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Placebo-Controlled Trial of Zonisamide for the Treatment of Alcohol Dependence

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Abstract

Introduction—Zonisamide is an anticonvulsant medication with GABAergic, glutamatergic, and monoaminergic effects. Zonisamide has also been shown to reduce alcohol intake in rodents and in risky drinkers in the context of a laboratory study. This pilot clinical trial evaluated the safety, tolerability, and efficacy of zonisamide for the treatment of alcohol dependence.

Materials and Methods—Forty subjects (23 men) were randomly assigned to receive treatment with either placebo or zonisamide in a 12-week, double-blind trial. The dosage of zonisamide was initiated at 100 mg/day and increased by 100 mg/day every 2 weeks for 8 weeks to a maximum dosage of 500 mg/day. The medication was continued for 4 weeks at the target dosage and then tapered and discontinued. The primary outcomes were drinks per week, heavy drinking days per week, and abstinent days per week, which were measured using the Timeline Follow-back method.

Results—There was a significant medication by treatment week interaction effect favoring the zonisamide group for heavy drinking days (HDD) ($p = 0.012$), drinks per week ($p = 0.004$), and alcohol urge scores ($p = 0.006$), though there was not a significant effect on the number or rate of increase in abstinent days. There were no serious adverse events reported and zonisamide treatment was well tolerated.

Discussion—These findings provide preliminary support for the use of zonisamide to treat alcohol dependence. Efforts to replicate and extend these findings are warranted.

INTRODUCTION

Considerable progress has been made in the application of research on the neurobiology of alcohol dependence (AD) to the rational development of pharmacological treatments for the disorder. A particularly promising approach has been the use of anticonvulsants to treat heavy drinking and to promote abstinence [1]. Johnson et al. [2] demonstrated the efficacy of topiramate 300 mg/day in reducing a variety of drinking outcomes, findings that were supported in a subsequent, multi-center, randomized trial [3].

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Like topiramate, zonisamide blocks sodium channels, reduces glutamate transmission, and inhibits carbonic anhydrase [4, 5]. In contrast to the more direct effects of topiramate on GABA and glutamate transmission [6, 7], zonisamide appears to facilitate GABA indirectly and reduce glutamate neurotransmission via effects on the excitatory amino acid transporter (EAAT) system. Zonisamide also reduces glutamate release from neurons [8], at least in part, by reducing potassium-evoked glutamate release, thereby inhibiting glutamatergic transmission in hyperexcitable neurons [9]. Zonisamide also appears to have direct and biphasic effects on the neuronal release of dopamine and serotonin, which could help to restore proper monoaminergic tone and transmission in the chronically alcohol-exposed brain [10, 11]. By increasing GABAergic, dopaminergic, and serotonergic output and normalizing glutamatergic neurotransmission, zonisamide may reduce both the rewarding effects of alcohol consumption and the unpleasant effects of drinking cessation.

Rodents administered zonisamide chronically showed reduced consumption of an ethanol-sucrose solution, comparable to that seen with topiramate [12]. In a within-subjects, cross-over design in 10 risky drinkers who were given free access to alcohol, single-dose administration of zonisamide 100 mg reduced alcohol consumption relative to a placebo medication session [13].

The U.S. Food and Drug Administration has approved zonisamide for the adjunctive treatment of partial seizures in adults with epilepsy. The drug has also shown efficacy in weight reduction in overweight individuals [14] and in the treatment of binge eating [6, 15]. Benefits of zonisamide have also been seen in some patients with bipolar disorder [16–20]. However, the tolerability of zonisamide has been a limiting factor in some clinical trials [15, 18, 20, 21].

We examined the potential efficacy and tolerability of zonisamide for the treatment of AD. We hypothesized that during treatment, zonisamide would result in more abstinent days and fewer heavy drinking days than placebo.

MATERIALS AND METHODS

We conducted a double-blind, placebo-controlled study of zonisamide in alcohol-dependent subjects whose goal was to reduce or stop their drinking. We used block randomization implemented by the investigational pharmacy to ensure that the investigators and staff were blind to study group assignment. The pharmacist used a software program to assign groups of ten subjects to drug or placebo, without balancing on demographic variables. Subjects received 12 weeks of medication treatment and concomitant psychosocial therapy. The Institutional Review Board at the University of Connecticut Health Center approved the protocol and the consent form and all subjects gave written informed consent to participate.

Subjects

Forty subjects (23 men; 57.5%) were recruited primarily through advertisements. Subjects were: 18–65 years old, with DSM-IV AD (past month) and at least 2 heavy drinking days (men: >4 standard drinks/day; women: >3 standard drinks/day) per week between screening and baseline, able to read at an 8th grade or higher level, with no gross cognitive impairment. Women of childbearing potential were non-lactating and practicing a reliable method of birth control, with a negative serum pregnancy test prior to treatment.

Subjects were excluded if they had a current, clinically significant disease or abnormality, had participated in a pharmacotherapy study in the preceding 30 days, or were currently dependent on drugs other than nicotine. Because zonisamide is a sulfonamide medication, subjects with a history of hypersensitivity to any sulfonamide, a penicillin allergy, a severe

allergic reaction to any drug, or a systemic autoimmune disease were excluded. Because the medication has been associated with the formation of renal calculi, subjects with a history of renal calculi were also excluded.

Study Medication

Zonisamide 100-mg capsules were over-encapsulated to appear identical to a placebo capsule filled with lactose. The initial dosage of zonisamide was 100 mg/day, which was increased by 100 mg/day every two weeks to a target dosage of 500 mg/day. The target dosage was continued for the last 4 weeks of the trial, after which it was tapered and the medication discontinued. The dosage of medication was reduced if necessary for tolerability.

Brief Counseling/Skills Training

All subjects received 6 biweekly sessions of brief (20-minute) cognitive-behavioral counseling (BC) and psychoeducation. The same therapist, who was blind to medication condition, administered all therapy sessions.

Assessments

Prior to study enrollment, each subject received a physical examination and laboratory evaluation that included urinalysis, a urine drug screen, and hematology and serum chemistry panels. Urine pregnancy testing was conducted monthly during treatment. At the study midpoint and endpoint, serum chemistry, hematology, and serum gamma-glutamyl-transpeptidase (GGT) measurements were repeated. Weight and vital signs were measured at each treatment visit. Urine drug screens were repeated at the midpoint and endpoint of the study.

The Structured Clinical Interview for DSM-IV was used to determine the presence or absence of mood, anxiety, and substance use disorders according to DSM-IV criteria. The Timeline Follow-Back (TLFB) method was used to estimate alcohol consumption during the 12-week pretreatment period [22]. The TLFB was re-administered at each visit during the treatment trial as the primary indicator of drinking behavior. Desire (urge/craving) to drink was assessed at each treatment visit with the Alcohol Urge Questionnaire (AUQ)[23] .

The Beck Depression Inventory (BDI) a 21-item, self-report measure, was used to measure pretreatment depressive symptoms [24]. A medication questionnaire, administered at the study endpoint, asked subjects to identify whether they had received zonisamide or placebo.

Data Analysis

Frequencies and percent frequencies are used to describe the sample. Efficacy analyses were performed using linear mixed models implemented in SPSS v17. All efficacy analyses were by intention-to-treat, with all available data included. The primary outcomes were abstinent days per week and heavy drinking days per week. Secondary outcomes were drinks per week, alcohol urge score and GGT concentration.

Medication group was treated as a fixed factor and treatment week as a continuous covariate, with pretreatment drinking also included as a covariate in the model. The interaction of medication group by week was used to compare the effects of zonisamide with placebo on drinking outcomes over time. Subjects were modeled as a random effect. We used week, rather than biweekly treatment visit, to model drinking behavior to enhance power and for comparison with the literature. Other measures that were administered biweekly were modeled by visit. GGT activity was measured at the screening, midpoint and endpoint visits. The frequency of specific groups of adverse effects of a moderate-to-severe nature and the number of subjects for whom medication treatment was discontinued due to

adverse effects were tallied and compared by medication group using χ^2 analysis or Fisher's Exact Test (FET). All p-values are two-sided, with $\alpha = 0.05$.

RESULTS

Descriptive Statistics

There were no pretreatment differences between the zonisamide and placebo study arms on demographic or drinking measures (see Table 1). There were no statistical differences in the frequency of other Axis I diagnoses between groups. More than one-third (37.5%) of subjects were on a stable dosage of an antidepressant medication at the time of study enrollment and remained on that treatment throughout the study period.

Treatment and Research Adherence

All placebo subjects and 12 (60%) of the zonisamide subjects reached the target dosage of five capsules/day [FET = 0.003]. The mean maximal dosage of zonisamide was 430 mg (SD=108.1). Capsule counts revealed that medication adherence was high in both groups [placebo: 95.7% (SD = 7.9%); zonisamide: 98.1% (SD=5.5%); $t_{38} = -1.12$, $p = 0.27$].

Integrity of the Blind

Non-significantly more of the zonisamide subjects (76.5%) than placebo subject (52.6%) correctly identified their treatment [$\chi^2(1df) = 3.20$, $p = 0.074$].

Study Retention

Four subjects (10%) failed to complete the 12-week treatment period, 3 in the zonisamide group [2 due to adverse medication effects (AEs) and 1 due to a lack of efficacy] and 1 in the placebo group (who was lost to follow up).

Safety and Tolerability

There were no serious or severe AEs in either treatment group. Although 16 subjects in each of the two groups reported one or more mild or moderate AEs, the zonisamide group reported more total AEs than the placebo group [$n = 50$ and $n = 32$, respectively; $\chi^2(1df) = 3.95$, $p = 0.047$]. Gastrointestinal AEs were most common and were reported by 65% of zonisamide subjects and 20% of placebo subjects [$\chi^2(1) = 8.29$, $p = 0.004$]. Other AEs that occurred in at least 10% of subjects were neurologic (32.5%), psychiatric (30.0%), cognitive (15.0%), genitourinary (15.0%), fatigue/somnolence (12.5%), and musculoskeletal (10%). None of these differed significantly in frequency by medication group.

Drinking Outcomes

The medication groups did not differ significantly on the percentage of abstinent days ($p = 0.94$), the weekly rate of change in abstinent days ($p = 0.33$), or the aggregate number of heavy drinking days per week ($p = 0.54$). However, there was a significant medication by treatment week interaction ($F_{1,458} = 6.33$, $p = 0.012$), which reflected a reduction of 0.3 HDD per week in the zonisamide group vs. 0.2 HDD per week for the placebo group (see Figure 1). At the study endpoint, the difference in HDD showed a small effect size ($d = 0.27$).

The aggregate number of drinks per week did not differ significantly by group ($p = 0.60$). However, there was a significant medication by treatment week interaction ($F_{1,458} = 8.36$, $p = 0.004$), with the zonisamide group decreasing their drinking by 2.2 drinks during each week of the study compared with a reduction of 1.4 drinks per week in the placebo group

(see Figure 2). At the study endpoint, the difference in drinks per week showed a moderate effect ($d = 0.44$).

Other Outcome Measures

Consistent with a greater reduction in drinking, the zonisamide group showed a greater decrease in urge to drink [decreasing by 1.4-points on the AUQ per week, compared to a 0.6-point per week decrease for the placebo group ($F_{1,211} = 7.57$, $p = 0.006$)]. Although the zonisamide group showed a greater reduction in GGT activity (i.e., a mean decrease between each of the three measurement time points of 8.4 U/L compared with 2.9 U/L for the placebo group), the difference was not statistically significant ($p = 0.30$). Although the zonisamide group showed a significantly greater total weight loss [2.54 kg ($SD=2.18$)] than the placebo group [0.36 kg ($SD=2.13$); $t_{26}=2.65$, $p=0.014$], the inclusion of this variable as a factor in the analyses did not alter the effect of medication on any of the drinking outcomes.

Antidepressant Treatment

Fifteen subjects (38%) were on stable antidepressant treatment [9 (45%) in the zonisamide group and 6 (30%) in the placebo group]. Although antidepressant use did not significantly affect heavy drinking days or drinks per week, it moderated the medication by week interaction on the number of abstinent days per week ($F_{1,456} = 5.43$, $p = 0.020$). In the placebo group, antidepressant-treated subjects reported 0.15 more abstinent days per week than subjects not receiving antidepressant treatment. There was no effect of antidepressant treatment on abstinent days in the zonisamide group ($F_{1,43} = 2.94$, $p = 0.094$).

DISCUSSION

We compared the effects of zonisamide with an inactive placebo on drinking outcomes in alcohol-dependent subjects whose goal was to reduce their drinking to sensible levels or to stop drinking completely. Both the reduction in heavy drinking (a small effect) and the reduction in drinks per week (a moderate effect) support the potential efficacy of this medication for the treatment of AD. Although there was no effect of medication on abstinent days, this outcome was likely confounded by the fact that nearly 2/3 of subjects in the study were not committed to abstinence as a treatment goal. The medication was well tolerated and it appeared to be useful irrespective of whether the subject was receiving concurrent antidepressant treatment. Further evaluation of zonisamide for AD treatment is warranted.

A limitation of the study is the small sample size and the comparatively short duration of treatment. A larger study would provide greater statistical power and a longer study could provide more evidence of zonisamide's efficacy, since in the present study the beneficial effects of zonisamide were only evident after the target dosage of medication was achieved, which occurred only four weeks prior to the end of the trial. As with studies of topiramate to treat AD [4, 5], trials of zonisamide must balance the advantage of a slow increase in dosage (and better tolerability) with a longer period of treatment at the target dosage. Studies to identify the optimal dosage of zonisamide are also needed.

The high rates of retention in treatment and adherence to the medication regimen are strengths of the study. The inclusion of a substantial proportion of subjects receiving concurrent antidepressant treatment suggests that zonisamide may be efficacious in a diverse population of alcohol-dependent individuals. Effects of the medication were also seen despite the concomitant administration of coping skills therapy and the fact that a majority subjects in the study had as their goal the reduction of drinking to sensible limits, rather than abstinence, both of which could have limited the beneficial effects of the medication.

Although the results of this pilot study should be interpreted cautiously, zonisamide appears to hold promise as a medication to reduce drinking in alcohol-dependent individuals. Further study of zonisamide for the treatment of AD is warranted, since it may provide an additional treatment option for this disorder. Comparison of the effects of zonisamide with those of topiramate could provide new insights into the mechanism of action of anticonvulsants and other medications in the reduction of heavy drinking.

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Figure 1.
Heavy Drinking Days per Week

Figure 2.
Number of Drinks per Week

Table 1Demographic and Pretreatment Clinical Variables^{1, 2}

Variable	Zonisamide (n=20)	Placebo (n=20)
<u>Demographics</u>		
Gender (% Male)	60%	55%
Age	47.8 (9.9)	50.4 (11.0)
Race/Ethnicity		
European-American	95%	85%
Hispanic	5	5
African-American	0	10
Marital Status		
Married	70%	60%
Not Married	30%	40%
Employment Status		
Working	75%	85%
Not Working	25%	15%
Education		
High School	10%	20%
Some College	25%	30%
College Graduate	40%	45%
Advanced Degree	25%	5%
Income ³		
Less than \$30,000	0%	15%
\$30,000 – \$59,999	0%	15%
\$60,000 – \$79,000	26.3%	15%
\$80,000 or more	73.7%	55%
<u>Clinical Variables</u>		
Drinking (Past 60 Days)		
Total Drinks	413 (207)	396 (224)
Drinking Days	51.9 (12.1)	54.8 (9.1)
Heavy Drinking Days	43.5 (14.1)	46.7 (12.7)
Age of Onset of Alcohol Dependence	38.3 (11.6)	35.6 (13.9)
Past Alcohol Treatment		
Yes	45%	55%
No	55%	45%
AUQ ⁴ Score	18.9 (10.4)	18.3 (11.3)
BDI ⁵ Score	9.1 (5.4)	11.2 (7.0)
Lifetime Axis I Disorders		
Mood Disorder	25%	50%
Anxiety Disorder	10%	15%
Drug Use Disorder	45%	35%
Concomitant Antidepressant	45%	30%

¹ Values are mean (SD) or percentage

² No significant between-group differences

³ t-test for means (SDs); χ^2 for frequencies

⁴ One missing value in the zonisamide group

⁵ Alcohol Urge Questionnaire

⁶ BDI= Beck Depression Inventory