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SHORT RESEARCH ARTICLE

Clinical efficacy of low-dose Perampanel correlates with neurophysiological changes in familial adult myoclonus epilepsy 2

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Abstract

Familial adult myoclonus epilepsy (FAME) management relies on antiseizure medications (ASMs), which inadequately address myoclonus and cortical tremor. This study evaluates Perampanel (PER), an AMPA-receptor antagonist, for treating FAME symptoms. Fifteen FAME2 patients participated in an observational prospective study. They received up to 6 mg daily of PER and underwent Unified-Myoclonus-Rating-Scale (UMRS) before and after treatment. Neurophysiological evaluations, including somatosensory evoked potentials (SEPs) and transcranial magnetic stimulation (TMS), assessed PER's impact on cortical glutamatergic excitatory and GABAergic inhibitory circuits. PER treatment significantly reduced UMRS total scores ($p = 0.001$) and action-myoclonus subscores ($p = 0.002$), irrespective of disease duration, age at onset, or testing time ($p > 0.05$). Patients with more severe baseline myoclonus demonstrated significant improvements. Neurophysiological assessments revealed a PER-induced decrease in sensorimotor hyperexcitability, characterized by diminished N33 amplitudes, attenuated glutamatergic facilitation, and enhanced GABAergic inhibition in the motor cortex. In conclusion, low-dose PER is well tolerated and effective in alleviating myoclonus in FAME2 patients, supported by its modulatory effects on glutamatergic and GABAergic neuronal circuits.

Plain Language Summary: This study investigated the effects of low-dose perampanel in individuals with Familial Adult Myoclonus Epilepsy2 (FAME2), a hereditary condition characterized by epilepsy and tremors. Perampanel, an antiepileptic drug, blocks AMPA receptors in the brain, reducing excessive neural activity that causes seizures and abnormal movements. The results showed significant symptom improvement, which correlated with changes in brain activity as measured by neurophysiological tests. This study

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suggests that perampanel helps regulate abnormal brain signals and may help managing FAME2 symptoms.

KEYWORDS

myoclonus, Perampanel, somatosensory evoked potentials, transcranial magnetic stimulation

1 | INTRODUCTION

Familial Adult Myoclonus Epilepsy (FAME) is an autosomal dominant condition presenting with cortical tremor, myoclonus and epilepsy.[1] The association between cortical tremor, myoclonus and epilepsy was first recognized in Japanese families and named BAFME (Benign Adult Familial myoclonic epilepsy). This condition is now increasingly reported worldwide, and although it is described using different acronyms is mostly referred to by the acronyms FAME/BAFME.[1]

The treatment is based on Antiseizure Medications (ASMs)[2] that combine antiseizure and antimyoclonic properties. Valproate, levetiracetam, and benzodiazepines are the first-line treatments that completely control seizures while having a limited effect on myoclonus and cortical tremor.[3,4]

Importantly, sodium-channel-blockers and gabapentin can potentially lead to severe reactions.[5,6] Perampanel (PER) is a selective noncompetitive AMPA-antagonist that demonstrated anti-myoclonic efficacy in different epilepsies.[7,8] Lately, our group demonstrated an imbalance between excessive motor cortex facilitation and reduced cortical inhibition in FAME2 patients. Exaggerated motor facilitation was indexed by reduced motor thresholds and increased short-interval-intracortical-facilitation (SICF), both paradigms partly underpinned by glutamatergic NMDA-type and AMPA-type receptors[9] while impaired cortical inhibition was indexed by the reduction of short-interval-intra-cortical-inhibition (SICI), long-interval-intra-cortical-inhibition (LICI) and short-latency afferent inhibition (SAI) together with a shortening of the cortical silent period, all these protocols underpinned by GABAergic networks.[9] These experimental findings provide a rationale for treatment targeting glutamatergic receptors. Thus, PER could represent an ideal there in FAME.

We conducted a real-world study aiming at evaluating the effectiveness of PER in a cohort of FAME2 patients from Italian descendants by means of clinical and electrophysiological assessment.

Key points

- Low-dose Perampanel (PER) effectively reduces myoclonus and tremor in FAME2 patients.
- PER modulates glutamatergic and GABAergic circuits, as shown by SEPs and TMS.
- Significant reduction in myoclonus scores, independent of disease duration or onset age.
- Low-dose PER is well-tolerated, providing a new therapeutic option for FAME2.
- PER decreases sensorimotor hyperexcitability, enhancing inhibitory control in the motor cortex.

2 | METHODS

This is a prospective, observational, single-center cohort analysis. Fifteen genetically confirmed expanded *STARD7* patients (9 men; 6 women), ranging in age from 15 to 70 years (mean: 49.5 years) were recruited. The molecular characterization was performed according to the methods previously described by Corbett et al.[10,11] Clinical data are presented in Table S1.

To evaluate the severity of myoclonus, we employed prior to and following the addition of PER the Unified-Myoclonus-Rating-Scale (UMRS), a statistically validated clinical instrument.[12] We utilized the UMRS total score as an indicator of overall myoclonus severity, and section 4 sub-score to measure action myoclonus.

COVID-19-related restrictions impacted hospital visit schedules, leading to delays in completing the study visits. Consequently, some participants who began PER treatment per the protocol could not attend in-person visits at the specified intervals of 3 and 6 months. Their treatment continued until these visits were feasible. As a result, the post-PER follow-up analysis was conducted at

two time points: POST-1 (3.6 ± 1.32 months) and POST-2 (9.38 ± 1.03 months).

3 | ELECTROPHYSIOLOGICAL EVALUATION

Electrophysiological assessment was performed in eight patients at baseline and at POST-1. The electrophysiological battery consisted of C-reflex, somatosensory evoked potentials (SEPs) and TMS protocols to assess PER's impact on cortical excitatory and inhibitory circuits.[9,13] Neurophysiological protocols are described in supplementary files.

4 | TREATMENT DESIGN

PER was integrated into the existing treatment regimen. Initially, PER was administered at 2 mg once/day for 1 week and increased to 4 mg/day and maintained until the first follow-up. Subsequent adjustments were made according to clinical assessments. If intolerable side effects occurred, PER administration was ceased. The dosages of concomitant ASMs were kept unchanged throughout the study.

5 | STATISTICAL ANALYSIS

Data were analyzed using SPSS v. 29.0 (SPSS Inc.) and GraphPad Prismv.8.4.2 for Windows. Normal distribution was verified using the Shapiro Wilk test. Repeated-measure ANOVA was applied to assess any difference of UMRS total scores and UMRS subscore (section 4) over time, setting TIME (baseline vs. POST1 vs. POST2) as within-subject factor. If a significant main effect was obtained in the ANOVA model, group differences were examined with post hoc tests (Bonferroni correction for multiple comparisons). Different paired t-tests were applied to assess differences before and after PER for neurophysiological measures (i.e., SEP amplitudes, motor thresholds, grand mean SICI, intracortical facilitation-ICF, SAI, LICI, SICF). Correlations between clinical variables (disease duration, age at onset and age at testing, number of ASMs at baseline, UMRS total score and subscore at baseline) and the clinical improvement at both UMRS scales (delta score indexed by the difference between baseline scores and follow-ups scores) were evaluated using Pearson's correlation coefficient. Effects were considered significant if $P < 0.05$. All data are presented as mean + SD (standard deviation) if not stated otherwise.

6 | RESULTS

6.1 | Clinical evaluation

Of the 15 patients enrolled in the trial, 13 completed POST-1, and eight completed POST-2. None of the patients discontinued PER. At POST-1, all participants were on PER 4 mg/day. At POST-2, three patients maintained 4 mg/day; five increased to 6 mg/day (average dose: 5.25 mg/day).

In all patients, add-on PER was associated with clinical improvement of myoclonus with a reduction of UMRS total score both at POST-1 and at POST-2 (Figure S1 and S2). This clinical improvement was also confirmed by repeated-measure ANOVA with a significant effect of TIME for the total score (F [2, 10]=13.2, $p = 0.001$) and for the action myoclonus subscore (F [2, 10] =11.9, $p = 0.002$). Post-hoc analysis revealed that the UMRS total score and action myoclonus subscore were significantly reduced at POST1 ($p = 0.008$, $p = 0.031$) and POST2 ($p = 0.006$, $p = 0.006$), see Figure 1A,B. The clinical improvement is also highlighted by Video S1 and spiral drawings (Figure 2).

The effect of PER was not related to disease duration as highlighted by the lack of significant correlations between disease duration and delta score of UMRS total and action myoclonus subscore at POST-1 ($r = 0.109$, $p = 0.722$; $r = 0.261$, $p = 0.390$) and POST-2 ($r = -0.424$, $p = 0.295$; $r = 0.308$, $p = 0.458$). Same results were obtained for the correlations between delta scores and age at onset (all $p > 0.07$) and age at testing (all $p > 0.2$). In contrast, we found that patients with a more severe disease at baseline showed the greatest improvement at both follow-ups, indexed by the significant positive correlation between the UMRS total score at baseline and the delta score at POST-1 ($r = 0.952$, $p < 0.001$) and POST-2 ($r = 0.746$, $p = 0.034$), and between action myoclonus subscore and delta score at POST-1 ($r = 0.886$, $p < 0.001$) and POST-2 ($r = 0.882$, $p = 0.004$). Similarly, patients taking more ASMs at baseline had the greatest clinical improvement at follow-ups, although significant only for UMRS total delta score at POST-1 ($r = 0.651$, $p = 0.016$).

None of the patients reported seizures during the study. PER was well tolerated. One patient (NA10) reported aggressiveness and dysphoria at 4 mg/day, which resolved splitting the dose in two daily administrations.

6.2 | Electrophysiological study

At POST-1, the C-reflex disappeared in one patient, remaining stable in the others (Table S1).

Regarding SEP amplitude, we found a significant reduction of the N33 ($p = 0.028$) but not for P25 ($p = 0.124$) and N20 ($p = 0.372$) components (see Figure 1C). No

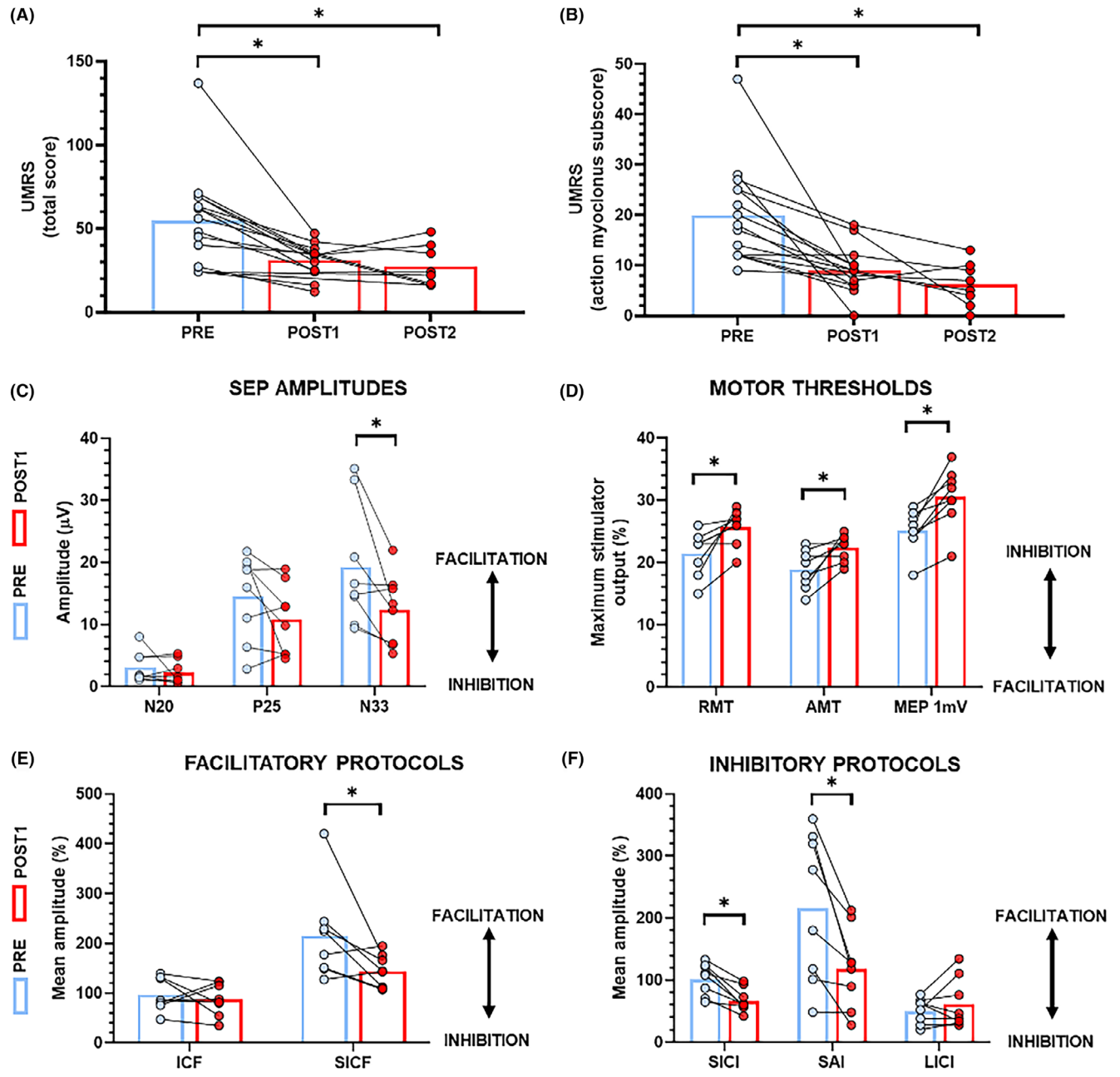

FIGURE 1 The UMRS total score (A) and the action myoclonus subscore (B) were significantly reduced following PER (PER) treatment at both follow-up assessments: POST1 (total score: $p = 0.008$; subscore: $p = 0.031$) and POST2 (total score: $p = 0.006$; subscore: $p = 0.006$). (C) Somatosensory evoked potentials showed a significant reduction in the amplitude of the N33 component ($p = 0.028$), with no significant changes in the P25 ($p = 0.124$) or N20 ($p = 0.372$) components. (D) The administration of PER induced a significant decrease in motor cortex facilitation, as indicated by increased motor thresholds (RMT: $p = 0.013$; AMT: $p = 0.019$; MEP1mV: $p < 0.001$), and (E) the reduction in SICF ($p = 0.048$), along with (F) a significant increase in motor cortex inhibition, as evidenced by reductions in SICI ($p = 0.001$) and SAI ($p = 0.022$) protocols. No significant effects were found for the ICF (E) and LICI (F) paradigms. *Statistical significance set at $p<0.05$.

significant difference was observed for N20, P25 and N33 latency after treatment (all $p > 0.174$) (Table S1).

Interestingly, the administration of PER induced a significant reduction of motor cortex facilitation, indexed by the increase of resting (RMT) and action (AMT) motor thresholds (RMT: $p = 0.013$; AMT: $p = 0.019$; motor evoked potentials-MEP1mV: $p < 0.001$), and the reduction of SICF ($p = 0.048$), along with a significant increase of motor cortex inhibition, evaluated by the reduction of SICI ($p = 0.001$) and SAI ($p = 0.022$) protocols. No significant effects were observed for ICF ($p = 0.463$) and LICI ($p = 0.335$) protocols. See Figure 1D–F.

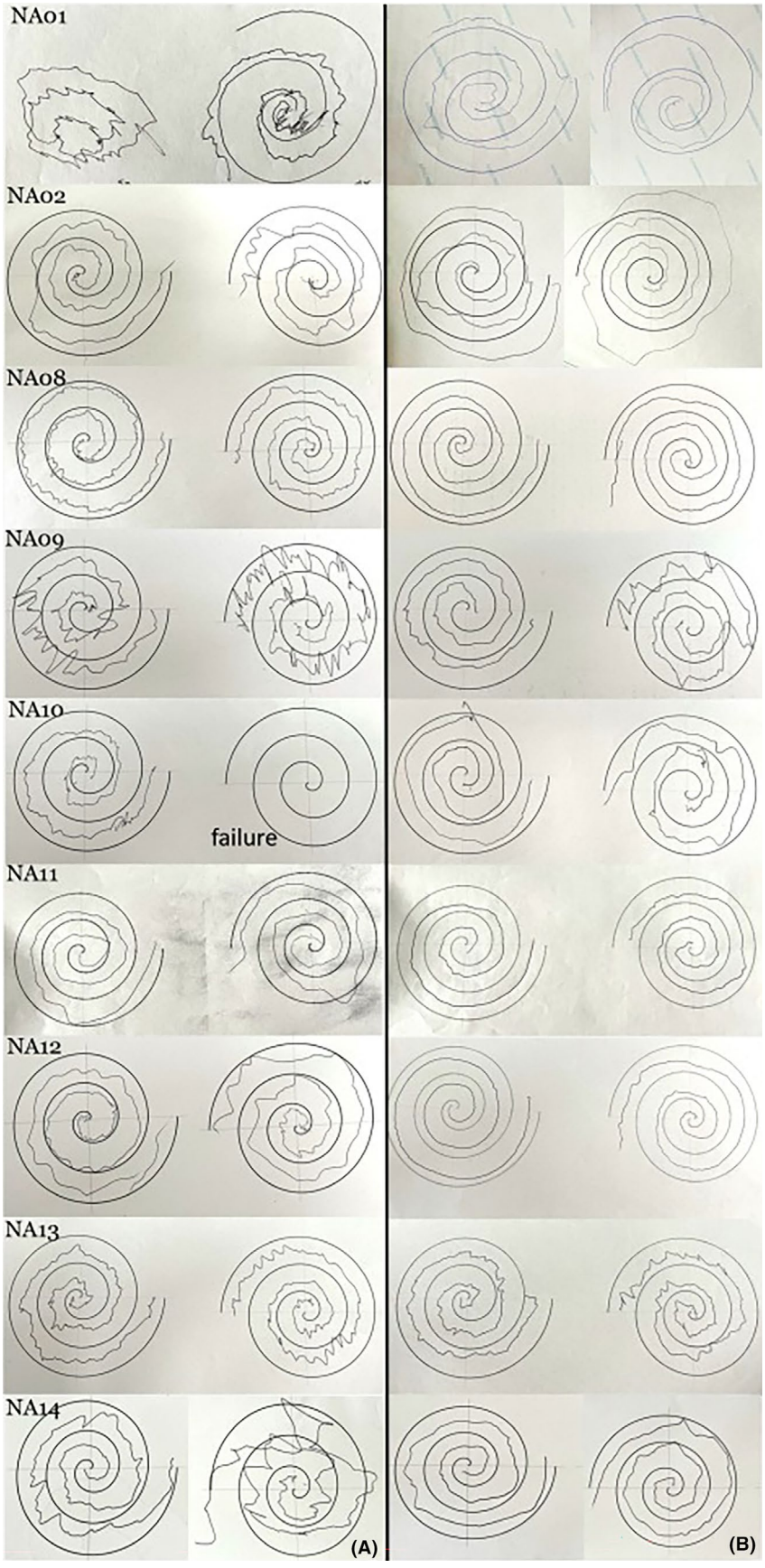

FIGURE 2 (A) Spiral Archimedes drawing executed at baseline and (B) at POST-1. Right-hand drawing is on the right and left-hand drawing is on the left. Note that subject NA10 could not initiate the task for the right hand at baseline.

7 | DISCUSSION

Myoclonus and cortical tremor occur in FAME as chronic symptoms doomed to get worsen over the years.[14] Chronic myoclonus, which impinges on all aspects of the patient's life, can be the main cause of disability.

We report the largest real-world study evaluating the effectiveness of PER in a FAME2 cohort.

PER at the maximum dose of 6 mg/day resulted in a significant improvement of myoclonus over time. Total and action myoclonus UMRS scores were significantly reduced at both follow-ups. Two patients did not show a sustained effect at second follow-up suggesting that individual variability in response to treatment might reflect differences in disease progression or tolerance to the drug. The effect of PER was not related to disease duration, age at onset of cortical tremor and age at evaluation suggesting that PER is effective at any stage of the condition. In addition, those patients with more severe myoclonus at baseline showed the greatest improvement at both follow-ups, reassuring that PER is effective even for the more disabling myoclonus. The clinical improvement was also supported by a reduction of the N33 component of the SEP, thus confirming the findings by Oi et al.[15]

We previously demonstrated that FAME2 patients have significantly larger N33 compared with healthy controls and juvenile myoclonic epilepsy patients, suggesting that PER normalizes this electrophysiological marker of FAME2. While the present study demonstrated that SEP amplitude decreased following PER administration, there was no significant change in SEP latency. This result contrasts with previous studies[16] reporting a prolongation of SEP latency as an effect of PER, consistent with its known action on AMPA receptors. Differences in patient populations, the specific methodology used for SEP measurement, or variability in the dosage and duration of PER treatment may contribute to these divergent findings. We also hypothesized that the enhanced efficacy in these patients could be related to the drug's action on AMPA receptors, which play a key role in modulating excitatory neurotransmission in the brain. In cases of more severe myoclonus, where cortical excitability is likely to be higher, PER's inhibitory effect on these receptors may be more pronounced, leading to greater clinical improvement.

Noteworthy, the PER effect was associated with a significant reduction of motor cortex facilitation, indexed by motor thresholds and the reduction of SICF. These results were accompanied by a significant increase of motor cortex inhibition (reduction of SICI) and sensory motor cortex interaction (reduction of SAI).[9]

We showed that PER positively affects the motor cortex excitability in FAME2 by improving the excitatory/inhibitory imbalance. Interestingly, previous studies in healthy controls[17] and patients with amyotrophic lateral sclerosis[18] showed that PER was able to increase motor thresholds in both cohorts, suggesting its effect on glutamatergic neurotransmission through antagonism of AMPA receptors. This result is also corroborated by the significant reduction in SICF protocol, that is underpinned by glutamatergic[9,19] and GABAergic circuits.[20] In addition to reducing hyperfacilitation, PER also boosted motor cortex inhibition by selectively enhancing GABA-A-mediated protocols (i.e., SICI and SAI) but not GABA-B protocols (i.e., LICI). Preclinical studies in animal models have suggested that PER might increase GABA-Aergic tone through AMPA receptor antagonism and thereby mediate anxiolytic activity in mice.[21]

Likewise, the antiseizure activity of PER was recently demonstrated in a patient with myoclonic epilepsy related to a mutation in the alpha1 subunit of the GABA-A receptor (GABRA1), through increasing inhibitory GABA inputs into neurons and thus reducing the excitability.[22] The results of the electrophysiological study coincide with the mean clinical improvement in our patients as evaluated by the UMRS. In most patients, however, giant SEPs did not necessarily become smaller even when the drug was associated with significant improvement of myoclonus.

This suggests that PER's antimyoclonic effect is not necessarily mediated through the mechanisms by which SEPs are enhanced. On the contrary, PER may exert its effect by reducing the exaggerated cortical facilitation and boosting cortical inhibition through NMDA-type and or AMPA-type glutamate transmission in FAME patients.[17]

PER was well-tolerated across our cohort. We acknowledge the lack of follow up at 6 months for certain individuals. Beyond the COVID-19 restrictions which rendered difficult the hospital visits this may be partly due to unreported side effects. PER blood concentration were not evaluated in this study. Although PER concentration has a linear regression relationship with PER dose, the lack of correlation data between PER blood concentrations and clinical outcomes might be a limitation of the present study. Furthermore, given the uncontrolled nature and short duration of this trial, these findings on PER's efficacy are preliminary and should be interpreted with caution. The limited follow-up period also precludes any assessment of the treatment's long-term stability. Future studies should address these aspects to provide a more comprehensive understanding of the drug's long-term efficacy and pharmacokinetics.

In addition, while the UMRS is a valuable tool for assessing action myoclonus, it does not specifically quantify cortical tremor. This limitation highlights the need for more precise measurement tools to evaluate the specific impact of PER on cortical tremor, which may be underrepresented in the current analysis. Yet, the enduring impact of this treatment warrants further exploration in more extensive, long-term controlled trials.

AUTHOR CONTRIBUTIONS

AC and RD: design of the study, execution, analysis of the data, writing of the manuscript, editing of final version of the manuscript. CC, MR, GS, VVI, LuB: acquisition of the clinical and neurophysiological data; images and video creation. FB and LV: genetic analysis and editing of final version of the manuscript. LB: editing of final version of the manuscript. PS: design of the study, writing of the manuscript, editing of final version of the manuscript.

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All the other authors report no conflict of interest relevant to this work.

CONFLICT OF INTEREST STATEMENT

Antonietta Coppola has received speaker's honoraria from Eisai, UCB and Jazz Pharmaceuticals, Angelini, and has served as a scientific consultant for advisory boards for Takeda, UCB, and Jazz Pharmaceuticals. Pasquale Striano received speaker's honoraria from UCB, Angelini, and Jazz Pharmaceuticals, and has served as a scientific consultant for advisory boards for Biomarin, Takeda, Proveca, UCB, and Jazz Pharmaceuticals. All the other authors report no disclosures relevant to the manuscript.

DATA AVAILABILITY STATEMENT

Anonymized data not published within this article will be made available by request from any qualified investigator.

ETHICS STATEMENT

This research was approved by local review boards or ethics committees (number 140/2023). Written informed consent for research use of clinical and genetic data was obtained from patients or their parents in the case of minors. We confirm that we have read the journal's position on issue involved in ethical publication and affirm that this work is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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