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Perampanel in post-stroke epilepsy: Clinical practice data from the PERampanel as Only Concomitant antiseizure medication (PEROC) study

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Abbreviations: AE, adverse event; ASM, anti-seizure medication; BRV, brivaracetam; Ei, enzyme-inducing; ESL, eslicarbazepine; LEV, levetiracetam; LCM, lacosamide; PER, perampanel; PEROC, PERampanel as Only Concomitant antiseizure medication; PSE, post-stroke epilepsy.

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ABSTRACT

Introduction: Post-stroke epilepsy (PSE) is one of the most common causes of acquired epilepsy. Nevertheless, there is limited evidence regarding the clinical profile of antiseizure medications (ASMs) in PSE. This study aims to evaluate the 12-month effectiveness and tolerability of perampanel (PER) used as only add-on treatment in patients with PSE in a real-world setting.

Methods: We performed a subgroup analysis of PSE patients included in a previous retrospective, longitudinal, multicentre observational study on adults. Treatment discontinuation, seizure frequency and adverse events were collected at 3, 6 and 12 months. Sub-analyses by early (≤1 previous ASM) or late PER add-on were also conducted.

Results: Our analysis included 56 individuals with PSE, characterized by varying initial treatment modalities and timeframes relative to disease onset. We found notable retention rates (92.8%, 83.7%, and 69% at 3, 6, and 12 months), with treatment withdrawal mainly due to poor tolerability. One year after PER introduction, seizure frequency significantly reduced, with a responder rate (≥50% reduction) of 83.9% and a seizure-free rate of 51.6%. Adverse events occurred in 25 (46.3%) patients, mainly dizziness, irritability, and behavioural disorders. No major statistical differences were found between early (30 patients, 53.6%) and late add-on groups, except for a higher 6-month responder rate in the early add-on group.

Conclusion: Adjunctive PER was effective and well-tolerated in patients with PSE in a real-world setting. Perampanel demonstrated good efficacy and safety as both early and late add-on treatment, making it a compelling option for this unique patient population.

1. Introduction

Stroke represents a frequent cause of new onset epilepsy in adults and the elderly [1,2]. Post-stroke epilepsy (PSE) is defined as one or more unprovoked seizures occurring >7 days after a stroke [2,3], affecting about 4–6% of stroke survivors [2,4]. It accounts for approximately 11% of all epilepsy cases and 55% of newly diagnosed seizures in older individuals [1,5,6], and it is associated with a significantly increased risk of mortality, disability rates, dementia and poor functional outcome [7]. While PSE generally has a good prognosis and responds well to anti-seizure medications (ASMs), approximately 20% of PSE patients are pharmaco-resistant [8,9]. Currently, evidence-based guidelines specifically addressing the management and choice of ASMs for PSE are lacking, primarily due to limited evidence on the effectiveness and safety profile of ASMs in this particular population [6,10,11].

Perampanel (PER) is a third-generation anti-seizure medication (ASM) that acts as a highly selective, non-competitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [12]. To date, it is approved as adjunctive therapy for focal onset seizures with or without evolution to bilateral tonic–clonic seizures and for primary generalized tonic–clonic seizures, and as monotherapy for focal onset seizures with or without bilateral tonic–clonic evolution in the United States and Japan [13]. In recent years, numerous real-world clinical practice studies highlighted the favourable safety and efficacy of adjunctive PER for patients with refractory epilepsy across a wide range of epileptic syndromes [14–17], aetiologies [18,19] and age groups [20–22]. However, to the best of our knowledge, no study focusing on PER use in PSE is available. Given the well-known role of glutamate-mediated excitotoxicity in the pathophysiology of both epilepsy and stroke [13,23], the adoption of a glutamate receptor-blocking agent such as PER may represent a suitable therapeutic strategy.

The PEROC (PERampanel as Only Concomitant antiseizure medication) study investigated the clinical profile of PER in patients with epilepsy aged >12 years on monotherapy receiving adjunctive PER in a real-world context [24]. This study demonstrated the good efficacy and safety of PER for focal and generalized epilepsy when used as the only concomitant adjunctive ASM [24]. Additionally, PER showed effectiveness both as early and late adjunctive treatment. [24–28]. Since the PEROC study included a subset of patients with PSE, we performed a sub-analysis to provide new insight into the use of PER in this specific subgroup of patients.

2. Methods

2.1. Participants

The PEROC study was a retrospective, longitudinal, multicenter observational study conducted across 52 epilepsy or neurology centers in Italy, focusing on individuals aged ≥12 years with either focal or generalized epilepsy [24]. Participants in the study were patients who

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were receiving treatment with PER as the only ASM in addition to a single concurrent ASM (as per standard clinical practice), who had experienced at least one seizure within the year prior to initiating the PER supplementary treatment, who maintained stable treatment during the preceding 90 days, and who had a follow-up period of at least 3 months at the time of database closure. Patients enrolled in clinical trials during the period of retrospective observation as well as those with inaccurate or unreliable clinical records, were excluded from the study [24].

For this sub-analysis, we specifically selected patients diagnosed with PSE, defined as the occurrence of one or more unprovoked seizures at least one week after an ischemic or haemorrhagic event [3].

2.2. Procedure

Data on demographics and clinical history, including age at epilepsy onset, type of epilepsy, aetiology, monthly seizure frequency during the previous 3 months, previous/concomitant ASM treatment and psychiatric history, were collected at baseline. Three, 6 and 12-month assessments and final evaluation (in cases of dropout) data were collected retrospectively based on medical records and included: a) date of assessment; b) current PER dose, titration schedule and dose of concomitant ASM; c) number of seizures since the last evaluation; d) side effects (open/general questions, not solicited for specific AEs, recorded verbatim and coded using MedDRA). To ensure data consistency, all visits performed between 1.5 and 4.5 months from baseline were referred as visit 1; all visits performed between 4.5 and 9 months from baseline were referred to as visit 2; all visits performed between 9 months and 15 months from baseline were referred to as visit 3.

Based on the number of prior ASMs, patients were stratified in two groups: 1) "early (primary or first two) add-on", indicating a history of 0–1 previous adjunctive ASM; 2) "late (secondary or following) add-on", indicating a history of ≥2 previous ASMs). Additionally, concomitant ASMs were grouped by mechanism of action into four groups: a) sodium channel blockers, b) GABAergic, c) SV2A ligands, and d) others. They were further distinguished as enzyme-inducing (Ei) ASMs (Ei-ASMs, such as carbamazepine, oxcarbazepine, phenobarbital and phenytoin) and non-EiASMs (any other ASM); patients were included in the EI-ASM group if taking at least one Ei-ASM.

2.3. Outcomes

The efficacy of PER was assessed by evaluating retention, responder rate (defined as a ≥ 50% reduction in baseline seizure frequency, normalized per 28 days) and seizure freedom (defined as the absence of seizures since the previous visit). Effectiveness outcomes were evaluated after 3, 6 and 12 months of PER treatment and at the final follow-up (i.e. the last available observation - last observation carried forward -, independently of the time point when it occurred, defined as the 'last visit'). Safety and tolerability outcomes included the rate of treatment discontinuation due to AEs and the incidence of PER-related AEs during the treatment.

Outcome measures were also evaluated within subgroups of patients defined by the number of prior ASMs ("early" vs "late add-on") and concomitant ASM, grouped by mechanism of action.

2.4. Standard protocol approval

The study received approval from the local Ethical Committee (Comitato Etico Sezione Area Centro Regione Calabria, Prot. N. 126, dated April 16, 2020) and was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from each patient or their parents or a legal representative.

2.5. Statistical analysis

Descriptive data were presented by counts and percentages for categorical variables, and as mean ± SD or median and interquartile range for continuous variables, as appropriate. Retention rates were calculated, at different time points, as the proportion of patients still receiving PER treatment. The Retention Population included all subjects whose PER status was known at the time point of the follow-up visit (including those continuing PER treatment and those who stopped PER before the follow-up visit). The Effectiveness Population included all patients who had at least one effectiveness measurement available. The Tolerability Population included all subjects for whom data on AEs were available. Data were analysed by Chi-square or *t*-test, as appropriate. Kaplan–Meier curves were constructed for time-dependent analyses. To obtain estimates adjusted for patient characteristics, exploratory multivariate analyses were also conducted. Retention was explored through Kaplan-Meier curves inspection stratified by early and late add-on treatment, and by proportional hazard regression. Effectiveness was assessed by classifying patients as "seizure-free," "responder," "non-responder," and "worsened," and using ordered logistic regression analysis. Lastly, a binomial logistic regression was used to investigate the odds of adverse events. In all three regression models, all potential predictors of the outcome previously identified in the literature were included. Results were considered significant for p values <0.05 (two sided). Data analysis was performed using SPSS 29.0.2.0 (IBM StataCorp LP, TX, USA) and STATA.17 (www.stata.com).

3. Results

3.1. Whole sample

Among the 503 participants in the PEROC study, 56 had PSE and received at least one visit during the observation period. The sample comprised 30 (53.6%) females. The median age was 49 years (IQR: 18.5–68.0; range: 12.1–90.3 years). Demographic and clinical details are summarized in Table 1. The median duration of epilepsy was 6 years (IQR: 3–14). Thirty (53.6%) patients were previously treated with 0 or 1 add-on ASMs ("early add-on" group), with 10 (17.8%) receiving PER as their first add-on. Levetiracetam (LEV, 32.1%), lacosamide (LCM, 14.3%) and oxcarbazepine (14.3%) were the most frequent concomitant drugs.

Visit 1 was performed by 39 subjects, visit 2 by 34 subjects, and visit 3 by 31 subjects. At the last visit, the median daily PER dose was 4 mg/day (IQR 4–6; range: 2–10). The median daily dose of PER was 4 mg (IQR: 4–6) at 3 months and 6 months, and 5 mg (IQR: 4–6) at 12 months. Retention rate was 92.8% (52 out of 56 patients evaluable for retention) at the 3-month follow-up, 83.7% (41/49) at the 6-month follow-up and 69% (29/42) at the 12-month follow-up. Fig. 1 shows the Kaplan–Meier curve of the overall retention time (timeline cut to 12 months). Thirteen out of 56 (23.2%) patients withdrew PER due to poor tolerability (9 patients, 16.1%), lack of efficacy (2 patients, 3.6%) or both (2 patients, 3.6%).

The median seizure number normalized for 28 days significantly decreased from 1.9 (IQR: 0.9–3.7; range: 0.3–280) at baseline to 0 (IQR 0–0.6; range 0–171.4) at last visit (−100%; $p < 0.001$). Seizure frequency also significantly diminished compared to visit 1 (median seizure number: 0; IQR 0–1.9; range: 0–36.2; −100%), visit 2 (median seizure number: 0; IQR 0–0.6; range 0–171.4; −100%), and visit 3 (median seizure number: 0; IQR 0–0.2; range 0–141.3; −100%; all $p < 0.001$; Fig. 2a).

Responder rates were 66.7% (26/39 patients), 84.8% (29/34) and 83.9% (26/31) at visit 1, 2 and 3, with a percentage of seizure-free subjects of 51.3% (20/39), 57.6% (20/34) and 51.6% (16/31) at each time-point (Fig. 3a). At the last available visit, the responder rate was 78.6% (44/56), with 53.6% (30/56) of patients being seizure-free.

Both responder and seizure-free rates did not statistically differ

Table 1
Demographic and clinical data of the study population at the baseline.

	Whole cohort ($n = 56$)		Early add-on ($n = 30$)		Late add-on ($n = 26$)		
Characteristics	N	%	N	%	N	%	*p*
Sex (female/male)	30/26	53.6/46.4	14/16	46.7/53.3	16/10	61.5/38.5	0.295
Age: median (IQR) years	49 (18.5–68)	–	59.5 (35–72.2)	–	30.6 (16.5–56.2)	–	0.730
Disease duration: median (IQR) years	6 (3–14)	–	4 (1–7.3)	–	10 (4.8–19.3)	–	0.003*
Age at epilepsy onset: median (IQR) years	42.5 (9.7–62.8)	–	55 (18.2–69)	–	12.7 (1.4–51.1)	–	0.006*
Patients aged ≤18 years at epilepsy onset (n.)	21	37.5	7	23.3	14	53.8	
Type of seizures							0.088
Focal onset	43	76.8	22	73.3	21	80.8	
Focal to bilateral tonic-clonic	4	7.1	4	13.3	0	0	
Both focal onset and focal to bilateral tonic-clonic	9	16.1	4	13.3	5	19.2	
Number of previous ASMs: mean (SD)	1.9 (1.7)	–	0.7 (0.5)	–	3.3 (1.5)	–	<0.001*
Number of previous ASMs							
0	10	17.9	10	33.3	–	–	<0.001*
1	20	35.6	20	66.7	–	–	
2	12	21.4	–	–	12	46.2	
3	3	5.4	–	–	3	11.5	
4	5	8.9	–	–	5	19.2	
5	3	5.4	–	–	3	11.5	
6	3	5.4	–	–	3	11.5	
Concomitant ASMs at baseline							
Carbamazepine	6	10.7	3	10	3	11.5	0.164
Clonazepam	1	1.8	1	3.3	–	–	
Lacosamide	8	14.3	2	6.7	6	23.1	
Levetiracetam	18	32.1	13	43.3	5	19.3	
Lamotrigine	4	7.1	1	3.3	3	11.5	
Oxcarabzepine	8	14.3	3	10	5	19.3	
Phenobarbital	2	3.6	2	6.7	–	–	
Topiramate	3	5.4	1	3.3	2	7.7	
Valproic acid	5	8.9	4	13.4	1	3.8	
Zonisamide	1	1.8	–	–	1	3.8	
Concomitant ASM by mechanism of action							
Sodium blocker	21	37.4	8	26.7	13	50	0.182
GABA agonist	1	1.8	1	3.3	–	–	
SV2A ligand	17	30.4	12	40	5	19.2	
Various	17	30.4	9	30	8	30.8	
Concomitant EiASMs	9	16.1	5	16.7	4	15.4	0.594

ASM: antiseizure medication; GABA: gamma-amino-butyrric acid; EiASMs: enzyme-inducing ASMs; IQR: interquartile range; SD: standard deviation; SV2 A: synaptic vesicle 2 A. *Significantly statistical difference.

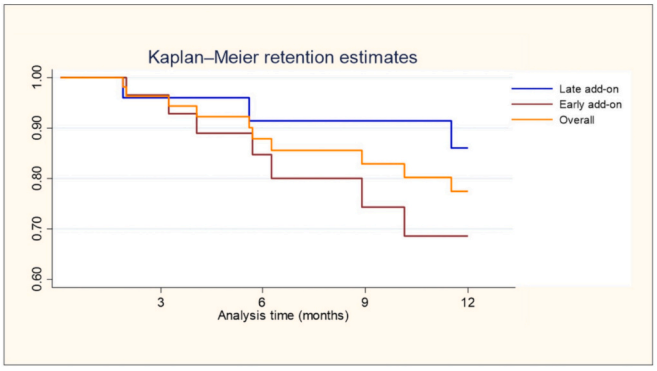

Fig. 1. Kaplan–Meier retention curves over 12 months of the whole study population and by early and late add-on subgroups. The graph illustrates the proportion of patients remaining on perampanel over time (timeline cut to 12 months) for the entire population, and for the early and late add-on subgroups.

according to the seizure type groups (i.e., focal, focal to bilateral tonic-clonic or both) at 3, 6, 12 months and the last visit (all $p > 0.05$). Notably, most patients (12/13) with focal to bilateral tonic-clonic seizures at baseline did not experience bilateral tonic-clonic during the 12-months observation. There was no difference in terms of responder rate according to epilepsy age at onset (children/adolescents, i.e. aged ≤18 years at epilepsy onset; adults, i.e. aged >18 years at epilepsy onset) (at all visits, $p > 0.05$). Higher seizure-free rate was observed in adults as compared to the children/adolescent group at the 12 months follow-up visit (70.6% vs 28.6%; $\chi^2 = 5.427$, $p = 0.011$; see supplementary table 1 for further details).

Safety data were available for 54 patients during the one-year period of observation (37 at visit 1, 30 at visit 2, and 29 at visit 3). Occurrence of AEs was registered in 25 patients (46.3%). Specifically, AEs were reported by 13/37 (35.1%), 9/30 (30%) and 7/29 (24.1%) patients at visits 1, 2, and 3, leading to PER discontinuation in 4, 3 and 4 cases within 3, 6 and 12 months, respectively. Table 2 provides details about the types of AEs. Patients experiencing AEs were significantly older than those without (55.7 ± 22.2 vs 33.0 ± 26.8 years; p: 0.007). No deaths or hospitalizations were reported. No significant difference in terms of outcomes or safety measures (all $p > 0.05$) was observed among patients grouped according to the mechanism of action of concomitant ASM. Likewise, there was no statistically significant difference in all endpoint measures between subjects receiving EiASM and those receiving non-EiASM (all $p > 0.05$).

Regarding the multivariate analysis, the Cox model revealed a significantly higher risk of PER discontinuation in patients with adverse effects (HR: 9.91; 95% CI: 1.52–64.56; $p = 0.016$) and a lower risk in those taking a concomitant EiASM (HR: 0.02; 95% CI: 0.00–0.65; $p = 0.028$; Supplementary Table 2). Binomial logistic regression analysis of AEs occurrence (Supplementary Table 3) and logistic regression analysis of PER-efficacy (Supplementary Table 4) did not show statistically significant association with analysed variables.

3.2. Early add-on and late add-on subgroups

Thirty patients (median age 59.5 years; IQR: 35–72.2) received none or one add-on ASM before PER (early add-on group), whereas 26

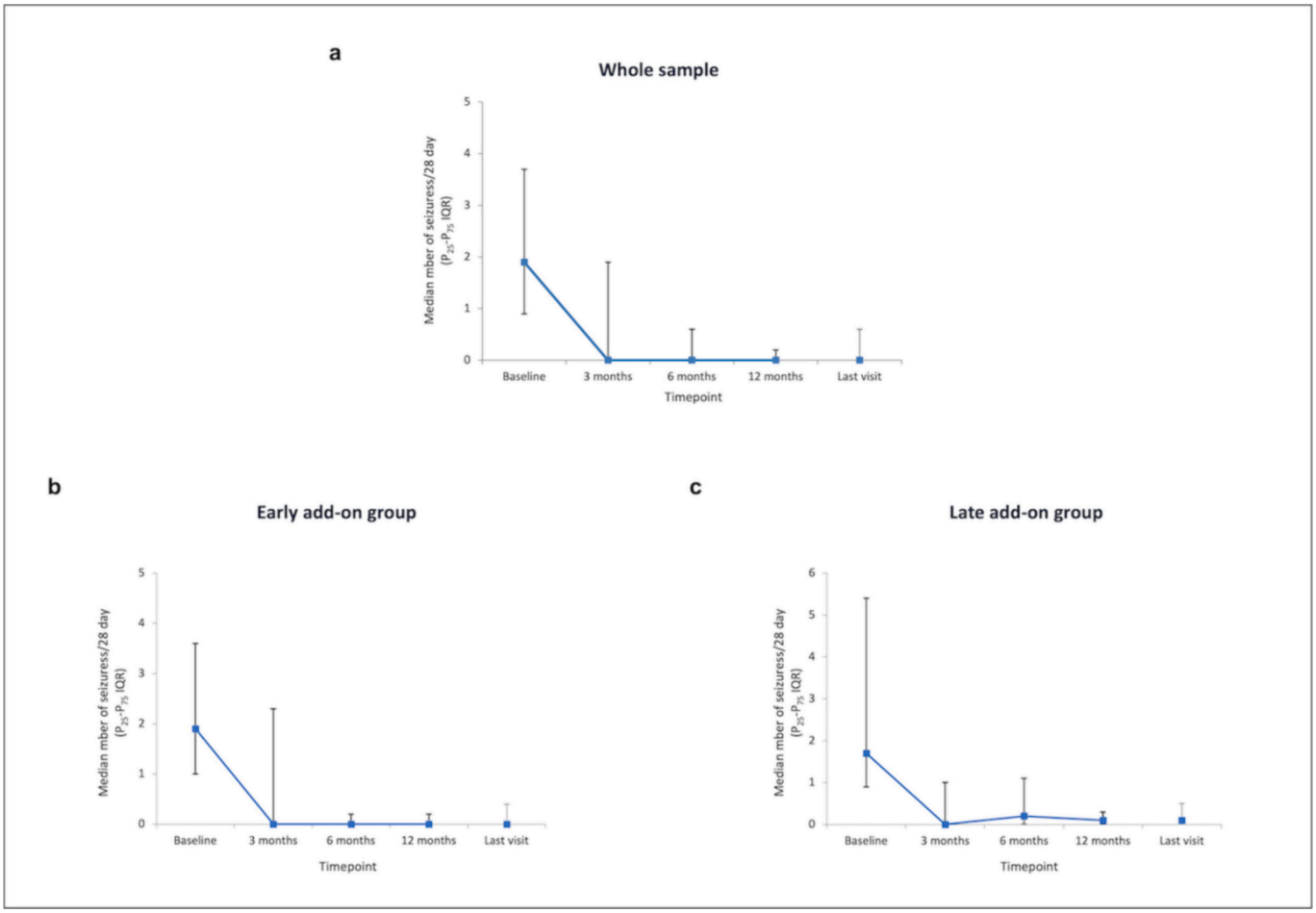

Fig. 2. Median 28 days normalized seizure frequencies (with P25 and P75 IQR) at baseline, 3-, 6-, 12-month and last follow-up visit.
The figure shows the median 28-day normalized seizure frequencies at baseline and subsequent follow-up visits in the whole population (a), early add-on group (b) and late add-on group (c). The frequency of seizures significantly decreased at the 3-, 6-, 12-month and last visit compared to baseline in the whole study population as well as in both subgroups.

subjects (median age 30.6 years; IQR: 16.5–56.2) added PER after ≥2 previous ASMs (late add-on group, Table 1).

Among the early add-on group, visit 1 was performed by 22 subjects, whereas visit 2 and 3 were performed by 16 subjects. The mean daily dose of PER was 4 mg (IQR: 4–6) at visit 1 and visit 2, and 6 mg (IQR: 4–6) at visit 3. Considering the last visit, the median PER dose was 4 mg/day (IQR 4–6). Retention rates were 90% (27/30 evaluable patients), 77.8% (21/27) and 59.1% (13/22) at 3-, 6- and 12-month follow-up visits. The Kaplan–Meier curve of the overall retention time (timeline cut to 12 months) is shown in Fig. 1. Treatment withdrawal occurred in 9 (16%) patients because of poor tolerability (7 subjects, 77.8%) or both insufficient efficacy and poor tolerability (2 subjects, 22.2%).

The total seizure frequency normalized per 28 days decreased from a median of 1.9 (IQR 1–3.6; range 0.3–112) at baseline to 0 (IQR 0–0.4; range 0–141) at the last visit (Fig. 2b). The median number of seizures decreased to 0.4 (IQR 0–2.3; range 0–36.2) at visit 1 (−100%), to 0 (IQR 0–0.2; range 0–30) at visit 2 (−100%) and to 0 (IQR 0–0.2; range 0–141) at visit 3 (−100%). The number of seizures significantly decreased from baseline for visit 1 ($p < 0.001$), visit 2 ($p < 0.001$) and visit 3 ($P = 0.008$). The difference between visit 2 and visit 1 was statistically significant ($p = 0.043$), while no difference resulted when comparing visit 3 with visit 1 and 2. The responder rate was 83.3% (25 out of 30 patients) considering the last visit, with a percentage of seizure-free subjects of 63.3% (19/30). Responder rate was also high at visits 1, 2 and 3 (63.6%, 14/22 patients; 100% (16/16); 87.5% (14/16), respectively), with a proportion of seizure-free individuals of 50% (11/22), 68.7% (11/16) and 62.5% (10/16), at 3, 6 and 12 months (see Fig. 3b).

Data about AEs were available for 28 patients. Specifically, AEs occurred in 9/21 (42.8%) at visit 1, in 4/13 (30.8%) at visit 2 and 5/14 (35.7%) at visit 3, causing drug discontinuation in 9 patients (3 at visit 1, 3 at visit 2 and 3 at visit 3).

In the late add-on group, visit 1 was performed by 17 subjects, visit 2 was performed by 18 subjects, and visit 3 by 15 subjects. The median daily dose of PER was 6 mg (IQR: 4–8) at 3 months, 4 mg (IQR: 4–8) at 6 months and 6 (IQR: 4–8) mg at 12 months. Considering the last available visit, the mean PER dose was 6 mg/day (IQR: 4–8). In this group, retention rates were 96.1% (25/26), 90.9% (20/22) and 80% (16/20) at visit 1, visit 2, and visit 3, respectively. Complete details about demographic, clinical, efficacy outcome and safety data are displayed in Tables 1 and 2, and in Fig. 1, 2c and 3c.

Comparing the two groups, the early add-on and late add-on groups did not statistically differ in terms of age, sex and age at epilepsy onset. Perampanel was prescribed at a higher dose in the late add-on patients at the 3 months ($p = 0.045$), but the drug dose did not differ between the two groups at subsequent follow-up visits. The two groups did not significantly differ regarding the concomitant ASM at baseline: LEV was the most frequent concomitant drug in the early add-on group (13/30, 43.3%), whereas LCM was the most frequent in late add-on group (5/26, 17.8%, Table 1). Retention rates were comparable. Normalized median seizure numbers showed a similar trend of reduction in the two groups at each follow-up visit. The percentage of responders was significantly higher in the early add-on group ($p = 0.046$) at the 6-month visit,

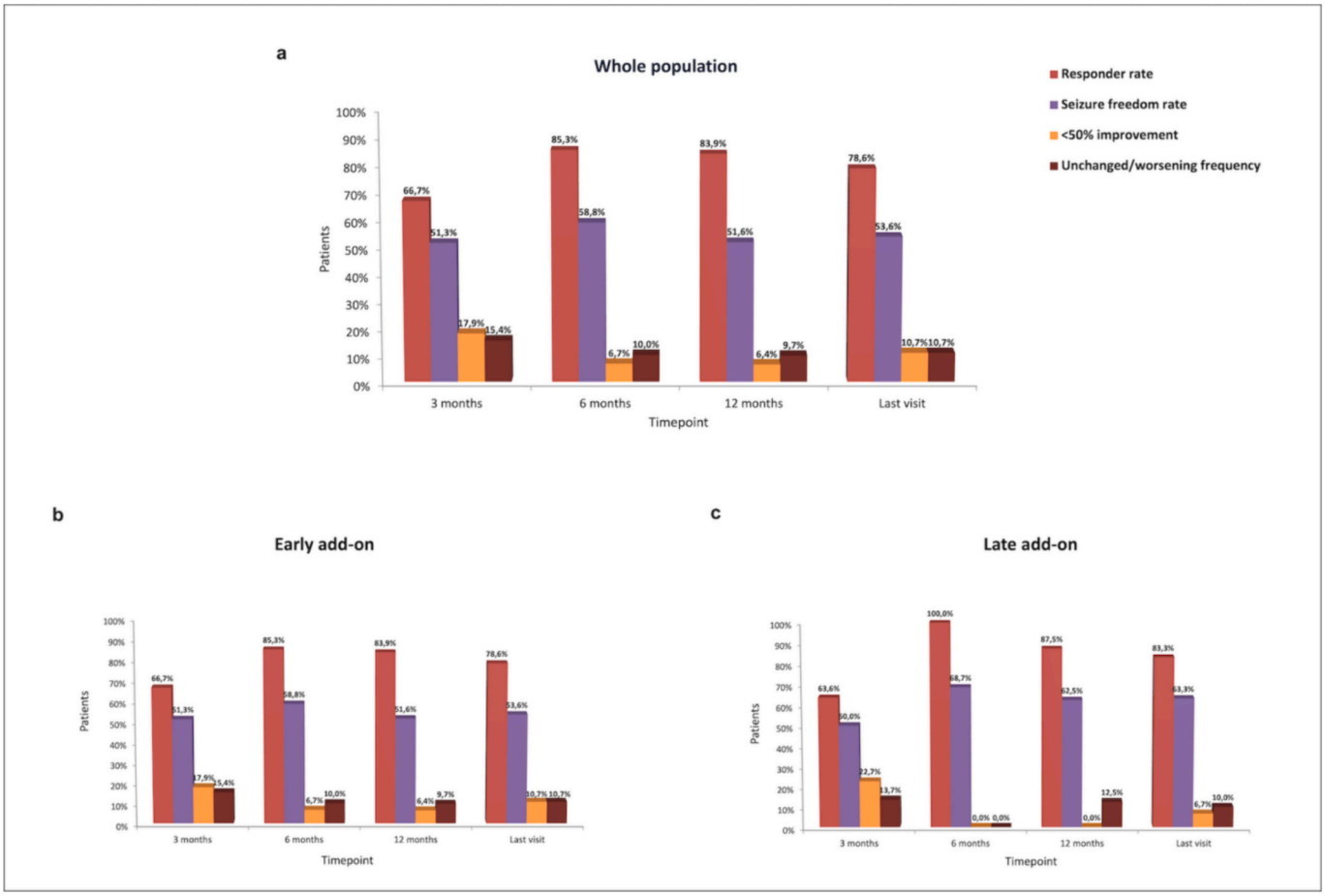

Fig. 3. Clinical response to add-on perampanel treatment.
The figure displays the proportion of responder patients, patients achieving seizure freedom, patients with <50% improvement in seizure frequency and patients with unchanged/worsening seizure frequency at 3, 6, and 12 months and at the last visit in the whole cohort (a), in the early (b) and late add-on (c) subgroups.

Table 2
Adverse events of the whole population and by early and late add-on subgroup.

	Whole population	Early add-on	Late add-on
Tolerability population, n. (%)	54	28	26
Subjects with any adverse events	25 (46.3)	16 (57.1)	9 (34.6)
Withdrawal due to adverse events	11 (20.4)	9 (32.1)	2 (7.7)
Type of adverse event			
Irritability/Nervousness	7 (13.0)	3 (10.7)	4 (15.4)
Dizziness/Vertigo	5 (9.2)	4 (14.3)	1 (3.8)
Agitation	4 (7.4)	3 (10.7)	1 (3.8)
Aggression	3 (5.5)	3 (10.7)	0
Instability/Ataxia	3 (5.5)	3 (10.7)	0
Psychosis/hallucinations	2 (3.7)	0	2 (7.7)
Mood disorders	2 (3.7)	0	2 (7.7)
Drowsiness	1 (1.8)	1 (7.1)	0
Other	3 (5.5)	1 (7.1)	2 (7.7)

whereas no significant difference was found at 3- and 12-month follow-up (all $p > 0.05$, Fig. 3). Likewise, the percentage of seizure-free-subjects was not statistically different at all visits. Finally, the two groups did not significantly differ in terms of AEs incidence ($p > 0.05$).

4. Discussion

The present study investigated the efficacy and tolerability of PER as the only concomitant adjunctive ASM for the treatment of PSE in a real-world context. Studies specifically evaluating the effectiveness and safety of different ASMs in patients with PSE are currently poor [11,12,29–41]. Table 3 reports the main available data about add-on ASMs treatment in PSE [35–37,41].

In our study PER was shown to be effective and well tolerated in PSE patients, as evidenced by the high observed retention rates. Notably, more than two thirds of patients remained on PER at the 12-month follow-up, with treatment withdrawal mainly due to poor tolerability. The retention rate observed in our sample was higher than those reported for old-generation ASMs [34,36,39] and generally consistent with the rates reported for new-generation ASMs [34,36–39], confirming that new ASMs should be preferred in PSE patients. In literature, the highest retention rates have been reported for LEV [31,40], LCM [36,40], eslicarbazepine (ESL) [37] and lamotrigine [40]. However, the patients included in those studies were either drug-naïve or on monotherapy [31,40], with a shorter history of epilepsy [31] and shorter follow-up period [36].

We found a good retention rate in both early and late add-on groups, although lower retention was observed in the early add-on group. Previous studies have demonstrated a higher retention rate when PER is used as an early add-on [26–28], including in elderly patients [22]. In this study, the higher age of early add-on patients compared to late add-on may partially account for this discrepancy. Indeed, the primary reason for discontinuing PER was the occurrence of adverse effects, which are known to be more common in the elderly [42].

In this study, PER was highly effective in reducing seizure frequency. At 6 months after PER introduction, >80% of our patients experienced a ≥ 50% reduction in seizure frequency, with more than half of them

Table 3
Available literature data on add-on ASMs treatment in PSE.

Study	ASMs	Design	Follow-up duration	N° of patients	Retention Rate	Responder rate	Seizure freedom	Adverse events
Villanueva et al., 2018[35]	BRV	Retrospective observational multicenter real-world study	12 months	22	n.a.	n.a.	40.9%	50.5%
Rosenow et al., 2019[36]	LCM	Observational, prospective	Up to 6 months	82	84.1% (69/82)	80%	56%	43.4% (36/83)
Sales et al., 2020[37]	ESL	Pooled analysis of 14 retrospective/prospective real-world study	12 months	76	87.8%	79% (49/62)	53.2% (33/62)	36.0% (27/75)
Lattanzi et al., 2022[21]	BRV	Retrospective observational real-world study	12 months	75	n.a.	42.7% (32/75)	34.7% (26/75)	20.3% (13/64)

Legend: ASMs: anti-seizure medications; BRV: brivaracetam; ESL: eslicarbazepine; LCM: lacosamide; n.a.: not available; PSE: post-stroke epilepsy.

being seizure-free; these percentages remained unchanged at the 12-month follow-up. Data on responder rates are very scarce in the literature [36,37,41], as the majority of studies considered seizure freedom as the outcome measure. The responder rates observed in our population are very high. Similar rates have been reported for ESL (79% at 12 months) [37] and for LCM (80% at 6-months follow-up) [36], whereas Lattanzi and al. reported a lower responder rate (42.7%) at 12 months in patients treated with brivaracetam (BRV) [41]. Seizure-freedom rates in PSE after add-on ASM treatment reported in other real-world studies ranged from 34% to 56% (Table 3) [35–37,41], which are in line with our findings. Moreover, we found a good seizure response at 12 months both in the early (87.5%) and late (80%) add-on groups. These results are in line with our previous studies [22,24] and demonstrate the usefulness of PER when administered as add-on in PSE.

Adverse events occurred in less than half of our patients, mainly during the first months after PER introduction, leading to drug withdrawal in 16,1% of patients. Similar rates of AEs have been demonstrated in real-world studies on PSE patients treated with BRV (50,5%) [35] and LCM (43.4%) [36], while a lower incidence of AEs was reported for ESL (36%) [37] and BRV (20,3%) [41]. According to the literature [43–46], dizziness, irritability and behavioural problems were the most common reported PER side effects. Interestingly, AEs occurrence was higher in the early (57.1%) than the late (34.6%) add-on group, contrary to recent literature data [24,44]. The most likely reason for this discrepancy could be the higher (although not statistically significative) median age of the early add-on group (59 years) as compared to late add-on group (30 years). The mechanism of action of the concomitant ASM (EiASM vs non-EiASM) did not impact the occurrence AEs. Perampanel could be a suitable therapeutic approach in patients with PSE given the typical patient profile. Indeed, PER has demonstrated good effectiveness and tolerability in elderly patients [22] who represent the majority of those with PSE. Another advantage of PER is its once-daily dosing, which can enhance adherence in patients that usually require polypharmacy due to common comorbidities. Of course, drug-drug interaction should also be considered due to PER CYP3A4/5 inducer activity [47].

Our study has some limitations. First, the open-label, retrospective design might have introduced potential sources of biases. Second, since this study represents a subgroup analysis of data from a previous research, relevant information about variables like stroke type and aetiology, concomitant medical conditions and treatments other than ASMs, is lacking, thus limiting the evaluation of their influence on PER safety and efficacy outcomes. The collection of AEs through open/general questions during clinical visits rather than using standardized questionnaires might represent a cause of underreporting. Lastly, the interpretation of the statistical analysis, especially the multivariate analysis, needs caution due to the small sample size.

5. Conclusions

This is the first study to investigate the use of PER in patients with PSE. Over a 12-month observational period in a real-world setting, our findings affirm both the efficacy and safety of PER. The observed significant seizure control and favourable tolerability profile suggest that PER could be an effective early treatment option for individuals with PSE.

Ethical statement

The study was performed following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study protocol was approved by the local Ethics Committee (Comitato Etico Sezione Area Centro Regione Calabria; Prot. N. 126, dated April 16, 2020). Informed consent was obtained from all individual participants or legal representatives included in the study.

Competing interests and funding

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Umberto Aguglia received speaker honoraria from Eisai; Fedele Dono received travel support and speaker honoraria from EISAI; Alfredo D'Aniello received Research grant for UCB Pharma and Speaker/Honoraria for Eisai, UCB Pharma, Angelini Pharma and Lusofarmaco; Giancarlo Di Gennaro received speaker honoraria from EISAI, UCB-Pharma, Livanova, Lusofarmaco, GW Pharmaceuticals. Served on advisory boards for Bial, Arvelle Therapeutics, Angelini Pharma; Edoardo Ferlazzo received speaker honoraria and advisory board from Arvelle Therapeutics, UCB Pharma, Eisai Pharma, Angelini Pharma; Sara Matricardi has served on an advisory board from Eisai outside the submitted work; Marta Piccioli received speaker honoraria from EISAI, UCB Pharma, Angelini Pharma, Jazz Pharmaceuticals, Italfarmaco; Orsini Alessandro received speaker honoraria and advisory boards by Jazz Pharmaceuticals; Pasquale Striano received speaker honoraria and advisory boards for BioMarin, Zogenyx, Poveca, research funding by Jazz Pharmaceuticals, Kolfarma Srl.

All other authors have no competing interests to declare that are relevant to the content of this article.

CRediT authorship contribution statement

Angelo Pascarella: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lucia Manzo:** Writing – original draft, Data curation. **Sara Gasparini:** Methodology, Investigation, Data curation, Conceptualization. **Oreste Marsico:** Investigation, Data curation. **Domenico Abelardo:** Formal analysis, Data curation. **Claudia Torino:** Formal analysis. **Vittoria**

Cianci: Investigation, Data curation. **Alfonso Iudice:** Investigation, Data curation. **Francesca Bisulli:** Investigation, Data curation. **Paolo Bonanni:** Investigation, Data curation. **Emanuele Caggia:** Investigation, Data curation. **Alfredo D'Aniello:** Investigation, Data curation. **Carlo Di Bonaventura:** Investigation, Data curation. **Jacopo C. DiFrancesco:** Investigation, Data curation. **Elisabetta Domina:** Investigation, Data curation. **Fedele Dono:** Investigation, Data curation. **Antonio Gambardella:** Investigation, Data curation. **Carla Marini:** Investigation, Data curation. **Alfonso Marrelli:** Investigation, Data curation. **Sara Matricardi:** Investigation, Data curation. **Francesco Paladin:** Investigation, Data curation. **Rosaria Renna:** Investigation, Data curation. **Marta Piccioli:** Investigation, Data curation. **Pasquale Striano:** Investigation, Data curation. **Michele Ascoli:** Investigation, Data curation. **Angela La Neve:** Investigation, Data curation. **Emilio Le Piane:** Investigation, Data curation. **Alessandro Orsini:** Investigation, Data curation. **Gianfranco Di Gennaro:** Formal analysis. **Umberto Aguglia:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Edoardo Ferlazzo:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2024.123106.

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