

## Case reports

# Successful Treatment of Primary Orthostatic Tremor Using Perampanel

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## Abstract

**Background:** Primary orthostatic tremor (POT) remains a therapeutic conundrum. Various medication classes have been tried, yielding modest results at best.

**Case Report:** A 62-year-old female with a 13-year history of POT, refractory to clonazepam up to 20 mg/day, was treated with perampanel 1–2 mg/day. She reported 90% subjective symptomatic improvement.

**Discussion:** This case highlights the potential for use of perampanel, a novel AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonist for the treatment of POT. There has been one prior report citing its use for POT with complete resolution of symptoms. We encourage further studies to highlight its efficacy for POT.

**Keywords:** Orthostatic tremor; leg tremor; instability; treatment; perampanel; antiepileptic

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## Introduction

Orthostatic tremor is a rare condition, characterized by unsteadiness while standing but relieved when sitting, walking, or lying down. Diagnosis is based on electromyography (EMG), which reveals a 13–18 Hz fast tremor in the legs, and occasionally in the trunk and arms as well.<sup>1</sup> Neuroimaging and laboratory testing are typically unremarkable in primary orthostatic tremor (POT).<sup>2</sup> Cases of secondary orthostatic tremor due to brainstem/cerebellar lesions, paraneoplastic disease, autoimmune causes, vitamin deficiencies, and side effects to dopamine-blocking medications have been reported.<sup>2</sup> Various pathophysiologic mechanisms for POT have been postulated. These include the presence of a central oscillator in the brainstem and/or cerebellum, and the possibility of POT being a neurodegenerative condition.<sup>2</sup>

POT continues to remain a therapeutic conundrum. Evidence supports the use of various medication classes such as benzodiazepines, beta blockers, and antiepileptic agents.<sup>3</sup> However, results remain modest at best. To date, there has only been one case report of marked improvement

of symptoms using perampanel.<sup>4</sup> We present a case that re-demonstrates similar findings using perampanel for the treatment of this condition, at doses that are subtherapeutic for the treatment of epilepsy.

## Case report

A 62-year-old female with a history significant for adrenal insufficiency had a 13-year history of instability and tremors in her legs when standing that improved when walking but caused her to have an overwhelming urge to sit or lie down. She had been previously diagnosed at an outside facility with orthostatic tremor within a year of symptom onset with surface EMG revealing 17–18 Hz tremor in her legs and back when standing. When she walked, the tremor “went away significantly” per the report. When she leaned on a chair, the tremor was noted in her arms.

Other investigations included MRI brain which had revealed T2 hyperintense lesions in the periventricular white matter. MRI C- and T-spine did not demonstrate any lesions. CSF analysis was negative for oligoclonal bands when tested on two separate occasions, 6 years apart. CSF was

otherwise unremarkable, including negative VDRL and Lyme titers. Serum studies were remarkable for elevated EBV IgG titers and a homozygous MTHFR mutation, which were obtained as part of workup for the white matter lesions on MRI brain. Titers for CMV, ANA, RF, SSA, SSB, Babesia, and Lyme antibodies were negative. Vitamin D and TSH levels were within normal limits. She reported a history of depression related to her disability from the orthostatic tremor.

She had been treated with clonazepam, up to 20 mg/day, without any symptomatic benefit. She subsequently had it tapered down to 0.25 mg/day. She requested a trial of perampanel citing the report by Ruiz-Julian et al.<sup>4</sup> We started her on perampanel 2 mg/day after counseling on possible psychiatric side effects, and the patient returned for follow-up on 1 mg/day with an additional 1 mg/day as needed (rarely). She immediately reported significant subjective symptomatic improvement, up to 90%. She did not report any side effects. Repeat needle EMG testing showed persistence of 17–18 Hz tremor when standing. Amplitude and burst synchronicity comparisons could not be made given differences in EMG techniques (surface vs. needle) and those characteristics not noted on her previous EMG done at an outside facility.

### Discussion

Orthostatic tremor presents significant motor as well as non-motor challenges to affected patients. While instability on standing and tremor are hallmarks of this disorder, symptoms such as fear of falling, social phobia, anxiety, and depression are also common and cause significant morbidity.<sup>5</sup> Due to its rare nature, there has been a dearth of well-designed randomized controlled trials.<sup>2</sup> Of the medications that have been trialed, clonazepam has been shown to be the most beneficial. However, on a retrospective chart review of 184 patients, clonazepam provided at least a mild benefit in 55% of the patients, followed by gabapentin (33%).<sup>3</sup> Other medication groups tried with lesser success were other antiepileptics and benzodiazepines, beta blockers, anti-Parkinsonian medications, antispasmodics, anticholinergics, antidepressants, calcium channel blockers, and carbonic anhydrase inhibitors.

Based on our review of literature, there has only been one reported case of perampanel (2–4 mg/day) used for POT which led to complete resolution of symptoms.<sup>4</sup> Our case replicates the findings with significant symptomatic benefit at a lower dose (1–2 mg/day).

Perampanel is a first-in-class, high potency, orally active, non-competitive AMPA receptor antagonist.<sup>6</sup> Fast glutamatergic neurotransmission is primarily mediated by postsynaptic AMPA and NMDA receptors. By blocking the former, perampanel inhibits glutamate-mediated excitation. As a result, it has been successfully used as an antiepileptic agent for both focal onset and generalized epilepsy. The half-life is long (105 hours) which argues against its use as an as-needed medication, despite our patient's experience.

Gironell and Marin-Lahoz have proposed that an increase in excitatory neurotransmitter activity could be an underlying mechanism for essential tremor (ET).<sup>7</sup> Increased input to the deep nuclei of the cerebellum could induce oscillatory activity and subsequently propagate to thalamic nuclei and the motor cortex. While ET and POT are distinct entities, the role of a central oscillator has been proposed as an

underlying mechanism for both. One possible mechanism for perampanel's effect in POT is interference with glutamatergic neurotransmission to central oscillators; perampanel may therefore be a valuable treatment option in other forms of tremors, such as ET.<sup>8</sup>

It is interesting to note that our patient did not have complete resolution of POT on electromyography nor any change in frequency following treatment with perampanel. This duplicates the findings of Ruiz-Julian et al. and raises the possibility that modulating glutamate only has a dampening effect on the symptoms of POT, perhaps by reducing the amplitude rather than the frequency of tremor, as postulated previously, although this could not be confirmed as amplitude comparisons were not available.<sup>4</sup>

Perampanel has a black box warning based on studies in epilepsy for serious neuropsychiatric side effects, including major depression and suicidal and homicidal thoughts. Our patient and many patients with POT have psychiatric disorders, in some cases as a reaction to the physical limitations of the disease. It is important to counsel patients on this potential concern. It is worth noting that dosing of perampanel for epilepsy is 2–12 mg/day; our case demonstrates efficacy at lower doses, and it is not known whether the risk of side effects is similar at those doses.

In conclusion, perampanel offers a novel strategy to combat POT. Given the now reproducible evidence of significant symptomatic improvement in POT, it would be reasonable to consider an early therapeutic trial of this medication rather than having patients accrue years of morbidity while cycling through other medications, which have thus far yielded suboptimal results. Of course, the possibility of a placebo effect is present, especially as the patient requested the medication. Therefore, blinded, placebo-controlled trials to establish its efficacy, dosing requirements, and side effect profile at those doses are recommended to further our understanding of optimal treatment for these patients.

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