Treatment of Binge-Eating Disorder With Topiramate: A Clinical Case Series

Nathan Andrew Shapira, M.D., Ph.D.;
Toby D. Goldsmith, M.D.; and Susan L. McElroy, M.D.

Background: Reduced appetite and weight loss were found in clinical trials of topiramate for epilepsy. Binge-eating disorder is characterized by recurrent episodes of binge eating that are not associated with regular use of inappropriate compensatory behaviors. Overweight and obesity may be common complications. To explore the effectiveness and tolerability of topiramate in binge-eating disorder, we describe the response of 13 consecutive outpatients with binge-eating disorder to naturalistic, open-label treatment with topiramate.

Method: The response of 13 female outpatients with binge-eating disorder by DSM-IV criteria to naturalistic, open-label treatment with topiramate (100–1400 mg/day) was reviewed. Response of binge-eating disorder symptoms was clinically assessed as none, mild, moderate, marked, or remission. Weight and side effects were also evaluated.

Results: All 13 patients had comorbid Axis I psychiatric disorders along with binge-eating disorder and were receiving psychotropic medications at the time of topiramate administration. After beginning topiramate treatment, 9 patients displayed a moderate or better response of binge-eating disorder symptoms that was maintained for periods ranging from 3 to 30 months (mean ± SD = 18.7 ± 8.0 months). Two other patients displayed moderate or marked responses that subsequently diminished. The remaining 2 patients had a mild or no response. The mean ± SD weight of the 13 patients decreased from 99.3 ± 26.4 kg to 87.5 ± 20.4 kg ($z = -2.4$, $df = 1$, $p = .02$), but only 7 patients lost ≥ 5 kg of weight. The mean topiramate treatment dose was 492.3 ± 467.8 mg/day for all 13 patients. The mean topiramate dose was higher in patients who lost ≥ 5 kg than in patients who lost < 5 kg. Also, topiramate dose correlated significantly with weight loss ($p < .01$). In general, topiramate was well tolerated, with neurologic side effects the most common. Of 3 patients who discontinued topiramate because of side effects, 2 resumed the drug at a later date without significant recurrence of these effects.

Conclusion: Topiramate may be an effective treatment for binge-eating disorder. Controlled studies of topiramate in binge-eating disorder appear warranted.

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Received April 13, 1999; accepted Oct. 19, 1999. *From the Department of Psychiatry, University of Florida, Gainesville (Drs. Shapira and Goldsmith); and the Biological Psychiatry Program, University of Cincinnati College of Medicine, Cincinnati, Ohio (Dr. McElroy).*

Reprint requests to: Susan L. McElroy, M.D., University of Cincinnati College of Medicine, Department of Psychiatry, P.O. Box 670559, 231 Bethesda Ave., Cincinnati, OH 45267-0559.

Binge-eating disorder is classified as an eating disorder not otherwise specified in the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* (DSM-IV), where it is defined as recurrent episodes of binge eating that are not associated with the regular use of inappropriate compensatory behaviors (e.g., purging, fasting, excessive exercise).[1] Binge-eating disorder is common among obese individuals (body mass index [BMI] > 30 kg/m^2) seeking treatment, occurring in approximately 30% of obese individuals in weight-loss treatment programs and 70% of individuals in Overeaters Anonymous.[2–4] It may also be common among the general population.[3,4]

Topiramate [2,3:4,5-bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate] is a novel agent approved for the treatment of epilepsy.[5] Several possible mechanisms of action of topiramate have been identified[5]: (1) state-dependent blockade of voltage-activated Na^+ channels, (2) enhancement of GABAergic activity at a nonbenzodiazepine site on $GABA_A$ receptors, and (3) antagonism of kainate/c-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) type glutamate receptors.

Several preliminary reports suggest that, like other antiepileptic drugs, topiramate may have mood-stabilizing properties.[6,7] Topiramate was initially prescribed in our clinic to several patients with treatment-refractory bipolar disorder who were inadequately responsive to other psychotropic agents in an attempt to stabilize residual affective symptoms. Serendipitously, several of these patients had comorbid binge-eating disorder, and it was noted that the patients' binge-eating disorder symptoms improved with topiramate treatment.

Several lines of evidence then suggested to us that topiramate might reduce binge eating in persons with binge-eating disorder. First, in controlled trials in patients with epilepsy, topiramate was associated with appetite suppression and weight loss.[5] The binge-eating episodes of binge-

eating disorder are associated with a sense of lack of control over eating (i.e., excessive appetite or impaired satiety), and binge-eating disorder is associated with overweight and obesity.[2] Second, in animal studies, stimulation of the lateral hypothalamus by glutamate agonists, including kainate/AMPA agonists, causes an intense rapid dose-dependent increase in food intake.[8,9] It is therefore conceivable that an antagonist of kainate/AMPA glutamate receptors such as topiramate might suppress appetite. Third, some persons with bulimia nervosa have been reported to have electroencephalographic abnormalities and to display reduced binge eating in response to the antiepileptic drug phenytoin.[10,11]

On the basis of this rationale and our initial clinical observations, we treated other patients with binge-eating disorder with topiramate and had favorable results. To obtain a preliminary assessment of the effectiveness and tolerability of topiramate in binge-eating disorder, we reviewed the naturalistic, open-label treatment with topiramate of 13 consecutive outpatients with binge-eating disorder.

METHOD

Thirteen female outpatients with DSM-IV binge-eating disorder were treated with topiramate in a naturalistic, open-label fashion with a dose range of 100 to 1400 mg/day. All patients provided informed consent to receive treatment with topiramate. For the one patient who was 17 years of age when she began topiramate, informed consent for her to receive the drug was given by both the patient and her legal guardian.

We reviewed the treatment with topiramate of these 13 patients. Topiramate was usually begun at 25 mg at night and subsequently increased by 25 to 50 mg per week according to the patient's response and side effects to a maximum dose of 1400 mg/day, usually given b.i.d. or q.h.s. as tolerated. Response and side effects were evaluated in face-to-face interviews via retrospective recall at approximately monthly appointments. Response of binge-eating disorder symptoms was assessed clinically as none (0% to < 25% decrease in binge-eating episodes), mild (25% to < 50% decrease in binge-eating episodes), moderate (50% to < 75% decrease in binge-eating episodes), marked (75% to < 100% decrease in binge-eating episodes), or remission (complete cessation of binge-eating episodes). Patient weight and BMI at the start and end of topiramate treatment were recorded and compared using the Wilcoxon signed-rank test and the Pearson product-moment correlation.

RESULTS

Thirteen outpatients with binge-eating disorder received naturalistic, open-label treatment with topiramate. The clinical characteristics of these patients are summarized in Table 1. All patients had comorbid Axis I diagnoses, and topiramate was added to preexisting psychotropic regimens in all patients. After topiramate addition, 9 patients displayed a moderate or better response of binge-eating disorder symptoms that was maintained over a period of time ranging from 3 to 30 months (mean ± SD = 18.7 ± 8.0 months). Patients 6 and 8, who responded for 17 and 3 months, respectively, did not return to clinic after those time periods. The initial response of 2 other patients subsequently declined despite continuation of topiramate: the marked response of 1 patient (patient 7) attenuated to mild and the initial moderate response of the other (patient 10) ceased when she began smoking marijuana. One patient each had mild or no response. Eight patients continue taking topiramate currently, 1 (patient 7) because it stabilizes her bipolar disorder and the other 7 because it decreases their binge-eating disorder symptoms. The latter 7 patients displayed a moderate or better response for a mean ± SD duration of topiramate treatment of 21.1 ± 6.0 (range, 13–30) months.

The mean ± SD weight of the patients decreased from 99.3 ± 26.4 kg to 87.5 ± 20.4 kg ($z = -2.4$, $df = 1$, $p = .02$). The mean ± SD BMI for 12 of 13 patients (height was not obtained for 1 patient) decreased from 36.5 ± 8.5 to 32.2 ± 7.7 ($z = -2.3$, $df = 1$, $p = .02$). However, only 7 patients accounted for this substantial weight loss. Indeed, 3 patients lost essentially no weight, 2 patients gained weight, and 1 other patient lost less than 5 kg. The mean ± SD treatment dose of topiramate was 492.3 ± 467.8 mg/day. Of note, the mean ± SD treatment dose of topiramate in the 7 patients who lost ≥ 5 kg (725.0 ± 529.3 mg/day) was higher than that (220.8 ± 156.9 mg/day) in the 6 patients who lost < 5 kg ($z = -1.9$, $df = 1$, $p = .05$). Moreover, in the 13 patients as a group, there was a statistically significant correlation between topiramate dose and amount of weight loss, accounting for about 55% of the variance ($r = -.75$, $df = 11$, $p < .01$).

In general, topiramate was well tolerated (see Table 1). Side effects were most commonly neurologic and often transient. However, 1 patient (patient 2) with an original moderate response of binge-eating disorder symptoms discontinued topiramate after approximately 9 months owing to sedation and cognitive dulling; she was later able to restart topiramate with a marked response without significant recurrence of these side effects. Another patient (patient 9) discontinued after 2 weeks owing to gastrointestinal distress. She was later able to restart topiramate at a lower dose with remission of binge-eating disorder and no occurrence of these side effects. Two patients (patients 9 and 11) had worsening of comorbid bipolar (manic) symptoms with topiramate. In patient 9, manic symptoms resolved with reduction of topiramate dose, but patient 11 chose to discontinue topiramate because of this side effect.

Table 1. Patients With Binge-Eating Disorder (BED) Treated Clinically With Open-Label Topiramate[a]

Patient No.	Age (y)	Psychiatric Diagnoses	Start Date	Date Discontinued	Effective Treatment Dose (mg/d)	Other Psychiatric Medications	Response[b]	Starting Weight		Final Weight	
								kg	BMI	kg	BMI
1	45	BED, BD, OCD	2/28/97	Continuing	1400	Clonazepam, thyroxine, lithium[c]	Remission of BED, remission of BD, remission of OCD	145.4	43.4	88.9	26.7
2	46	BED, BD	1. 5/27/97 2. 1/10/99	1. 2/18/98 (due to sedation, cognitive dulling) 2. Continuing	500	Paroxetine, divalproex, clozapine, propranolol	1. Moderate improvement of BED 2. Marked improvement of BED, no improvement of BD	74.3	32.1	73.6	31.3
3	44	BED, BD	7/30/97	Continuing	1200	Thyroxine, divalproex, tranylcypromine, gabapentin, liothyronine	Remission of BED, moderate improvement of BD	120.2	44.2	92.3	33.9
4	47	BED, BD	8/20/97	Continuing	600	Fluoxetine, clonazepam, quetiapine, methylphenidate, thyroxine, glipizide, metformin, tiamterene/ hydrochloro-thiazide conjugated estrogens	Moderate improvement of BED, moderate improvement of BD	147.7	54.3	126.8	46.5
5	43	BED, BD	9/2/97	Continuing	1200	Clozapine, lorazepam, thyroxine	Moderate improvement of BED, moderate improvement of BD	83.0	32.4	70.0	27.3
6	22	BED, BD	9/8/97	2/2/99 (did not return to clinic)	100	Bupropion	Moderate improvement of BED, moderate improvement of BD	63.4	23.5	62.7	23.3
7	39	BED, BD	10/9/97	Continuing	200	Venlafaxine	Initial marked improvement of BED attenuated to mild improvement over time, remission of BD	94.1	33.3	105.4	37.5
8[d]	33	BED, MDD	11/12/97	2/25/98 (did not return to clinic)	300	Fluoxetine, thyroxine	Moderate improvement of BED, mild improvement of MDD	109.6	…	105.4	…
9	54	BED, BD (in remission), CB	1. 12/5/97 2. 7/10/98	1. 12/17/97 (due to GI distress) 2. Continuing	175	Divalproex, trazodone, estrogen	1. No improvement of BED 2. Remission of BED, initial worsening followed by marked improvement of BD, remission of CB	89.1	37.1	80.0	33.3
10	19	BED, MDD, MA	1/27/98	5/12/98 (due to no continued benefit)	300	Venlafaxine	Moderate improvement of BED attenuated to no response when began smoking marijuana, no improvement of MDD	70.0	28.4	62.3	25.3
11	32	BED, BD	1/28/98	5/22/98 (due to worsening BD)	125	Lithium	Mild improvement of BED, worsening of BD	106.8	43.3	107.3	43.5
12	40	BED, MDD, OCD	2/20/98	3/2/98 (due to no response)	100	Estrogen, trazodone	No improvement of BED, no improvement of MDD, no improvement of OCD	97.7	35.4	97.7	35.4
13	38	BED, MDD (in remission)	3/18/98	Continuing	200	Venlafaxine	Remission of BED	90.0	30.4	65.6	22.1

[a]Abbreviations: BD = bipolar disorder, BMI = body mass index, CB = compulsive buying, GI = gastrointestinal, MA = marijuana abuse, MDD = major depressive disorder, OCD = obsessive-compulsive disorder. All patients were female.
[b]Response = none (0%–< 25% decrease in binge-eating episodes), mild (25%–< 50% decrease in binge-eating episodes), moderate (50%–< 75% decrease in binge-eating episodes), marked (75%–100% decrease in binge-eating episodes), or remission (complete cessation of binge-eating episodes).
[c]Lithium discontinued without relapse of BED, BD, or OCD symptoms.
[d]Height was not obtained for this patient.

Unlike many other antiepileptics, topiramate is not associated with any known hematologic or hepatic abnormalities, and routine monitoring is not required.[5] Seven patients therefore did not receive these laboratory tests coincident with their topiramate therapy. Of the 6 patients who did, none showed clinically significant changes in hematologic or hepatic parameters. One patient (patient 1), however, displayed an increased serum glutamic-pyruvic transaminase level of 61 U/L (normal range, 6–46 U/L) while taking 1200 mg/day of topiramate, although this was thought to be due to her birth control medication.

Table 1 shows the medications to which topiramate was added. These agents primarily included antidepressants and mood stabilizers. No adverse interactions between these drugs and topiramate were observed.

Regarding response of comorbid diagnoses to topiramate treatment, 7 patients (patients 1, 3–7, 9) demonstrated moderate response, marked response, or remission of comorbid bipolar affective symptoms, and 1 patient (patient 2) had no response. By contrast, 2 patients (patients 9 and 11) displayed worsening of bipolar affective symptoms with topiramate treatment. Patient 9's initial worsening of bipolar affective symptoms was followed by a marked improvement. Of the 3 patients with major depressive disorder, 1 had a mild response and 2 had no response of active depressive symptoms. Of the 2 patients with comorbid obsessive-compulsive disorder, 1 patient (patient 1) displayed a remission of her symptoms, but the other (patient 12) displayed no apparent response to topiramate treatment. One patient (patient 9) experienced complete remission of severe compulsive buying while taking topiramate.

Case Summary

Patient 1 (the first patient our group treated with topiramate) was a 45-year-old woman with long-standing bipolar I disorder, severe binge-eating disorder, mildly to moderately severe obsessive-compulsive disorder, and severe migraine headaches. Both her bipolar I disorder and binge-eating disorder had been resistant to many different medical and psychological treatments, including lithium, carbamazepine, gabapentin, lamotrigine, various serotonin reuptake inhibitors, tricyclics, bupropion, monoamine oxidase inhibitors, and supportive psychotherapy.

Topiramate was begun on February 28, 1997, when added to lithium and thyroxine for manic symptoms and extremely rapid mood swings. She weighed 320 lb (145 kg) and was bingeing 2 or 3 times a day. In the past, divalproex sodium had stabilized her mood swings to some degree, but the patient refused further treatment with divalproex because she felt it increased her appetite and exacerbated her binge eating, and she had gained clinically significant weight while taking the drug. After 10 days of topiramate therapy, on March 10, 1997 (25 mg once a day for 1 week, then 25 mg twice a day), she reported that her manic symptoms had improved, that she had stopped binge eating, and that she had "lost 20 lb in 2 weeks." By March 24, 1997, she reported that her mood swings had worsened to some degree, but that her binge eating was still in remission. Topiramate was increased to 75 mg twice a day, but her neurologist stopped the drug because she also developed increased migraines, and he thought topiramate might be contributing to her headaches. However, on April 10, 1997, this patient reported that after she stopped the topiramate, she experienced increased appetite and a return of her urges to binge as well as a return of manic symptoms, and that she had stopped losing weight. She requested that treatment with topiramate be restarted. Topiramate was reinitiated at 25 mg twice a day for 1 week followed by 50 mg twice a day for 1 week.

On April 21, 1997, she reported that although her migraines continued, she felt better since restarting the topiramate, with remission of her mood swings, no binge eating, and decreased appetite. Over the next several months, the topiramate dose was slowly increased several times, and the patient was able to discontinue her lithium with continued remission of binge eating and manic symptoms and further weight loss. When topiramate was discontinued and resumed on one other occasion (after the patient lost her insurance and ran out of the drug), her binge eating and mood swings started and stopped, respectively. She has since stayed on topiramate treatment, which has been gradually increased to a stable dose of 1400 mg/day to successfully treat reemergent binge-eating symptoms, with a continued remission of binge-eating and bipolar disorders, losing a total of 56.5 kg from February 28, 1997, to August 20, 1999.

DISCUSSION

In this review of the naturalistic, open-label topiramate treatment of 13 outpatients with binge-eating disorder, 9 patients showed at least moderate improvement in their binge-eating symptoms after the addition of topiramate to ongoing psychotropic regimens, which was maintained for 3 to 30 months. Of 8 patients who have continued topiramate therapy to the present, 7 have maintained a moderate or better response in their binge-eating symptoms for a mean ± SD duration of 21.1 ± 6.0 (range, 13–30) months. Seven patients have lost ≥ 5 kg in weight. Side effects on topiramate have usually been neurologic and transient in nature.

These findings are limited by several methodological flaws. Most importantly, topiramate treatment was naturalistic and open-label and, thus, nonrandomized, unblinded, and uncontrolled. Also, standardized assessment instruments were not used. The possibility that the observed favorable response to topiramate was in fact due to placebo response, clinician or patient bias, or spontaneous

remission cannot be excluded. Second, topiramate was added to ongoing psychotropic regimens. It is therefore unknown whether the observed favorable effect on binge eating was due to the topiramate alone, to concurrently administered psychotropic medications, or to a synergistic response between the two. (However, in patient 1, concomitant lithium was discontinued, and both her binge-eating disorder and bipolar disorder remained in remission on topiramate monotherapy.) Third, although binge-eating disorder was a major complaint of all of these patients, they all had other major psychiatric disorders, particularly mood disorders. Thus, it is unclear whether topiramate would reduce binge-eating symptoms in the absence of a mood disorder. Topiramate, though, did alleviate binge eating in 2 patients, patients 9 and 13, whose mood disorders were in remission.

Yet another limitation is that 7 patients were taking medications known to cause hyperphagia and/or weight gain. The relationship between binge eating and psychotropic-induced hyperphagia/weight gain has been unexplored. Indeed, if psychotropic-induced hyperphagia/weight gain occurs via binge eating, topiramate's apparent effectiveness in binge-eating disorder in this small group of patients could be due to its being effective in the former and not the latter. These findings must therefore be regarded as highly preliminary pending outcome of controlled trials in populations of medication-free patients with binge-eating disorder without various comorbid disorders.

Even when these limitations are considered, the sustained response observed in 9 of 13 patients with binge-eating disorder suggests that topiramate may have utility for at least a subset of patients with binge-eating disorder. Antidepressants have previously been shown to be superior to placebo in the treatment of binge-eating disorder.[12] However, antidepressants possess a significant risk of inducing or worsening manic symptoms when used in bipolar disorder.[13,14] If topiramate is proved to have both mood-stabilizing and anti–binge-eating properties, it may offer a novel approach to those patients with comorbid bipolar and binge-eating disorders.[15] Moreover, if topiramate has anti–binge-eating properties in patients without mood disorders, its novel mechanism(s) of action would make it an extremely useful addition to the therapeutic armamentarium for binge-eating disorder and other disorders characterized by binge eating including, possibly, bulimia nervosa and some forms of obesity.[16]

Drug names: bupropion (Wellbutrin), carbamazepine (Tegretol and others), clonazepam (Klonopin and others), clozapine (Clozaril and others), divalproex sodium (Depakote), fluoxetine (Prozac), gabapentin (Neurontin), glipizide (Glucotrol and others), lamotrigine (Lamictal), liothyronine (Cytomel), lorazepam (Ativan and others), metformin (Glucophage), methylphenidate (Ritalin), paroxetine (Paxil), phenytoin (Dilantin and others), propranolol (Inderal and others), quetiapine (Seroquel), topiramate (Topamax), tranylcypromine (Parnate), trazodone (Desyrel and others), venlafaxine (Effexor).

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