Efficacy and Tolerability of Open-Label Topiramate in the Treatment of Sleep-Related Eating Disorder: A Retrospective Case Series

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Objective: Determine the efficacy and tolerability of topiramate in the treatment of sleep-related eating disorder (SRED).

Method: This is a retrospective chart review of consecutive patients treated in an open-label trial of topiramate for SRED in a sleep disorders clinic. Patients were diagnosed according to the second edition of the International Classification of Sleep Disorders. Patients with a Clinical Global Impressions of Improvement (CGI-I) rating of "very much" or "much" improved were considered treatment responders.

Results: 30 subjects were prescribed topiramate, of whom 25 had at least 1 postbaseline follow-up appointment. The mean age of these 25 patients was 44 ± 12 years, 76% were female, and the mean age at onset of SRED was 25.2 ± 12.8 years. The mean dose of topiramate was 135 ± 61.6 mg (range, 25–300 mg) over a mean period of 11.6 ± 11.4 months (range, 1–42 months). Over two thirds of the patients (17/25 or 68%) were considered topiramate responders. Twenty-eight percent (7/25) of the patients lost more than 10% of body weight. Adverse events were reported by 84% (21/25) of patients. Nearly half (7/17 or 41%) of the responders discontinued topiramate after a mean of 12.4 months.

Conclusion: In this open-label retrospective trial, topiramate was found to be very effective in reducing nocturnal eating in patients with chronic SRED. The tolerability of topiramate was an issue in some patients. Given the promise of this approach, but the limitations of this study, prospective, double-blind study of topiramate in a larger sample of patients with SRED is warranted.

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Sleep-related eating disorder (SRED) is a behavioral disorder combining the repetitive nocturnal awakenings of a sleep disorder with the driven, compulsive eating of a daytime eating disorder.[1,2] Sleep-related eating disorder is characterized by partial or full awakenings from sleep with compulsive eating, usually of high calorie foods. Individuals report little control over the behavior, which may occur multiple times per night. Partial or complete amnesia may be present afterward.[3] Prevalence data on SRED are preliminary, although some evidence suggests that up to 1% to 1.5% of adults have manifested this behavior.[4,5] The majority of sufferers are female; roughly one half are overweight; and daytime eating disorders (either frank or subclinical), mood disorders, and sleep disorders are not uncommon. Onset of the disorder is often in the 20s, and the disorder is usually chronic.

A variety of treatments have been employed in case series of patients with nocturnal eating, including dopaminergic agents,[6,7] opioids,[6] and sedative-hypnotics[6] or selective serotonin reuptake inhibitors.[8] I recently reported good success with the use of topiramate in 2 patients with SRED and 2 with night eating syndrome (NES) who were refractory to other pharmacologic and behavioral approaches.[16] All of the patients had at least a 50% reduction in nocturnal eating episodes and 3 had at least a 75% reduction, at doses of 75 to 400 mg at bedtime. Substantial weight loss was observed in all 4 patients (mean = 11.1 kg). Side effects were generally mild, though they limited the planned dose escalation in 2 patients.

Topiramate is an anticonvulsant agent indicated for the management of partial complex seizures.[9] The pharmacologic profile of topiramate is complex and involves increasing the inhibitory activity of γ-aminobutyric acid, blocking the effect of glutamate receptors, inhibiting carbonic anhydrase, and, potentially, blocking the activity of state-dependent sodium channels.[9] In clinical trials of topiramate for the treatment of epilepsy,[10] bipolar disorder,[11] and essential tremor,[12] appetite suppression and substantial weight loss have been observed in some patients. Furthermore, 2 open series[13,14] and 1 double-blind trial[14] have demonstrated that topiramate is an effective treatment for binge-eating disorder.

I now report a retrospective longitudinal analysis of the efficacy and tolerability of topiramate in the treatment

Table 1. Current ICSD-2 Definition and Diagnostic Criteria for Sleep-Related Eating Disorder[a]

A. Recurrent episodes of involuntary eating and drinking occur during the main sleep period
B. One or more of the following must be present with the recurrent episodes of involuntary eating and drinking:
   1. Consumption of peculiar forms or combinations of food or inedible or toxic substances
   2. Insomnia related to sleep disruption from repeated episodes of eating, with a complaint of nonrestorative sleep, daytime fatigue, or somnolence
   3. Sleep-related injury
   4. Dangerous behaviors performed in pursuit of food or while cooking food
   5. Morning anorexia
   6. Adverse health consequences from recurrent binge eating of high-caloric food
C. The disturbance is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder (hypoglycemic states, peptic ulcer disease, reflux esophagitis, Kleine-Levin syndrome, Klüver-Bucy syndrome, and nighttime extension of daytime anorexia nervosa [binge/purge subtype], bulimia nervosa, and binge-eating disorder)

[a]From the International Classification of Sleep Disorders (ICSD), second edition (pages 174–175), with permission.[3]

of a larger consecutive series of patients with SRED than previously studied.

METHOD

Subjects

The study sample consisted of consecutive patients diagnosed with SRED by the author according to the International Classification of Sleep Disorders, second edition[3] (see Table 1 for diagnostic criteria), from June 2002 to June 2005. Only patients for whom topiramate was prescribed for SRED were included in this series. The study was approved by the Institutional Review Board of Partners Healthcare, the parent organization of Brigham and Women's Hospital, Boston, Mass.

Procedure

Demographic, clinical, and nocturnal eating information was recorded from medical records prior to and after topiramate prescription. Characteristics of nocturnal eating recorded were number of episodes per night, estimated number of calories consumed, level of consciousness during episodes, duration of episodes, types of food or inedible substances consumed, and presence of amnesia for episodes.

Topiramate dose titration was standardized for all patients: 25 mg 1 hour prior to bedtime for the first week and subsequent increase by 25 mg per week until 100 mg per night was achieved or until side effects became intolerable or night eating was eliminated. If symptoms remained at 100 mg, dosage was increased by 25- or 50-mg increments (if tolerated) until symptoms were relieved. Patients were seen at follow-up every 2 to 6 months, depending upon clinical need. Subjects were encouraged to keep a night eating diary to better document nocturnal eating.

The primary efficacy outcome measure was the Clinical Global Impressions of Improvement (CGI-I),[15] addressing change in SRED symptoms from baseline (the period immediately prior to initiation of topiramate) to the final visit at which the patient was seen while taking topiramate. The CGI-I was determined retrospectively at chart review. The CGI-I is a 7-point scale describing change as 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), or 7 (very much worse). The CGI-I for patients with SRED was based on the following criteria: > 75% reduction in nocturnal eating (in terms of number of episodes or number of calories) was considered "very much improved," 50% to 75% reduction was rated as "much improved," 25% to 49% reduction was considered "minimally improved." If subjects had worsened eating in terms of number of episodes, number of calories, or reduction of level of consciousness or worsened amnesia for the episode, they were considered "much worse" or "very much worse." This schema is similar to that used in my previous case series on SRED and topiramate.[16] Patients achieving a 1 (very much improved) or 2 (much improved) were considered treatment responders.

Polysomnography was performed prior to initiation of topiramate for 17 of 25 subjects, according to previously described methods.[16]

Data Analysis

Identifying information was removed from the data, which were then entered into an Excel (Microsoft Corp.) spreadsheet. Continuous data are presented as means ± standard deviation and range. Statistical analysis was performed using the Student t test for continuous variables and the χ^2 test for categorical variables.

RESULTS

Thirty patients with SRED were prescribed topiramate by the author (2 of whom were treated by colleagues under the supervision of the author). Five of these patients had no postbaseline follow-up data, due to either not taking topiramate (N = 1) or having been lost to follow-up (N = 4). Thus, the treatment group consisted of 25 patients for whom efficacy and tolerability data are available (Table 2). Their mean age was 44 ± 12 years (range, 17–62 years), and 76% were female. Mean age at onset of SRED was 25.2 ± 12.8 years (range, 6–56 years). Thirty-two percent (8/25) were overweight (body mass index [BMI] 25 to < 30; range, 19.0–58.2) and 28% (7/25) were obese (BMI ≥ 30). Twenty-eight percent (7/25) had a history of a daytime eating disorder (1 bulimia, 1 anorexia,

Table 2. Summary Demographics and Topiramate Treatment Outcomes of Patients With Sleep-Related Eating Disorder (SRED) (N = 25)

Characteristic	Value
Female, N (%)	19 (76)
Age, mean (range), y	44 ± 12 (17–62)
Body mass index, mean ± SD, kg/m^2	27.9 ± 7.6
Age at onset of SRED, mean ± SD, y	25.2 ± 12.8
Family history of SRED, N (%)	3 (12)
Sleep disorders, N (%)	18 (72)
Daytime eating disorders, N (%)	7 (28)
Previous treatment for SRED, N (%)	12 (48)
Frequency of sleep-related eating, mean ± SD (range), episodes/wk	16 ± 8 (1.5–40)
Amnesia, N (%)	11 (44%)
Topiramate dose, mean ± SD (range), mg	
Responders	147.1 ± 66.9 (50–300)
Nonresponders	109.4 ± 37.4 (25–150)
Treatment outcome (very much/much improved), N (%)	17 (68%)
Adverse events, N (%)	21 (84%)
Discontinued medication, N (%)	15 (60%)

2 binge-eating disorder, 3 eating disorder not otherwise specified [NOS]), though in all cases the disorder had resolved by the time of this trial.

Prior to initiation of topiramate, nocturnal eating occurred on a nightly basis for all patients, and multiple episodes of eating per night were present (mean ± SD = 16 ± 8 episodes per week; range, 1.5–40 episodes) for the majority of patients. Forty-four percent (11/25) of them reported altered level of consciousness and/or amnesia during at least some episodes of nocturnal eating. Forty-eight percent (12/25) of patients had had previous pharmacologic treatment for SRED, of which only 2 reported a (transient) positive treatment response. Over 50% of the patients (13/25) were taking concomitant central nervous system (CNS)–active medications during the topiramate trial, though such medications were not changed during the period of assessment of topiramate's effect on night eating. Description of patients, characteristics of nocturnal eating, and treatment response are included in Table 3.

Polysomnographic Data

Seventy percent (12/17) of patients had sleep efficiency less than 85%, 5 of 17 had sleep onset latency greater than 30 minutes, and 70% (12/17) had less than 10% slow wave sleep. Twenty-nine percent (5/17) of subjects had an apnea-hypopnea index greater than 15 per hour (46.1, 30.5, 21.5, 16.4, 15.1). Three of these 5 patients with sleep apnea either were on continuous positive airway pressure (CPAP) at the time of the topiramate trial (1 patient) or had discontinued CPAP due to inability to tolerate the device (2 patients). Three of the 17 patients had periodic leg movement of sleep indices greater than 15 per hour (51.5, 43.9, 16.5). These 3 patients either had had previous trials of dopaminergic agents without benefit for SRED (2 patients) or were taking a dopaminergic agent prior to, and throughout, the topiramate trial (1 patient). Six patients had episodes of nocturnal eating on the night of the polysomnographic assessment. All episodes followed awakenings from non–rapid eye movement (non-REM) sleep and occurred during electroencephalogram (EEG)-defined wakefulness.

Topiramate Dosing and Duration

The mean topiramate dosage was 135 ± 61.6 mg (range, 25–300 mg) over a mean period of 11.6 ± 11.4 months (range, 1–42 months). All but 2 patients took at least 75 mg for a period of at least 2 weeks. Only 2 patients took more than 200 mg (250, 300 mg).

Clinical Efficacy of Topiramate for SRED

Analysis of CGI-I scores revealed that 17 (68%) of 25 patients were considered responders, 7 (28%) of 25 were unchanged, and 1 (4%) of 25 was worse (Table 3). The mean ± SD topiramate dose for responders was 147 ± 67 mg (median = 125 mg; range, 50–300 mg) and 109.4 ± 37.4 mg (median = 112.5 mg; range, 25–150 mg) for nonresponders. The mean duration of topiramate use in patients stratified by CGI-I outcome was as follows: "very much improved" (mean = 11.9 months; median = 14.5 months; range, 1–22 months); "much improved" (mean = 19.3 months; median = 21 months; range, 1–42 months); "no change" (mean = 2.9 months; median = 2 months; range, 1–8 months). Once patients achieved an effective dose, optimal response of nocturnal eating episodes was reported as being nearly immediate. In the 7 patients who were considered responders but discontinued topiramate (6 of whom had follow-up information available), 2 maintained remission, 2 had a partial relapse, and 2 had a complete relapse, usually within days of discontinuing topiramate.

Response to topiramate in those with a history of amnesia and altered level of consciousness while eating (7/11) was similar to response in those who reported eating while wide awake and with full recollection (10/14). Pretreatment values of age, gender, BMI, and number of eating episodes per night did not predict response to topiramate (all p values > .10). Twenty-eight percent (7/25) of patients lost greater than 10% of body weight (15 kg, 13.6 kg, 9.1 kg, 8.6 kg, 6.8 kg, 6.4 kg, 5.0 kg).

Adverse Events

Adverse events were reported by 84% (21/25) of patients (Table 3). The most common were paresthesias (20%), excessive daytime sleepiness (16%), and sexual dysfunction (12%). No serious adverse events occurred. Sixty percent (15/25) of patients discontinued topiramate after a mean period of 7.3 months (range, 1–33 months), and 3 (12%) of 25 discontinued due to adverse events. Of those discontinuing topiramate, 7 (47%) of 15 were considered responders, of whom 2 of 7 discontinued due to

Table 3. Clinical Demographics and Treatment Outcomes With Sleep-Related Eating Disorder (SRED)

Patient	Age (y)/Sex	Body Mass Index (kg/m^2)	Age at Onset, y	Night Eating Episodes (per wk)	Sleep Disorder	Daytime Eating Disorder	Diagnostic Criteria Met for SRED[a]	Amnesia	Dose of Topiramate, mg	Duration of Topiramate, mo	Discontinued Topiramate	Adverse Events	CGI-I (1–7)[b]
1	33/F	40.1	10	20	Sleep walking, night terrors, nightmares	Eating disorder NOS	1, 2, 3, 5, 6	+	200	42	No	None	2
2	54/F	31.1	19	1.5	Insomnia	BED	2	+	125	18	No	Tachyphylaxis	1
3	41/F	24.9	39	10	Insomnia	None	2, 5	+	100	2	No	Headaches	1
4	53/M	31.1	6	15	Insomnia	None	1, 2, 6	+	250	5	No	Visual illusions	2
5	62/F	27.1	56	20	Insomnia	None	2, 6	+	125	3	Yes	None	4
6	48/M	27.1	43	5	RLS, OSA, insomnia, night terrors, sleep walking	None	2	+	75	1	Yes	Anxiety	1
7	56/F	58.2	53	21	OSA, RLS	None	6	–	125	22	No	EDS, dream enactment, weight loss (27 lb)	1
8	52/M	25.0	44	21	Insomnia	None	2, 6	–	100	1	Yes	Irritable	4
9	17/F	23.0	11	40	Insomnia	None	2, 6	+	25	2	Yes	EDS	4
10	44/M	29.3	23	7	None	None	5, 6	–	150	16	No	Paresthesias, decreased memory, sexual dysfunction	1
11	39/F	28.2	24	21	None	Bulimia	5, 6	–	150	23	No	Decreased cognitive function	2
12	44/M	30.1	23	14	OSA	None	6	–	125	2	Yes	None	4
13	48/M	31.7	24	7	OSA	None	2, 6	–	200	33	Yes	Sexual dysfunction	2
14	26/F	28.3	21	21	None	None	1, 2, 5, 6	–	50	1	Yes	Nausea, EDS, paresthesias	2
15	31/F	28.2	27	10	Bruxism	None	6	–	150	6	No	Bicarbonate reduction	2
16	41/F	23.8	25	28	EDS	Anorexia	2, 5, 6	+	300	31	No	None	2
17	61/F	20.3	20	14	None	None	2	–	75	13	Yes	Weight loss, paresthesias	1
18	31/F	21.3	20	14	None	None	5	–	150	21	Yes	Weight loss (14 lb), paresthesias	2
19	53/F	24.8	19	14	Nightmares	None	2, 5, 6	–	125	12	Yes	Eye twitching, tolerance	2
20	47/F	20.8	41	7	Sleep walking, night terrors, nightmares	None	1, 4	+	150	2	Yes	Worsened amnesia	5
21	55/F	27.4	21	14	PLMS	BED	6	–	100	2	Yes	Depression	4
22	50/F	22.5	25	21	Sleep walking	None	3, 5, 6	+	150	8	Yes	Paresthesias, decreased memory, sexual dysfunction	4
23	33/F	19.0	18	12	None	Eating disorder NOS	1, 5, 6	+	125	17	No	Hair loss	1
24	26/F	30.4	21	21	Sleep walking	Eating disorder NOS	5, 6	–	100	6	Yes	EDS	1
25	61/F	26.0	7	21	None	None	6	–	100	2	Yes	Did not feel well	4

[a]Diagnostic criteria met for SRED: 1 = Consumption of peculiar forms or combinations of food or inedible or toxic substances; 2 = Insomnia related to sleep disruption from repeated episodes of eating, with a complaint of nonrestorative sleep, daytime fatigue, or somnolence; 3 = Sleep-related injury; 4 = Dangerous behaviors performed in pursuit of food or while cooking food; 5 = Morning anorexia; 6 = Adverse health consequences from recurrent binge eating of high caloric food.

[b]CGI-I: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), or 7 (very much worse).

Symbols: + = present, – = absent.

Abbreviations: BED = binge eating disorder, CGI-I = Clinical Global Impressions of Improvement, EDS = excessive daytime sleepiness, NOS = not otherwise specified, OSA = obstructive sleep apnea, PLMS = periodic limb movements of sleep, RLS = restless legs syndrome.

adverse events and 1 of 7 discontinued due to development of tolerance to the therapeutic effect. Of the 17 responders, 7 (41%) discontinued medication after a mean period of 12.4 months (range, 1–33 months).

DISCUSSION

These data confirm and extend my previous small case series[16] suggesting that topiramate may be of value in the treatment of SRED. It also nearly doubles the world's published literature on the treatment of this complex disorder. However, given the lack of a placebo comparison and the use of a retrospective, clinical measure of SRED severity, our results remain preliminary. My original study[16] demonstrated substantial or complete response of nocturnal eating with doses of topiramate 75–300 mg before bedtime. The current larger series of patients again suggests that topiramate may reduce the number of nocturnal eating episodes and, in some patients, reverse the weight gain associated with this disorder.

Other treatments that have shown some promise in the treatment of nocturnal eating in open-label studies include sertraline,[8] *d*-fenfluramine,[17] and *l*-dopa.[6] These medications have disparate mechanisms of action in the CNS and may exert their therapeutic effects in night eating by different means: by improving sleep continuity (*l*-dopa in patients with restless legs syndrome or sertraline in those with mood or anxiety disorders) or by appetite suppression (*d*-fenfluramine). It has also been postulated that sertraline may act by reentraining the circadian control of appetite to a normal daytime pattern, potentially through serotonergic actions at the suprachiasmatic nucleus.[8]

The mechanism by which topiramate improves SRED is unclear, though it has 2 properties that may contribute: enhancement of sleep and appetite suppression. Although topiramate is mildly sedating, it is not clear that sedatives alone are of therapeutic value in the treatment of SRED. In fact, the new onset of SRED in patients given zolpidem for a variety of sleep disorders, particularly restless legs syndrome,[18,19] demonstrates that hypnotic effects alone are probably not sufficient to treat SRED. On the other hand, the efficacy of topiramate in the reduction of daytime binge episodes in binge-eating disorder and bulimia suggests that topiramate may promote control of undesirable eating, both day and night. The mechanism by which this occurs is unclear; however, its sensitization of adipocytes to insulin[20] and its promotion of insulin release by pancreatic cells[21] may be relevant.

In my previous small case series,[16] 2 subjects were described as having SRED and 2 with NES. This distinction was based upon whether nocturnal eating occurred with (SRED) or without (NES) alterations in level of consciousness. Other features that are characteristic of SRED (as opposed to NES) include the higher prevalence of primary sleep disorders, the occasional ingestion of nonedible substances, and the impaired recollection for nocturnal eating episodes. However, for a diagnosis of SRED, the recently revised International Classification of Sleep Disorders, second edition,[3] requires episodes of undesirable eating during full or partial arousals from sleep, associated with secondary consequences, but does not specify that level of consciousness be reduced during such episodes. Thus, all subjects in the current report were considered to have SRED. Further supporting the integration of these 2 nocturnal eating disorders (NES and SRED) is our finding that level of consciousness during nocturnal eating did not predict treatment benefit from topiramate, with both groups responding at similar, high rates.

The patients treated with topiramate in the current study were similar to those with SRED previously described in sleep clinic settings.[1,2,6,8,10] For instance, they were predominantly 30- to 50-year-old women, with a young adult onset of nightly nocturnal eating with prominent resultant sleep disruption and weight gain. In distinction to some other reports,[1,2] but consistent with others,[7,18] a diagnosis of sleepwalking and amnesia for nocturnal eating was present in a minority of patients. The similarity of our patient sample to previously reported patients with SRED provides some confidence that our findings with topiramate treatment may be relevant to other patients with similar complaints.

Consistent with my previous case series[16] and with published data on tolerability of topiramate in eating disorders[13] and epilepsy[22] studies, treatment-emergent adverse events were common. Although only 3 of 25 patients explicitly discontinued topiramate due to an adverse event, a number of other patients had adverse events of moderate intensity that may have outweighed treatment benefit if they had been treatment responders or may have contributed to their decision to discontinue treatment.

The current data should be interpreted in light of a number of important limitations. Most importantly, this was an open-label study, and nocturnal eating may be subject to expectation, suggestion, and other components of the placebo response in both the patients and investigators. Clearly, double-blind, randomized, placebo-controlled studies are required to demonstrate efficacy. In the present study, each subject served as their own control compared to their immediate baseline period. Although there is clearly variability in this baseline, we are more confident in the data, given the long history of nocturnal eating (average of 19.1 years) in these subjects and the relative refractoriness of the patients to previous therapies. Another important caveat is that treatment response was based upon retrospective analysis of charts, rather than prospective measures of nocturnal eating. Similarly, though some patients did provide diaries of nocturnal eating, treatment response was often based upon patients' recollection of nocturnal eating at the time of the appoint-

ment, which may have produced inaccuracies in the data. Future studies should employ sleep and eating diaries to better quantify treatment response. Such diaries will necessarily be the primary outcome variable in treatment studies of SRED until reliable and validated measures of disease severity are developed.

In summary, topiramate was found to be of substantial benefit in patients with SRED in this open-label case series, though adverse events limited its tolerability. Given the paucity of effective medication treatments for SRED, a controlled trial of topiramate in a larger sample of patients is indicated.

Drug names: sertraline (Zoloft and others), topiramate (Topamax), zolpidem (Ambien).

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