Topiramate in the Long-Term Treatment of Binge-Eating Disorder Associated With Obesity

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Background: This study assessed the long-term effectiveness and tolerability of topiramate in binge-eating disorder (BED) with obesity.

Method: Sixty-one patients with BED (DSM-IV-TR criteria) and obesity enrolled in a 14-week, single-center, randomized, double-blind, placebo-controlled study. Completers (N = 35) were offered participation in a 42-week, open-label extension trial of topiramate. Fifteen patients who received topiramate and 16 patients who received placebo in the double-blind study entered the open-label trial. Topiramate was titrated from 25 mg/day to a maximum of 600 mg/day. The primary endpoint was change from baseline to final visit in weekly binge frequency using the last observation carried forward for all patients who received topiramate. Baseline for patients receiving double-blind topiramate was the beginning of the controlled study; for patients receiving placebo, baseline was the beginning of the open-label trial. Open-label data were gathered from December 1998 to November 2000.

Results: Forty-four patients (31 who received topiramate in the open-label trial plus 13 who received topiramate in the double-blind study only) received at least 1 dose of topiramate; 43 patients provided outcome measures at a median final dose of 250 mg/day. Mean weekly binge frequency declined significantly from baseline to final visit for all 43 patients (–3.2; $p < .001$), for the 15 patients who received topiramate during the controlled and open-label studies (–4.0; $p < .001$), and for the 15 patients who received topiramate only during the open-label trial (–2.5; $p = .044$). Patients also exhibited statistically significant reduction in body weight. The most common reasons for topiramate discontinuation were protocol nonadherence (N = 17) and adverse events (N = 14).

Conclusion: Topiramate treatment was associated with enduring improvement in some patients with BED and obesity but was also associated with a high discontinuation rate.

(J Clin Psychiatry 2004;65:1463–1469)

Received April 20, 2004; accepted Sept. 2, 2004. From the Psychopharmacology Research Program (Drs. McElroy and Keck) and the Women's Health Research Program (Dr. Arnold), Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, Ohio; the Department of Psychiatry, University of Florida, Gainesville (Dr. Shapira); Ortho-McNeil Pharmaceutical, Inc., Raritan, N.J. (Drs. Rosenthal, Wu, and Fazzio and Ms. Capece); the Biological Psychiatry Laboratory, McLean Hospital, Belmont, Mass. (Dr. Hudson); and the Department of Psychiatry, Harvard Medical School, Boston, Mass. (Dr. Hudson).

Supported in part by funding from Ortho-McNeil Pharmaceutical, Inc. Employees of Ortho-McNeil Pharmaceutical, Inc. (Drs. Rosenthal, Wu, and Fazzio and Ms. Capece) assisted in the preparation of the manuscript for publication.

This study was presented at the 156th annual meeting of the American Psychiatric Association, May 17–22, 2003, San Francisco, Calif.

Financial disclosure appears at the end of the article.

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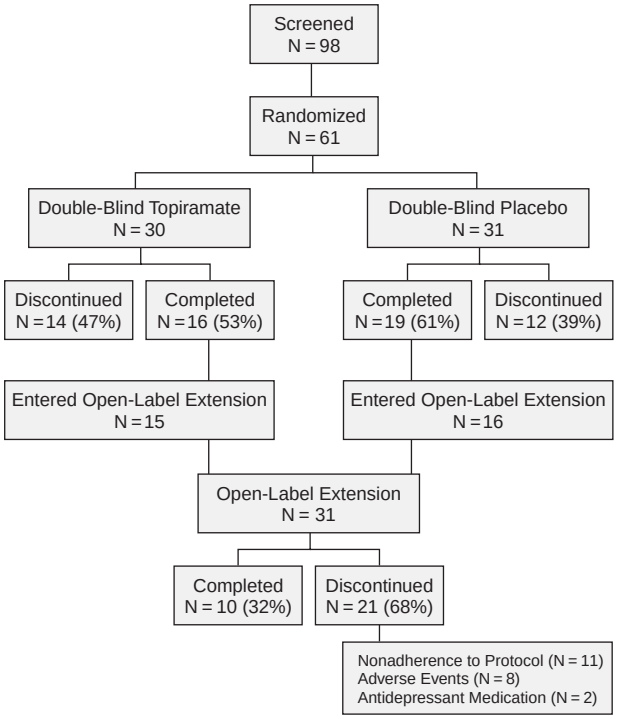
Binge-eating disorder (BED) is characterized by recurrent, uncontrollable, and distressing episodes of excessive food consumption without compensatory inappropriate weight loss behaviors.[1–4] Its prevalence in the general population is estimated to be 1.5% to 2.0%.[2–7] Many persons who seek treatment for BED are overweight or obese.[2–4] Conversely, a significant proportion of persons seeking weight management have BED, including approximately 8% to 30%[2–6] of obese individuals in weight loss treatment programs, 70% of individuals in Overeaters Anonymous,[5] and up to 50% of those seeking bariatric surgery.[8,9]

The pharmacotherapy of BED is an area that has shown promising development in the last several years.[10,11] Double-blind, placebo-controlled trials have shown that some antidepressants,[12–15] antiobesity agents,[16] and anticonvulsants[17] may reduce both binge-eating behavior and body weight in patients with BED over the short term. However, no study was longer than 14 weeks, and thus little is known about the long-term effectiveness of pharmacotherapy in BED.

Topiramate is a novel anticonvulsant[18–22] associated with therapeutic weight loss properties.[21,23,24] Preliminary data suggest that topiramate may be effective for binge-eating behavior and obesity associated with BED.[25–27] In an earlier controlled study in 61 patients, we reported that

Figure 1. Participant Flow



topiramate was efficacious in the short-term treatment of BED associated with obesity.[17] Specifically, topiramate was superior to placebo in reducing binge frequency, global severity of illness, obsessive-compulsive features of binge-eating symptoms, body weight, and body mass index (BMI). To evaluate the long-term effectiveness, tolerability, and safety of topiramate in BED associated with obesity, we report results from a 42-week open-label extension trial for those 35 patients who completed the controlled study.[17]

METHOD

Patients

As described in detail in our earlier report,[17] patients were included in the controlled study if they were between 18 and 60 years of age, met the DSM-IV-TR[1] criteria for BED, and were obese (BMI of ≥ 30 kg/m^2).[28] Patients were excluded if they had a diagnosis of a substance use disorder by DSM-IV-TR criteria within the past 6 months; unstable bipolar disorder by DSM-IV-TR criteria within the past 3 months; clinically significant suicidality; a history of any psychiatric disorder that could interfere with diagnostic assessment, treatment, or study adherence; a score < 15 on the Yale-Brown Obsessive Compulsive Scale modified for binge eating (YBOCS-BE); clinically unstable medical illness; a history of nephrolithiasis or seizures (including febrile seizures in childhood); or clinically significant abnormal laboratory results. Patients were also excluded if they required treatment with any medication that might adversely interact with or obscure the action of topiramate (e.g., stimulants, antidepressants, or carbonic anhydrase inhibitors), received psychoactive medications (other than mood stabilizers or zolpidem) within 2 weeks before randomization, received an experimental drug or used an experimental device within 30 days before randomization, or previously received treatment with topiramate.

Patients were included in the open-label extension trial if they completed the controlled study and indicated that they wanted to pursue open-label treatment with topiramate.

The controlled and open-label study protocols were approved by the University of Cincinnati Medical Center Institutional Review Board. Both studies were conducted in compliance with the Declaration of Helsinki. All patients signed approved informed consent forms after the study procedures had been fully explained. Patients were enrolled in the controlled study from September 2, 1998, through June 4, 2000; they were enrolled in the open-label extension trial from December 16, 1998, to November 27, 2000.

Study Design

A randomized, parallel-group, placebo-controlled, double-blind, flexible-dose 14-week trial with a 2-week tapering period from study medication (weeks 1 through 16, described in detail previously[17]) was followed by an open-label, 42-week extension study for patients who completed the placebo-controlled trial (Figure 1). At the initial screening visit, the following was obtained or performed: the Structured Clinical Interview for DSM-IV[29] (to assess whether the patient met DSM-IV criteria for BED and any comorbid Axis I psychiatric disorders); the number of binges and binge days during the previous week; psychiatric history; medical history; physical examination; vital signs; routine blood chemical and hematologic tests; fasting blood levels of glucose, insulin, and lipids; electrocardiogram; and urinalysis. Patients were provided with take-home diaries at this and each of the following visits (during the controlled and open-label studies) in which to record on a daily basis any binges and, once study medication was initiated, the number of medication tablets taken.

Evaluations during the double-blind treatment study occurred after 1, 2, 4, 6, 8, 10, and 14 weeks and after weeks 15 and 16 during the 2-week treatment taper and discontinuation period. During the extension trial (weeks 16 through 56), patients were evaluated every 4 weeks. The baseline for the patients who received topiramate during the controlled study was defined as the beginning of the controlled study (week 1). The baseline for the patients who received placebo during the controlled study was defined as the beginning of the open-label trial (week 16).

Topiramate was titrated upward from an initial dose of 25 mg/day to a maximum dose of 600 mg/day according to response and tolerability. At each visit, patients were assessed through review of their diaries for the number of binges experienced since the last visit. Other outcome measures were also assessed (see Outcome Measures), as were topiramate dose and compliance (through diary review and tablet count), any adverse events, use of any nonstudy medications, weight, and vital signs.

Outcome Measures

The primary outcome measure was the weekly frequency of binge-eating episodes (binge frequency) before each clinic visit. As in the earlier report, binge-eating episodes were defined using DSM-IV-TR criteria. Secondary outcome measures were weekly frequency of days with at least 1 binge-eating episode (binge day frequency), Clinical Global Impressions-Improvement (CGI-I) and -Severity of Illness (CGI-S) scores,[30] YBOCS-BE scores, Hamilton Rating Scale for Depression (HAM-D) scores,[31] BMI, weight, and percent and total body fat as measured by bioelectrical impedance (Health Management System 1000, Bio/Analogics, Beaverton, Ore.). The YBOCS-BE is a modified version of the Yale-Brown Obsessive Compulsive Scale[32] that measures the obsessiveness of binge-eating thoughts and the compulsiveness of binge-eating behaviors (questionnaire available from S.L.M. upon request). Weight was measured with a calibrated balance beam scale. Height was measured with a vertical ruler attached to the scale.

Safety measures assessed included adverse events, clinical laboratory data, physical examination findings, and vital signs.

Statistical Analysis

The mean change in outcome measures from baseline (defined as the visit at which topiramate was started) to the final visit was assessed using a 1-sample paired t test.

Efficacy analyses were performed for all patients with at least 1 efficacy evaluation after double-blind or open-label topiramate treatment (the intent-to-treat population [ITT]), with missing data imputed using a last-observation-carried-forward (LOCF) method. This test was used to determine if the mean change was significantly different from zero. For patients who completed the open-label extension, the change from baseline to week 56 was also analyzed.

RESULTS

Thirty-five of 61 patients completed the double-blind study,[17] and 31 of these patients entered the open-label extension trial. Of these 31 patients, 15 received topiramate during the double-blind study (the topiramate double-blind/open-label [TPM DB/OL] group) and 16 received placebo (the placebo double-blind/topiramate open-label [PBO DB/TPM OL] group). In total, 44 patients took at least 1 dose of topiramate: the 31 patients described above plus 13 patients who took topiramate only during the double-blind study (Table 1). The median duration of open-label and/or double-blind topiramate treatment was 21 weeks. One patient from the PBO DB/TPM OL group never returned for an evaluation after taking topiramate, thereby leaving 43 patients with at least 1 post-topiramate outcome measure. The mean ± SD and median final doses of topiramate in this population were 342 ± 257 mg and 250 mg, respectively.

Thirty-five patients discontinued topiramate during the controlled study (N = 14) or the extension trial (N = 21). During the controlled study, the reasons for topiramate discontinuation were protocol nonadherence (N = 6), adverse events (N = 6), lack of efficacy (N = 1), and reemergence of a previous medical condition (N = 1). During the extension trial, 11 patients were nonadherent with the study protocol (TPM DB/OL, N = 5; PBO DB/TPM OL, N = 6), 8 patients discontinued owing to adverse event (TPM DB/OL, N = 1; PBO DB/TPM OL, N = 7), and 2 patients dropped out from the TPM DB/OL group to receive antidepressant medication. Median duration of topiramate use by open-label extension study participants was 40 weeks (range, 20–56 weeks) in the TPM DB/OL group and 17 weeks (range, 1–37 weeks) in the PBO DB/TPM OL group. Ten patients completed 56 total weeks of

Table 1. Demographic and Baseline Characteristics of 44 Binge-Eating Disorder Patients Receiving at Least 1 Dose of Topiramate[a]

	Double-Blind Treatment Group			
	Topiramate[b] (N = 28)		Placebo[c,d] (N = 16)	
Variable	Mean	SD	Mean	SD
Age, y	40.9	8.08	40.5	9.55
Binge frequency (per week)	5.0	2.93	4.1	4.48
Binge days (per week)	4.1	1.72	2.6	2.72
CGI-S score	4.6	0.87	3.9	1.73
HAM-D score	5.9	5.31	1.5	2.07
YBOCS-BE score	21.4	4.04	15.4	7.32
Obsessions	10.5	2.13	7.8	3.41
Compulsions	11.0	2.13	7.6	4.12
Body mass index, kg/m^2	43.78	6.15	43.37	6.45
Weight, kg	120.1	18.81	126.3	27.09

[a]Thirteen patients received topiramate in the double-blind study only, 15 patients received topiramate in both the double-blind and extension studies, and 16 patients received topiramate in the extension study only.
[b]The baseline values for the patients who received topiramate during the double-blind phase were defined as those at the beginning of the double-blind phase of the study (week 1).
[c]The baseline values for the patients who received placebo during the double-blind phase were defined as those at the beginning of the open-label trial (week 16).
[d]Only 15 patients in the placebo group provided baseline efficacy measures.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, YBOCS-BE = Yale-Brown Obsessive Compulsive Scale modified for binge eating.

Table 2. Effect of Topiramate Treatment on Outcome Measures (mean change from baseline)[a]

	Final Visit (LOCF; N = 43)		Week 56 (completers; N = 10)	
Outcome Measure	Mean Change	p Value	Mean Change	p Value
Binge frequency (binges/week)	–3.2	< .001	–5.0	.002
Binge days (per week)	–1.2	.002	–2.0	.070
CGI-S score	–1.8	< .001	–2.5	< .001
HAM-D score	–0.1	NS	0.4	NS
YBOCS-BE score	–10.7	< .001	–12.8	.001
Obsessions	–5.2	< .001	–6.4	.002
Compulsions	–5.6	< .001	–6.4	.001
Body mass index, kg/m^2	–2.1	< .001	–5.1	< .001
Weight, kg	–6.0	< .001	–14.2	< .001

[a]Thirteen patients received topiramate in the double-blind study only, 15 patients received topiramate in both the double-blind and extension studies, and 16 received topiramate in the extension trial only.

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, NS = nonsignificant ($p \geq .05$), YBOCS-BE = Yale-Brown Obsessive Compulsive Scale modified for binge eating.

treatment in both the controlled study and the open-label extension study.

Table 2 shows the mean change from baseline to the final study visit (LOCF) for each outcome measure for the 43 patients who received at least 1 post-topiramate effectiveness evaluation, as well as the mean change from baseline to week 56 for the 10 patients who completed the extension trial. Treatment with topiramate was associated with statistically significant changes from baseline in mean binge frequency for all patients receiving topiramate during either the controlled or extension studies (N = 43, –3.2, $p < .001$) and for the patients who completed treatment (N = 10, –5.0, $p = .002$). In addition, mean binge frequency was statistically significantly decreased from baseline in those 15 patients receiving topiramate during both the controlled and extension studies (TPM DB/OL; –4.0, $p < .001$) and in those 15 patients receiving topiramate only during the extension phase (PBO DB/TPM OL; –2.5, $p = .044$).

Patients treated with topiramate during either the double-blind study or the open-label extension trial appeared to exhibit comparable and time-dependent reductions in binge-eating frequency (Figure 2). For TPM DB patients, the mean weekly binge frequency decreased from 5.0 at DB baseline (week 0) to 0.6 at the end of the DB study (week 14). For TPM DB/OL patients, the mean binge frequency decreased further to 0.3 during the OL extension (week 56). For PBO DB/TPM OL patients, the mean weekly binge frequency during the OL extension decreased from 4.1 to 0.7. For those subjects who had at least 1 postbaseline evaluation after receiving topiramate (N = 43), the mean duration of therapy was 23.5 weeks.

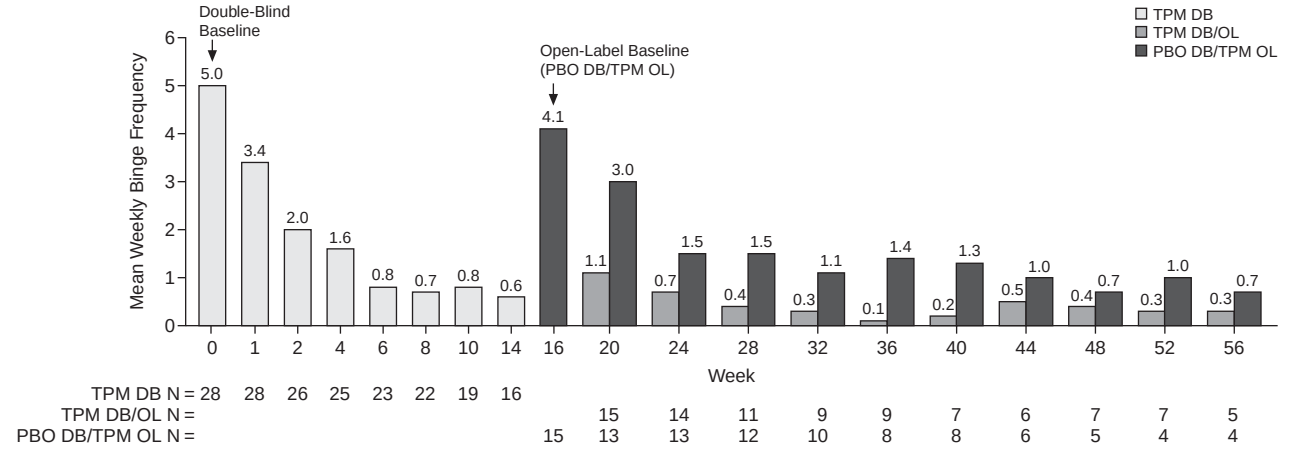
Analysis of secondary outcome measures showed that the 43 patients treated with topiramate during either the controlled study or the open-label extension exhibited statistically significant reductions from baseline in CGI-S scores ($p < .001$), YBOCS-BE total scores ($p < .001$) (including YBOCS-BE obsession [$p < .001$] and YBOCS-BE compulsion [$p < .001$] subscale scores), body weight ($p < .001$), and BMI ($p < .001$) (Table 2). Mean HAM-D score was not changed significantly from baseline at final visit. The mean reductions from baseline for the same outcome measures for the 10 patients who completed the open-label extension were also significant (Table 2). Most patients reported that their BED symptoms were either very much improved or much improved as measured by CGI-I score at final visit (69% [29/42] of all available patients, including 67% [18/27] in the TPM DB/OL group and 73% [11/15] in the PBO DB/TPM OL group). CGI-I scores were significantly improved on the basis of within-subject change ($p < .001$).

In the 14-week double-blind study, the mean weight loss in the ITT population was 5.9 kg (13.0 lb) in the topiramate group and 1.2 kg (2.6 lb) in the placebo group. In the OL extension, the weight loss experienced by the PBO DB/TPM OL group (–14.5 kg [–31.9 lb], $p = .002$) after a mean 19.3 weeks of treatment (range, 1–37 weeks) was similar to that experienced by the TPM DB/OL group (–14.1 kg [–31.0 lb], $p = .023$) after a mean 23.0 weeks of treatment (range, 20–56 weeks) (Figure 3). The mean weight loss for the 10 patients who completed the open-label extension was 14.2 kg (31.2 lb). Similarly, the change in mean BMI from baseline was significant at week 56 for both the TPM DB/OL group ($p = .003$) and the PBO DB/TPM OL group ($p = .022$). Patients treated with topiramate demonstrated significant changes from baseline in percent body fat (–2.2%, $p = .011$) and total body fat (–5.4 kg [–11.9 lb], $p < .001$) at final visit. Notable changes from baseline that did not reach statistical significance included reduced blood glucose (–5.3 mg/dL) and triglyceride (–28.1 mg/dL) concentrations. There were no consistent, clinically significant changes in diastolic blood pressure, low-density lipoprotein cholesterol, or total cholesterol.

Safety Data

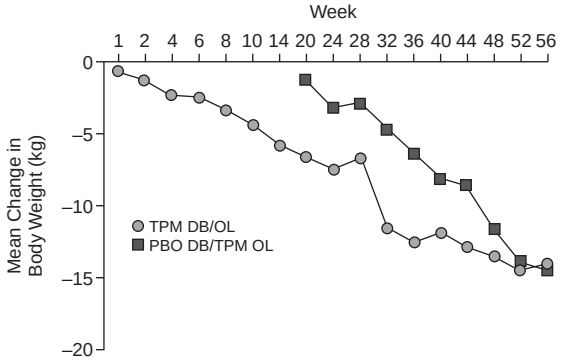
Fourteen (32%) of 44 patients discontinued topiramate due to adverse events; 6 patients discontinued during the controlled study, and 8 patients withdrew during the open-label extension trial. Patients who discontinued topiramate did not differ from those who completed the open-label trial on any baseline variables except for BMI and body weight. Specifically, completers had a significantly higher baseline mean ± SD BMI (47 ± 6 vs. 42 ± 6 kg/m^2, $p = .021$) and body weight (136 ± 21 vs. 118 ± 21 kg [299 ± 46 vs. 260 ± 46 lb], $p = .023$) than noncompleters. Patients discontinuing because of adverse events were not taking a higher dose of topiramate than those discontinuing the drug for other reasons (225 ± 179 vs. 326 ± 282 mg/day, $p = .262$).

Figure 2. Weekly Binge Frequency Through Week 56 in Binge-Eating Disorder Patients Receiving Topiramate[a]



[a]Data based on available observations at each time point. In the PBO DB/TPM OL group, 1 subject did not return for evaluation and thus was not included in the analysis for this figure.
Abbreviations: PBO DB/TPM OL = placebo double-blind/topiramate open-label, TPM DB = topiramate double-blind, TPM DB/OL = topiramate double-blind/open-label.

Figure 3. Change in Body Weight Through Week 56 in Binge-Eating Disorder Patients Receiving Topiramate



Abbreviations: PBO DB/TPM OL = placebo double-blind/topiramate open-label, TPM DB/OL = topiramate double-blind/open-label.

Table 3. Adverse Events Reported by ≥ 15% of Patients With Binge-Eating Disorder Receiving Topiramate (N = 44)

Adverse Event	N	%
Paresthesias	33	75
Dry mouth	20	46
Headache	16	36
Taste perversion	15	34
Cognitive problems NOS	14	32
Dizziness	13	30
Somnolence	11	25
Fatigue	11	25
Dyspepsia	11	25
Diarrhea	9	21
Confusion	8	18
Nausea	8	18
Nervousness	7	16

Abbreviation: NOS = not otherwise specified.

Most adverse events were mild to moderate in nature. There was 1 serious medical event of depression possibly related to topiramate. There were no changes in physical examination findings, vital signs, or clinical laboratory values suggestive of drug-related toxicity. The most common adverse events included paresthesias, dry mouth, headache, taste perversion, and cognitive problems (Table 3). The adverse event profile of topiramate in the open-label extension trial was similar to that for the controlled phase of the study.[17]

DISCUSSION

In this group of patients with BED and obesity, topiramate was associated with clinically significant reductions in binge frequency, global severity of illness, obsessive-compulsive features of binge eating, body weight, and BMI that persisted over an extended period of time. Thus, patients who received topiramate during the controlled study showed maintenance of anti–binge-eating response and continued weight loss with topiramate during the open-label extension. Specifically, mean weekly binge frequency was reduced from 5.0 at baseline, to 1.1 at week 20, to 0.3 at week 56. These long-term data compare favorably with a mean reduction of weekly binge-eating frequency of 4.4 during the double-blind part of the trial. Patients' mean weight loss at week 20 was 6.7 kg (14.7 lb), and at week 56 it was 14.1 kg (31.0 lb). Patients who received placebo during the controlled study showed a reduction in binge eating and weight when treated with open-label topiramate. With continued topiramate treatment, they displayed continued reduced binge eating and

progressive weight loss. Specifically, their baseline mean weekly binge frequency was decreased from 4.1 at baseline, to 1.4 at week 36 (after 20 weeks of treatment), to 0.7 at week 56 (after 52 weeks of treatment). Their mean weight loss from baseline at week 36 was 6.4 kg (14.1 lb), and at week 56 it was 14.5 kg (31.9 lb).

Thus, long-term treatment with topiramate was associated with sustained reductions in binge frequency and body weight in a subset of patients with BED and obesity. Although uncontrolled, this study represents the longest prospective trial of a pharmacologic agent in the treatment of BED to show beneficial effects in both binge-eating behavior and body weight.[10,11]

The mechanism of action of topiramate in BED is unknown but might involve the drug's antagonism of glutamate receptors. Stimulation of the lateral hypothalamus of rats by glutamate or glutamatergic agonists elicits a rapid, intense eating response.[33–36] Conversely, selective antagonists of the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor in certain brain regions produce anorexia in animal models.[34,37] Topiramate may, therefore, reduce binge eating by decreasing appetite or enhancing satiety through glutamate antagonism. Although the selective serotonin reuptake inhibitors[12–15] and *d*-fenfluramine[38] have been hypothesized to decrease binge eating through their serotonergic properties, topiramate is not known to have a direct effect on central serotonergic systems.[20,22,39]

Several limitations of this study should be considered. First, the extension trial was open-label, nonrandomized, and uncontrolled. The possibility that the observed favorable effects on binge-eating behavior, global severity of illness, obsessive-compulsive features of binge-eating symptoms, and/or weight loss were in fact due to placebo response, investigator or patient bias, or spontaneous remission[40] cannot be excluded. Second, the sample size was small and the attrition rate was high. Specifically, of 61 patients initially entered into the 14-week controlled study, only 10 (16%) completed the 42-week open-label extension. However, the primary analysis was based on all open-label patients at all time points and may have led to an underestimate of effect due to the need to impute missing data using an LOCF design. Another limitation is that this study excluded patients with certain psychiatric disorders, limiting the ability to generalize these findings to patients with BED and comorbid disorders (e.g., unstable bipolar disorder, active substance use disorders, psychotic disorders, or severe personality disorders).

The high attrition rate in this study deserves special comment. The most common reasons for study discontinuation were nonadherence with the protocol (N = 17) and adverse events (N = 14). Because there are no long-term double-blind, placebo-controlled pharmacotherapy trials in BED, little is known about adherence with long-term pharmacotherapy in patients with this disorder. Completers differed from noncompleters at baseline only in that they had a significantly higher mean BMI and body weight. Although this difference may be clinically insignificant, another interpretation is that greater obesity in BED is associated with greater adherence to pharmacotherapy. In the only other prospective 1-year pharmacotherapy study of an eating disorder characterized by binge eating, only 19 (13%) of 150 outpatients with bulimia nervosa randomly assigned to fluoxetine or placebo after successful fluoxetine treatment completed the 1-year study.[41] Increasing research indicates that binge eating may be associated with pathologic impulsivity.[42] It was our clinical impression that patients' impulsivity played a role in having difficulty adhering to study protocol procedures. Future BED pharmacotherapy studies should address potential factors associated with nonadherence, including measures of adiposity and impulsivity.

The second most common reason for premature study termination was topiramate discontinuation due to adverse events. Adverse events, however, were mild to moderate in severity and consistent with the established tolerability profile of topiramate in controlled trials of epilepsy and open-label reports of BED.[25–27] Topiramate intolerability may have been caused in part by an overly aggressive dosage titration of topiramate and by the uncertainty regarding the minimum effective dose of topiramate in this disorder. Indeed, with increased experience with topiramate, our group now usually increases the drug at the slower rate of 25 mg/day per week for at least the first month of administration. For patients with adverse events, the dosage titration can be slowed, or even reduced to 15 mg/day every few weeks. Regarding minimum effective dose, we usually titrate to an initial target dose of 100 to 200 mg/day and reserve dosages of 600 mg/day and above for those patients who are resistant to, but tolerant of, lower doses. Use of a less aggressive dosage titration schedule and a lower target dose might therefore have attenuated the dropout rate without sacrificing the clinical benefit in the present study.

Regarding our finding that completers had a higher mean baseline BMI and body weight, another hypothesis is that more severely obese patients with BED tolerate topiramate better than less severely obese patients. However, there are no data from available trials of topiramate in epilepsy or obesity to support this hypothesis.

In short, despite several limitations, this 42-week, open-label extension of a 14-week, double-blind, placebo-controlled study suggests that topiramate may have enduring therapeutic effects in some persons with BED associated with obesity. Controlled trials of topiramate in the long-term treatment of BED appear warranted. However, such trials should address potentially high attrition rates and consider fixed-dose designs to establish the minimally effective and maximally tolerated doses of topiramate in the treatment of this disorder.

Drug names: fluoxetine (Prozac and others), topiramate (Topamax), zolpidem (Ambien).

Financial disclosure: Dr. McElroy is a consultant to or member of the scientific advisory boards of Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Ortho-McNeil, and Wyeth-Ayerst and is a principal investigator or coinvestigator on research studies sponsored by Forest, Eisai, Eli Lilly, Ortho-McNeil, Pfizer, Sanofi-Synthelabo, AstraZeneca, and Bristol-Myers Squibb. Dr. Shapira has received grant/research support from and participated in speakers/advisory boards for Ortho-McNeil. Dr. Arnold has been a consultant for, received grant/research support from, and participated in speakers/advisory boards for Eli Lilly and Pfizer. Dr. Keck is a consultant to or member of the scientific advisory boards of Abbott, AstraZeneca, Bristol-Myers Squibb, Corcept, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Ortho-McNeil, Pfizer, UCB Pharma, Shire, and Wyeth and is a principal investigator or coinvestigator on research studies sponsored by Abbott, the American Diabetes Association, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Elan, Eli Lilly, Janssen, Merck, National Institute of Mental Health, National Institute of Drug Abuse, Organon, Ortho-McNeil, Pfizer, the Stanley Medical Research Institute, and UCB Pharma. Dr. Fazzio and Ms. Capece are major stock shareholders in Johnson & Johnson. Dr. Hudson has been a consultant for and received grant/research support from Ortho-McNeil and Eli Lilly.

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