A Preliminary Open-Label Study of Zonisamide Treatment for Bipolar Depression in 10 Patients

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Objective: The purpose of this study was to investigate the effectiveness of zonisamide in the treatment of bipolar depression.

Method: Ten patients with DSM-IV bipolar disorder, depressed phase, who had either not tolerated or not responded to previous treatments were given zonisamide in this add-on open-label study. Zonisamide treatment was started at 100 mg/day and increased by 100 mg every 2 weeks to a maximum of 300 mg/day in divided doses (b.i.d. or t.i.d.). Subjects underwent weekly visits at which they were administered the 17-item Hamilton Rating Scale for Depression (HAM-D), Young Mania Rating Scale (YMRS), and Clinical Global Impressions scale (CGI). Every 2 weeks, subjects also underwent laboratory tests, a urine examination, and a verbal memory test. Outcome measures were analyzed with repeated-measures analysis of variance.

Results: Eight subjects completed all 8 weeks of the study. Two subjects completed more than 4 weeks of the study, and their data were analyzed using the last observation carried forward. Bipolar depression subjects had a significant reduction in HAM-D scores ($p < .001$) and in CGI-Improvement (CGI-I) scores ($p < .001$). Five of 8 subjects who completed all 8 weeks of the study had more than a 50% decrease in HAM-D scores and were rated much improved on the CGI-I at the end of 8 weeks of treatment. There was no significant drug effect on YMRS scores, weight, or verbal memory.

Conclusion: Zonisamide may be a useful drug in the treatment of bipolar depression. Further controlled clinical trials are needed.

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Bipolar disorder is a serious mental illness characterized by periods of mania and depression interspersed with periods of normal mood. The aim in the treatment of bipolar disorder is to reverse mania or depression and to maintain long-term mood stability.[1] In this regard, antidepressants such as selective serotonin reuptake inhibitors and tricyclics are effective in the treatment of depression but can precipitate mania if not given with a mood stabilizer such as lithium or valproate.[1] Use of multiple medications can lead to noncompliance and more side effects. Therefore, an ideal medication for bipolar depression would have both antidepressant and mood-stabilizing properties. Until recently, there was no medication approved by the U.S. Food and Drug Administration for the treatment of bipolar depression.

Zonisamide is a new anticonvulsant that is structurally similar to serotonin and has a pharmacologic profile similar to those of carbamazepine (control of kindled and shock-induced seizures) and lamotrigine (inhibition of ion channels).[2,3] Furthermore, zonisamide has been shown to facilitate dopaminergic and serotonergic transmission at low doses.[4,5] Therefore, low-dose (100–300 mg) zonisamide may be an ideal candidate for treatment of bipolar depression. At higher doses, zonisamide may have mood-stabilizing properties, possibly due to its ion channel–inhibiting properties.[2] Furthermore, zonisamide has been shown to decrease dopamine neurotransmission at higher doses.[5] Therefore, zonisamide could potentially be useful both for treatment of bipolar depression and for

long-term mood stabilization,[6] thereby providing a comprehensive management strategy for bipolar disorder with a single medication. There has been 1 report of use of open-label zonisamide in the treatment of mania, and that study reported that zonisamide was efficacious as an antimanic agent in doses up to 600 mg/day.[7] In addition, although weight gain is a frequent problem with many other medications, recent studies have reported that zonisamide can be useful for inducing weight loss and decreasing binge eating.[8,9]

In this open-label add-on design study, we investigated the effectiveness of low-dose zonisamide (up to 300 mg/day) for treatment of bipolar depression.

METHOD

Subjects were recruited by advertisement and from an outpatient clinic. Subjects participated in the study after providing informed consent using a form approved by the Indiana University Investigational Review Board. Patients initially underwent a screening process in which they had a full psychiatric evaluation including a structured interview to confirm their diagnosis of bipolar disorder. Patients also underwent a physical examination, electrocardiogram, and laboratory tests including a comprehensive metabolic panel, urine toxicology, and microscopic urine examination. Inclusion criteria for the study were as follows: male or female, 18 to 65 years of age; satisfy DSM-IV criteria for bipolar disorder, depressed phase; no significant change in psychotropic medication or doses within at least 4 weeks of inclusion in the study; history of being inadequately responsive to or intolerant of prior pharmacotherapy for previous episodes of depression; 17-item Hamilton Rating Scale for Depression (HAM-D)[10] score of > 18; and Young Mania Rating Scale (YMRS)[11] score of < 10.

Exclusion criteria were as follows: history of or currently suffering from serious medical illness; taking medication that may interact with zonisamide; history or family history of nephrolithiasis; history of allergies to sulfonamides; history of substance abuse within 3 months or substance dependence within 6 months of the study; pregnant, planning to become pregnant, or not using adequate contraception; electroconvulsive therapy received in the past year; significant suicidal or violence risk at the time of the study; renal or hepatic dysfunction; and history of decreased sweating or heatstroke.

Seven to 10 days after the screening visit, subjects underwent their baseline visit and were started on treatment with zonisamide 100 mg p.o. q.d. Subsequently, subjects were seen weekly (± 3 days) for behavioral and laboratory assessments for a total of 8 weeks. Zonisamide dosage was increased by 100 mg every 2 weeks to a maximum of 300 mg p.o. in divided doses (b.i.d. or t.i.d.) by the end of week 6.

The following ratings were performed at both baseline and weekly visits: the 17-item HAM-D, YMRS, and Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I)[12] as assessed by a physician. The following were performed every 2 weeks: Selective Reminding Test (SRT)[13] for verbal learning (12 words given with selective reminding of words forgotten until patient was able to remember all the words once; different versions were given at each visit), blood chemistry, complete blood count, and urine dipstick and microscopic examination.

RESULTS

Thirteen patients were deemed eligible for the study and were dispensed at least 1 dose of medication. Three patients dropped out of the study within 2 weeks. One patient complained of excessive sedation, and the others dropped out due to personal reasons. Ten patients completed more than 4 weeks of the study, and their results are presented. Patients' characteristics are depicted in Table 1. The mean ± SD age of subjects was 44 ± 16 years (1 male and 9 female; 8 white, 2 African American). The mean ± SD number of years of illness was 23 ± 13. Patients had experienced multiple episodes of depression and mania/hypomania and had tried multiple mood stabilizers and/or antidepressants without significant response for depressive episodes or had experienced side effects and desired a new type of treatment. One patient stopped medication after 4 weeks due to development of a rash, which subsided upon stopping treatment. One patient withdrew from the study after 6 weeks due to lack of significant mood response to the drug and complaints of tingling and coldness in the feet. Data for these patients have been included with the last observation carried forward. The remaining 8 subjects completed all 8 weeks of the study.

Response of these 10 subjects on the 17-item HAM-D is presented in Figure 1. Overall, the 17-item HAM-score for 10 patients decreased from baseline during the 8 weeks of the study. Results of repeated-measures analysis of variance of weekly HAM-D scores for 8 weeks of treatment were significant ($F = 6.3$, $df = 8$, $p < .001$) (mean ± SD scores, baseline: 21 ± 4, eighth week: 10 ± 9) (Figure 1). On repeated-measures analysis of variance, there were significant decreases in mean CGI-S ($F = 7.5$, $df = 8$, $p < .001$) (baseline: 4 ± 0, eighth week: 2 ± 1) and CGI-I scores ($F = 4.9$, $df = 7$, $p < .001$; first week: 3 ± 1, eighth week: 2 ± 1) (Figure 2). Five of 8 subjects who completed all 8 weeks of the study had a decrease of more than 50% in HAM-D scores and were rated much improved on the CGI-I at the end of 8 weeks of treatment. There was no significant change in mean YMRS scores (baseline: 4 ± 3, eighth week: 3 ± 3).

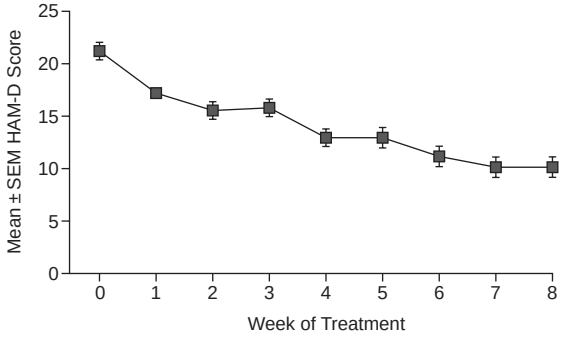
Some of the medication side effects seen were reversible rash (1 subject), asymptomatic decreased white blood

Table 1. Characteristics of 10 Subjects With Bipolar I Disorder, Depressed Phase

Patient	Gender	Age (y)	Years of Illness	Weeks Treated	HAM-D Score		Previously Tried Medications	Concomitant Psychotropic Medications
					Baseline	Endpoint		
1	M	54	23	8	19	10	Fluoxetine, imipramine, lithium, sertraline, olanzapine, methylphenidate	Sodium valproate, bupropion SR
2	F	37	22	4	21	20	Fluoxetine, sodium valproate, topiramate, sertraline	Gabapentin, sertraline
3	F	63	13	8	16	9	Sodium valproate, lithium, citalopram, venlafaxine, bupropion, fluoxetine, sertraline, nefazodone	None
4	F	63	44	8	28	25	Bupropion, sodium valproate, lithium, sertraline, phenelzine, fluoxetine, mirtazapine, topiramate, nortriptyline	Bupropion, lamotrigine, citalopram, lorazepam
5	F	39	23	8	26	1	Sodium valproate, sertraline	None
6	F	23	4	8	24	1	Paroxetine, fluoxetine, olanzapine, escitalopram	None
7	F	28	16	8	18	4	Paroxetine, alprazolam, clonazepam, fluoxetine, venlafaxine XR	Venlafaxine, alprazolam
8	F	57	22	8	21	2	Sertraline, lithium, trazodone	None
9	F	56	46	6	20	24	Lithium, bupropion, methylphenidate, lamotrigine, fluoxetine	Lorazepam
10	F	22	12	8	18	5	Sodium valproate, venlafaxine, escitalopram, bupropion	None

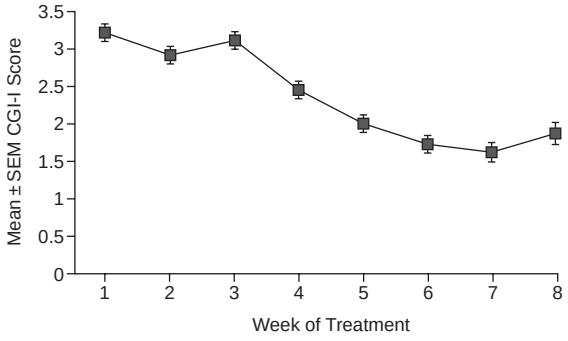
Abbreviations: F = female, HAM-D = Hamilton Rating Scale for Depression, M = male, SR = sustained release, XR = extended release.

Figure 1. Weekly 17-Item HAM-D Scores in 10 Bipolar Depression Patients During 8 Weeks of Zonisamide Treatment



Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Figure 2. Clinical Global Impressions-Improvement (CGI-I) Scores in 10 Bipolar Depression Patients During 8 Weeks of Zonisamide Treatment



cell count (2 subjects) and neutrophil counts (1 subject), tremor (1 subject), coldness and tingling of the feet (1 subject), increased urinary frequency (3 subjects), and anorexia (1 subject). No signs or symptoms of nephrolithiasis were reported by any patient. There were also no reports of significant change in weight except for 1 subject who had anorexia and weight loss. For 7 subjects for whom weight measurements were available before and after the study, there was no significant change in weight with up to 300 mg/day of zonisamide treatment (mean ± SD weight, baseline: 205 ± 50 lb, after treatment: 204 ± 51 lb). Immediate verbal recall as measured by the SRT also showed no significant change during the course of the study (mean ± SD scores, baseline: 108 ± 22, eighth week: 106 ± 22).

DISCUSSION

In this open-label study, a significant decrease in HAM-D scores was seen in patients with bipolar depression treated with zonisamide. As this study was open-label and had a small number of subjects, the results of the study should be interpreted with caution until they are confirmed with larger scale placebo-controlled trials. The improvement in depression scores could also be due to spontaneous resolution of the depressive episode in the 8-week study period. However, patients had tried other medications in previous depressive episodes and reported that they felt better on zonisamide treatment. Five patients who had a significant decrease in depression elected to continue with zonisamide after the study was completed.

Patients who were taking no other medications or who had not tried multiple medications in the past did very well with zonisamide treatment, with near-complete remission of symptoms after 8 weeks of treatment. On the other hand, patients who were taking multiple medications at the time of study did less well than patients for whom zonisamide was used as monotherapy. This is expected, as patients taking multiple medications, even though their depression may be less severe, are likely to have more treatment-resistant depression.

Zonisamide was associated with a number of side effects in some patients; however, patients who tolerated it well did report significant improvement with this medication. Therefore, zonisamide may be a useful alternative for bipolar patients who can tolerate it and are not responding to other medications. Additional useful attributes of the drug include lack of weight gain or even weight loss with higher doses[8,9] and decreased likelihood of marked cognitive effects. Finally, zonisamide's potential ability to decrease dopaminergic neurotransmission in higher dosages may also make it useful for the treatment of mania and mood stabilization. If future placebo-controlled trials confirm these effects of zonisamide, it may prove to be a useful drug for the treatment of bipolar disorder.

Drug names: alprazolam (Xanax and others), bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Tegretol, and others), citalopram (Celexa), clonazepam (Klonopin and others), escitalopram (Lexapro), fluoxetine (Prozac and others), gabapentin (Neurontin and others), imipramine (Tofranil and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), methylphenidate (Ritalin, Metadate, and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), paroxetine (Paxil and others), phenelzine (Nardil), sertraline (Zoloft), topiramate (Topamax), trazodone (Desyrel and others), venlafaxine (Effexor), zonisamide (Zonegran).

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