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Perampanel, a new hope for Essential tremor: An open label trial

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Essential tremor (ET) is one of the most common neurological disorders. Drug treatment for ET is often unsatisfactory, with first-line drugs only achieving 50%–60% improvement [1].

Although neurotransmitter systems underlying ET have not as yet been identified, an increase in excitatory transmitters such as glutamate has been hypothesized [2,3]. Perampanel, licensed and marketed as an antiepileptic drug, is a first-in-class selective, noncompetitive AMPA receptor antagonist that functions by blocking glutamate activity in the postsynaptic AMPA receptors [4].

We explored the effects of perampanel on ET in an open-label trial with the aim of determining whether perampanel warrants further investigation as a treatment for ET.

We enrolled 12 consecutive, moderate to severe (Glass Scale II or higher), patients diagnosed of ET according to the Movement Disorders Society consensus statement. Exclusion criteria included hepatic disease, substance abuse and epilepsy. The study protocol was approved by the Hospital Ethics Committee. Informed consent to participate was obtained from all patients.

Eight of the 12 patients were taking anti-tremor medication (mean daily doses in brackets): 5 propranolol (80 mg), 2 gabapentin (1200 mg) and one primidone (300 mg). The anti-tremor drug dose was not changed in the month before or during the trial.

Perampanel was dosed over a period of 8 weeks (56 days) according to the typical regime for myoclonic epilepsy [5]. Dosage was titrated at 2 mg daily at night for the first month, rising to 4 mg daily at night from the second month.

The main outcome measure was the severity of ET as quantified by the validated Tremor Clinical Rating Scale (TCRS) (Fahn et al., 1998) and the validated Glass Scale (Gironell et al., 2010). Scores were compared for day 1 (before drug intake) and day 56 (last dose taken the night before. To evaluate the main outcomes we used the nonparametric asymptotic Wilcoxon-Pratt signed-rank test. Any $p < 0.05$ was considered significant. All statistical tests were performed using R 3.4.3.

The 12 included patients had a mean (± SD) age of 69.5 ± 9.7 years (range, 52–85 years) and a mean history of tremor of 30.3 ± 15.7 years (range, 8–60 years). Most patients were male (83%) and all had a positive family history of tremor (100%). Four of the 12 patients were not taking anti-tremor medication. Dizziness, nausea and instability reported by 4 patients while on perampanel led these to withdraw from the trial. Results for the 8 patients who completed the study are summarized in Table 1.

According to the TCRS, there was a significant improvement in tremor, from a mean baseline (day 1) score of 73.75 ± 7.07 to 38.75 ± 12.69 by day 56, representing a relative reduction of 47% ($p < 0.001$). There were also significant improvements in clinical scores in the first 3 components of the TCRS, as follows: TCRS Parts 1 + 2, 52.13 ± 5.84 at baseline to 26.1 ± 9.46 at 56 days for a relative reduction of 50% ($p < 0.001$); and TCRS Part 3, 21.63 ± 1.85 at baseline to 12.63 ± 4.14 at 56 days for a relative reduction of 42% ($p < 0.001$). Finally, findings for TCRS Part 4 (self-reported global appraisal) were marked improvement (+3) in 3 patients, moderate improvement (+2) in 3 patients and a slight improvement (+1) in 2 patients.

The Glass Scale score also showed a statistically significant improvement, from 2.63 ± 0.52 at baseline to 1.75 ± 0.71 at day 56 ($p = 0.039$). Interestingly, 7 of the 8 patients achieved a 1-point reduction in the Glass Scale after perampanel. Subjective tremor improvement in percentage terms was 61%, with 4 of the 8 patients achieving an improvement of over 70%. All 8 patients who completed the study opted to continue with perampanel treatment.

In this pilot study we found that perampanel improved tremor in all 8 patients who tolerated the medication, with a subjective tremor improvement of over 70% in half of these patients. In terms of tremor improvement, perampanel would appear to be more effective than current first-line anti-tremor drugs for ET, namely, propranolol and primidone [1]. Interestingly, the subjective improvement in tremor in 2 of the 8 patients was above 80%.

Four main mechanisms, mainly involving the thalamus and cerebellum, have been implicated in ET: decreased GABA, increased catecholamine levels, T-type calcium channel dysfunction, and, finally, increased excitatory amino acid (EAA) activity [2,3]. Perampanel functions by blocking glutamate activity in the postsynaptic AMPA receptors (the predominant mediator of excitatory neurotransmission in the brain) [4]. Positive effects have been reported for some patients with myoclonic epilepsy and for one patient with primary orthostatic tremor [5].

In conclusion, in this pilot study we found that perampanel had a markedly positive anti-tremor effect in patients with ET, which would suggest that this drug has potential as a first-line anti-tremor treatment. Blinded, randomized trials are needed, however, to confirm its effectiveness.

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Table 1
Baseline and post-intervention scores for TCRS and Glass Scale.

Day 1				Day 56				
Patient	TCRS 1 + 2	TCRS 3	GLASS	TCRS 1 + 2	TCRS 3	TCRS 4	GLASS	SUBJ
1	45	19	II	15	8	+3	I	80%
2	55	20	II	18	8	+3	I	75%
3	60	24	III	40	15	+1	III	35%
5	55	22	III	18	13	+3	II	90%
6	50	24	III	35	21	+1	II	40%
9	58	22	III	20	12	+2	II	70%
10	44	20	II	30	12	+2	I	45%
12	50	22	III	33	12	+2	II	55%
Mean	52.13	21.63	1.75	26.10*	12.63*	+1.41	1.16**	61.2%

TCRS: Tremor Clinical Rating Scale; GLASS: Glass Scale; SUBJ: subjective improvement %. *p < 0.001; **p < 0.05.

Conflicts of interest

None of the authors of this manuscript have any potential conflict of interest related to the content of the study.

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