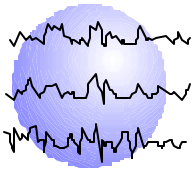
DECLINE IN COGNITIVE FUNCTIONING ASSOCIATED WITH ZONISAMIDE (ZNS) THERAPY

Gretchen Weatherly, PhD
Gail L. Risse, PhD
Britt E. Carlson, BS
Mary C. Gustafson, PharmD
Patricia E. Penovich, MD



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Minnesota Epilepsy Group, P.A.®
225 Smith Avenue N., Suite 201
St. Paul, MN 55102
Phone: (651) 241-5290
Fax: (651) 241-5248

REVISED ABSTRACT

RATIONALE

The introduction of a new antiepileptic drug (AED) necessitates careful evaluation of its effect on cognition. However, since its introduction there have been few empirical studies published that investigate cognitive effects of zonisamide (ZNS) therapy, although cognitive complaints are not uncommon with AEDs, as a class. Reported here are the preliminary findings from a group of 20 epilepsy patients who were administered neuropsychological measures prior to and during treatment with ZNS. The objective is to investigate the effects of ZNS on cognitive functioning.

METHODS

Twenty epilepsy patients (mean age=39.6 years, 35.0% male) who had been administered a battery of neuropsychological tests prior to and during ZNS therapy for partial onset seizures, were selected from clinic files. Patients were included in the study if they had a baseline full-scale intelligence quotient greater than 70. Length of time from initiation of ZNS ranged from 3 to 429 days, with the majority of participants being on ZNS for a minimum of 58 days at the time of testing. ZNS dosage ranged from 100 to 800 mg (mean dosage at the time of testing=405 mg). The majority of patients (19 of 20) were on multiple AEDs, and their dosage may have been adjusted during the course of ZNS treatment. The cognitive battery included measures of working memory, verbal fluency, visuomotor processing speed, and psychomotor speed. Paired t-tests were calculated to compare mean performances at baseline and during ZNS therapy.

RESULTS

Mean scores on cognitive tests declined for all tests relative to baseline, with the exception of one measure of motor speed and dexterity (Grooved Pegboard). Statistically significant decline was observed on measures of verbal fluency (Controlled Oral Word Association) and working memory (Digit Span). There was a trend toward lower scores on measures of visuomotor processing speed (Digit Symbol-coding) and verbal fluency (Animal Naming), although these comparisons did not reach statistical significance.

CONCLUSIONS

These preliminary results suggest ZNS, when used with other AEDs, may be associated with cognitive decline in some patients. Performance may be more affected on tasks requiring cognitive processing as opposed to psychomotor speed. Additional research is needed to further investigate the possible effects of dose, titration, and duration of adjunctive ZNS therapy on cognitive test performance and to determine the incidence of patients' subjective complaints of cognitive change.

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INTRODUCTION

Antiepileptic drugs (AEDs), as a class, are commonly associated with cognitive effects, including impaired attention, vigilance, and psychomotor speed.[1] Older AEDs, such as carbamazepine, phenytoin, and valproate, have been shown to affect cognition; however the cognitive effects of many newer AEDs have yet to be established.[1] Zonisamide (Zonegran®, ZNS) is a novel AED with a broad spectrum of action, which was approved in 2000 for the adjunctive treatment of partial seizures in adults with epilepsy. Few empirical studies have investigated cognitive effects of ZNS therapy, although cognitive complaints associated with the drug are not uncommon in clinical practice. In one study with a limited number of subjects by Berent et al[2] adverse effects of ZNS on verbal learning were observed, but no effects of ZNS on previously learned material or on visual-perceptual learning were noted. The present study was conducted to investigate the effects of ZNS on various aspects of cognitive function in epilepsy patients. In nearly every case, ZNS was used as an adjunctive treatment to other AEDs, which is representative of normal clinical practice in highly intractable cases.

METHODS

Twenty epilepsy patients (7 males and 13 females), ranging in age from 20 to 76 years (mean=39.6 years), were selected from clinic files. All patients had been administered a battery of neuropsychological tests prior to and during ZNS therapy for partial onset seizures. Patients were included in the study if they had a baseline full-scale intelligence quotient greater than 70. Length of time from initiation of ZNS to time of the second battery ranged from 3 to 429 days (mean=117 days), with the majority of participants being on ZNS for a minimum of 58 days at the time of testing. ZNS dosage at the time of testing ranged from 100 to 800 mg/d (mean=405 mg/d). Eighteen patients (90.0%) were on other AEDs at the time of baseline neuropsychological testing (median=2 AEDs, mode=2 AEDs), and 19 patients (95.0%) were on other AEDs at the time of testing during ZNS therapy (median=2 AEDs, mode=2 AEDs) (Table 1). The neuropsychological test battery included measures of working memory, verbal fluency, visuomotor processing speed, and psychomotor speed (Table 2). Paired t-tests were used to compare mean scores on the neuropsychological tests at baseline and during ZNS therapy. Values of $P<0.05$ were considered statistically significant.

RESULTS

Mean scores on all neuropsychological tests declined relative to baseline (Table 3). A statistically significant decline was observed on measures of verbal fluency (COWA, $P=0.001$) and working memory (Digit Span, $P<0.001$). There was a trend toward lower scores on measures of visuomotor processing speed (Digit Symbol-Coding) and verbal fluency (Animal Naming) during ZNS treatment. The

figure shows the percentage of patients demonstrating a clinically significant (i.e., ≥25%) decline in performance on each neuropsychological measure.

CONCLUSIONS

- These results suggest that ZNS, when used as adjunctive treatment with other AEDs, may be associated with cognitive decline.
- Cognitive processing, as opposed to psychomotor speed, appears to be the most sensitive to ZNS as adjunctive therapy.
- Confounding factors could have influenced patients' change in cognitive function, such as the addition and/or the change in dosing of concomitant medications, possible interactions between ZNS and the other AEDs, and variations in the time from initiation of ZNS therapy to final testing.
- Additional research is warranted to further investigate the possible effects of dosage, titration, and duration of ZNS therapy as monotherapy and adjunctive therapy on cognitive test performance and to determine the incidence of patients' subjective complaints of cognitive change.

REFERENCE

1. Meador, K Jr. Cognitive outcomes and predictive factors in epilepsy. *Neurology*. 2002;58(suppl 5): S21-S26.
2. Berent S, Sackellares JC, Giordani B, Wagner JG, Donofrio PD, Abou-Khalil B. Zonisamide (CI-912) and cognition: results from preliminary study. *Epilepsia.* 1987;28:61-67.

Table 1 **Concomitant AEDs at Baseline and at the Time of Testing During ZNS Therapy**

AED	Patients n (%)	
	Baseline	**ZNS**
Carbamazepine	6 (30.0)	2 (10.0)
Clonazepam	1 (5.0)	2 (10.0)
Divalproex/valproic acid	5 (25.0)	3 (15.0)
Felbamate	3 (15.0)	4 (20.0)
Gabapentin	3 (15.0)	3 (15.0)
Lamotrigine	5 (25.0)	5 (25.0)
Levetiracetam	1 (5.0)	3 (15.0)
Oxcarbazepine	2 (10.0)	3 (15.0)
Phenobarbital	4 (20.0)	1 (5.0)
Phenytoin	9 (45.0)	2 (10.0)
Tiagabine	1 (5.0)	0 (0)
Topiramate	1 (5.0)	4 (20.0)

Table 2 **Battery of Neuropsychological Tests**

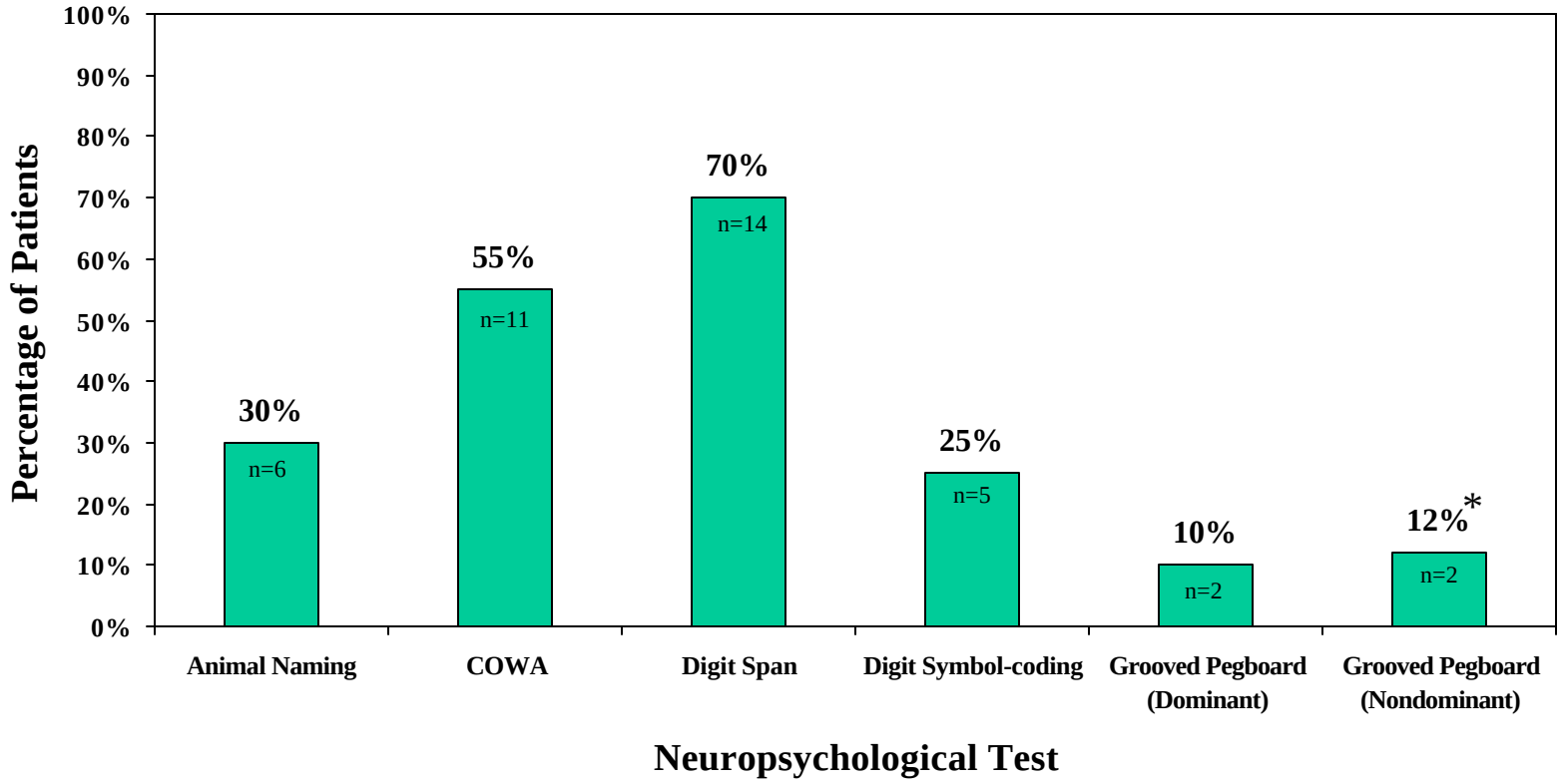
Test	Parameter Measured
Animal Naming	Verbal fluency
Controlled Oral Word Association (COWA)	Verbal fluency
Digit Span	Working memory
Digit Symbol-coding	Visuomotor processing speed
Grooved Pegboard (for dominant and nondominant hand)	Motor speed and dexterity

Table 3 **Percentage Changes From Baseline in Neuropsychological Test Scores (N=20)**

Test	Mean (Standard Deviation) Percentage Change in Score From Baseline
Animal Naming	-6% (48.7%)
COWA	-29% (32.3%)*
Digit Span	-28% (24.0%)*
Digit Symbol-coding	-8% (28.6%)
Grooved Pegboard	
Dominant hand	-2% (35.0%)
Nondominant hand**	-3% (34.7%)

*Statistically significant decrease in score from baseline, $P \leq 0.001$
**17 patients took the Grooved Pegboard test for the nondominant hand

Figure **Percentage of Patients Showing a ³25% Decline in Neuropsychological Test Scores\ Since Initiation of ZNS Treatment (N=20)**



*17 patients took the Grooved Pegboard test for the nondominant hand