Zonisamide in the Treatment of Binge-Eating Disorder: An Open-Label, Prospective Trial

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Background: Binge-eating disorder is characterized by recurrent episodes of uncontrollable overeating without compensatory weight-loss behaviors. It commonly co-occurs with obesity. Zonisamide is a novel antiepileptic drug associated with weight loss. The purpose of this study was to preliminarily assess zonisamide in the treatment of binge-eating disorder.

Method: Fifteen outpatients with DSM-IV-TR binge-eating disorder were enrolled from Jan. 25, 2002, through Sept. 10, 2002, in an open-label, prospective, 12-week, flexible dose (100–600 mg/day) study of zonisamide. The primary outcome measure was binge-eating episode frequency. Secondary measures included binge day frequency, body mass index (BMI), weight, Clinical Global Impressions-Severity of Illness scale (CGI-S) scores, Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating (YBOCS-BE) scores, Three Factor Eating Questionnaire (TFEQ) scores, and Hamilton Rating Scale for Depression scores. Safety measures included adverse events, routine blood chemical and hematology laboratory values, urinalyses, plasma zonisamide levels, physical examination findings, and electrocardiograms. Outcome measures were analyzed by a repeated-measures random regression analysis using all data and an endpoint analysis using last observation carried forward.

Results: Eight subjects completed the 12 weeks of treatment. The mean (SD) zonisamide daily dose at endpoint evaluation was 513 (103) mg/day. Both the random regression and endpoint analyses found a highly significant decrease in binge-eating episode frequency, binge day frequency, BMI, weight, CGI-S scores, YBOCS-BE total scores, and TFEQ hunger and disinhibition scores ($p < .0001$ for all measures in both analyses except $p = .001$ for endpoint analysis of binge eating frequency, $p = .0001$ for endpoint analysis of TFEQ disinhibition, and $p = .0008$ for endpoint analysis of TFEQ hunger). The 7 subjects who discontinued zonisamide prematurely did so due to lack of response (N = 1), protocol nonadherence (N = 2), and adverse events (N = 4).

Conclusion: Zonisamide was effective in reducing binge-eating frequency, severity of illness, and weight and was generally well tolerated in an open trial of binge-eating disorder. Controlled trials appear warranted.

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Binge-eating disorder is characterized by recurrent, uncontrollable, and distressing episodes of excessive food consumption (binge eating) without compensatory weight-loss behaviors.[1,2] It is associated with overweight and obesity.[1–6] Indeed, although its prevalence in the general population of the United States is estimated to be 1.5% to 2%,[1–5,7] approximately 8% to 30% of those seeking standard weight-loss treatments,[1–4] up to 50% of those seeking bariatric surgery,[8,9] and 70% of those participating in Overeaters Anonymous[3] are estimated to have binge-eating disorder.

Various psychological treatments, particularly cognitive-behavioral therapy and interpersonal therapy, have been shown to be effective in reducing binge-eating episodes in binge-eating disorder, both acutely and over the long term.[7,10,11] These treatments, however, have been less effective for the associated overweight and obesity. Selective serotonin reuptake inhibitors (SSRIs)[12–15] and the novel antiepileptic topiramate[16] have been found to be superior to placebo in reducing both binge-eating episodes and overweight in outpatients with binge-eating disorder.[17] These trials, however, have ranged from only 6 to 14 weeks in duration. Their long-term antibinge-eating and weight loss effects are therefore unknown. Moreover, both SSRIs and topiramate are associated with side effects that some patients find intolerable (e.g., sexual dysfunction for SSRIs and cognitive impairment for topiramate). Novel treatments that reduce both binge eating and overweight are therefore needed for binge-eating disorder.

Zonisamide is a structurally and pharmacologically novel antiepileptic drug—a sulfamate-substituted monosaccharide—with proven anticonvulsant efficacy when used adjunctively in refractory partial epilepsy.[18–20] Mechanisms hypothesized to account for zonisamide's antiepileptic properties include antagonism of voltage-gated sodium and T-type calcium channels, blockade of potassium-evoked glutamate release, modulation of central dopaminergic and serotonergic function, and carbonic anhydrase inhibition.[18–25]

Several lines of evidence suggest that zonisamide might be a useful treatment for binge-eating disorder. First, like the anticonvulsant topiramate,[26,27] zonisamide has been associated with anorexia and weight loss in clinical trials with epilepsy patients.[19,20,28] Both agents have also been shown to be superior to placebo in inducing weight loss in patients with obesity.[29,30] In addition, as noted, topiramate has been shown to reduce overweight in binge-eating disorder associated with obesity.[16] Although zonisamide and topiramate have distinct pharmacologic profiles, both drugs share several pharmacologic actions. These include sodium channel blockade, carbonic anhydrase inhibition, and reduction of glutamate neurotransmission.[18,19,21,24–26] Regarding the latter property, animal studies have shown that stimulation of the lateral hypothalamus by glutamate and glutamate agonists causes an intense, rapid, dose-dependent increase in food intake,[31] whereas glutamate antagonism of the nucleus tractus solitarius reduces food intake.[32]

Second, unlike topiramate, zonisamide also modulates the function of serotonin and dopamine,[22,23,25] 2 neurotransmitters involved in the regulation of feeding behavior[33] and in the mechanisms of some medications with efficacy in either binge-eating disorder (SSRIs, d-fenfluramine, sibutramine)[12–15,34,35] or obesity (sibutramine, stimulants).[36]

Third, a broad range of antidepressants have been reported to reduce binge eating in both bulimia nervosa[37] and binge-eating disorder,[12–15,17] and preliminary observations suggest zonisamide may have thymoleptic properties.[38–40]

Because of these observations, we conducted an open-label trial of zonisamide in 15 patients with binge-eating disorder.

METHOD

Study Design

The study was a single-center, open-label, flexible-dose study. After a week of medication-free evaluation, subjects were treated with zonisamide for a 12-week period. Zonisamide was dispensed in 100-mg capsules. Zonisamide was begun at 100 mg/day for the first 7 days. The dosage was then increased, as tolerated, by 100 mg/day every 7 days to a maximum of 600 mg/day. Study medication could be reduced to a minimum of 100 mg daily because of bothersome side effects at any time during the 12-week treatment period. Subjects who were classified as responders (≥ 50% reduction in binge eating frequency from baseline) at the end of the 12-week treatment period could continue in an open-label maintenance trial. (These results will be described in a later report). Those who wanted to discontinue treatment were tapered off the drug.

Table 1. Baseline Characteristics of 15 Subjects With Binge-Eating Disorder Receiving Zonisamide

Characteristic	Mean	SD
Age, y	36.8	8.2
	N	%
Women	14	93
White	15	100
Major depressive disorder		
Current	2	13
Major depressive disorder		
Lifetime (current or past)	8	53
Anxiety disorder		
Lifetime (current or past)	2	13
Alcohol abuse or dependence		
Past	1	7

Subject Selection Criteria

Subjects were outpatients recruited through advertisements for a binge eating medication trial. Subjects were eligible for the study if they met DSM-IV-TR criteria for binge-eating disorder,[2] reported experiencing ≥ 3 binge-eating episodes weekly for at least the prior 6 months, and were between 18 and 60 years of age.

Subjects were excluded if they had a current body mass index (BMI) < 19; were pregnant or lactating; had concurrent anorexia nervosa or bulimia nervosa; had a substance use disorder within 1 year of study entry; had a lifetime history of a psychotic disorder, bipolar disorder, or dementia or other cognitive disorder; had a personality disorder that could interfere with diagnostic assessment, treatment, or compliance; displayed clinically significant suicidality or homicidality; had received psychotherapy or behavioral therapy within 3 months of entry into the study; had clinically unstable medical illness; had a history of seizures, including childhood febrile seizures; had a history of nephrolithiasis; had clinically significant laboratory or electrocardiogram abnormalities; received psychoactive medication (other than hypnotics, e.g., zolpidem or zaleplon, as needed for insomnia) within 2 weeks of initiation of study medication; had previously been treated with zonisamide; or had < 3 binges in the week before receiving study medication.

Fifteen subjects were enrolled in the study from January 25, 2002, through September 10, 2002, and received treatment with zonisamide. Their baseline characteristics are summarized in Table 1. Major depressive disorder was the most common co-occurring psychiatric disorder.

It occurred in 8 subjects as a lifetime diagnosis and was current in 2 subjects.

Subject Evaluation

The Institutional Review Board at the University of Cincinnati Medical Center (Cincinnati, Ohio) approved the protocol, and all subjects provided written informed consent before administration of any study procedures. All subjects underwent a screening evaluation that included an interview for demographic information and medical, psychiatric, and family histories; the Structured Clinical Interview for DSM-IV[41] to establish binge-eating disorder and comorbid Axis I diagnoses; a physical examination; vital signs; height and weight; electrocardiogram; routine fasting blood chemical and hematological tests; and urinalysis. At this evaluation and each of the following visits, subjects were given take-home diaries in which to record any binges and, once medication was initiated, the number of capsules taken on a daily basis. Subjects were seen weekly during the study for the first 6 weeks and then every 2 weeks for the remainder of the trial.

At each visit following the screening visit, subjects were assessed for number of binges experienced since the last visit, other outcome measures, medication dose, medication compliance ascertained by capsule count, adverse events, use of nonstudy medications, vital signs, and weight.

Outcome Measures

The primary outcome measure was the weekly frequency of binge-eating episodes (binge frequency), defined as the mean number of binges per week in the interval between visits (total number of binges divided by number of days in the interval, and then multiplied by 7). Binges were defined using DSM-IV-TR criteria[2] and assessed via clinical interview and review of subject take-home diaries, in which subjects recorded binges, duration of binges, and food consumed during binges (so that binges could be confirmed by the investigator). The interviews and diary reviews were performed by the physician investigator (S.L.M., R.K., E.B.N., or P.E.K.) working with that particular subject. Secondary outcome measures were weekly frequency of binge days (days when there were 1 or more binges), BMI (body weight in kg divided by height in m^2), weight (kg), Clinical Global Impressions-Severity of Illness scale (CGI-S) scores, Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating (YBOCS-BE) scores,[42] Three Factor Eating Questionnaire (TFEQ) scores,[43] and Hamilton Rating Scale for Depression (HAM-D) total scores.[44] The CGI-S is a 7-point scale on which a score of 1 = normal, 2 = borderline ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, and 7 = among the most extremely ill patients. The YBOCS-BE is a modified version of the Yale-Brown Obsessive-Compulsive Scale[42] (available from the authors on request) that measures obsessiveness of binge-eating thoughts and compulsiveness of binge-eating behaviors. The TFEQ (also called the Eating Inventory)[43] is a self-report questionnaire that measures 3 dimensions of eating behavior thought to be dysregulated in eating disorders and obesity: cognitive restraint in eating (cognitive restraint), susceptibility to periodic disinhibition of control over eating (disinhibition), and perceived hunger (hunger). We also tabulated categories based on percentage decrease in frequency of binges from baseline (the week before treatment) to endpoint (the final week of treatment) and defined as follows: remission = cessation of binges, marked = 75%–99% decrease, moderate = 50%–74% decrease, and none = less than 50% decrease. These response categories have been used in previous pharmacologic treatment studies of binge-eating disorder.[12–16]

The following safety measures were assessed: adverse events, routine blood chemical and hematology laboratory values, plasma zonisamide levels, physical examination findings, and electrocardiograms.

Statistical Methods

For each outcome measure except response categories, we performed a repeated-measures random regression analysis using modifications of analyses we have used in previous placebo-controlled studies of binge-eating disorder.[12–16] This "time trend" analysis was our primary analysis and assessed the rate of change of each outcome measure during the treatment period. We used a model for the mean of the outcome variable that included a term for time. We modeled time as a continuous variable, expressed as weeks, with weeks ranging from 0 at baseline to 12 at the week 12 visit after beginning treatment with zonisamide. The measure of effect was the rate of change (change per week) in the outcome. For the analysis of binge frequency and binge day frequency, we used the logarithmic transformation log ([binges/week] + 1) to normalize the data and stabilize the variance.

To account for the correlation of observations within individuals in the random regression analysis, we used PROC GENMOD in SAS software (version 6.12, Cary, N.C.) to calculate the standard errors of the parameter estimates using compound symmetry as the working covariance structure. The random regression analysis is intent-to-treat, using available observations on all subjects who completed a baseline evaluation.

We also performed an endpoint analysis of the change from baseline, applying a 1-sample t test to the last observation carried forward (LOCF).

For the results of response categories, we present the data in 2 ways: one using only subjects completing the 12 weeks of treatment (completers) and the other, an intent-to-treat analysis, using LOCF.

We set alpha at .05 for statistical significance. All tests were 2-tailed.

Table 2. Outcome Measures Before and After 12 Weeks of Treatment With Zonisamide and Analysis of Change in Outcome Measures

Outcome Measure	Baseline (N = 15) Mean (SD)	Last Observation (N = 15[a]) Mean (SD)	Week 12 (N = 8) Mean (SD)	Time Trend Analysis Rate of Change[b] Estimate	SE	p Value	Endpoint Analysis Change From Baseline[c] Estimate	SE	p Value
Binges/wk	8.0 (6.6)	1.1 (2.5)	0.1 (0.3)	–0.175[d]	0.008	< .0001	–6.93	1.73	.001
Binge days/wk	5.0 (1.0)	0.8 (1.5)	0.1 (0.3)	–0.156[e]	0.006	< .0001	–4.14	0.43	< .0001
BMI, kg/m^2	40.0 (6.8)	37.6 (6.2)	39.0 (4.4)	–0.251	0.037	< .0001	–2.35	0.45	< .0001
Weight, kg	106.5 (21.5)	100.5 (21.2)	98.3 (12.2)	–0.641	0.095	< .0001	–6.06	1.13	< .0001
CGI-S score	5.0 (0.8)	2.3 (1.3)	1.6 (0.5)	–0.306	0.019	< .0001	–2.73	0.34	< .0001
YBOCS-BE score									
Total	19.8 (5.2)	6.2 (6.3)	2.1 (3.1)	–1.46	0.12	< .0001	–13.6	1.56	< .0001
Obsessions	9.9 (3.0)	3.3 (3.5)	1.1 (2.1)	–0.673	0.064	< .0001	–6.60	0.83	< .0001
Compulsions	9.9 (2.7)	2.9 (3.0)	1.0 (1.2)	–0.785	0.070	< .0001	–7.00	0.83	< .0001
TFEQ score									
Cognitive restraint	6.5 (4.4)	10.6 (5.2)	9.1 (5.3)	0.321	0.173	.064	4.43	1.87	.034
Disinhibition	13.7 (2.1)	7.2 (4.7)	5.4 (4.2)	–0.748	0.109	< .0001	–6.43	1.12	.0001
Hunger	9.7 (4.2)	4.1 (4.0)	3.1 (2.9)	–0.591	0.122	< .0001	–5.50	1.07	.0008
HAM-D score	6.8 (4.6)	4.5 (4.2)	4.5 (3.1)	–0.123	0.123	.31	–2.27	1.49	.15

[a]N = 14 for TFEQ measures.
[b]Random regression model includes all available observations on all subjects at all time points, including those who terminated the study prematurely (see text for explanation of model).
[c]One-sample t test using last observation carried forward.
[d]Estimate and SE displayed is for log [(binges/wk) + 1] used in statistical analysis; corresponding estimate for binges/week at week 12 is 0.3.
[e]Estimate and SE displayed is for log [(binge days/wk) + 1] used in statistical analysis; corresponding estimate for binge days/week at week 12 is 0.2.
Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, TFEQ = Three Factor Eating Questionnaire, YBOCS-BE = Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating.

RESULTS

During the course of the study, 7 subjects withdrew prematurely for the following reasons: lack of response (N = 1), nonadherence with the protocol (N = 2), and adverse events (N = 4). The latter included: altered taste (N = 1), development of depressive symptoms (N = 1), development of a panic attack (N = 1), and presumed nephrolithiasis with hydronephrosis and pyelonephritis (N = 1), which was considered a serious adverse event (see below). The remaining 8 patients completed the 12 weeks of treatment.

The mean (SD) daily dose at endpoint evaluation for all 12 subjects was 513 (102.7) mg. The mean (SD) daily dose for the 8 patients who completed the 12-week trial was 562.5 (74.4) mg.

The observed mean values for the outcome variables at week 12 are presented in Table 2. Both the time trend and endpoint analyses found a highly significant decrease in frequency of binges, frequency of binge days, BMI, weight, CGI-S scores, YBOCS-BE total scores, YBOCS-BE obsession scores, YBOCS-BE compulsion scores, TFEQ disinhibition scores, and TFEQ hunger scores ($p < .0001$ for all measures in both analyses except $p = .001$ for endpoint analysis of frequency of binge eating, $p = .0001$ for endpoint analysis of TFEQ disinhibition, and $p = .0008$ for endpoint analysis of TFEQ hunger; Table 2). TFEQ cognitive restraint scores were significantly increased in the endpoint ($p = .034$) but not the time trend analysis ($p = .064$; Table 2). The change in HAM-D scores was not significant in either analysis ($p = .31$ for time trend, $p = .15$ for endpoint; Table 2).

Table 3. Response Categories for Percentage Decrease in Frequency of Binges and Frequency of Binge Days From Baseline to Endpoint in Patients Treated With Zonisamide for 12 Weeks

	Frequency of Binges				Frequency of Binge Days			
	Endpoint[a] (N = 15)		Completers (N = 8)		Endpoint[a] (N = 15)		Completers (N = 8)	
Response	N	%	N	%	N	%	N	%
None (< 50%)	1	7	0	0	1	7	0	0
Moderate (50%–74%)	1	7	0	0	2	13	0	0
Marked (75%–99%)	5	33	1	13	4	27	1	13
Remission (100%)	8	53	7	88	8	53	7	88

[a]Last observation carried forward.

The great majority of subjects either achieved a remission of binge eating or a marked level of response either at the end of 12 weeks or at the last point of observation (Table 3). The estimated mean weight loss at week 12 was 7.6 kg (16.8 lb) from the time trend analysis. The observed mean weight loss for completers at week 12 was 8.2 kg (18.1 lb).

The most common adverse events reported by the subjects were altered taste, fatigue, dry mouth, and cognitive impairment (Table 4). One subject developed a serious adverse medical event: presumed nephrolithiasis (an actual stone was never recovered) with hydronephrosis and pyelonephritis 3 weeks after beginning zonisamide. Because kidney stones are a known side effect of zonisamide,[18,19,28] the presumed kidney stone was attributed to

Table 4. Side Effects Reported by ≥ 10% of 15 Subjects Treated for 12 Weeks With Zonisamide for Binge-Eating Disorder

Side Effect	N	%
Altered taste	7	47
Fatigue	7	47
Dry mouth	7	47
Cognitive impairment	6	40
Insomnia	5	33
Nausea	5	33
Drowsiness	5	33
Dyspepsia	5	33
Irritability	4	27
Headache	4	27
Memory impairment	4	27
Parasthesia	3	20
Impaired concentration	2	13
Urinary tract infection	2	13
Panic symptoms[a]	2	13
Depression[b]	2	13

[a]Includes 1 subject who experienced a panic attack and 1 subject who experienced a limited symptom panic attack; the first subject had no comorbid Axis I disorders and the second had current minor depression.
[b]Includes 1 subject who had a past history of major depressive disorder, recurrent; the other subject (who is also the subject who developed the panic attack) had no other psychiatric disorders.

the zonisamide. The subject's zonisamide was discontinued and she recovered fully with antibiotics. Because it was unknown if the presumed kidney stone was due to zonisamide (since it had occurred after only 3 weeks of treatment) and the subject believed that zonisamide had relieved her binge eating, she resumed zonisamide under the supervision of her family physician and nephrologist.

There were no changes in physical examination findings, vital signs, or clinical laboratory values suggestive of drug-related toxicity. The mean (SD) plasma zonisamide level in the 14 subjects who were assessed was 32 (9.3) μg/mL (range, 16–47 μg/mL; normal range, 10–40 μg/mL). The mean (SD) plasma zonisamide level for completers was 34 (10.1) μg/mL (range, 16–43 μg/mL); the level for noncompleters was 29 (8.5) μg/mL (range, 17–47 μg/mL). There was no evidence of withdrawal symptoms in the 7 subjects in whom zonisamide was either abruptly discontinued (N = 4) or gradually withdrawn (per protocol, N = 3).

DISCUSSION

Using a time trend analysis (based on the estimated rate of change of outcome measures) and an endpoint analysis (based on LOCF), open-label treatment with zonisamide of 15 subjects with binge-eating disorder was associated with a significant reduction in frequency of binges, frequency of binge days, BMI, weight, obsessive-compulsive features of binge-eating symptoms, and severity of illness. Change in TFEQ subscale scores suggested improvement in susceptibility to periodic disinhibition of control over eating and perceived hunger, and possibly an increase in cognitive restraint over eating. There was no significant change in HAM-D scores with either analysis, but the mean HAM-D score was low at baseline. These findings provide preliminary evidence for the effectiveness of zonisamide in binge-eating disorder.

The potential mechanism of action of zonisamide in binge-eating disorder is unknown. Weight loss may occur through a decrease in energy intake due to a reduction in binge eating. Zonisamide may reduce binge eating via its side effects such as dyspepsia, nausea, and taste perversion. Alternatively, zonisamide may reduce binge eating by correcting an abnormality of serotonin neurotransmission. Although there has been limited study of serotonin neurotransmission in binge-eating disorder,[45] there is considerable evidence of dysfunctional serotonergic neurotransmission in bulimia nervosa,[45,46] a condition related to binge-eating disorder.[1,6,7] Further support for serotonergic dysfunction occurring in binge-eating disorder comes from 4 positive placebo-controlled studies of SSRIs[12–15] and from a positive placebo-controlled study of a serotonin releasing agent, *d*-fenfluramine, in the treatment of binge-eating disorder.[34]

Alternatively, zonisamide may decrease binge eating and overweight through some of its mechanisms on other neurotransmitter systems. The drug enhances dopamine transmission[22] and inhibits glutamate transmission[21]; both of these properties have been shown to reduce feeding behavior.[32,33] Indeed, the former is a characteristic of psychostimulants and the latter is a characteristic of topiramate—both of which are associated with antibinge-eating[16,47] and weight-loss effects.[29,36] Yet another possibility, therefore, is that zonisamide may decrease binge eating and overweight through some combination of its effects on the serotonin, dopamine, and glutamate systems.

Several limitations of this study should be considered. First, because the study was uncontrolled, the observed improvement could represent placebo response, rater bias, and/or subject bias. Indeed, binge eating in binge-eating disorder has been associated with substantial response to placebo in many randomized, controlled trials.[17] However, as the overweight associated with binge-eating disorder has generally not responded to placebo, the significant weight loss seen in this trial suggests zonisamide may be associated with real therapeutic effects.

Second, because the study group was small and primarily female and the duration of treatment was short (12 weeks), the results may not generalize to larger groups of persons with binge-eating disorder or to longer treatment periods. (A maintenance trial with 7 of the 8 subjects who completed the 12-week acute trial is ongoing.)

Third, the dropout rate of the study was high (47%)—much higher than in the Gadde et al.[30] study of zonisamide in obese adults in which 3 (10%) of 30 patients randomized to zonisamide dropped out (before completing the 16-week treatment period). The most common reason for

dropout in this study was adverse events; reasons for dropout in the Gadde et al.[30] study were not listed. It is unknown if the different dropout rates in the 2 studies reflect chance variation, differences in dose titration (zonisamide was increased at a slightly faster rate in our study), other differences in study design (subjects in the Gadde et al.[30] study received ancillary counseling with a registered dietician, whereas subjects in this study received no ancillary treatment), or differences in subject populations. Nonetheless, the high dropout rate in this study may have implications for future controlled trials of zonisamide in binge-eating disorder.

Fourth, individuals with several forms of psychopathology were excluded. Thus, the results may not generalize to binge-eating disorder with these forms of comorbid psychopathology, such as bipolar disorder or severe personality disorder.

In summary, in an open-label, prospective, 12-week, flexible-dose trial, zonisamide was found to be effective and relatively well tolerated in reducing binge frequency, weight, and severity of illness in subjects with binge-eating disorder. Because the study used an open-label design, these results should be considered preliminary and should be replicated in a placebo-controlled trial.

Drug names: sibutramine (Meridia), topiramate (Topamax), zaleplon (Sonata), zolpidem (Ambien), zonisamide (Zonegran).

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