Zonisamide for the Management of Essential Tremor: An Illustrative Case Report on Long-Term Effectiveness

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Abstract
Essential tremor, a common adult pathologic tremor disorder, is characterized by action tremors. Mainstays of treatment include gabapentin, primidone, and propranolol. However, many patients obtain insufficient benefit or do not tolerate these medications (especially the elderly). Short-term studies demonstrate that zonisamide may be effective for essential tremor; however, long-term data are lacking. This is a case report of an 83-year-old, right-handed man with essential tremor of the upper extremities and head who previously failed several pharmacological treatments (defined as obtaining inadequate benefit from maximum tolerated dose) with gabapentin, nadolol, propranolol, and primidone and was initiated on zonisamide monotherapy. Long-term zonisamide therapy (200 mg daily) was well tolerated in this elderly patient and associated with clinically significant improvement of upper extremity tremor and clinically modest improvement in head tremor. The beneficial effects and tolerability were sustained over nearly 28 months of follow-up treatment.

Introduction and Case Report
Essential tremor (ET) is a common pathologic tremor characterized by action tremors, particularly kinetic and postural tremors. The term “essential” implies that ET is an inherent or inherited condition. In general, approximately 50% of patients will report a positive family history of tremor. Pathologic action tremors occur with voluntary contraction of a muscle and are further subdivided into postural, isometric, and kinetic tremors. A postural tremor is triggered upon voluntarily attempting to maintain a position against the force of gravity. For example, postural tremor of the upper extremities can be detected by having the patient extend their arms forward with fingers extended. An isometric tremor occurs with muscle contraction against a rigid stationary object (e.g., when making a fist, flexing the wrist against a flat surface, or squeezing the examiner’s fingers). A kinetic tremor occurs during voluntary movement and can be elicited by having the patient perform a finger-to-nose test, having patients sign their name, write a sentence, draw freehand spirals, or drink water from a cup. When severe, these tremors can be functionally disabling.

The hallmark symptom of ET is a bilateral postural or kinetic tremor affecting the distal upper extremities characterized by an insidious onset. However, tremor at rest (i.e., tremor present when a body part is fully supported against gravity in a manner not necessitating voluntary activation of skeletal muscles) is not uncommon. The second most frequent body part affected is the head. Essential tremor of the head is characterized by a horizontal “no-no” tremor pattern or a vertical “yes-yes” pattern. Other body parts, such as the legs, chin, trunk, tongue, soft palate, and, rarely, the lips and eyebrows, may also be affected.

The severity of ET is often assessed by the use of drawing or writing samples (e.g., having the patient draw spirals or write sentences). These tests provide an illustration of tremor fluctuation and magnitude. For patients with tremor that significantly interferes with daily activities, long-term pharmacotherapy should be considered. Gabapentin, propranolol, and primidone have been...
HD was an 83-year-old, right-handed male with essential tremor who obtained clinically significant long-term improvement from zonisamide monotherapy.

HD was started on zonisamide 100 mg at bedtime for two weeks. Aside from a transient and mild daytime sleepiness, the dose was well tolerated and increased to 200 mg at bedtime. At the subsequent follow-up two weeks later, the patient’s handwriting and spiral and line drawings had significantly improved (Figure 1). The patient reported satisfactory control of upper extremity tremor, but his mild head tremor persisted. The dose of zonisamide was increased to 300 mg at bedtime and associated with additional symptomatic benefit but was not tolerated due to excessive daytime sleepiness. Therefore, the dose was reduced back to 200 mg, and levetiracetam 500 mg twice daily was added. The patient noticed additional improvement of upper extremity tremor and levetiracetam was increased to 1,000 mg twice daily. However, the patient experienced onset of depressive symptoms attributed to levetiracetam, and the medication was discontinued. After 10 months of zonisamide treatment, the patient ran out of medication for approximately one week and reported significant worsening of hand and head tremor. He was restarted on zonisamide 200 mg with improvement of symptoms. The patient was maintained on zonisamide 200 mg at bedtime with good tolerability and improvement in handwriting and spiral and line drawings, which were sustained over 28 months, at which time the patient was lost to follow-up.

Discussion

In the United States, zonisamide is indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy, and in Japan, it is indicated for treatment of Parkinson’s disease. The exact mechanism of action for these conditions of interest is unknown, but may involve blockade of sodium and calcium channel and weak carbonic anhydrate inhibition. Another antiepileptic drug, topiramate, has a similar mechanism of action.
In a double-blind, placebo-controlled randomized trial, the efficacy and tolerability of zonisamide for ET was evaluated. Twenty patients (mean age=60 years) were randomized to receive zonisamide or a placebo for four weeks. Zonisamide was initiated at a dosage of 100 mg per day and increased to 200 mg per day after two weeks. At study end, the mean dose of zonisamide was 160 mg per day. There were no significant improvements in clinical rating scale scores, and the majority of patients felt that their tremor was unchanged. However, tremor amplitude as assessed by accelerometry significantly improved in the zonisamide group. Zonisamide was modestly well tolerated, with 30% of patients discontinuing the study due to side effects (fatigue, headache, paresthesias).³

In a randomized, crossover study of propranolol and zonisamide for isolated head tremor in 12 female patients with ET (mean age=72.3 years), zonisamide was found to be more effective than propranolol. Zonisamide was initiated at 50 mg per day and titrated to 200 mg as tolerated. Propranolol was initiated at 40 mg per day and titrated up to 160 mg as tolerated. Patients were treated for two weeks with either zonisamide or propranolol, then underwent a two-week washout prior to undergoing exchange of zonisamide for propranolol (i.e., patients initially receiving zonisamide were crossed over to propranolol and vice versa). The mean doses of zonisamide and propranolol were 100 and 126.67 mg per day, respectively. In eight patients, side effects occurred during treatment with zonisamide and included mild sedative effects, diarrhea, and abdominal discomfort. With propranolol treatment, nine patients developed bradycardia.¹⁰

In an evaluator-blinded, open-label study, 25 patients with moderate to severe upper limb ET were treated with zonisamide as monotherapy or as adjunctive therapy in a 12-week “treatment” phase, followed by a 12-week “extension” phase. Zonisamide treatment significantly reduced tremor scores at the end of the “treatment” and “extension” phases at mean doses of 252 and 225 mg per day, respectively. Doses up to 300 mg per day produced no additional benefit and were associated with more adverse symptoms, especially somnolence, poor energy, imbalance, and altered taste.¹¹

In an open-label, crossover trial of zonisamide for ET, 14 patients were randomized to receive either zonisamide or arotinolol for two weeks. After a two-week washout period, patients switched medications. Compared to baseline, both drugs significantly improved tremor, and there was no significant difference in the antitremor effect between zonisamide and arotinolol. The mean doses of zonisamide and arotinolol were 136 and 11.4 mg per day, respectively. However, zonisamide was noted to be more effective for tremors of cranial nerve areas (e.g., tremor affecting voice, tongue, and head). Mild sleepiness was observed in three patients after zonisamide administration and mild bradycardia was noted in four patients after arotinolol administration.¹²

This case report illustrates use of zonisamide monotherapy in a very elderly patient who previously failed (defined as obtaining inadequate benefit from maximum tolerated dose) several medications for essential tremor. The patient experienced clinically significant improvement of upper extremity tremor and modest improvement of head tremor with zonisamide that was sustained over approximately 28 months of follow-up. One of the most important limitations to a case report is lack of controls and ability to generalize. Nevertheless, this case report indicates that zonisamide monotherapy may be a well-tolerated and effective therapy for essential tremor in a very elderly patient who failed or did not tolerate several other medications.

About the Author
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