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BRIEF COMMUNICATION

Long-term effectiveness of add-on perampanel in patients with Lennox–Gastaut syndrome: A multicenter retrospective study

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Abstract

This retrospective study assessed long-term effectiveness of add-on perampanel (PER) in patients with Lennox–Gastaut syndrome (LGS). Outcomes included time to PER failure and time to seizure relapse in responders. PER failure was defined as either discontinuation of PER or initiation of another treatment. Seizure relapse in responders was defined as occurrence of a seizure in seizure-free patients and increase of at least 50% in average monthly seizure frequency for those who were responders. Eighty-seven patients were included. Treatment failure occurred in 52 (59.8%) subjects at a median time of 12 months. Treatment failure was due to lack of efficacy in 27 (52.0%) patients, lack of tolerability in 14 (27.0%), and both reasons in 11 (21.0%). A slower titration was associated with a lower risk of PER failure compared to faster titration schedules, and the occurrence of adverse events increased the risk of treatment failure. Thirty-six patients (41.4%) were responders during a median follow-up of 11 months. Seizure relapse occurred in 13 of 36 (36.1%) patients after a median time of 21 months. The overall rate of seizure responders was 23 of 87 (26.4%) at the end of follow-up. This study provides real-world evidence on the effectiveness of PER as adjunctive treatment in LGS patients.

KEYWORDS

developmental and epileptic encephalopathy, Lennox–Gastaut syndrome, LGS, perampanel, real-world evidence

1 | INTRODUCTION

Lennox–Gastaut syndrome (LGS) is a developmental and epileptic encephalopathy (DEE) that usually responds poorly to pharmacological and nonpharmacological therapies. The onset is between 18 months and 8 years of age, and LGS persists into adulthood in nearly all cases. The etiology of LGS can be highly variable, including structural, genetic, and metabolic causes.[1,2]

To date, evidence on treatment is limited, and only a few randomized controlled trials on antiseizure medications (ASMs) in this population have been undertaken.[3] Despite the increasing number of approved drugs and new, repurposed compounds, there are still unmet needs for the management of this epileptic condition in clinical practice. Valproate remains a major therapeutic option in LGS patients, although lamotrigine, rufinamide, topiramate, cannabidiol, and clobazam are popular therapeutic options in Italy, allowing for a tailor-made antiseizure therapy.[4]

Perampanel (PER) is a first-in-class, selective, noncompetitive α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate receptor antagonist and acts as a potentially broad-spectrum ASM.[5–7]

This study aimed to assess the long-term effectiveness of PER as an adjunctive treatment of seizures in a cohort of children and adults with LGS.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

A retrospective observational cohort study was carried out at 19 Italian epilepsy centers All LGS patients who started treatment with PER from December 2019 to December 2022 were enrolled. LGS diagnosis was based on mandatory criteria: (1) multiple, drug-resistant seizure types with onset before 18 years, including at least tonic seizures; (2) cognitive and behavioral impairment; and (3) electroencephalographic abnormalities including at least diffuse slow spike-and-wave complexes and diffuse paroxysmal fast activity.[2] Patients with insufficient or incomplete information, subjects with other DEE or drug-resistant epilepsy syndromes, and cases with other concomitant add-on or treatment changes simultaneously with PER initiation were excluded.

2.2 | Study setup and data collection

Medical records of all patients were evaluated by the referring clinician to collect demographic and clinical data, including current age, gender, age at seizure onset, duration of epilepsy, etiology, structural abnormalities on

brain magnetic resonance imaging, cognitive and behavioral comorbidities, seizure types and frequency, drop attacks, previous and concomitant treatments, PER titration schedule, and highest total daily dose.

Seizure frequency at baseline was defined as the average monthly number of seizures during the previous 3 months before starting PER. Data on seizure frequency were obtained from the seizure diary used by parents/caregivers of all patients. Seizure response was defined as a ≥50% reduction in baseline frequency of all countable seizure types and drop attacks; seizure worsening was defined as a >25% increase in baseline frequency of all countable seizure types and drop attacks.[8,9]

The primary endpoint was the time to treatment failure in the whole study cohort. The secondary endpoint was the time to seizure relapse among responders. Treatment failure was defined as either discontinuation of PER, or initiation of another treatment, including the prescription of a new ASM, starting of the ketogenic diet, or implantation of vagal nerve stimulation. Seizure relapse was defined as the occurrence of a seizure or a seizure cluster (for patients who reached seizure freedom for at least 1 month) or an increase of at least 50% in the average monthly seizure frequency of all countable seizure types and drop attacks after a period of ≥50% reduction for at least 1 month (for those who were seizure responders but did not reach seizure freedom). The occurrence of adverse events (AEs) and the reduction in dosage and/or discontinuation of other treatments after PER introduction were also considered.

In patients who have withdrawn from therapy, the date of PER discontinuation was defined as the day of starting a weaning schedule. For all the others, observations were censored on December 2, 2022, with the last observation carried out at least 3 months before this date.

The study has been conducted according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. Each dataset was approved by the local independent ethics committee, and letters were sent to these ethics committees to inform them of the study. The need for informed consent was waived due to the retrospective nature of the study.

2.3 | Statistical analysis

Values are presented as median (interquartile range [IQR]) for continuous variables and number (%) of subjects for categorical variables. The study outcomes were assessed by Kaplan–Meier survival analyses. Simple and multivariable Cox proportional hazard models were performed to identify baseline characteristics of patients associated with the study outcomes. Preselected independent variables entered into multivariable models included current age, gender, duration of epilepsy, etiology, baseline monthly seizure frequency, previous and concomitant treatments, titration schedule, and the occurrence of AEs.

Exploratory analyses were performed to evaluate the impact of concomitant use of sodium channel blockers (SCBs; carbamazepine, phenytoin, lamotrigine, oxcarbazepine, eslicarbazepine acetate, lacosamide, rufinamide), γ-aminobutyric acidergic (GABAergic) drugs (benzodiazepine, phenobarbital, vigabatrin, stiripentol), and strong enzyme-inducing ASMs (EiASMs; carbamazepine, phenytoin, phenobarbital, primidone) on the primary outcome.

Logistic regression analysis was performed to assess the independent predictors of the occurrence of behavioral disturbances. Results were considered significant for p values ≤ .05 (two-sided). Data were analyzed using Stata/IC version 15 (StataCorp).

3 | RESULTS

During the study period, 87 patients with LGS who received PER as adjunctive treatment were included. Demographics and clinical data are summarized in Table 1. The median age was 22 (IQR = 15–34) years, and 52 (60%) were male. All patients had multiple seizure types, and 67 (77%) had drop attacks. Baseline monthly seizure frequency was daily in 57 (65.5%), weekly in 24 (27.6%), and monthly/sporadic in six (6.9%) patients. The median number of treatments tried before PER was eight (IQR = 5–12), and the median number of concomitant treatments was 3 (IQR = 2–3). The titration of PER was ≤2 mg every week in 20 (23.0%) patients, 2 mg every 2 weeks in 52 (59.7%), and 2 mg every 3–4 weeks in 15 (17.3%) patients. The maximum dose given was 6 (IQR = 4–8) mg/day.

Treatment failure occurred in 52 (59.8%) patients over 36 months. The median time to PER failure was 12 months. The probability of not failing PER treatment was 67.8% (95% confidence interval [CI] = 56.9–76.5) at 6 months, 49.9% (95% CI = 38.8–59.9) at 12 months, 45.8% (95% CI = 34.8–56.1) at 18 months, 41.3% (95% CI = 30.4–51.8) at 24 months, and 35.8% (95% CI = 24.9–46.7) at 36 months (Figure S1). The reasons for treatment failure were lack of efficacy in 27 (52.0%) patients, lack of tolerability in 14 (27.0%), and both reasons in 11 (21.0%). The median times to PER failure because of lack of efficacy and poor tolerability were 6 (IQR = 5–10) and 5 (IQR = 3–12; p = .841) months, respectively.

Titration schedule (hazard ratio [HR] = .5, 95% CI = .2–.9, p = .049 for 2 mg every 2 weeks; HR = .1, 95% CI = .1–.3, p < .0001 for 2 mg every 3–4 weeks) and the occurrence of AEs (HR = 1.9, 95% CI = 1.0–3.8, p = .042) were independent predictors of treatment failure. A slower titration schedule was associated with a lower risk of treatment

TABLE 1 Demographics and clinical characteristics of the study cohort.

Characteristics	Patients, *N* = 87
Male gender	52 (60%)
Current age, years	22 [15–34]
Patients in pediatric age, <18 years old	35 (40%)
Age at seizure onset, months	18 [6 months–4 years]
Duration of epilepsy prior to PER, years	17 [12–31]
Etiology	
Structural	23 (26.5%)
Genetic	19 (21.8%)
Infectious	2 (2.3%)
Unknown	43 (49.4%)
Structural abnormalities on brain MRI	34 (39.0%)
Comorbidities	
Moderate to severe ID/behavioral disturbances	75 (86.2%)
Mild ID/borderline functioning	12 (13.8%)
Seizure frequency	
Daily	57 (65.5%)
Weekly	24 (27.6%)
Monthly/sporadic	6 (5.7%)
Number of previous treatments	8 [5–12]
Number of concomitant treatments	3 [2–3]
Titration of perampanel	
2 mg every week	20 (23.0%)
2 mg every 2 weeks	52 (59.7%)
2 mg every 3–4 weeks	15 (17.3%)
Maximum perampanel dose, mg/day	6 [4–8]

Note: Data are expressed as median [interquartile range] for continuous variables and *n* (%) for categorical variables.

Abbreviations: ID, intellectual disability; MRI, magnetic resonance imaging; PER, perampanel.

failure, whereas the occurrence of AEs was associated with a higher risk (Table S1). Among 35 patients who did not fail treatment, nine were not seizure responders over a median treatment duration of 11 months (IQR = 6–26). In addition, AEs occurred in 9 of 35 patients who did not fail PER.

Thirty-six of the 87 (41.4%) patients of the whole study cohort (including patients who either remained on or discontinued PER) were responders for all countable seizure types, and 22 of 36 (61.1%) experienced a ≥50% reduction in the frequency of drop attacks during a median follow-up of 11 months (IQR = 6–26). Seizure relapse occurred in 13 of 36 (36.1%) patients over 36 months. The median time to seizure relapse was 21 (IQR = 7–29) months. The probability of remaining responders was 88.9% (95% CI = 73.05–95.68) at 3 months, 77.8% (95% CI = 60.44–88.21) at 6 months, 66.1% (95% CI = 47.89–79.14) at 12, 18, and 24 months, and 62.15% (95% CI = 43.52–76.19) at 36 months (Figure S2). At the end of the follow-up, 23 of 87 (26.4%) patients of the whole study cohort were responders and did not have seizure relapse. The occurrence of AEs was an independent predictor of time to seizure relapse (HR = 10.8, 95% CI = 2.0–58.5, $p = .006$; Table S2).

Overall, AEs were reported by 39 (44.8%) patients and included behavioral disturbances in 19, somnolence in 11, fatigue in six, dizziness in six, gait imbalance in three, and anorexia in one patient. A shorter duration of epilepsy (odds ratio [OR] = .8, 95% CI = .6–.9, $p = .025$), a high number of previous ASMs (OR = 1.5, 95% CI = 1.2–2.0, $p = .001$), and a faster PER titration (OR = .1, 95% CI = .02–.6, $p = .014$ for 2 mg every 2 weeks; OR = .04, 95% CI = .003–.4, $p = .010$ for 2 mg every 3–4 weeks) were associated with the occurrence of behavioral disturbances (Table S3).

None of the patients experienced seizure worsening during PER treatment.

Among patients who experienced AEs, 30 of 39 (76.9.%) discontinued PER treatment; in the remaining cases, PER dose was reduced with the resolution of AEs, particularly somnolence, fatigue, dizziness, and gait imbalance.

The most commonly concomitant ASMs were valproate (50/87, 57.4%), clobazam (23/87, 26.4%), lamotrigine (21/87, 24.1%), and rufinamide (21/87, 24.1%; Table S4). SCBs, GABAergic drugs, and EiASMs were taken by 52 of 87 (59.7%), 45 of 87 (51.7%), and 14 of 87 (16%), respectively. The concomitant use of SCBs, GABAergic drugs, and EiASMs was not associated with the time to PER failure (Tables S5–S7).

The reduction in dosage and/or discontinuation of one or more concomitant treatments after the initiation of PER occurred in 32 (36.8%) patients.

4 | DISCUSSION

This study provides real-world evidence on the effectiveness of PER as an adjunctive treatment for seizures associated with LGS. At the end of the study period, 40% of the included subjects were continuing PER treatment. Approximately 41% of the patients were responders and experienced a significant reduction in all countable seizure types, and more than half of them also experienced a significant reduction in drop attacks. Approximately two thirds of the patients who were responders maintained responder status in the long term.

Add-on PER allowed the reduction in dosage and/or discontinuation of other treatments in approximately one

third of the patients. These aspects are relevant for rational polytherapy in LGS, in which seizure freedom might be unachievable and side effects often affect the quality of life more than seizures themselves.[1]

In approximately three quarters of patients who experienced AEs, PER was withdrawn, whereas AEs were no longer detectable following downtitration in the remaining cases. The inverse association between the occurrence of AEs and the time to seizure relapse among responders may be due to the reactive reduction in PER dosage to improve treatment tolerability.

Behavioral and psychiatric side effects are frequently reported with PER treatment.[10,11] In this cohort, approximately 20% of the patients experienced irritability and aggression, particularly in association with rapid titration, duration of epilepsy, and numerous previous treatments. This percentage is consistent with that already reported by other real-world studies assessing people with epilepsy and epileptic encephalopathies.[12–15] Psychiatric AEs were experienced more often by patients with previous psychiatric comorbidity and intellectual disability.[15]

PER has recently been investigated in a phase 3, multicenter, double-blind, randomized controlled trial as adjunctive therapy in patients with inadequately controlled seizures associated with LGS (NCT02834793). The study was terminated early by the sponsor due to a recruitment challenge, further impacted by COVID-19 pandemic. The participants enrolled numbered 70, and variability in treatment response was observed.[16]

The real-world evidence coming from observational studies can complement data from clinical trials and has value for understanding outcomes in routine clinical practice.

Only a few reports about the use of PER in patients with LGS have been published so far, and they included a limited number of LGS subjects in mixed cohorts of patients with drug-resistant epilepsies.[12–14,17–21] Two real-world studies specifically investigated PER use in LGS patients, providing weak evidence that it may be efficacious and generally well tolerated.[12,13]

This study provides the largest cohort exploring the long-term effectiveness of PER in LGS patients. The main strengths include the recruitment at multiple sites and the real-world design, which reflects the everyday clinical approach and can increase the generalizability of the results. Furthermore, treatment failure, defined as either discontinuation of PER, or initiation of another treatment, represents a novel study outcome, which can provide a more reliable and informative measure of treatment effectiveness. Different shortcomings also need to be acknowledged. The main limits include the open-label and retrospective design, which may have introduced potential sources of bias. The lack of a control group did not allow any definitive conclusions about the comparative efficacy and tolerability of PER with other therapeutic options. Furthermore, no standardized questionnaires have been used to assess AEs, the impact of the drug on behavior and cognitive skills, and the clinical global changes according to the caregiver's impression.

5 | CONCLUSIONS

In this real-world study, PER appears to be effective in patients with LGS and generally well tolerated, with a possible partial loss of efficacy in a few patients over time. Despite these encouraging results suggesting how PER may represent a valuable therapeutic option for patients with LGS with inadequately controlled seizures, we cannot draw firm conclusions on its use as a first-line treatment. The results of this study are consistent with those on other licensed adjunctive treatments, including rufinamide, topiramate, felbamate, cannabidiol, and most recently, fenfluramine.[3,22,23] More studies, including head-to-head clinical trials and PROBE (prospective randomized open, blinded end-point) studies, may be worthwhile to provide more robust evidence about the use of PER in LGS, compare the currently available therapies and their long-term effects, investigate the efficacy of treatments according to age and underlying etiologies, and provide evidence for a more tailored treatment. Additional information about the underlying pathophysiological mechanisms of LGS may contribute further to a more personalized approach and, hopefully, the development of disease-modifying treatments.

AUTHOR CONTRIBUTIONS

Sara Matricardi and Simona Lattanzi contributed to the conceptualization and design of the study, data acquisition and analysis, and drafting of the manuscript. All authors contributed to the data acquisition, review, and editing.

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None.

CONFLICT OF INTEREST STATEMENT

S.M. has received speaker's or consultancy fees from Eisai and has served on advisory boards for Zogenix–UCB Pharma outside the submitted work. A.D. has participated in pharmaceutical industry-sponsored clinical trials for UCB Pharma, received speaker honoraria from Eisai, UCB, Angelini Pharma, and Neuraxpharm, and has served on advisory boards for Angelini Pharma outside the submitted work. G.D.G. has served on advisory boards and in pharmaceutical industry-sponsored symposia for Eisai, UCB Pharma, Bial, Lusofarmaco,

LivaNova, Arvelle, and Angelini outside the submitted work. P.S. has received speaker's or consultancy fees from Angelini Pharma, Jazz Pharmaceuticals, Neuraxpharm, Kolfarma, and UCB Pharma and has served on advisory boards for Angelini Pharma, Angelini Pharma, Jazz Pharmaceuticals, and UCB Pharma outside the submitted work. A.Ve. has received speaker's or consultancy fees from Angelini Pharma, Eisai, GW Pharmaceuticals, Kolfarma, UCB Pharma, Proveca, and Neuraxpharm outside the submitted work. S.L. has received consultancy fees from Angelini Pharma, Eisai, GW Pharmaceuticals, and UCB Pharma and has served on advisory boards for Angelini Pharma, Arvelle Therapeutics, BIAL, Eisai, and GW Pharmaceuticals outside the submitted work. None of the other authors has any conflict of interest to disclose.

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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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