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ORIGINAL RESEARCH

Key Words: mood disorder, treatment efficacy, mood stabilizer, Adjuvant treatment, Bipolar Disorder

Zonisamide for Bipolar Disorder, Mania or Mixed States: A Randomized, Double Blind, Placebo-Controlled Adjunctive Trial

By Deborah Dauphinais, Michael Knable, Joshua Rosenthal, Mark Polanski, Norman Rosenthal

ABSTRACT ~ Objective: *This is the first multicenter, double blind, randomized, placebo-controlled trial to evaluate the safety and efficacy of adjunctive zonisamide for the treatment of bipolar mania or mixed state.* ***Experimental design:*** *One hundred four patients with Bipolar Disorder, Type I, II or NOS, in a manic, hypomanic or mixed state of illness were randomized to either adjunctive zonisamide or placebo. The study consisted of three phases: a 7 to 30 day screening and stabilization phase, 6 weeks of blinded treatment and a 1 to 3 week discontinuation phase. The primary outcome variable for manic and hypomanic patients was the Young Mania Rating Scale (YMRS) both the YMRS and Montgomery Asberg Depression Rating Scale (MADRS) served as primary outcome variables for patients in mixed states. Secondary outcome measures included the Clinical Global Impression for Bipolar Disorder (CGI-BP), the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and an a priori analysis of response and remission. Metabolic parameters including weight, waist-hip ratio, body mass index, fasting glucose, cholesterol and triglyceride levels were also analyzed. Side effects were measured using the SAFTEE.* ***Principal observations:*** *There were no statistically significant differences for any of the primary or secondary outcome measures between zonisamide and placebo-treated patients.* ***Conclusions:*** *In contrast to previous studies that suggested efficacy of adjunctive zonisamide in bipolar mania or mixed state, these results were not confirmed in this double blind controlled study.* Psychopharmacology Bulletin. *2011;44(1):5–17.*

INTRODUCTION

The prevalence of Bipolar I Disorder is approximately 1.6% to 5.5% depending on the diagnostic criteria used.[1,2] The risk for recurrence of illness is

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increased in patients with residual symptoms of depression, mania, hypomania or mixed state.[3] Treatment strategies that target residual and sub-threshold symptoms are needed to improve patient outcome and reduce morbidity. There is preliminary evidence suggesting that zonisamide administered adjunctively to standard mood stabilizers may be one such option.[4–9]

Zonisamide, a broad-spectrum anticonvulsant, became available in Japan in 1989 and received FDA approval in 2000 as an adjunctive treatment for adults with partial seizures. Although its exact mechanism of action is unknown, several mechanisms have been proposed for its anticonvulsant effects. These include dose related blockade of sodium channels, blockade of T-type calcium channels,[10] low dose facilitation of serotonergic and dopaminergic transmission, dopaminergic inhibition at higher doses and carbonic anhydrase inhibition.[11]

Several preliminary studies of zonisamide have been conducted in bipolar disorder with promising results for efficacy in both the manic[4–6] and depressed phases of the illness.[5–9] In addition to the putative mood stabilizing properties of zonisamide, beneficial effects on weight and metabolic parameters have been reported.[12–15] Because weight gain and obesity are frequent side effects of the standard treatments of bipolar disorder, medications without these properties are highly desirable.[15]

Zonisamide offers the advantage of fewer significant drug interactions than several currently available mood stabilizers. It is inactivated by CY3A4 dependent reduction and drug clearance is increased by co-administration of carbamazepine, phenytoin and phenobarbital; a higher dose of zonisamide may be required in patients taking these medications.[16] Zonisamide appears to be generally well tolerated with a favorable side effect profile; sedation and dizziness are reported as common side effects with rare reports of more serious adverse events.[10]

The primary objective of this multicenter, controlled study was to further evaluate the safety and efficacy of zonisamide, given adjunctively with a mood stabilizer, in the hypomanic, manic or mixed state phases of bipolar disorder.

MATERIALS AND METHODS

Subjects

One hundred four patients with bipolar disorder, type I, type II or NOS in a hypomanic, manic or mixed state of illness who met all inclusion and exclusion criteria were randomized to either zonisamide or placebo at a 1:1 ratio. The ten participating sites recruited subjects from June 2, 2008 through November 2, 2008. All study sites were private

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outpatient research centers within the United States. Capital Clinical Research Associates (CCRA) was both a study site and the coordinating site for the study. All subjects were volunteers, age 18 to 65, who signed written informed consent. Diagnosis was made using DSM-IV criteria[17] as determined by the Mini International Neuropsychiatric Interview.[18]

Subjects were required to have symptoms of hypomania, mania or mixed state that began at least one week prior to the screening visit. Scores on the Young Mania Rating Scale (YMRS)[19] and a structured interview version of the Montgomery Asberg Depression Rating Scale (MADRS)[20–21] at screening were used to define phase of illness using the following criteria: YMRS score between 12 and 20 and a MADRS score <10 was hypomania, YMRS score >20 and a MADRS score <10 was mania and a mixed state was defined by YMRS score >12 and MADRS score >10. Subjects were required to be taking a stable regimen of psychotropic medication for at least two weeks prior to the baseline visit. Subjects who were not taking psychotropic medications at entry could be treated by the research psychiatrist during the screening phase and were subsequently enrolled provided they continued to meet all inclusion and exclusion criteria. All subjects taking lithium or valproic acid were required to have minimum blood levels of 0.4 mEq/L and 50 mEq/L respectively.

Subjects with a decrease in YMRS score of 25% or more between the screening and baseline visits were excluded from the study. In addition, subjects were excluded if any of the following conditions applied: there was another Axis I disorder as a principal diagnosis in the 6 months prior to screening, there was a positive urine screen for illicit drugs, there was a history of substance abuse or dependency requiring specialized treatment in the 6 months prior to screening, there were significant medical problems or significantly abnormal laboratory values, there was a history of allergy to sulfonamides or related drugs, there was a history of recurrent nephrolithiasis, pregnancy or lactation. Subjects were also excluded if they had initiated a course of Cognitive Behavior Therapy within one month prior to screening, had been in another research study within 2 weeks of screening or had prior treatment with zonisamide.

Study Design and Procedures

The study consisted of a screening and stabilization phase of up to 30 days, a treatment phase of six weeks, and discontinuation phase of one to three weeks. All medications taken within 30 days of baseline were documented and all medications for the current episode of illness

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were recorded and required to be at a stable dose for at least two weeks prior to baseline. Adjunctive medications were kept at consistent dosages for the duration of the study. Patients were permitted adjunctive use of benzodiazepines (up to 2 mg of lorazepam-equivalents per day), zolpidem (5 to 10 mg at bedtime), zaleplon (5 to 10 mg at bedtime), eszopiclone (1–3 mg), or ramelteon (8 mg) as needed for insomnia. If benzodiazepines were being used for anxiety, they could be taken at higher doses as long as the dose was constant for two weeks prior to enrollment and throughout the study. Stimulant medications such as amphetamines, methylphenidate and modafinil were not allowed. No new therapies, pharmacological or non-pharmacological, such as light therapy or cognitive behavioral therapy, were permitted during the study. Patients were seen at Weeks 1, 2, 4 and 6 during the treatment phase. Telephone visits were scheduled at Weeks 3 and 5. During the discontinuation phase of the study, a telephone visit was scheduled at Week 7 (and Week 8 if needed) with a final study visit at Week 9. Table 1 presents a summary of study procedures at each visit.

At baseline, subjects were randomly assigned to either zonisamide or placebo in a 1:1 ratio. Study medication was started at 100 mg a day and increased after one week to 100 mg twice a day (V3, week 1) and then to 100 mg each morning and 200 mg each evening after another week (V4, week 2). The dose of study medication was maintained at 300 mg a day for the remainder of the 6-week study. Patients unable to tolerate more than 100 mg per day were allowed to remain at that dosage. Likewise, patients who could not tolerate more than 200 mg per day were able to stay at that dosage. Patients whose dosage had been raised, but were unable to tolerate the higher dosage, had their daily dose lowered by 100 mg a day. At the end of the treatment phase, the dose of study medication was tapered by 100 mg every seven days.

A central pharmacy prepared identical capsules containing study drug or placebo. Generic zonisamide was purchased from Apotex. The placebo was Avicel PH 105, a microcrystalline cellulose manufactured by CMF BioPolymer. The randomization sequence was managed by a centralized IVRS facility. All study subjects, staff, raters and clinicians remained blind to allocated treatment. The central pharmacy was the only party not blinded during the study and at the conclusion of the study sent randomization codes directly to the statistician.

Outcome Measures

The YMRS was the primary outcome measure for manic and hypomanic patients; the YMRS and MADRS scores were used for patients in mixed states. Efficacy was assessed using a mixed model repeated

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TABLE 1

SUMMARY OF STUDY PROCEDURES AT EACH VISIT
ZONISAMIDE AUGMENTATION FOR BIPOLAR HYPOMANIA, MANIA AND MIXED STATES

WEEK	0	DAY 1	1	2	3	4	5	6	7 (+8)	7–9
Visit	1	2	3	4	TC	5	TC	6	TC	7 (follow up)
Informed Consent	X									
MINI	X									
DSM-IV Criteria	X									
Labs[1,2]	X							X		
Physical exam	X							X		
ECG	X									
YMRS	X	X	X	X		X		X		X
MADRS	X	X	X	X		X		X		X
CGI-BP	X	X	X	X		X		X		X
QIDS	X	X	X	X		X		X		X
Q-LES-Q	X	X	X	X		X		X		X
SAFTEE (SYMPTOM CHECKLIST)		X	X	X		X		X		X
Vital Signs	X	X	X	X		X		X		X
Weight/Height	X							X		
Waist-hip ratio	X							X		
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Dispense IP		X	X	X		X		X		
Collect IP			X	X		X		X		X

[1]Screening and endpoint labs: serum chemistry, hematology, urinalysis, free T4, TSH, Lithium and Valproic acid levels for subjects taking these meds, serum pregnancy test for women of childbearing potential, urine drug test at screening only.
[2]Serum metabolic measures: fasting glucose, total cholesterol, HDL, VLDL, LDL and triglycerides.

measures analysis of variance (ANOVA) for the primary outcome variables as well as the Clinical Global Impressions scale modified for bipolar disorder (CGI-BP).[22] Responders were defined as subjects showing a decrease of ⩾50% on the MADRS and/or YMRS. Remission was defined as a score of less than 10 on the MADRS and a score of less than 7 on the YMRS at endpoint.

The secondary outcome measures were CGI-BP and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[23] Metabolic outcome measures were weight, waist-hip ratio, Body Mass Index (BMI)[24,25] and levels of plasma lipids, glucose and triglycerides. Safety was assessed using the Systematic Assessment for Treatment Emergent

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Effects (SAFTEE),[26] a rating scale for reported adverse events. Basic descriptive statistics including the mean, standard deviation, variance and range were performed for all variables. Paired T-tests were used to compare differences between groups for vital signs and metabolic measures.

Based on data from previous studies, it was estimated that 34 subjects in each of the two groups, zonisamide vs. placebo, were needed for 80% statistical power to detect an effect size of 0.7 at a statistical significance level of 0.05. We planned to screen up to 200 subjects in order to enroll 100 and in order to ensure that 68 patients would complete the trial.

RESULTS

One hundred and seventy-six subjects were screened and 104 were randomized to treatment. Eighty-nine subjects were diagnosed with bipolar disorder type I, with 60 in a mixed state. Thirteen subjects were diagnosed with bipolar disorder type II, with 9 in a mixed state. Two subjects had a diagnosis of bipolar disorder, NOS, with 1 in a mixed state. Table 2 shows the characteristics of the two treatment groups. There were no statistical differences between groups at baseline for demographic measures, vital signs, metabolic measures, or the primary and secondary outcome measurements.

Fifty subjects were allocated to treatment with zonisamide and 54 were allocated to placebo. The mean dose of zonisamide was 263.6 mg/d, S.D. 71.8 mg. Three subjects were excluded from analysis. Two from the zonisamide group were excluded for clinical reasons and 1 from the placebo group was excluded because psychotropic medications were not at stable doses for 2 weeks prior to baseline. One subject allocated to treatment with zonisamide withdrew consent after randomization and did not start the study drug. Diagram 1[27, 28] shows subject flow through the trial. Ninety-two subjects completed the trial, 43 from the zonisamide group and 49 from the placebo group.

The zonisamide and placebo treatment groups showed no statistically significant difference in change from baseline to study end point on either the YMRS or MADRS scores. Graph 1 shows the mean YMRS scores vs. time for both groups; Graph 2 shows mean MADRS scores vs. time for both groups. There was no group-by-time interaction demonstrated using the mixed model repeated measure ANOVA at any time point for the YMRS, MADRS or secondary outcome variables. Table 3 lists the results for the YMRS, MADRS and CGI-BP. There were no statistically significant differences between groups for

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TABLE 2

BASELINE CHARACTERISTIC TABLE: DEMOGRAPHICS
ZONISAMIDE AUGMENTATION FOR BIPOLAR HYPOMANIA, MANIA AND MIXED STATES

	ZONISAMIDE (N = 48) N = 40 BIPOLAR I N = 7 BIPOLAR II N = 1 BIPOLAR, NOS	PLACEBO (N = 52) N = 46 BIPOLAR I N = 5 BIPOLAR II N = 1 BIPOLAR, NOS	CHI SQUARE; DEGREES OF FREEDOM; PROBABILITY
Age (s.d.)[a]	41.2 (10.6)	41.1 (11.2)	0.06; 99; 0.95[b]
Gender	23 female 25 male	30 female 22 male	0.96; 1; 0.33
Race	0 Asian 23 Black 0 Hispanic 2 Other 23 White	1 Asian 21 Black 1 Hispanic 0 Other 29 White	4.63; 4; 0.33
Employment	8 full time 12 part time 1 retired 27 unemployed	6 full time 10 part time 0 retired 36 unemployed	2.60; 3; 0.46
Education (highest grade or degree)	1 grade 8 or less 10 some high school 13 high school 17 some college 5 college 1 post grad 0 other	2 grade 8 or less 13 some high school 15 high school 15 some college 4 college 2 post grad 1 other	2.19; 6; 0.90

[a]Two sample t-test for age analysis, Chi square test for all other demographics.
[b]T-value; degrees of freedom; probability.
Education level data missing for 1 subject in zonisamide group.
Baseline characteristics data was analyzed for all except 4 subjects: 3 subjects were excluded from analysis for clinical reasons (2 zonisamide, 1 placebo). There was no demographic data for 1 Placebo subject included in the analysis.

the Q-LES-Q, vital signs, waist hip ratio, BMI, fasting blood glucose or lipid profiles.

Sixty-two percent of study completers treated with zonisamide were YMRS responders at week 6 verses 45% of placebo recipients ($P < 0.1$). Forty-six percent of the zonisamide group subjects were MADRS responders compared with 50% of the placebo group ($P < 0.73$). The YMRS remission rates were 36% for the zonisamide group and 20% for placebo group ($P < 0.10$). MADRS remission rates were 55% verses 56%, respectively ($P < 0.89$). The mean dose of zonisamide in YMRS responders was higher than YMRS nonresponders, 285.2 mg/d (S.D. 45.6 mg) compared with 229.4 mg/d (S.D. 92.0 mg), respectively. The mean dose of zonisamide in MADRS responders was 290 mg/d (S.D. 71.8 mg) and 239.1 mg/d (S.D. 89.1) mg in the nonresponders.

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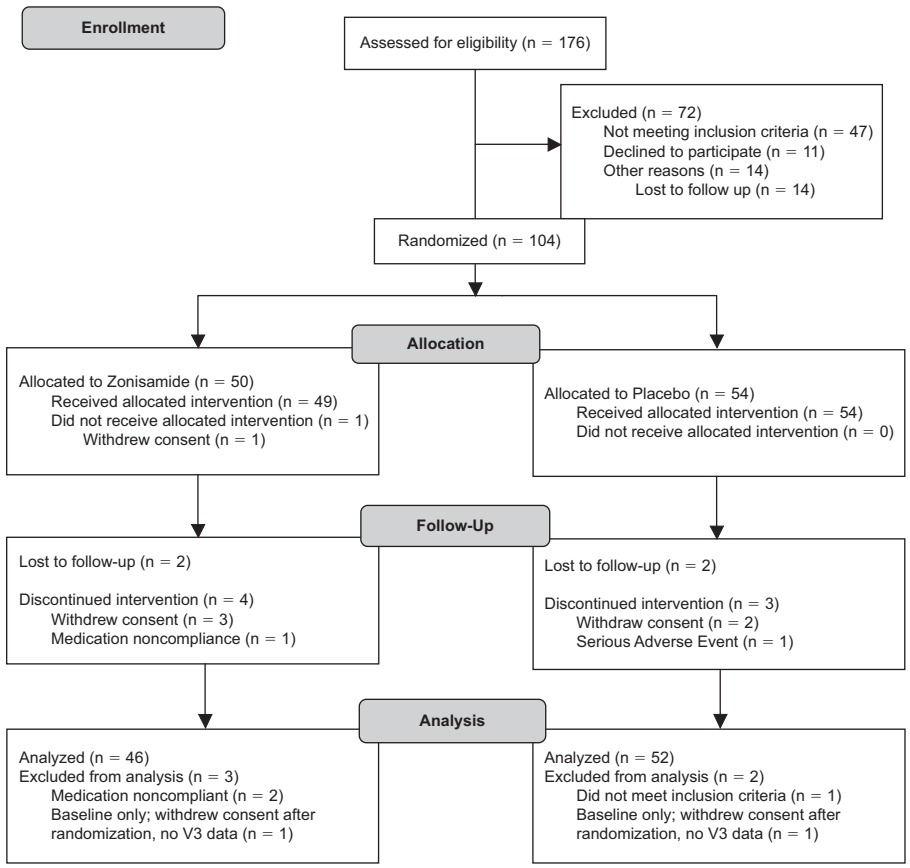
DIAGRAM 1

SUBJECT FLOW DIAGRAM
ZONISAMIDE AUGMENTATION FOR BIPOLAR HYPOMANIA, MANIA AND MIXED STATES



Prepared using CONSORT format.[27,28]

Treatment with zonisamide was well tolerated. The two most common adverse events reported were dry mouth, occurring in 12.5% of patients taking zonisamide versus 9.6% of patients taking placebo, and increased anxiety, occurring in 10.4% vs. 3.8%, for zonisamide and placebo, respectively. Nausea and headache occurred a bit more frequently in the placebo group (15.4%) than in zonisamide (14.6% and 12.5%, respectively). Two Serious Adverse Events (SAE) were reported. One subject from the zonisamide group was hospitalized after a possible suicide attempt. Another subject in the placebo group was hospitalized at week 3 due to increased manic behavior.

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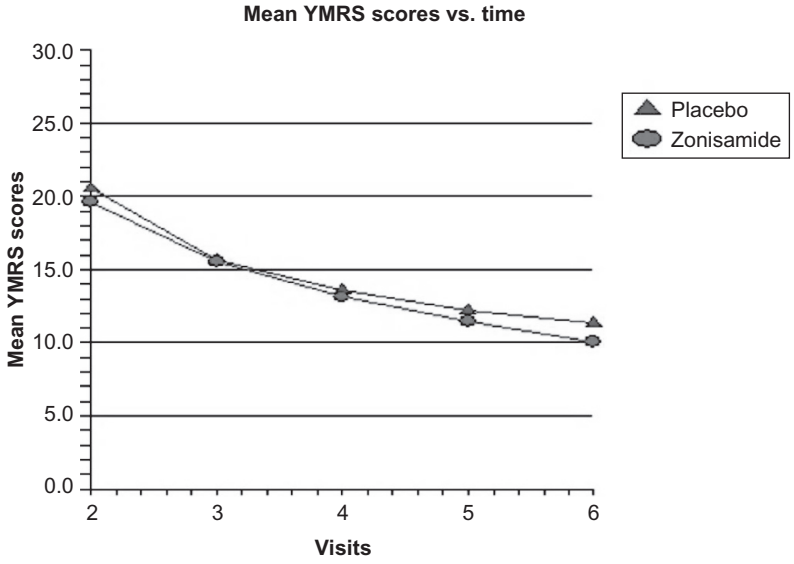
GRAPH 1

MEANS OF YMRS SCORES
ZONISAMIDE AUGMENTATION FOR BIPOLAR HYPOMANIA, MANIA AND MIXED STATES



GRAPH 2

MEANS OF MADRS GRAPH
ZONISAMIDE AUGMENTATION FOR BIPOLAR HYPOMANIA, MANIA AND MIXED STATES

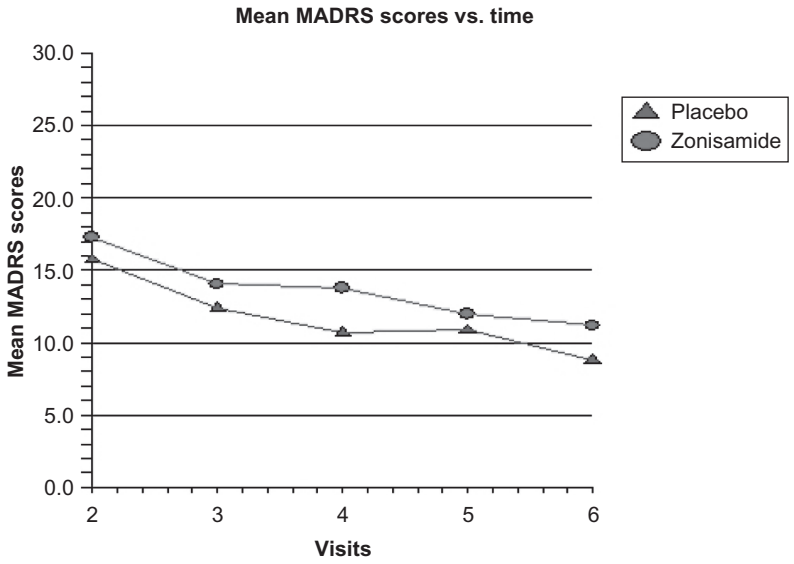


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TABLE 3

STUDY OUTCOME MEASURES AT SCREENING/BASELINE AND END POINT ZONISAMIDE AUGMENTATION FOR BIPOLAR HYPOMANIA, MANIA AND MIXED STATES

	RATING SCALE SCORES AT BASELINE AND END POINT: MEAN (S.D.)		
	ZONISAMIDE	PLACEBO	F VALUE; D.F.; PROBABILITY
MADRS Baseline	17.3 (8.8)	15.8 (10.1)	$F(4,353) = 0.55, p < 0.70$
MADRS V6	11.2 (10.4)	8.8 (7.3)	
YMRS Baseline	19.6 (4.2)	20.5 (4.3)	$F(4,358) = 0.23, p < 0.92$
YMRS V6	10.1 (7.4)	11.4 (6.3)	
CGI-Mania Baseline	4.1 (0.4)	4.3 (0.6)	$F(6,530) = 0.37, p < 0.90$
CGI-Mania V6	2.8 (1.2)	2.8 (1.2)	
CGI-Depression Baseline	3.3 (1.4)	3.1 (1.5)	$F(6,523) = 0.23, p < 0.97$
CGI-Depression V6	2.6 (1.4)	2.3 (1.3)	
CGI-Overall Baseline	4.2 (0.5)	4.4 (0.5)	$F(6,531) = 0.33, p < 0.92$
CGI-Overall V6	3.0 (1.1)	3.1 (1.0)	

DISCUSSION AND CONCLUSION

This multicenter, placebo-controlled study did not demonstrate superior efficacy of adjunctive zonisamide compared with placebo in bipolar patients with hypomania, mania or mixed states. This stands in contrast to preliminary studies that were open-label or retrospective chart reviews, which showed favorable results using similar doses of zonisamide.[4–6]

Additionally, we did not find zonisamide to offer any benefits for weight reduction as had been reported by other investigators.[6,29–32] Studies of zonisamide that examined weight loss as a principal outcome measure used a higher dose of zonisamide than in the present study, enrolled subjects with obesity and included diet and an exercise program in the protocol.[30–32]

Of particular interest for the treatment of bipolar disorder is the study by McElroy, et al.[6] of open-label adjunctive zonisamide in patients with bipolar disorder in which 34 patients with bipolar mania or mixed state entered an 8-week acute treatment phase. The mean dose of zonisamide in this study was 247 mg a day (range 100 to 600 mg a day). Significant reduction in CGI-BP-Mania-S and YMRS scores were reported ($P < 0.0001$ and $P < 0.001$ respectively), with improvement noted as early as one week after initiation of zonisamide treatment. There was no significant reduction in CGI-BP-Depression-S ($P < 0.44$) or IDS ($P < 0.47$) in this study group. During the continuation phase of the study, the CGI-BP-Mania-S reduction seen in the acute phase was maintained but the manic patients with depression showed return of the

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mean CGI-BP-Depression-S and IDS scores to baseline. In addition, a trend was observed that zonisamide responders in the manic group were taking a higher dose of medication than nonresponders (mean dose 300 ± 96 verses 213 ± 136, respectively, $P < 0.06$). This effect was not seen within the depressed group. Significant weight loss was found to be a beneficial side effect of zonisamide in this study.

Kanba et al.,[4] was the first group to report an open-label trial of zonisamide. Twenty-four patients with bipolar mania, schizoaffective mania or schizophrenia were treated with the addition of zonisamide with doses of 100 mg to 600 mg a day. They reported marked global improvement in 33% of patients with bipolar mania and moderate or greater global improvement in 80% of the bipolar group. Ghaemi et al.[5] conducted chart reviews of 35 outpatients with bipolar disorder treated with the addition of zonisamide using the CGI-I score as the measure of response (mean dose 130 mg/day ± 72.7, range 50–400 mg). They reported moderate to marked effectiveness in 9 subjects and concluded there was modest benefit in these 35 patients. The mean dose of zonisamide in the responders was higher than the group as a whole at 172.2 ± 97.2 mg/day, range 100–400 mg.

Our study, the only double blind, placebo-controlled study of adjunctive zonisamide for treatment of the manic spectrum of bipolar disorder, demonstrated no statistically significant efficacy for this treatment. Factors possibly contributing to a false-negative result must be carefully considered when interpreting these data. The placebo effect was strong in the present study, 45 % on the YMRS and 50% on the MADRS, consistent with results found in other clinical trials of affective disorders. The mean dose of zonisamide administered in this study was similar to mean doses in the preliminary studies of bipolar disorder. In the present study, we did find the mean dose of zonisamide in treatment responders to be higher than in nonresponders for both the YMRS and MADRS ratings. This was not found in our study of zonisamide augmentation for bipolar depression (in press). Recent studies have suggested efficacy of zonisamide for the treatment of bipolar disorder, obesity and alcohol dependence at daily doses of up to 600 mg a day.[4,6,29–34] Given these data it is possible that zonisamide given in daily doses above 300 mg may be effective for the treatment of bipolar disorder, especially the manic phase. ✤

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