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Efficacy, tolerability, and retention rates of zonisamide in older adult patients with focal-onset epilepsy: Experiences from two tertiary epilepsy centers

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ABSTRACT

Objective: The objective of this study was to evaluate the efficacy, tolerability, and retention rates for zonisamide (ZNS) in older adult patients with focal-onset epilepsy.

Patients and methods: Chart reviews of patients aged 60 years and older with focal-onset epilepsy treated with ZNS in two tertiary epilepsy centers were analyzed retrospectively.

Results: Eighty-five patients (41 males, 44 females) aged over 60 years (range: 60–81) with focal-onset epilepsy treated with ZNS were identified; 55.3% of the patients (n = 47) were on monotherapy. The median and average doses of ZNS doses were 200 mg/day (range: 100–400) and 212.9 ± 84.2 mg/day, respectively. With ZNS treatment, 67.1% of the patients (n = 57) were seizure-free for a median of 28 months (range: 10–56) whereas 20% (n = 17) of the patients had seizures that were unresponsive to ZNS treatment. Best seizure control was achieved in patients with poststroke epilepsy; seizure freedom was 80% in this subgroup.

Overall retention rate was found to be 83.5%. There was no significant relation between receiving poly- or monotherapy and discontinuation of ZNS (p = 0.18).

Thirty-two of the patients (37.6%) lost weight. Median weight loss was 8 kg (range: 2–16). There was no significant correlation between weight loss and the administered doses of ZNS (r = 0.34; p = 0.12).

Conclusion: Despite limitations due to the retrospective design of the study, the results show that ZNS is a well-retained drug with high efficacy in older adult patients with epilepsy.

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1. Introduction

Epilepsy is the third most common neurologic disease following dementia and stroke in older adult people [1]. Seizures are usually focal-onset and although a higher remission rate is expected, recurrence of seizures is more frequent, and mortality is higher when compared with young adults [2–4]. Treatment of older individuals with epilepsy is very important since this group is forming an increasingly larger part of the population [5,6].

Anatomical and physiological changes that take place may easily influence the pharmacokinetics and the pharmacodynamics of the drugs and lead to a variety of outcomes in older patients [7]. Therefore, age-related physiological changes as well as comorbidities should always be taken into account before deciding for an antiepileptic drug (AED) in this particular group of patients.

Zonisamide is an AED approved as mono- and adjunctive treatment for focal-onset seizures. Approved therapeutic doses in adults range between 200 and 500 mg/day. Zonisamide has a clear dose–response

relationship with a long half-life of approximately 60 h which provides once-a-day dosing [8].

Data regarding the treatment of epilepsy in older adults are limited. In our study, we aimed to investigate the efficacy, tolerability, and retention rates of ZNS in older adult patients with focal-onset epilepsy.

2. Methods

This was a retrospective study conducted in two tertiary epilepsy centers in Turkey. Chart reviews of patients aged 60 years and older treated with ZNS at Akdeniz University, School of Medicine and Necmettin Erbakan University, School of Medicine were performed. A total of 85 patients who had a history of two or more unprovoked focal-onset seizures (with or without secondary generalization) were eligible for the study. All of the patients underwent magnetic resonance imaging (MRI) or computerized tomography (CT). Clinical information and detailed histories were obtained from hospital charts.

The starting dose of ZNS was 100 mg on a once-daily schedule. Hospital charts included all clinically relevant parameters which had been captured at regular time points in the first year (baseline, after a month, and every 6 months). However, because of the retrospective

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design of the study, no exact visit windows could be defined after the first year, and the visit schedules were up to the physician's discretion and the patients' health conditions.

Hospital charts included neurological and physical examinations in addition to laboratory tests including complete blood counts and kidney and liver functions. Seizure control, adherence, tolerability, and side effects, which were assessed by direct questioning, were also in the database. Lack of efficacy was defined as the occurrence of further seizures despite the maximum tolerable dose of ZNS. Response was defined as seizure freedom for 6 months on a stable dose of ZNS. The primary outcomes were response and/or remission besides retention rates at last follow-up and the discontinuation due to side effects.

The study was conducted with the approval of the Ethics Committee.

2.1. Statistical analysis

Statistical analysis was carried out using SPSS 18 Software (SPSS Inc., Chicago, IL, USA). Continuous data were characterized by median and range. Categorical data were characterized by number and percentage. The statistical difference in response (seizure freedom rates at 6 months follow-up) between distinct etiologies was determined by using a one-sided Chi-square test. A Pearson correlation test was used to analyze the correlation between the dose of ZNS and loss of weight. The level of significance was set at 0.05.

2.2. Results

Eighty-five patients (41 males, 44 females) were identified who met the inclusion criteria with a median age of 63 years (range: 60–81). The overall median ZNS dose was 200 mg/day (range: 100–400), and the average dose was 212.9 ± 84.2 mg/day. Median duration of therapy was 28 months (range: 10–56). Cerebrovascular lesions were found to be the most frequent imaging findings (47.1%) whereas 18 patients (21.2%) had brain tumor documented on brain MRI or CT. Ten patients (11.8%) had dementia, and no cause was identified in 17 of the patients (20.0%). With ZNS treatment, 67.1% of the patients ($n = 57$) were seizure-free for a median of 28 months. Distribution of the ZNS dose administered in seizure-free patients is illustrated in Fig. 1. Twenty percent ($n = 17$) of the patients had seizures that were unresponsive to ZNS treatment despite the maximum tolerable dose. Seizure freedom and unresponsiveness according to etiology are summarized in Table 1.

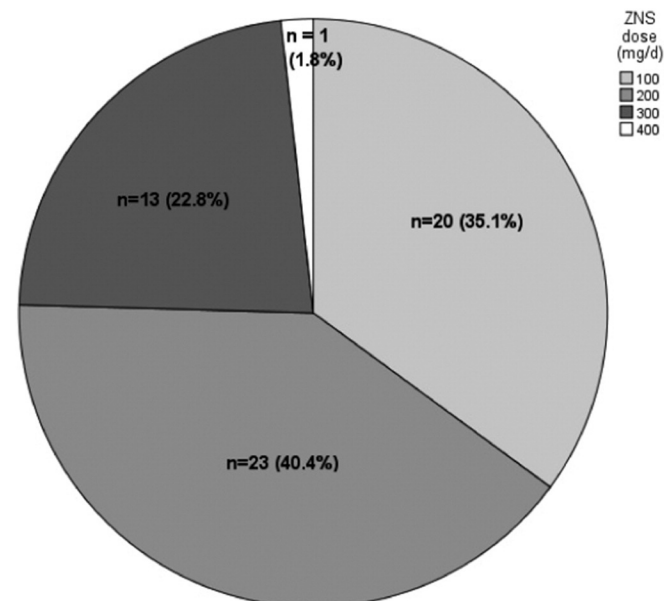


Fig. 1. Distribution of the zonisamide (ZNS) dose administered in seizure-free patients.

Table 1
Response rates to zonisamide treatment according to etiology.

	N (%)	Seizure freedom	No response	Retention
Stroke	40 (47.1)	32 (80.0%)	3 (7.5%)	36 (90.0%)
Brain tumor	18 (21.2)	9 (50.0%)	7 (38.9%)	12 (66.7%)
Dementia	10 (11.8)	6 (60.0%)	2 (20.0%)	8 (80.0%)
Unknown cause	17 (20.0)	10 (58.8%)	5 (29.4%)	15 (88.2%)

When seizure control was evaluated based on etiologies; best seizure control was achieved in patients with poststroke epilepsy (PSE). Remission rates were high (80.0% vs. 55.6%), and unresponsiveness was low (7.5% vs. 31.1%) in patients with PSE when compared with other subgroups (p values were 0.017 and 0.007, respectively). Twenty-four of the patients (60%) with PSE were on combination therapy.

A total of 26 patients (30.6%) experienced side effects, and 14 patients (16.5%) discontinued ZNS (Table 2). Two patients discontinued ZNS due to weight loss. Actual ZNS doses at the time of discontinuation of the drug are represented in Fig. 2, individually.

The number of patients receiving combination therapy was 38 (44.7%). Adjunctive AEDs and their doses are represented in Fig. 3. The majority of the patients were on ZNS monotherapy ($n = 47$; 55.3%). There was no significant relation between receiving combination or monotherapy and discontinuation of ZNS ($p = 0.18$). None of the patients in our study population received more than 2 AEDs.

Thirty-two of the patients (37.6%) lost weight. Median weight loss was 8 kg (range: 2–16). There was no significant correlation between weight loss and the administered doses of ZNS ($r = 0.34$; $p = 0.12$).

3. Discussion

The results of our study conducted in patients aged 60 years and over demonstrated that ZNS is an effective and a well-tolerated AED in older patients. Zonisamide was able to achieve seizure control in 67.1% of patients ($n = 57$) with relatively low daily doses (overall median and average dose was 200 mg/day and 212.9 ± 84.2 mg/day, respectively), and retention rates were high 83.5%. Zonisamide was associated with weight loss in approximately one-third (37.6%) of the patient population.

According to the demographic studies, seizures in older individuals are more frequently observed as compared with middle-aged and young adults. The annual incidence of epilepsy sharply increases and reaches to 0.9/1000 around ages 60 to 69 years and to 1.5/1000 for those over 80 years [1].

Seizures in older adults are usually focal-onset but although very rarely, late-onset generalized seizures can also be encountered. Therefore, an AED with a broad-spectrum efficacy and the least drug interactions should be the drug of choice in older [9,10].

According to the literature, the most common etiology of epilepsy in older adults is stroke which accounts for 30–40% of all cases [11,12]. Concordant with the available data, in our study population, cerebrovascular lesions were also found to be the most frequent imaging findings (47.1%) suggesting PSE to be the most likely leading etiology.

Table 2
Side effects after zonisamide treatment.

Side effects	n
Fatigue	9 (10.6%) ^a
Drowsiness	13 (15.3%) ^b
Elevated serum creatinine	2 (2.4%) ^c
Behavioral problems	2 (2.4%) ^d

^a Treatment was discontinued in 3 patients.

^b Treatment was discontinued in 5 patients.

^c Treatment was discontinued in 2 patients. Renal functions recovered after the discontinuation.

^d Treatment was discontinued in 2 patients.

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