Open-Label Adjunctive Zonisamide in the Treatment of Bipolar Disorders: A Prospective Trial

Susan L. McElroy, M.D.; Trisha Suppes, M.D.; Paul E. Keck, Jr., M.D.; David Black, Ph.D.; Mark A. Frye, M.D.; Lori L. Altshuler, M.D.; Willem A. Nolen, M.D.; Ralph W. Kupka, M.D.; Gabriele S. Leverich, M.S.W.; Jorg Walden, M.D.; Heinz Grunze, M.D.; and Robert M. Post, M.D.

Background: The response of 62 outpatients with DSM-IV bipolar disorders to open-label adjunctive zonisamide was evaluated in a prospective 8-week acute trial, followed by a 48-week continuation trial, conducted from June 2001 through May 2002.

Method: During the acute trial, response to zonisamide was assessed weekly for the first 4 weeks and every 2 weeks for the second 4 weeks with the Clinical Global Impressions scale modified for bipolar illness (CGI-BP), the Young Mania Rating Scale (YMRS), and the Inventory for Depressive Symptomatology (IDS). During the continuation trial, patients were assessed with these scales every 4 weeks. Patients' weights and side effects were also evaluated. Outcome measures were analyzed with repeated-measures analyses of variance.

Results: Patients with manic symptoms at study entry (N = 34) displayed significant reductions in CGI-BP-Mania Severity and YMRS scores in the acute and continuation (N = 19) trials (p values < .0001 and < .001, respectively). Patients with depressive symptoms at study entry (N = 22) showed significant decreases in CGI-BP-Depression Severity and IDS scores in the acute trial (p values < .001 and < .05, respectively), but only 9 patients entered the continuation trial. Among these 9 patients, maintenance of antidepressant response was mostly maintained. Initially euthymic patients (N = 6) showed no change in any rating scale scores acutely, but 2 of 4 patients who entered the continuation trial developed depressive symptoms. The 62 patients as a group showed significant weight loss in both trials (p values < .001). However, 20 patients (32%) discontinued zonisamide for worsening mood symptoms.

Conclusion: Adjunctive zonisamide was associated with beneficial effects on mood and body weight in some patients with bipolar disorders, but was also associated with a high discontinuation rate due to worsening mood symptoms. Double-blind, placebo-controlled studies are necessary to determine zonisamide's thymoleptic properties, if any, in bipolar disorders.

(J Clin Psychiatry 2005;66:617–624)

Received July 30, 2004; accepted Oct. 5, 2004. *From the Psychopharmacology Research Program, University of Cincinnati College of Medicine, Cincinnati, Ohio (Drs. McElroy and Keck); the University of Texas Southwestern Medical Center, Dallas (Dr. Suppes); the University of California Los Angeles Neuropsychiatric Institute and the West Los Angeles VA Medical Center, Los Angeles (Drs. Black, Frye, and Altshuler); the University Hospital Groningen, Groningen (Dr. Nolen), and Altrecht Institute for Mental Health Care, Utrecht (Dr. Kupka), the Netherlands; the Biological Psychiatry Branch, National Institute of Mental Health (NIMH), Bethesda, Md. (Ms. Leverich and Dr. Post); Zentrum fur Innovative Therapie Bipolarer Storungen am Universitats Klinikum, Freiburg (Dr. Walden), and Psychiatrische Klinik der LMU, Munich (Dr. Grunze), Germany.*

Funding was provided by the Stanley Medical Research Institute. Elan Corp., San Francisco, Calif., provided study medication.

Financial disclosure appears at the end of this article.

Corresponding author and reprints: Susan L. McElroy, M.D., Psychopharmacology Research Program, Department of Psychiatry, P.O. Box 670559, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Cincinnati, OH 45267-0559 (e-mail: susan.mcelroy@uc.edu).

Zonisamide is a structurally and pharmacologically novel antiepileptic drug—a sulfamate-substituted monosaccharide—with documented adjunctive anticonvulsant efficacy in refractory partial epilepsy.[1–4] Mechanisms hypothesized to account for zonisamide's antiepileptic properties include blockade of voltage-gated sodium and T-type calcium channels, modulation of central dopaminergic and serotonergic function, indirect reduction of glutamatergic activity and enhancement of GABAergic activity, and carbonic anhydrase inhibition.[1,2,4–9]

Several lines of evidence suggested that zonisamide might be a useful treatment for bipolar disorder. First, several other antiepileptic drugs have established efficacy in the manic (valproate, carbamazepine, and possibly phenytoin)[10–13] or depressive (lamotrigine)[10,11,14–16] phases of bipolar disorder. Second, there are several preliminary reports of the successful use of zonisamide in the treatment of bipolar disorder.[17–19] For example, Kanba et al.[17] evaluated the open-label addition of zonisamide (100–600 mg/day) to other psychotropics in 15 patients with acute bipolar mania. Eighty percent of patients displayed at least moderate global improvement; 33% displayed marked global improvement. Baldassano et al.[19] evaluated 12 patients with treatment-resistant bipolar disorders

(type I, type II, not otherwise specified [NOS], and cyclothymia) who received adjunctive zonisamide (mean dose = 249 mg/day) for 4 weeks. Seven patients (58%) were considered responders, defined as a ≥ 2-point improvement on the Clinical Global Improvement scale. Third, consistent with other anticonvulsants with antimanic or antidepressant properties, zonisamide blocks voltage-gated sodium channels, modulates both dopaminergic and serotonergic function, and may indirectly reduce glutamatergic and enhance GABAergic activity.[1,2,4–10] All of these mechanisms have been hypothesized to play a role in mood stabilization in bipolar disorder.[10,12,20] Fourth, zonisamide has been associated with weight loss in patients with epilepsy,[2] obesity,[21] and binge-eating disorder.[22] Weight gain, overweight, and obesity frequently complicate the treatment of bipolar disorder.[23–27] Agents associated with therapeutic weight loss that may also be mood stabilizing—or at least not mood destabilizing—are needed for the treatment of bipolar disorder.[27] Zonisamide therefore represents a potential novel treatment for bipolar disorder, including forms of the illness associated with drug-induced weight gain, overweight, or obesity.

To preliminarily explore the potential spectrum of clinical effectiveness and tolerability of zonisamide in bipolar disorder, we conducted an open-label, prospective, 8-week trial of adjunctive zonisamide in 62 outpatients with DSM-IV[28] bipolar disorder or schizoaffective disorder, bipolar type, who were either inadequately responsive to or poorly tolerant of standard psychotropic regimens. In addition, 32 patients who completed the 8-week acute trial participated in a 48-week open-label continuation trial.

METHOD

Subjects

Patients were eligible to participate if they (1) were participating in the Stanley Foundation Bipolar Treatment Network[29]; (2) were 18 years of age or older; (3) had a DSM-IV diagnosis of bipolar disorder I, II, or NOS or schizoaffective disorder, bipolar type (as determined by the Structured Clinical Interview for DSM-IV [SCID-P][30]); (4) were either inadequately responsive to or poorly tolerant of at least 1 standard mood stabilizer (i.e., lithium, divalproex, carbamazepine, or an atypical antipsychotic); (5) did not meet current DSM-IV criteria for a substance dependence disorder that required specialized treatment; (6) had no unstable general medical conditions; (7) had no clinically significant prestudy physical examination, laboratory, electrocardiogram, or urinalysis abnormalities; (8) had no history of clinically significant nephrolithiasis; and (9) were not allergic to sulfa drugs.

Adequate mood stabilizer treatment was defined as at least 2 weeks of treatment with a blood level or daily dose as indicated for the following: lithium, 0.7 mEq/L; carbamazepine, 4 μg/mL; divalproex, 50 μg/mL; olanzapine, 5 mg/day; risperidone, 2 mg/day; and clozapine, 25 mg/day. The institutional review boards at the sites that enrolled patients (University of Cincinnati College of Medicine, University of Texas Southwestern Medical Center, and University of California Los Angeles Neuropsychiatric Institute) approved the protocol, and all patients provided written informed consent to receive treatment with zonisamide. Patients were enrolled from June 11, 2001, through May 2, 2002.

Procedure

Zonisamide was added to preexisting psychotropic regimens at an initial dose of 100 mg/day, generally given at night, and subsequently typically increased by 100 mg/day every 7 days according to patient response and side effects. Zonisamide could be increased to a maximum dose of 800 mg/day.

During the acute phase, patients were seen every week for the first 4 weeks of treatment, and then every 2 weeks for the next 4 weeks, to assess response, weight, and side effects. Response was evaluated at each visit by unblinded raters with the Clinical Global Impressions scale modified for bipolar illness (CGI-BP)[31] to rate severity and degree of improvement in index mood symptoms and overall illness, the Young Mania Rating Scale (YMRS)[32] to rate severity of manic symptoms, and the Inventory for Depressive Symptomatology (IDS)[33] to rate severity of depressive symptoms. The CGI-BP assessed patients' symptoms over the past 1 to 2 weeks (depending on the time of the patient's last rating), the YMRS assessed symptoms over the past 48 hours, and the IDS assessed symptoms over the past week.

At the end of the acute phase, subjects were given the opportunity to enroll in a 48-week continuation trial, during which patients were seen every 4 weeks. The CGI-BP, IDS, and YMRS were completed using the same procedures as in the acute phase, except the CGI-BP assessed patients' symptoms over the past 4 weeks. Termination from either the acute or continuation trial was defined as discontinuation of zonisamide for any reason, an addition of another psychotropic, or an increase in the dosage of a concomitant psychotropic to further control the patient's affective symptoms.

To assess for potential toxicity, routine blood laboratory tests were collected at baseline and termination of the acute phase. Serum zonisamide levels were obtained at the end of the acute and continuation trials.

Data Analytic Plan

Frequencies were utilized for analyses of the demographic and clinical features of the patient population. Means were calculated using the descriptives function for continuous demographic and clinical variables at baseline. Acute trial outcome measures were analyzed with

repeated-measures analyses of variance (ANOVAs) using the SAS PROC MIXED, version 8.02, procedure (SAS Institute Inc., Cary, N.C.). Missing data were estimated with the maximum likelihood method. For the continuation trial, outcome measures from the last visit were compared to baseline and end of the acute trial visits using repeated-measures ANOVAs. The analysis was utilized to evaluate whether treatment patterns observed during the acute phase persisted into the continuation phase.

Categorical response to zonisamide was tabulated based on degree of change at the end of the acute phase (8 weeks) and at the last visit of the continuation phase, as assessed by the CGI-BP-Improvement score compared with baseline. Responders in the acute phase were defined as patients who completed this phase and who displayed much or very much improvement. During the continuation phase, patients were classified as responders if (1) they were responders in the acute phase and there was no worsening of their symptoms during the continuation phase or (2) they were not responders during the acute phase but they subsequently displayed much or very much improvement in the continuation phase.

t Tests were used to assess for changes in laboratory test parameters from baseline to the end of the 8-week trial and for differences in serum zonisamide levels between responders and nonresponders.

RESULTS

Sample Characteristics

Sixty-two outpatients with bipolar I (N = 42), bipolar II (N = 16), bipolar NOS (N = 2), or schizoaffective, bipolar type (N = 2) disorders received at least 1 dose of zonisamide. The clinical characteristics of the patients are summarized in Table 1. Patients were assigned to a baseline group based on their dominant mood symptom presentation at study entry. Specifically, 34 patients had predominately manic (N = 2) or mixed (N = 32) mood symptoms (from here forth referred to as manic symptoms), 22 had predominately depressive mood symptoms, and 6 were relatively euthymic at trial entry.

All patients with manic or depressive symptoms elected to receive zonisamide because they were inadequately responsive to their current pharmacologic regimens. The 6 euthymic patients entered the trial to see if the drug's putative weight loss effects[21] would alleviate psychotropic drug–induced weight gain. In addition, 6 patients whose primary reason for receiving zonisamide was persistent mood symptoms also identified weight gain as a problematic side effect of their current pharmacologic regimen and an additional reason for entering the study. Thus, a total of 12 patients identified weight loss as an important treatment goal.

The mean ± SD number of psychotropic medications per patient at the time of zonisamide addition was 2.75 ± 1.36. The most common concomitant medications were antidepressants (N = 43), antipsychotics (N = 32), divalproex (N = 21), anxiolytics (N = 21), lithium (N = 12), thyroxine and/or triiodothyronine (N = 9), topiramate (N = 9), lamotrigine (N = 6), and gabapentin (N = 4).

Protocol Completion

Forty patients (65%) completed the 8-week acute trial. Thirty-two patients enrolled in the continuation trial and attended at least 1 study visit; 11 patients (18%) completed the 48-week continuation trial and thus received zonisamide for 56 weeks. Table 2 shows the reasons for early study discontinuation during the acute and continuation phases, which included worsening of mood state (N = 20), side effects (N = 5), lack of improvement (N = 8), and study protocol nonadherence (N = 7). Three additional patients discontinued the study prematurely because of an unrelated medical condition (N = 1) and administrative reasons (N = 2). Eight patients who completed the acute trial did not enroll in the continuation trial.

Response of Patients' Mood Symptoms to Zonisamide

Response of patients with manic symptoms. Patients with manic symptoms at trial entry (N = 34) showed significant decreases in CGI-BP-Mania Severity ($F = 22.24$, $df = 5,230$; $p < .0001$) and YMRS ($F = 10.14$, $df = 5,227$; $p < .001$) scores over the 8-week trial (see Figures 1 and 2). These decreases were evident 1 week after beginning zonisamide. However, there was no concurrent reduction in CGI-BP-Depression Severity ($F = 0.95$, $df = 5,230$; $p = .44$) or IDS ($F = 0.92$, $df = 5,227$; $p = .47$) scores. Also, only 14 (41%) of the 34 patients completed the acute trial and displayed much or very much improvement on the CGI-BP-Mania Improvement score and were therefore considered treatment responders.

Nineteen patients subsequently participated in the continuation trial for a mean ± SD of 152 ± 124.6 days (range, 9–369 days). Both CGI-BP-Mania Severity and YMRS score reductions achieved over the course of the acute 8-week trial were maintained during the continuation trial (all F values > 17.1, df = 2,34; all p values < .001; CGI-BP-Mania Severity scores: baseline 3.4 ± 0.78, end of acute trial 1.7 ± 0.96, end of continuation trial 1.6 ± 1.09; YMRS total scores: baseline 13.1 ± 6.43, end of acute trial 5.3 ± 5.33, end of continuation trial 5.6 ± 6.04). Results from both the CGI-BP-Depression Severity and IDS showed that after an initial decrease in depressive symptoms during the acute phase, mean scores returned to baseline levels by the end of the continuation phase (F values > 3.60, df = 2,34; p values < .05; CGI-BP-Depression Severity: baseline = 3.7 ± 1.13, end of acute phase = 3.1 ± 1.26, end of continuation phase = 4.0 ± 1.50; IDS total scores: baseline = 25.6 ± 11.18, end of acute phase = 20.3 ± 10.07, and end of continuation phase = 27.8 ± 13.20). Thirteen of the 19 patients who en-

Table 1. Baseline Demographic and Clinical Features of 62 Bipolar Outpatients Grouped by Mood Symptoms Before Treatment With Adjunctive Zonisamide

Variable	Manic[a] (N = 34)	Depressed (N = 22)	Euthymic (N = 6)	All (N = 62)
Bipolar diagnosis, N (%)				
Bipolar I	26 (76)	12 (55)	4 (67)	42 (68)
Bipolar II	7 (21)	8 (36)	1 (17)	16 (26)
Bipolar NOS	1 (3)	1 (5)	0 (0)	2 (3.2)
Schizoaffective	0 (0)	1 (5)	1 (17)	2 (3.2)
Women, N (%)	21 (62)	12 (55)	5 (83)	38 (61)
White, N (%)	32 (94)	19 (86)	6 (100)	57 (92)
Age at entry, mean (SD), y	37.7 (10.65)	40.1 (9.75)	41.8 (16.0)	39.2 (10.7)
CGI-BP score (mania), mean (SD)	3.45 (0.9)	1.1 (0.35)	1.2 (0.4)	2.4 (1.4)
Range	2–5	1–2	1–2	1–5
YMRS score, mean (SD)	12.4 (5.7)	3.2 (2.4)	1.8 (3.1)	8.1 (6.6)
Range	2–29	0–8	0–8	0–29
CGI-BP score (depression), mean (SD)	3.7 (1.1)	4.0 (0.8)	1.2 (0.4)	3.6 (1.2)
Range	2–6	3–6	1–2	1–6
IDS score, mean (SD)	24.9 (10.0)	27.0 (8.8)	8.0 (3.95)	24.0 (10.6)
Range	8–46	15–44	4–13	4–46
DSM-IV rapid cycling, N (%)	5 (15)	6 (27)	1 (17)	12 (19)
Treatment duration, mean (SD), d	131 (121.5)	127 (119.7)	177 (158.4)	134 (123.3)
Weight, mean (SD), kg	93.2 (21.6)	87.5 (20.1)	100.9 (33.7)	91.9 (22.5)
BMI, mean (SD)[b]	30.8 (7.2)	31.5 (7.83)	35.3 (10.7)	31.6 (7.8)

[a]Includes patients with manic (N = 2) or mixed (N = 32) mood symptoms.
[b]BMI = weight in kg/height in m^2.
Abbreviations: BMI = body mass index, CGI-BP = Clinical Global Impressions scale modified for bipolar illness, IDS = Inventory for Depressive Symptomatology, NOS = not otherwise specified, YMRS = Young Mania Rating Scale.

Table 2. Reasons for Zonisamide Discontinuation During Acute and Continuation Trials[a]

Baseline Mood Symptoms	N	Worsening Mood State, N (%)	Side Effects, N (%)	No Improvement, N (%)	Nonadherent, N (%)
Manic[b]	34	13 (38)[c]	3 (9)	3 (9)	5 (15)
Depressive[b]	22	7 (32)[d]	1 (5)	3 (14)	1 (5)
Euthymic	6	0	1 (17)	2 (33)	1 (17)
Total	62	20 (32)	5 (8)	8 (13)	7 (11)

[a]Eight patients who completed the acute trial did not enroll in the continuation trial.
[b]One additional patient from the manic group discontinued drug for a non–study-related medical condition, and 2 additional patients discontinued drug for administrative reasons, 1 from the manic group and 1 from the depressive group.
[c]One patient discontinued drug for worsening manic symptoms, 1 for development of mixed mania, 2 for development of rapid cycling, and 9 for development of depression.
[d]Four patients discontinued drug for worsening depressive symptoms, 2 for development of mixed mania, and 1 for development of mania.

tered the continuation phase were classified as treatment responders during the continuation phase. Twelve of the 14 acute trial responders enrolled in the continuation trial; 11 patients showed no change or an improvement in symptom severity, and 1 patient showed a mild worsening of symptoms during the continuation phase. Of the remaining 7 patients who were not treatment responders during the acute trial, 2 subsequently met response criteria during the continuation phase.

Response of patients with initial depressive symptoms. Patients with depressive symptoms at baseline (N = 22) showed a significant decrease in mean CGI-BP-Depression Severity total score ($F = 4.46$, $df = 5,230$; $p < .001$) and IDS total score ($F = 2.70$, $df = 5,227$; $p < .05$) over the 8-week acute trial. They did not show any change in mean CGI-BP-Mania Severity score ($F = 0.57$, $df = 5,230$; $p = .73$) or in mean YMRS score ($F = 0.64$, $df = 5,227$; $p = .67$). However, only 7 (32%) of the depressed patients completed the acute trial and were classified as responders.

Nine patients participated in the continuation trial for a mean ± SD of 218 ± 126.3 days (range, 18–350 days). Among this subgroup of depressed subjects, significant improvement in both CGI-BP-Depression Severity and IDS scores from baseline to the end of the acute phase was mostly maintained during the continuation phase (F values > 8.3, $df = 2,16$; p values $\leq .01$; CGI-BP-Depression Severity scores: baseline 4.0 ± 0.71, end of acute trial 2.0 ± 1.32, end of continuation trial 2.9 ± 1.36; IDS scores: baseline 25.8 ± 10.41, end of acute trial 13.1 ± 13.00, end of continuation 15.33 ± 9.80). Six of the 9 patients who entered the continuation phase were

Figure 1. Mean Clinical Global Impressions Scale Modified for Bipolar Illness (CGI-BP) Mania Severity Scores for Patients With Manic Symptoms During Acute Treatment With Adjunctive Zonisamide

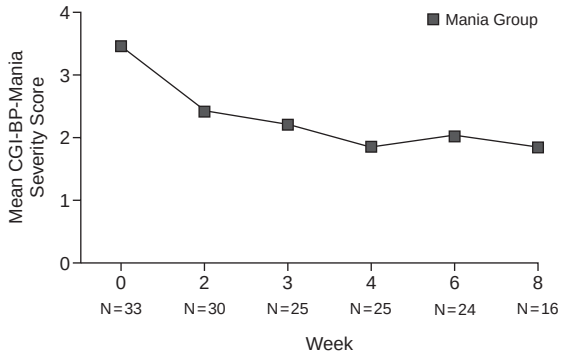
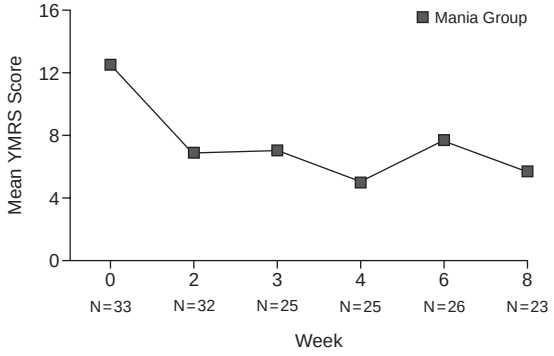


Figure 2. Mean Young Mania Rating Scale (YMRS) Scores for Patients With Manic Symptoms During Acute Treatment With Adjunctive Zonisamide



acute trial treatment responders. All continuation trial responders were acute trial responders; thus no additional antidepressant benefits occurred during the continuation trial that were not already realized during the acute trial. However, 2 acute trial responders experienced a worsening of symptoms ("minimally" and "much worse," respectively) during the continuation trial. Thus, 4 of the 9 patients who pursued continuation treatment were considered responders.

Response of patients with initial euthymia. Patients with relative euthymia at trial entry (N = 6) showed no changes in CGI-BP-Mania or Depression Severity, YMRS, or IDS scores over the 8-week trial (F values < 0.55, p values > .74). Four of these patients participated in the continuation trial for a mean of 226 ± 157.4 days (range, 28–378 days). None of the patients experienced an increase in CGI-BP-Mania Severity or YMRS scores (all F values < 0.29, p values > .75). Two patients, however, experienced mild increases in depressive symptoms (1 patient developed a CGI-BP-Depression Severity score of mildly ill with an IDS score of 15, and the other developed a CGI-BP-Depression Severity score of moderately ill and an IDS score of 20), but both were rated as minimally worsened on the CGI-BP-Improvement scale.

Zonisamide Effects on Weight

Patients as a group displayed significant weight loss over the 8-week acute trial, losing a mean of 0.96 ± 2.27 kg (2.11 ± 5.00 lb), or 0.15 ± 0.40 kg (0.33 ± 0.89 lb) per week (F = 4.39, df = 5,211; p < .001). Although patients who identified weight loss as a treatment goal were heavier as a group than the rest of the sample (100 ± 24.81 kg [220 ± 54.7 lb] vs. 90 ± 21.60 kg [198 ± 47.63 lb]), this difference was not significant (t = 1.37, df = 54, p = .18). There were no significant differences between these subjects and the rest of the sample in weight loss over the course of the study (t = 0.45, df = 54, p = .66).

Weight data at baseline, end of the acute phase, and end of the continuation phase were available for 28 (88%) of 32 patients who enrolled in the continuation phase. Results indicated that the weight-loss effects observed during the 8-week acute trial continued during the continuation phase (F = 22.0, df = 2,54; p < .001) (see Tables 3 and 4). Specifically, patients lost a mean of 0.15 ± 0.25 kg (0.33 ± 0.55 lb) per week during the continuation trial.

Zonisamide Dose and Level

The mean ± SD dose of zonisamide at the end of the acute trial was 247 ± 122 mg/day (range, 100–500 mg/day). Within the manic group, treatment responders tended to have higher doses of zonisamide than nonresponders (mean dose: t = 1.97, df = 27, p = .06, 300 ± 96 vs. 213 ± 136 mg/day; highest dose: t = 2.76, df = 29, p = .01, 357 ± 109 vs. 235 ± 132 mg/day). Within the depressed group, there were no significant differences in the mean (233 ± 82 vs. 254 ± 151 mg/day) or highest (300 ± 89 vs. 335 ± 178 mg/day) zonisamide doses between responders and nonresponders (t values < 0.5, p values = NS).

Serum zonisamide levels were available for 38 patients at the end of the acute trial. The mean serum zonisamide level for the whole sample was 14.57 ± 9.76 μg/mL (range, < 0.50–40.01 μg/mL). There were no significant differences between responders and nonresponders in either the mania or the depressed group (t values < 0.96; mania group: responder = 14.81 ± 9.34 μg/mL vs. nonresponder = 11.49 ± 10.03 μg/mL; depressed group: responder = 16.77 ± 9.71 μg/mL vs. nonresponder = 17.24 ± 12.77 μg/mL).

Tolerability and Side Effects

Most patients tolerated zonisamide well. Side effects experienced by more than 1 patient included sedation/tiredness/lack of energy (N = 8), cognitive impairment

Table 3. Change in Weight in Patients With Bipolar Disorders Receiving Adjunctive Zonisamide

Time of Evaluation	N[a]	Weight (kg), Mean (SD)	Range (kg)	Weight Loss (kg), Mean (SD)	% Change in Weight[b]
Study entry	56	91.94 (22.46)	46.3–142.9	NA	NA
4 wk	44	94.30 (23.02)	45.4–145.2	–0.81 (1.89)	–0.9
8 wk	38	89.24 (21.40)	44.9–140.2	–1.11 (2.58)	–1.2
6 mo	15	94.65 (25.81)	49.9–142.9	–5.25 (5.41)	–5.8
1 y	6	94.76 (30.03)	56.5–138.4	–9.00 (4.85)	–9.7
Last evaluation	56	89.57 (21.95)	44.9–138.4	–2.37 (4.05)	–2.5

[a]Reflects number of patients available at each time point. Patients who missed the relevant visit but did not discontinue from the study were omitted.
[b]Compared with baseline weight for patients with available data at each measurement point.

Table 4. Change in Body Mass Index (BMI)[a] in Patients With Bipolar Disorders Receiving Adjunctive Zonisamide

Time of Evaluation	N[b]	BMI, Mean (SD)	Range	Change in BMI, Mean	% Change[c]
Study entry	55	31.57 (7.82)	17.48–51.14	NA	NA
4 wk	43	32.01 (7.89)	17.48–49.88	–0.29	–1.0
8 wk	38	30.81 (7.13)	17.45–47.16	–0.39	–1.2
6 mo	15	31.27 (7.52)	19.49–46.66	–1.86	–5.8
1 y	6	32.45 (8.78)	21.26–45.17	–3.24	–9.7
Last evaluation	55	30.74 (7.69)	17.48–49.79	–0.83	–2.6

[a]BMI = weight in kg/height in m^2.
[b]Reflects patients available at each time point. Patients who missed the relevant visit but did not discontinue from the study were omitted.
[c]Compared with baseline BMI for patients with available data at each measurement point.

(N = 5), dry mouth/thirst (N = 4), tremors (N = 4), nausea (N = 2), diarrhea (N = 2), constipation (N = 2), and unsteady gait (N = 2). These effects often occurred when zonisamide was initiated or increased in dose, frequently resolved or lessened with time and/or dosage reduction, and usually did not result in drug discontinuation. Only 5 patients (8%) discontinued zonisamide because of side effects. These patients reported the following: increased heart rate and tremors, sedation and cognitive impairment, fatigue and backache, and unsteady gait and poor coordination (by 2 patients).

The only laboratory differences found were a marginally significant decrease in potassium from 4.16 mEq/L to 4.04 mEq/L ($t = 1.8$, $df = 13$, $p = .09$) and a marginally significant decrease in alanine aminotransferase from 31.18 U/L to 23.00 U/L ($t = 1.92$, $df = 16$, $p = .07$) at the end of the acute trial compared with baseline. There were no reports of significant alterations in lithium or valproate levels associated with zonisamide administration.

DISCUSSION

Sixty-two outpatients with bipolar disorders who either were inadequately responsive to standard pharmacotherapy regimens or had psychotropic-associated weight gain and who received prospective, open-label, adjunctive treatment with zonisamide for up to 56 weeks were evaluated. Patients with manic or mixed mood symptoms at zonisamide initiation displayed significant and rapid decreases in ratings of manic but not depressive symptoms. Those who entered the continuation phase displayed continued improvement in manic symptoms. Depressive symptoms, however, persisted.

Patients with depressive symptoms at zonisamide initiation showed some acute improvement, but it was more modest and delayed in onset. Also, two thirds of the patients who displayed an acute antidepressant response appeared to maintain the response. The euthymic patients who received zonisamide showed no changes in ratings of illness severity in manic or depressive symptoms acutely, but 2 patients developed mild depressive symptoms over the long term.

Zonisamide treatment was associated with statistically significant weight loss, which all patients identified as favorable. Adverse effects of zonisamide were usually neurologic or gastrointestinal, often mild and transient, and infrequently led to drug discontinuation. Adjunctive zonisamide has not been reported to significantly alter valproate levels in epilepsy patients,[34,35] but as a carbonic anhydrase inhibitor, it theoretically could increase lithium levels.[36] There were no reports of zonisamide adversely affecting valproate or lithium levels in our bipolar patients.

The interpretations of these findings are limited by several methodological shortcomings. Most importantly, this was a nonrandomized, open-label study. Thus, the possibility that the observed favorable response to zonisamide therapy was instead due to clinician or patient bias, a placebo response, or spontaneous improvement cannot be ex-

cluded. Another important limitation is that zonisamide was added to other medications. It is therefore unknown whether the apparent antimanic response after zonisamide addition was due to zonisamide alone or to a combination with concurrently administered mood stabilizers and/or antidepressants. Moreover, the manic patients' mean ± SD baseline YMRS score of only 12.4 ± 5.7 reflected a mild level of manic symptomatology; effectiveness in more severe manic pathology was not assessed in this trial. Yet another important limitation is the high study discontinuation rate. Despite the apparent beneficial effects of zonisamide on manic and depressive symptoms according to rating scales, along with the drug's favorable effects on body weight and generally benign side effect profile, only 11 patients (18%) completed the entire 56-week trial. Moreover, 20 patients (32%) discontinued zonisamide because of a worsening mood state, and 8 (13%) stopped the drug because of lack of improvement (2 for lack of weight loss). Indeed, there have been reports of induction of mania and behavioral difficulties by zonisamide in patients with epilepsy.[37–39]

In summary, this open-label, prospective study suggests that adjunctive zonisamide may have beneficial acute and long-term thymoleptic effects in a subgroup of bipolar patients with hypomanic or mixed symptoms inadequately responsive to standard pharmacotherapy. Acute antidepressant effects were less pronounced but possibly evident in a small subset of patients. In addition, zonisamide was associated with therapeutic weight loss for bipolar patients with and without psychotropic-associated weight gain. However, a substantial number of patients discontinued the drug because of worsening mood symptoms. Double-blind, placebo-controlled studies of zonisamide in the different phases of bipolar disorder will be necessary to definitely establish whether or not this drug has antimanic, antidepressant, or long-term mood-stabilizing properties in this illness.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote), gabapentin (Neurontin and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), phenytoin (Dilantin and others), risperidone (Risperdal), topiramate (Topamax), zonisamide (Zonegran).

Financial disclosure: Dr. McElroy is a consultant to or a member of the scientific advisory boards of Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Ortho-McNeil, and Wyeth-Ayerst and is a principal or coinvestigator on research studies sponsored by Forest, GlaxoSmithKline, Esai, Eli Lilly, Merck, Ortho-McNeil, Pfizer, Sanofi-Synthelabo, AstraZeneca, and Bristol-Myers Squibb. Dr. Suppes has received grant/research support from Abbott, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, NIMH, Novartis, Robert Wood Johnson Foundation, and the Stanley Medical Research Institute and has served as a consultant for and/or on the speakers or advisory boards of Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Johnson & Johnson, Novartis, Pfizer, Pharmaceutical Research Institute, Ortho-McNeil, Shire, and UCB Pharma. Dr. Keck is a consultant to or a member of the scientific advisory boards of Abbott, AstraZeneca, Bristol-Myers Squibb, Corcept, GlaxoSmithKline, Janssen, Jazz, Eli Lilly, Novartis, Ortho-McNeil, Pfizer, UCB Pharma, Shire, and Wyeth and is a principal or coinvestigator on research studies sponsored by Abbott, the American Diabetes Association, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Elan, Eli Lilly, Janssen, Merck, NIMH, National Institute of Drug Abuse, Organon, Ortho-McNeil, Pfizer, the Stanley Medical Research Institute, and UCB Pharma. Dr. Frye has served as a consultant for Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, Elan, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Novartis, Ortho-McNeil, Otsuka, Pfizer, and UCB Pharma; has received grant/research support from Abbott, the American Foundation for Suicide Prevention, GlaxoSmithKline, NIMH, Pfizer, Solvay, and the Stanley Medical Research Institute; and has served on the speakers bureau of Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Novartis, Ortho-McNeil, and Otsuka. Dr. Altshuler has served as a consultant for Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, and Janssen; has received grant/research support from and serves on the speakers bureau of Abbott; has received honoraria from Abbott, Bristol-Myers Squibb, Eli Lilly, Forest, and Janssen; and serves on the advisory boards of Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, Janssen, and Pfizer. Dr. Post has been a consultant for Abbott, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Elan, Novartis, Shire, and UCB Pharma.

REFERENCES

1. Oommen KJ, Mathew SS. Zonegran: a new antiepileptic drug. Clin Neuropharmacol 1999;22:192–200
2. Leppik IE. Zonegran: a novel antiepileptic agent. Today's Therapeutic Trends 1999;17:181–195
3. Faught E, Ayala R, Montouris GG, et al. Randomized controlled trial of zonisamide for the treatment of refractory partial-onset seizures. Neurology 2001;57:1774–1779
4. Seino M, Fujitani B. Zonisamide: clinical efficacy and use in epilepsy. In: Levy RH, Mattson RH, Meldrum BS, et al, eds. Antiepileptic Drugs. 5th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2002:885–891
5. Rho JM, Sankar R. The pharmacologic basis of antiepileptic drug action. Epilepsia 1999;40:1471–1483
6. Okada M, Kaneko S, Hirano T, et al. Effects of zonisamide on dopaminergic system. Epilepsy Res 1995;22:193–205
7. Okada M, Hirano T, Kawata Y, et al. Biphasic effects of zonisamide on serotonergic system in rat hippocampus. Epilepsy Res 1999;34:187–197
8. Okada M, Kawata Y, Mizuno K, et al. Interaction between Ca^{2+}, K^{+}, carbamazepine and zonisamide on hippocampal extracellular glutamate monitored with a microdialysis electrode. Br J Pharmacol 1998;124: 1277–1285
9. MacDonald RL. Zonisamide: mechanisms of action. In: Levy RH, Mattson RH, Meldrum BS, et al, eds. Antiepileptic Drugs. 5th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2002:867–872
10. Wang PW, Ketter TA, Becker OV, et al. New anticonvulsant medication uses in bipolar disorder. CNS Spectr 2003;8:930–932, 941–947
11. Keck PE Jr, McElroy SL. Treatment of bipolar disorder. In: Schatzberg AF, Nemeroff CB, eds. Textbook of Psychopharmacology. 3rd ed. Washington, DC: American Psychiatric Press Publishing; 2003
12. Mishory A, Yaroslavsky Y, Bersudsky Y, et al. Phenytoin as an antimanic anticonvulsant: a controlled study. Am J Psychiatry 2000;157:463–465
13. Weisler RH, Kalali AH, Ketter TA, and the SPD417 Study Group. A multicenter, randomized, double-blind, placebo-controlled trial of extended release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. J Clin Psychiatry 2004; 65:478–484
14. Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. J Clin Psychiatry 1999;60:79–88
15. Bowden CL, Calabrese JR, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry 2003;60:392–400
16. Calabrese JR, Bowden CL, Sachs G, et al. A placebo-controlled

18-month trial of lamotrigine and lithium maintenance therapy in recently depressed patients with bipolar I disorder. J Clin Psychiatry 2003;64:1013–1024
17. Kanba S, Yagi G, Kamijima K, et al. The first open study of zonisamide, a novel anticonvulsant, shows efficacy in mania. Prog Neuropsychopharmacol Biol Psychiatry 1994;18:707–715
18. Berigan TR. Zonisamide treatment of bipolar disorder: a case report [letter]. Can J Psychiatry 2002;47:887
19. Baldassano CF, Lipari MA, Ghaemi SN, et al. Adjunctive zonisamide as acute treatment of bipolar disorder outpatients [abstract]. Presented at the annual meeting of the American Epilepsy Society; December 6–11, 2002; Seattle, Wash
20. Post RM, Weiss SRB, Clark M, et al. Lithium, carbamazepine, and valproate in affective illness. In: Manji HK, Bowden CL, Belmaker RH, eds. Bipolar Medications Mechanisms of Action. Washington, DC: American Psychiatric Press; 2000:219–248
21. Gadde KM, Francisy DM, Wagner R. Zonisamide in obesity. JAMA 2003;289:1820–1825
22. McElroy SL, Kotwal R, Hudson JI, et al. Zonisamide in the treatment of binge-eating disorder: an open-label, prospective trial. J Clin Psychiatry 2004;65:50–56
23. Elmslie JL, Silverstone JT, Mann JL, et al. Prevalence of overweight and obesity in bipolar patients. J Clin Psychiatry 2000;61:179–184
24. McElroy SL, Frye MA, Suppes T, et al. Correlates of overweight and obesity in 644 patients with bipolar disorder. J Clin Psychiatry 2002; 63:207–213
25. Fagiolini A, Frank E, Houck E, et al. Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. J Clin Psychiatry 2002;63:528–533
26. Fagiolini A, Kupfer DJ, Houck PR, et al. Obesity as a correlate of outcome in patients with bipolar I disorder. Am J Psychiatry 2003; 160:112–117
27. Keck PE Jr, McElroy SL. Bipolar disorder, obesity, and pharmacotherapy-associated weight gain. J Clin Psychiatry 2003;64:1426–1435
28. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
29. Leverich GS, Nolen WA, Rush AJ, et al. The Stanley Foundation Bipolar Treatment Outcome Network, 1: longitudinal methodology. J Affect Disord 2001;67:33–44
30. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders (Research Version, 2/96 Final). New York, NY: Biometrics Research, New York State Psychiatric Institute, 1996
31. Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 1997;73:159–171
32. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429–435
33. Rush AJ, Giles DE, Schlesser MA, et al. The Inventory for Depressive Symptomatology (IDS): preliminary findings. Psychiatry Res 1985;18: 65–87
34. Mather GC, Shah J. Zonisamide: drug interactions. In: Levy RH, Mattson RH, Meldrum BS, et al, eds. Antiepileptic Drugs. 5th ed. Philadelphia, Pa: Lippincott Williams & Williams; 2002:880–884
35. Shah J, Shellenberger K, Canafax DM. Zonisamide: chemistry, biotransformation, and pharmacokinetics. In: Levy RH, Mattson RH, Meldrum BS, et al, eds. Antiepileptic Drugs. 5th ed. Philadelphia, Pa: Lippincott Williams & Williams; 2002:873–879
36. Abraham G, Owen J. Topiramate can cause lithium toxicity [letter]. J Clin Psychopharmacol 2004;24:565–567
37. Charles C, Stoez L, Tollefson G. Zonegran-induced mania. Psychosomatics 1990;31:214–221
38. Kimura S. Zonegran-induced behavior disorder in two children. Epilepsia 1994;35:403–405
39. Ozaawa K, Kobayashi K, Noda S, et al. Zonisamide-induced depression and mania in patients with epilepsy [letter]. J Clin Psychopharmacol 2004;24:110–111