A WITHIN-SUBJECTS STUDY OF COGNITIVE EFFECTS IN PATIENTS WHO HAVE BEEN TREATED WITH BOTH TOPIRAMATE AND ZONISAMIDE

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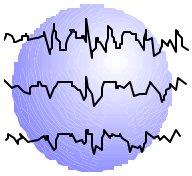

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REVISED ABSTRACT

RATIONALE: Two of the newer antiepileptic drugs (AEDs), topiramate (TPM) and zonisamide (ZNS) have a similar chemical structure and produce similar cognitive side effects (Weatherly et al., 2004). Yet providers continue to prescribe each of these drugs independent of patient response to the other medication. The current study aims to clarify whether patients who experienced cognitive side effects on one of the drugs are likely to experience similar side effects on the other drug.

METHODS: Adult neuropsychological files were retrospectively reviewed. Epilepsy patients were included if they had undergone neuropsychological testing during adjunctive therapy with TPM and again while on ZNS. All patients had a baseline IQ of 70 or greater and did not have a progressive neurological disorder. The cognitive test battery included measures of working memory, verbal fluency, visual-motor speed, and manual dexterity. A decline was defined as a decrease of one standard deviation or change of one descriptive category relative to baseline testing. Due to the limited number of subjects, neuropsychological data were reviewed without formal statistical comparisons.

RESULTS: Eight patients were identified who underwent neuropsychological testing while treated with TPM who had also been tested separately while on ZNS. The mean TPM dose was 200 mg and the mean ZNS dose was 312.5 mg daily. Impaired performance on both drugs independently was observed on measures of digit repetition (37% of patients), phonemic verbal fluency (37%), and mental sequencing (28%). Five patients also underwent baseline testing while on another medication regimen that did not include ZNS or TPM. Four of 5 (80%) of patients with baseline testing experienced a decline from baseline on two or more measures when taking TPM. Similarly, 4/5 (80%) of patients who underwent baseline testing experienced a decline on at least 2 measures when treated with ZNS. Three of the 5 subjects with baseline testing experienced measurable cognitive side effects (e.g., a decline on 2 or more measures) on both TPM and ZNS. One demonstrated side effects on TPM but not ZNS, and one showed a cognitive decline on ZNS but not TPM. These two patients were both treated with relatively low doses of the drugs in question.

CONCLUSION: Sixty percent of patients with baseline testing experienced a decline in cognition on both drugs, and patients who did not show such declines were treated with lower doses of the medication. Among all 8 patients, impairment on both drugs independently was observed most frequently on measures of phonemic verbal fluency and digit repetition. The observed impairments are consistent with previous studies suggesting these drugs are associated with deficits in cognitive processing rather than motor speed. Additional study with larger sample sizes is clearly needed to clarify factors contributing to cognitive side effects associated with these drugs.

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Introduction:

There is a growing body of literature suggesting that two of the newer antiepileptic drugs (AEDs), topiramate (TPM) and zonisamide (ZNS), may be associated with a decline in cognition. Recent evidence has shown that healthy volunteers and epilepsy patients treated with TPM may experience decreased visual-motor speed, verbal recall, verbal fluency, attention, and working memory (1 - 5). Less well-documented are cognitive side effects of ZNS, which may also include declines on neurocognitive measures of verbal memory, verbal intellectual abilities, verbal fluency, working memory, and visual-motor speed (6 – 8). Ojemann, et al (9) and Weatherly, et al (10) also noted that the pattern of cognitive deficits was similar between the two drugs, possibly due to the sulfa-containing properties of both. Despite these similarities, providers have continued to prescribe both of these drugs independent of the patient's response to the other medication. The current study aims to clarify whether patients who experienced cognitive side effects on one of the drugs are likely to experience similar side effects on the other drug.

Methods:

- Adult neuropsychological files were retrospectively reviewed. Epilepsy patients were included if they had undergone neuropsychological testing during adjunctive therapy with TPM and again while on ZNS.
- All patients had a baseline IQ or estimated IQ of 70 or greater and did not have a progressive neurological disorder.
- The cognitive test battery included measures of working memory, verbal fluency, visual-motor speed, and manual dexterity (see Table 1). A total of 7 measures were included.
- Eight patients were identified who underwent neuropsychological testing while treated with TPM who had also been tested separately while on ZNS.
- Demographic characteristics of the sample (n = 8) are listed in Table 2.
- Five of the 8 patients had also undergone neuropsychological testing while taking another medication combination that did not include TPM or ZNS. This was considered the patient's cognitive "baseline."
- A decline was defined as a decrease of one standard deviation or change of one descriptive category (e.g., average to low average) relative to baseline performance.

Results

- Of the 5 patients with baseline testing, 3 experienced measurable cognitive side effects (e.g., a decline on 2 or more measures) on both TPM and ZNS. One demonstrated side effects on TPM but not ZNS, and one showed a cognitive decline on ZNS but not TPM. These two patients were both treated with relatively low doses of the drugs in question (TPM 100 mg/day; ZNS 100 mg/day) compared to those who experienced declines. The number of patients showing a decline on each measure is presented in Figure 1.
- 4/5 patients with baseline testing experienced a decline from baseline on two or more measures when taking TPM. The mean number of tests showing a decline on TPM was 3.2 (range 1 – 5).
- 4/5 patients who underwent baseline testing experienced a decline on at least 2 measures when treated with ZNS. The mean number of tests showing a decline on ZNS was 3.4 (range 1 – 5).
- One patient who did not have baseline testing experienced a decrease from her estimated previous level of functioning on ZNS 500 mg.
- When data from all 8 subjects is considered, 37% of patients showed impaired performance on both TPM and ZNS independently on measures of digit repetition and phonemic verbal fluency, and 28% showed deficits in mental sequencing on both drugs. See Figure 2.

Conclusion:

Among patients with baseline testing, a majority (60%) experienced a decline in cognition on both drugs, and patients who did not show such declines were treated with lower doses of the medication. When all 8 patients are considered, impairment on both drugs independently was observed most frequently on measures of phonemic verbal fluency and digit repetition. The observed impairments are consistent with previous studies suggesting these drugs are associated with deficits in cognitive processing rather than motor speed. Additional study with larger sample sizes is clearly needed to clarify factors contributing to cognitive side effects associated with these medications.

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Table 1

List of Tests by Cognitive Domain

Domain	Test
Visual-motor speed	WAIS-III Digit-Symbol
Digit recall	WAIS-III Digit Span
Mental sequencing	WAIS-III Letter-Number Sequencing
Verbal fluency	Controlled Oral Word Association Test and animal naming *or* D-KEFS Verbal Fluency
Manual dexerity	Grooved Pegboard, dominant and nondominant hands

Table 2

Sample Characteristics (n = 8)

Mean age at 1st testing	44.75 years
Mean age at 2nd testing	46.625 years
Average baseline IQ	78
Number of women	8
Mean TPM dose	200 mg (100 – 300 mg)
Mean ZNS dose	312.5 mg (100 – 500 mg)
Number tested on TPM first	3
Number tested on ZNS first	5
Number of patients with additional "baseline" testing (not on TPM or ZNS)	5
Mean time between 1st and 2nd testing	23 months (2.5 – 58 mos.)

Figure 1

Number of patients (n=5) whose performance declined at least one standard deviation or one descriptive category from baseline testing on each measure

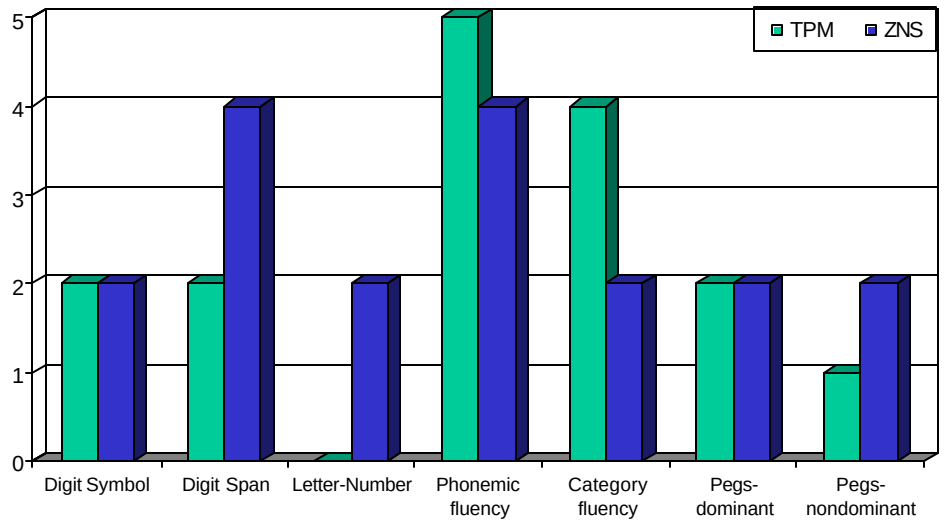

Figure 2

Percentage of patients (n = 8) showing impairment on TPM, ZNS, and both