A Double-Blind Placebo-Controlled Trial of Zonisamide (Zonegran) in the Treatment of Essential Tremor

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Abstract: **Medical therapy for essential tremor (ET), a common movement disorder, is often inadequate. We performed a double-blind placebo-controlled randomized trial to evaluate the efficacy and tolerability of zonisamide (ZNS), an antiepileptic agent, in treating ET. Twenty patients (mean age, 60 ± 15 years) with ET were randomized to receive ZNS or placebo. ZNS was initiated at a dosage of 100 mg/day and escalated to 200 mg/day at day 14. Patients were evaluated by accelerometry and the Fahn–Tolosa–Marin (FTM) rating scale at baseline and days 14 and 28, as well as the Clinical Global Impression (CGI-C) scale at day 28. At endpoint, subjects assigned to ZNS were taking a mean dosage of 160 ± 50 mg/day. There were no significant improvements in the FTM total score or its subsections. Tremor amplitude as assessed by accelerometry significantly improved in the ZNS group compared to the placebo group at endpoint relative to baseline (−0.50 ± 0.72 vs. 0.30 ± 0.79 m/s²; $P = 0.03$). On the CGI-C, 60% (n = 6) of patients in the ZNS group felt that their tremor was unchanged, while the remaining patients felt that their tremor was "minimally improved." Thirty percent (n = 3) of patients taking ZNS discontinued the study due to side effects (fatigue, headache, paresthesias) while taking 100 mg per day. ZNS did not provide significant improvements in clinical rating scales at study endpoint compared to placebo and was only modestly well tolerated. ZNS was effective in reducing tremor amplitude as measured by accelerometry.**

Key words: zonegran; zonisamide; essential tremor

Essential tremor (ET) is one of the most common adult tremor disorders and is characterized by postural and kinetic tremor that usually affects the hands, head, or voice. It has been referred to as a benign disorder, but symptoms are usually progressive and may be disabling. Propranolol and primidone are first-line medications that are used to treat limb tremor in ET, but it is estimated that approximately 30% of ET patients will not respond to either medication.[1] The use of other medications to treat ET is often limited by untoward side effects.[2] The difficulty of treating ET with currently available medications has prompted the search for additional medications to reduce tremor.

Zonegran (3-sulfamoylmethyl-1,2-benzisoxazole; zonisamide; ZNS) is an antiepileptic drug that is indicated as adjunctive treatment of partial seizures.[3] There is some evidence that ZNS can reduce tremor. A pilot open-label crossover study in 14 ET patients that compared ZNS to arotinolol, a β-adrenergic blocker, found that patients taking ZNS demonstrated a significant reduction in tremor compared to baseline as measured by Fahn–Tolosa–Marin (FTM) rating scales.[4] The mean dose of ZNS used in the study was 136 ± 50.0 mg per day. We sought to evaluate the tolerability and efficacy of ZNS in reducing tremor in ET patients in a double-blind pilot study.

PATIENTS AND METHODS

Patients diagnosed with ET and followed at a university movement disorders center were invited to participate in the study during a 3-month recruitment period. It was determined that 11 patients per group would be required to detect a 50% improvement in accelerometry measures at a significance level of 0.05 (two-sided) and 80% power. Eligibility criteria included age 18 to 80 years and a diagnosis of definite ET (as defined by the Tremor Investigator Group) that affected the upper extremities.[5] Further inclusion criteria included stable antitremor medications for at least 14 days prior to baseline, independent ambulation, and the ability to take oral medication. Exclusion criteria included the presence of severe renal disease or blood urea nitrogen (BUN) 50% greater than normal; subjective complaints of somnolence; Mini-Mental Status Exam (MMSE)[6] less than 24; hypersensitivity to sulfonamides; botulinum toxin treat-

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TABLE 1. *Baseline characteristics*

	ZNS (n = 10)	Placebo (n = 10)
Age (yr)	57.6 ± 12.8	61.5 ± 17.2
Gender	5 male, 5 female	4 male, 6 female
Time since ET diagnosis (yr)	7.4 ± 3.3	4.6 ± 1.6
Tremor amplitude: postural, worst affected hand (m/s^2)	0.74 ± 0.79	0.79 ± 1.01
Adjunct medications	Propranolol 40 mg (for heart conditions; n = 3); Primidone 75 mg (n = 1); Topamax 100 mg (n = 1)	Clonazepam 1 mg (n = 1); Topamax 25 mg (n = 1); Primidone 75 mg (n = 1)

ment for upper limb tremor in the prior 6 months; deep brain stimulation for ET or any other brain surgery; isolated physiological or psychogenic tremor; use of ZNS 30 days prior to study entry; alcohol or drug addiction; use of benzodiazepines other than in fixed doses for treatment of ET; and any major neurological, psychiatric, or medical disorders that were judged by the principal investigator (PI) to disqualify a patient from entering the study, including Parkinson's disease. Women of childbearing age were required to have a negative pregnancy test in the 7 days prior to study entry and were using birth control that was judged adequate by the PI. Patients who met inclusion and exclusion criteria provided written informed consent to enter the study. Institutional review board approval for the study was granted through the University of South Florida.

At baseline, patients were randomized to receive either ZNS 100 mg or placebo according to a computer-generated randomization schedule. Both patients and staff were blind to randomization. ZNS and placebo were supplied in identical containers that were marked with code numbers. On day 14, study medication was escalated to ZNS 200 mg/day or placebo. ET was evaluated by accelerometry and the FTM[7] at baseline and days 14 and 28, and the Clinical Global Impression (CGI-C)[8] scale at day 28. The primary outcome measure was the change in postural tremor intensity from baseline to endpoint in the worst affected limb as measured by accelerometry. The accelerometry device utilized in this study was a component of a portable PC-based test system (Catsys System) that measures coordination reaction time, tremor, and postural sway or stability (Danish Product Development).[9] A comprehensive sex- and age-separated normal material has been published using this apparatus and method of analysis.[9] The present study measured postural tremor in patients with clinically diagnosed ET. Neurological examinations and tremor measurements were conducted by a movement disorders specialist (T.A.Z.) and research assistant. To measure postural tremor, patients were asked to hold the pen in a writing posture but with the arms extended level with the shoulders. The pen was held with the long axis parallel to the ground, and hand vibrations were recorded and displayed in real time against a time axis plot on the computer screen.

Dosage adjustments were permitted at each office visit and further ZNS titration could be halted with a patient report of satisfactory tremor control or emergence of side effects. One assessment was made for each scale at each visit. Data were analyzed using nonparametric paired samples analysis. The mean ± standard deviation (SD) is reported. Last observation carried forward (LOCF) was used for analyses for patients who prematurely withdrew from the study.

RESULTS

Twenty patients (mean age, 60 ± 15 years) were randomized to either ZNS (n = 10) or placebo (n = 10). Baseline characteristics and medications are included in Table 1. Forty percent (n = 8) of study participants were taking therapy for ET at baseline. Of the patients who were not taking therapy, all patients reported previously taking medications that improved ET, but discontinued them in the past due to poor tolerability. Three patients randomized to ZNS discontinued the study due to side effects (headache and nausea in one patient on day 7, fatigue in one patient on day 12, diarrhea and headache in one patient on day 13), all while taking 100 mg per day, and two patients in the placebo group discontinued the study due to personal reasons. Three additional patients taking ZNS developed side effects while taking 200 mg/day (fatigue in one patient on day 15, mild sleepiness and headache in one patient on day 22, and paresthesias and fatigue in one patient on day 22), but none discontinued the study. All other subjects reached study endpoint and maximum study dosage.

Total FTM scores decreased from 21 ± 11.3 to 15.7 ± 8.7 in the ZNS group compared to 29.8 ± 10.4 to 26.7 ± 10.3 in the placebo group at study endpoint compared to baseline ($P = 0.36$). In the ZNS group, scores for FTM parts A, B, and C improved at study endpoint compared to baseline, but the differences from placebo were not significant (Table 2). Postural tremor amplitude in the worst affected limb significantly improved in the ZNS

TABLE 2. *FTM tremor rating scale scores*

	Zonegran	Placebo	*P*
Mean change in FTM scale: baseline to endpoint (LOCF)	−5.3 ± 3.9 points (25% reduction)	−3.1 ± 6.4 points (10% reduction)	0.36
Change in part A FTM scale[a]	−4.2 ± 2.90 (47% reduction)	−1.8 ± 3.33 (16% reduction)	0.10
Change in part B FTM scale	−.9 ± 1..37 (22% reduction)	−0.9 ± 1.97 (14% reduction)	1
Change in part C FTM scale	−.6 ± 1.17 (8% reduction)	−0.3 ± .95 (3% reduction)	0.54

[a]FTM part A includes ratings of resting, postural, and action tremor severity of the upper and lower extremities, face, tongue, voice, head, and trunk. FTM part B includes ratings of upper extremity tremor while writing, drawing, and pouring liquid. FTM part C assesses functional disability including tremor ratings while speaking, eating, taking liquids, hygiene, dressing, and working.

group compared to the placebo group at endpoint compared to baseline (−0.50 ± 0.72 vs. 0.30 ± 0.79 m/s^2; $P = 0.03$) at a mean dosage of 160 ± 50 mg/day (Figs. 1 and 2). There were no significant differences in accelerometry or FTM scores between patients who were taking ZNS as adjunct therapy or monotherapy. Drug treatment decreased postural tremor amplitude by 30% or greater as measured by accelerometry in six patients who were considered responders. In this group, total FTM scores improved by 28% compared to a worsening of 10% in patients who were not considered to be responders.

Evaluation of the CGI-C showed that at study endpoint, 60% (n = 6) of patients taking ZNS felt that their tremor was "unchanged" compared to baseline, while 20% (n = 2) of patients felt that their tremor was "minimally improved" (two patients who discontinued the study early on due to side effects did not have CGI scores). Two patients elected to remain on ZNS after completion of the study.

DISCUSSION

This randomized double-blind placebo-controlled study demonstrated that ZNS did not significantly improve FTM total and subsection scores compared to baseline. Evaluation of the CGI-C also showed that 60% of patients who took ZNS felt that they were unchanged at study endpoint. Only two patients elected to remain on ZNS after completion of the study. However, ZNS significantly reduced postural tremor intensity as assessed by accelerometry at study endpoint compared to baseline. Our results differ from those of a previous crossover pilot study by Morita and colleagues[4] in 14 ET patients that compared ZNS with arotinolol, a peripherally acting β-adrenergic blocker. In that study, ZNS significantly improved tremor scores on the FTM in patients with ET at a mean dose of 136 ± 50 mg/day. ZNS was more effective for tremors of cranial nerve areas, including voice, face, tongue, and head. The majority of patients treated with ZNS noticed "mild" global improvement of tremor disability.

In our trial, study design may have contributed to the apparent discord between significantly improved accelerometry results and those of the FTM and CGI-C, including mild baseline ET severity in several of the study participants and the small number of patients in the study. Accelerometry may have provided a more sensitive measure of the effect of ZNS on tremor intensity than the tremor rating scale. Study entry criteria did not specify a baseline tremor severity score as inclusion, and it is possible that some patients with relatively mild ET did not notice tremor improvement with ZNS. However, even patients with moderate ET did not report anything more than "minimal improvement" with ZNS use. The maximum ZNS dosage was 200 mg/day, lower than the conventional ZNS dosage in epilepsy (200–400 mg/day). It is possible that higher doses of ZNS would have produced greater efficacy in reducing tremor. However, because 60% of patients reported side effects from ZNS dosages ranging from 100 to 200 mg/day, higher titration of the drug might not have been feasible. This study

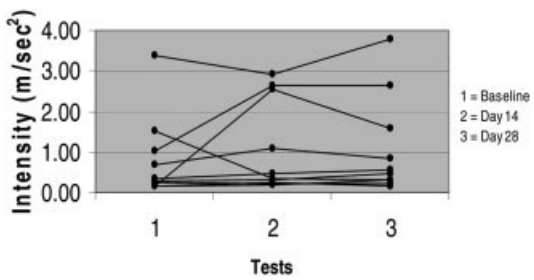

FIG. 1. Tremor intensity: placebo group.

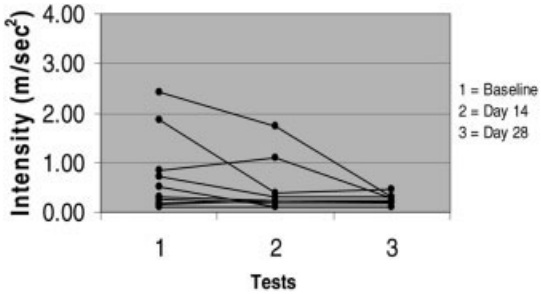

FIG. 2. Tremor intensity: active drug group.

found that although ZNS produced significant reduction in tremor amplitude in ET patients as assessed by accelerometry, it did not provide significant clinical improvement as measured by the FTM or CGI-C and was only modestly well tolerated.

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