge episodes, as well as dosing information, in a daily diary to assist in accurate reporting.

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.[24] 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 the occasional use of short-acting sedatives for sleep. Patients with a diagnosis of anorexia nervosa, a body mass index ≤ 17.5 kg/m^2, 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 permitted to continue if they had been on a stable regimen for 3 months prior to the study.

Efficacy Measures

At each visit, patients completed the EDI[25] and the EAT.[26] In addition, subjects rated their response to treatment using the Patient Global Improvement (PGI) scale[27] at weeks 1 through 10. Clinicians administered the

Hamilton Rating Scale for Depression (HAM-D)[28] at each visit and the Hamilton Rating Scale for Anxiety (HAM-A)[29] on entry and at weeks 5 and 10.

The EDI is a self-administered questionnaire[25] that contains 64 items related to attitudes and behaviors, which are rated on a 6-point scale on which 1 = always, 2 = usually, 3 = often, 4 = sometimes, 5 = rarely, and 6 = never. The 64 items are divided into 8 subscales such that each item is included in only 1 subscale score. The EDI subscales are drive for thinness, bulimia/uncontrollable overeating, body dissatisfaction, ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness, and maturity fears.

The EAT[26] contains 26 items rated on a 6-point scale, on which 1 = always, 2 = usually, 3 = often, 4 = sometimes, 5 = rarely, and 6 = never. The 26 items are divided into 3 subscales such that each item is included in only 1 subscale score. The EAT subscales are dieting, bulimia and food preoccupation, and oral control.

An electrocardiogram (ECG) was performed at screening and week 11, vital signs were recorded weekly, and laboratory testing was performed at screening and weeks 2, 6, and 11.

Statistical Analyses

Statistical analyses were conducted on the intent-to-treat (ITT) population, which included all randomized patients who received at least 1 dose of study medication and had at least 1 postbaseline efficacy measurement. Statistical analyses for the EDI and EAT measures employed the percent change from baseline, which was compared using a Wilcoxon rank sum test. HAM-A and HAM-D data were assessed using change in score from baseline to the final visit by analysis of covariance. The proportion of subjects reporting improvement on the PGI scale was assessed using a Cochran-Mantel-Haenszel test stratified by site.

RESULTS

Demographic and Baseline Characteristics

The mean age of the patients was similar between the groups treated with topiramate (29.0 years) and placebo (29.6 years). All patients were female, with the exception of 1 male in the group treated with topiramate. The mean body weight was 61.5 kg (135.4 lb) for patients in the topiramate group and 67.4 kg (148.5 lb) for those in the placebo group (safety population). Mean baseline scores on the bulimia/uncontrollable overeating, body dissatisfaction, drive for thinness, and perfectionism subscales of the EDI were elevated in both groups, while baseline scores on the ineffectiveness, interpersonal distrust, interoceptive awareness, and maturity fears subscales were at or near the normal range (Table 1). Mean baseline scores were also higher than normal for EAT subscales, with the exception of the oral control subscale (Table 2). Post hoc analyses indicated that there were no statistically significant differences between treatment groups for baseline HAM-A, HAM-D, total EAT, or EDI scores (all $p > .05$). Two 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

Sixty-nine patients were randomly assigned to receive 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 postbaseline visit and were included in the ITT 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 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, there was a statistically significant difference between groups only in the number of patients who discontinued due to patient choice (N = 7 placebo, N = 1 topiramate; $p = .028$).

Efficacy Data

Patients treated with topiramate exhibited a greater change in mean score than patients treated with placebo on 5 of the EDI subscales (Table 1). The magnitude of this change was statistically significant for scores on the bulimia/uncontrollable overeating ($p = .005$), body dissatisfaction ($p = .007$), and drive for thinness ($p = .002$) subscales. Mean scores at the last visit for the topiramate group were within normal range for each subscale, with the exception of body dissatisfaction and perfectionism.

Patients treated with topiramate exhibited a statistically greater change in mean score than patients treated with placebo on the bulimia/food preoccupation ($p = .019$) and dieting ($p = .031$) subscales of the EAT, as well as the total score ($p = .022$, Table 2). Baseline scores for both groups on the oral control subscale of the EAT were within normal limits and changed only marginally at the last visit.

The reduction from baseline to the last visit for HAM-A scores was significantly greater for patients treated with topiramate than for placebo-treated patients ($p = .046$, Figure 1). The change from baseline to last visit for HAM-D scores was numerically greater for patients

Table 1. Eating Disorder Inventory Scores in Bulimia Patients Treated With Topiramate or Placebo

	Topiramate (N = 31)		Placebo (N = 33)		
Subscale (normal score)	Mean	SD	Mean	SD	p Value[a]
Bulimia/uncontrollable overeating (< 8)					
Baseline	10.4	5.0	11.5	5.1	.005
Final	5.9	5.5	10.3	6.8	
Body dissatisfaction (< 13)					
Baseline	16.7	8.2	19.1	8.7	.007
Final	14.2	8.5	19.9	8.5	
Drive for thinness (< 12)					
Baseline	14.1	5.6	16.2	4.0	.002
Final	10.9	5.7	15.3	4.4	
Ineffectiveness (< 9)					
Baseline	8.8	7.9	7.7	6.5	.986
Final	5.5	6.2	6.9	8.4	
Perfectionism (< 6.5)					
Baseline	8.1	5.3	9.1	5.3	.852
Final	8.0	5.4	8.5	5.7	
Interpersonal distrust (< 3.5)					
Baseline	3.7	3.3	4.4	4.0	.887
Final	3.3	3.7	3.7	3.8	
Interoceptive awareness (< 8)					
Baseline	8.1	5.8	8.3	5.1	.351
Final	5.8	5.6	7.3	6.3	
Maturity fears (< 3.5)					
Baseline	4.7	5.3	3.1	3.0	.854
Final	3.5	5.4	2.2	2.6	

[a]Percent change from baseline for topiramate vs. placebo by Wilcoxon rank sum test.

Table 2. Eating Attitudes Test Scores in Bulimia Patients Treated With Topiramate or Placebo

	Topiramate (N = 31)		Placebo (N = 33)		
Scale (normal score)	Mean	SD	Mean	SD	p Value[a]
Bulimia/food preoccupation (< 5)					
Baseline	11.5	4.3	12.4	3.9	.019
Final	7.9	5.2	10.9	5.2	
Dieting (< 10)					
Baseline[b]	18.3	8.3	22.5	7.5	.031
Final	15.2	9.0	20.6	8.1	
Oral control (< 6)					
Baseline	2.8	3.4	3.3	3.5	.539
Final	2.5	3.1	2.8	3.4	
Total score (< 20)					
Baseline	32.5	12.8	37.8	12.0	.022
Final	25.6	14.6	33.8	13.6	

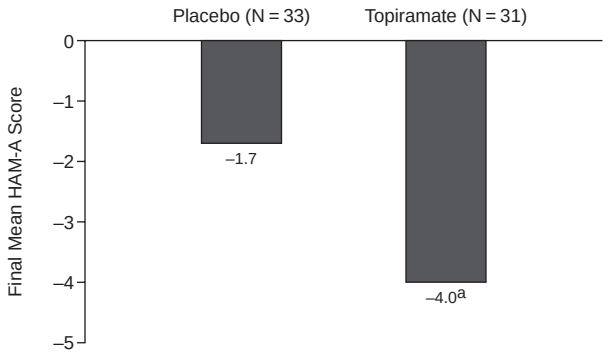
[a]Percent change from baseline for topiramate vs. placebo by Wilcoxon rank sum test.
[b]One placebo patient was excluded from this subscale only, as a result of missing data.

treated with topiramate than placebo but did not reach statistical significance (p = .069, Figure 2).

More patients treated with topiramate (61.3%) reported improvement in PGI scores than did those patients receiving placebo (36.4%, p = .004, Figure 3).

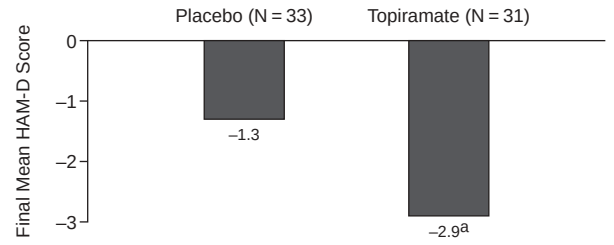
Reductions in bingeing and purging behaviors associated with the current study were previously reported.[23] The primary efficacy measure was the percent reduction

Figure 1. Change in Hamilton Rating Scale for Anxiety (HAM-A) Scores Among Bulimia Patients Treated With Topiramate or Placebo



[a]p = .046 based on change from baseline at final visit (analysis of covariance).

Figure 2. Change in Hamilton Rating Scale for Depression (HAM-D) Scores Among Bulimia Patients Treated With Topiramate or Placebo



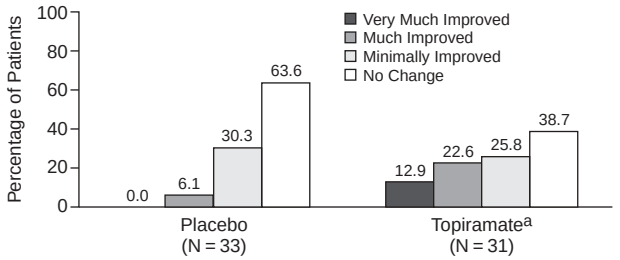
[a]p = .069 based on change from baseline at final visit (analysis of covariance).

in the mean number of days on which a patient binged and/or purged. Patients treated with topiramate exhibited significantly greater percent reductions in the mean number of days on which they binged and/or purged (–44.8% vs. –10.7% placebo, p = .004), the mean number of days on which they binged (–48.2% vs. –17.7% placebo, p = .015), and the mean number of days on which they purged (–43.4% vs. –16.6% placebo, p = .016). The median topiramate dose was 100 mg/day (range, 25–400 mg/day).

Safety Data

The most common treatment-emergent adverse effects in the topiramate group included fatigue (N = 11 [32%] topiramate, N = 8 [24%] placebo), flulike symptoms (N = 10 [29%] topiramate, N = 6 [18%] placebo), and paresthesia (N = 8 [24%] topiramate, N = 2 [6%] placebo). Additional adverse events with an incidence of at least 10% included hypoesthesia (N = 7 [21%] topiramate, N = 1 [3%] placebo), nausea (N = 6 [18%] topiramate, N = 3 [9%] placebo), constipation (N = 5 [15%] topiramate, N = 2 [6%] placebo), difficulty with concentration/

Figure 3. Patient Global Improvement at Final Visit Among Bulimia Patients Treated With Topiramate or Placebo



[a]p = .004 based on Cochran-Mantel-Haenszel test stratified by site.

attention (N = 5 [15%] topiramate, N = 2 [6%] placebo), and nervousness (N = 4 [12%] topiramate, N = 2 [6%] placebo). Headache was more common with placebo than with topiramate (N = 4 [12%] topiramate, N = 5 [15%] placebo). Adverse events in either treatment group did not typically lead to patient withdrawal from the study. The 1 patient treated with topiramate who withdrew due to an adverse event did so due to nausea, while the 2 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, or physical examination findings or clinical laboratory values suggestive of drug-related toxicity.

DISCUSSION

As we previously reported,[23] primary efficacy measures from this randomized, double-blind, placebo-controlled trial demonstrated that treatment with topiramate was associated with reductions in both binge and purge behaviors. The mean number of days on which patients binged and/or purged decreased 44.8% in the topiramate group compared with 10.7% in the placebo group. These results build on the findings of previous open-label studies in which topiramate was utilized for the treatment of binge-eating disorder[18,30] and bulimia nervosa.[20–22]

The data presented herein extend our primary findings and were gathered to address whether topiramate treatment alleviates other behavioral dimensions central to bulimia nervosa, including pathologic attitudes toward food, eating, body image, and weight. These results show that patients treated with topiramate exhibit significantly greater reductions on the subscales of the EDI and EAT that assess maladaptive attitudes and behaviors seen in patients with bulimia nervosa. Furthermore, patients treated with topiramate exhibited a significantly greater reduction in mean HAM-A scores than the placebo group, and a significantly greater proportion reported clinical improvement.

Baseline EDI scores for ineffectiveness, interpersonal distrust, interoceptive awareness, and maturity fears were already at or near normal values; this may well explain why changes to these values were not significant, while the subscales related to bulimia/uncontrollable overeating, body dissatisfaction, and drive for thinness showed significant improvements with topiramate treatment. Also, Garner et al.[25,31] have suggested that abnormally poor baseline scores on the ineffectiveness, interpersonal distrust, and interoceptive awareness subscales tend, at least in anorectic patients, to identify those who are less preoccupied by weight.

Similarly, on the EAT, the bulimia/food preoccupation subscale is most closely related to bulimia.[26] High scores on the dieting subscale are not necessarily related to bulimia per se, but reflect a pathologic avoidance of fattening foods. Improvement on this subscale, along with the previous demonstration of reduced carbohydrate craving,[23] suggests that patients experience a modulation in their macronutrient selection process while on topiramate treatment. Abnormal scores on the oral control subscale are more typically related to lower weight and self-control than to bulimia, and here the oral control baseline was within normal range. Thus, the baseline measures for the EDI and EAT subscales are consistent with the profile expected in a bulimic patient population, and subsequent improvements associated with topiramate therapy were most significant in the subscales most relevant to bulimia.

It is important to emphasize the clinical relevance of the results of this study. The improvements in the 2 eating disorder scales suggest a therapeutic effect of topiramate that extends beyond the modulation of bingeing and purging behaviors. The EAT results suggest relief from obsession with food, and the EDI results likewise show an amelioration of obsession with food and body weight, as well as an improvement in distorted body image. It is the coexistence of the loss of control over eating, the preoccupation with food, the dissatisfaction with body shape, and the drive to thinness that compels the bulimic to binge and purge.

Also, with the accompanying reduction of overall anxiety as reflected in the lowered HAM-A score, patients may have less of a need to seek the emotional relief that bingeing and purging provide. Topiramate appears to favorably impact core psychological symptoms as well as the physical aspects of bulimia. With these changes, it would be reasonable to expect that patients would have a considerably better chance of engaging in and benefiting from treatment, both pharmacologic and psychotherapeutic.

Topiramate has several mechanisms and sites of action that may contribute to its effect on bulimia. It modulates synaptic activity via voltage-dependent sodium and calcium channels, enhances γ-aminobutyric acid (GABA) activity at a nonbenzodiazepine site on $GABA_A$ receptors,

and blocks α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA)/kainate glutamate receptors.[32] The mechanism of action (or combination of actions) through which topiramate alleviates the behaviors associated with bulimia nervosa and binge-eating disorder is unknown. Animal studies have shown that injection of glutamate and glutamate agonists into the lateral hypothalamus causes a dose-dependent increase in food intake.[33,34] 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, a finding that may be of relevance to topiramate's proposed antagonism of AMPA/kainate glutamate receptors.[32]

The results of the current study represent the first controlled trial of topiramate for bulimia nervosa. Therapy with topiramate is associated with substantial improvements in the behaviors associated with bulimia and results in improvements in the pathologic eating attitudes and behaviors of the disorder. Longer-term multicenter trials are indicated.

This article is the second of a 2-part series. The first part appeared in the November 2003 issue (J Clin Psychiatry 2003;64:1335–1341).

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

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