



## Perampanel as only add-on epilepsy treatment in elderly: A subgroup analysis of real-world data from retrospective, multicenter, observational study

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### ABSTRACT

**Introduction:** Drug management of epilepsy in the elderly presents unique but data on this population are scarce. This study aimed to assess the effectiveness and tolerability of perampanel (PER) used as only add-on to a background anti-seizure medication (ASM) in the elderly in a real-world setting.

**Methods:** We performed a subgroup analysis of patients aged  $\geq 65$  years included in a previous 12-month multicenter study on adults. Treatment discontinuation, seizure frequency, and adverse events were recorded

**Abbreviations:** AE, adverse event; ASM, anti-seizure medication; Ei, enzyme-inducing; PER, perampanel; PEROC, PERampanel as Only Concomitant antiseizure medication.

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at 3, 6 and 12 months after PER introduction. Sub-analyses by early ( $\leq 1$  previous ASM) or late PER add-on were also conducted.

**Results:** The sample included 65 subjects (mean age:  $75.7 \pm 7.2$  years), with mainly focal (73.8%) epilepsy. The mean PER daily dose was  $\approx 4$  mg during all follow-up. Retention rates at 3, 6, and 12 months were 90.5%, 89.6%, and 79.4%. The baseline median normalized per 28-day seizure number significantly decreased at 3-, 6- and 12-month visits. One year after PER introduction, the responder rate ( $\geq 50\%$  reduction in baseline seizure frequency) was 89.7%, with a seizure freedom rate of 72.4%. Adverse events occurred in 22 (34.9%) patients with dizziness and irritability being the most frequent. No major differences between early (41 patients, 63.1%), and late add-on groups were observed.

**Conclusion:** Adjunctive PER was effective and well-tolerated when used as only add-on treatment in elderly people with epilepsy in clinical practice, thus representing a suitable therapeutic option in this age category.

## 1. Introduction

The management of epilepsy in elderly individuals represents a common situation in daily practice due to the rapid growth of this segment of the population [1,2]. The treatment of these patients is often challenging. Physiological age-related changes in pharmacokinetics and pharmacodynamics as well as drug interactions due to concomitant therapies for comorbidities must be well-thought-out in the choice of anti-seizure medications (ASMs) [3–5]. Few clinical data are available on the use of different ASMs in elderly patients with epilepsy. Indeed, elderly patients are usually underrepresented in regulatory epilepsy trials [6]; moreover, randomized-controlled protocols often diverge significantly from real routine clinical practice and results may not be generalizable to a wider population. Therefore, real-world studies are likely to represent the main source of data on the efficacy and safety of ASMs in this population. Older generation ASMs still widely used in the elderly pose safety concerns such as adverse events (AEs), drug interactions, and impacts on comorbidities [7]. As regards the use of newer ASMs in the elderly, the few available data show comparable effectiveness with a more favourable pharmacokinetic profile, better tolerability, and fewer drug interactions than older ones [5,7].

Perampanel (PER) is a third-generation ASM, highly selective, noncompetitive  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist [8], licensed, to date, for use as adjunctive therapy for focal onset seizures with or without evolution to bilateral tonic-clonic seizures and primary generalized tonic-clonic seizures and as a monotherapy for focal onset seizures with or without bilateral tonic-clonic evolution is allowed in the United States and Japan [9,10]. Data about the safety and efficacy of adjunctive PER for patients with refractory epilepsy have been provided by clinical randomized, double-blind, placebo-controlled trials [11–14], and open-label extension studies [15–17] as well as several real-world multicenter studies [18–25]. Moreover, recent data suggest PER effectiveness when used as an early rather than a late add-on option [26–34]. To date, very few studies, often based on small sample sizes, are available on PER use in elderly patients [35–40].

The PEROC (PERampanel as Only Concomitant antiseizure medication) study investigated the tolerability and effectiveness of PER over 12 months in people with epilepsy aged  $>12$  years receiving PER as adjunctive treatment to a background monotherapy in a real-world context [34]. As the study included a proportion of elderly patients (aged  $\geq 65$  years), we performed a sub-analysis to provide further evidence about the use of PER on this subgroup of patients.

## 2. Materials and methods

The PEROC study was an observational, multicenter, retrospective, longitudinal study that included patients with focal or generalized epilepsies recruited from 52 Italian epilepsy or neurology centers [34]. Data collection was performed from March 2020 to March 2021. Treatment with PER as the only ASM added to a single concomitant ASM according to the usual clinical practice and at least one seizure within the year before starting add-on treatment represented criteria of inclusion.

Patients with  $<3$ -month follow-up at the closing of the database were excluded [34].

### 2.1. Procedure

Data on demographics, medical history (duration of epilepsy, classification of epilepsy, monthly seizure frequency during the previous 3 months, historical ASM treatment, reason for discontinuation of previous ASM, reason for initiating PER, psychiatric history). Concomitant ASM and daily dose were collected at baseline. Three, 6 and 12-month assessments and final evaluation (i.e., if a patient dropped out) included: a) date of assessment; b) patient's height and weight; c) current PER dose, titration schedule and dose of concomitant ASM; d) number of seizures since last evaluation; e) side effects (open/general questions, not solicited for specific AEs).

Concomitant ASMs were stratified by the mechanism of action into four groups: a) sodium channel blockers, b) GABAergic, c) SV2A ligands, and d) others. Moreover, they were grouped as enzyme-inducing (Ei) ASMs (Ei-ASMs, i.e. carbamazepine, oxcarbazepine, phenobarbital and phenytoin) and non-EiASMs (any other ASM); patients were included in the Ei-ASMs group if taking at least one Ei-ASMs.

Seizure number at different time intervals was collected retrospectively based on medical records. Adverse effects were recorded verbatim and coded using MedDRA. To warrant data uniformity, all visits performed from 1.5 months to 4.5 months from baseline were considered as visit 1; all visits performed from 4.5 months to 9 months from baseline were considered as visit 2; all visits performed from 9 months to 15 months from baseline were considered as visit 3.

### 2.2. Outcomes

Retention rate at 3, 6, and 12 months was assessed. The efficacy of PER was assessed by quantifying changes in seizure frequency between the follow-up evaluations. We evaluated: the reduction in median number of seizures, normalized per 28 days; responders' rate (i.e., a decrease in median seizure frequency  $\geq 50\%$ ); seizure freedom (defined as absence of seizures since the previous visit). Effectiveness was assessed after 3, 6, and 12 months of PER treatment and the final follow-up (i.e. the last available observation - last observation carried forward -, independently of the timepoint when it occurred, defined as '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. Retention time, efficacy and safety and tolerability outcomes were also evaluated by subgroups of patients according to the number of prior ASMs (0–1, also defined as "early add-on"; or  $> 1$ ), and concomitant ASM, grouped by mechanisms of action.

### 2.3. Statistical analysis

Descriptive data were expressed as numbers and percentages for categorical variables, and as mean  $\pm$  SD or median and interquartile range for continuous variables. 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 with ongoing 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 analyzed by Chi-square or *t*-test, as appropriate. Kaplan–Meier curves were built for time-dependent analyses.

### 3. Results

#### 3.1. Whole sample

The analysis included 65 patients (33 female, 50.8%; mean age: 75.7 ± 7.2). Demographic and clinical details are reported in Table 1. The median duration of epilepsy was 7 years. Forty-eight (73.8%) subjects had focal epilepsy. Structural etiology was the most frequent (45 patients, 69.2%): vascular and neoplastic etiology was the most common (18 and 12 out of 45; 40% and 26.7%, respectively). Of note, 41 (63.1%) patients were previously treated with 0 or 1 add-on ASMs (“early add-on” group). The most co-prescribed drugs included levetiracetam (41.5%), lacosamide, carbamazepine and valproate (all 9.2%).

At the last visit, the mean PER dose was 4.4 ± 1.4 mg/day (range: 2–10; n: 65). Visit 1 was performed by 42 subjects, visit 2 was performed

by 44 subjects, and visit 3 by 29 subjects. The mean daily dose of PER was 4.3 ± 1.4 mg at 3 months, 4.6 ± 1.6 mg at 6 months and 4.7 ± 1.4 mg at 12 months.

At 12 months, 79.4% of the evaluable population for retention was still taking PER (27/34). Retention rates were 90.5% (38 out 42 evaluable patients) and 89.6% (43 out 48) at 3 and 6 months after PER introduction. Fig. 1a shows the Kaplan–Meier curve of the overall retention time. The timeline was cut to 12 months. The cumulative probability of remaining on treatment was 0.87 at 12 months. Treatment withdrawal occurred in 7 patients, due to poor tolerability in 5 (71.4%) and both insufficient efficacy and poor tolerability in 2 (28.6%) of them.

At baseline, the median seizure number normalized per 28 days was 1.5 (IQR 0.9–3.7; range 0.3–45.9). The total seizure frequency normalized per 28 days decreased significantly to 0 (IQR 0–0.4; range 0–10.7) at the last visit. Moreover, the median seizure number decreased to 0 (IQR 0–1.5; range 0–36.2) at visit 1 (–100%), to 0 (IQR 0–0.4; range 0–10.7) at visit 2 (–100%) and lastly to 0 (IQR 0–0.3; range 0–7) at visit 3 (–100%; Fig. 2a). Difference in number of seizures resulted statistically significant from baseline for visit 1 ( $p < 0.001$ ), visit 2 ( $p < 0.001$ ) and visit 3 ( $P = 0.007$ ). The differences between visit 2 and visit 1 and between visit 3 and visit 2 were not significant.

The responders’ rate was 86.2% considering the last visit, with a percentage of seizure-free subjects of 67.7%. Responders’ rate was also persistently high compared with baseline at visits 1, 2 and 3 (73.8%,

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

Characteristics	Whole cohort (n = 65)		Early add-on (n = 41)		Late add-on (n = 24)		p
	N	%	N	%	N	%	
Sex (female/male)	33/32	50.8/49.2	20/21	48.8/51.2	13/11	54.2/46.8	0.436
Age: mean (SD) years	75.7 (7.2)	–	75.5 (7.2)	–	76.1 (7.8)	–	0.721
Disease duration: median (IQR) years	7 (2–15)	–	6 (2–13)	–	9 (3–39)	–	–
Age at epilepsy onset: mean (SD) years	59.4 (20.2)	–	63.0 (18.1)	–	53.2 (22.5)	–	0.060
Psychiatric comorbidities <sup>#</sup>	4	7.5	2	5.8	2	10.5	0.391
Type of epilepsy							
Focal	48	73.8	32	78.0	16	66.7	0.135
Generalized	14	21.5	6	14.6	8	33.3	
Undetermined	3	4.7	3	7.4	0	0	
Etiology of epilepsy							
Structural	45	69.2	31	75.6	14	58.3	0.227
Genetic	4	6.2	1	2.4	3	12.5	
Unknown	16	24.6	9	22.0	7	29.2	
Number of previous ASMs: mean (SD)	1.6 (1.6)	–	0.7 (0.4)	–	3.1 (1.7)	–	<0.001*
Number of previous ASMs							
0	10	15.4	10	24.4	–	–	<0.001*
1	31	47.7	31	75.6	–	–	
2	14	21.5	–	–	14	58.3	
3	3	4.6	–	–	3	12.5	
4	2	3.1	–	–	2	8.3	
5	3	4.6	–	–	3	12.5	
6	0	0	–	–	–	–	
7	1	1.5	–	–	1	4.2	
8	1	1.5	–	–	1	4.2	
Concomitant ASMs at baseline							
Carbamazepine	6	9.2	4	9.8	2	8.3	0.018*
Clonazepam	1	1.5	1	2.4	0	0	
Lacosamide	6	9.2	1	2.4	5	20.8	
Levetiracetam	27	41.5	22	53.7	5	20.8	
Lamotrigine	5	7.7	4	9.8	1	4.2	
Oxcarbazepine	4	6.2	3	7.3	1	4.2	
Phenobarbital	5	7.7	3	7.3	2	8.3	
Phenytoin	2	3.1	–	–	2	8.3	
Valproic acid	6	9.2	3	7.3	3	12.5	
Zonisamide	3	4.6	–	–	3	12.5	
Concomitant ASM by mechanism of action							
Sodium blocker	18	27.7	8	19.5	10	41.7	0.065
GABA agonist	5	7.7	3	7.3	2	8.3	
SV2A ligand	27	41.5	22	53.7	5	20.8	
Various	15	23.1	8	19.5	7	29.2	
Concomitant EiASMs	17	26.1	10	24.4	7	29.2	0.433

ASM: antiseizure medication; GABA: gamma-amino-butyric acid; EiASMs: enzyme-inducing ASMs; IQR: interquartile range; SD: standard deviation; SV2A: synaptic vesicle 2 A. <sup>#</sup>Data available only for 54 patients.

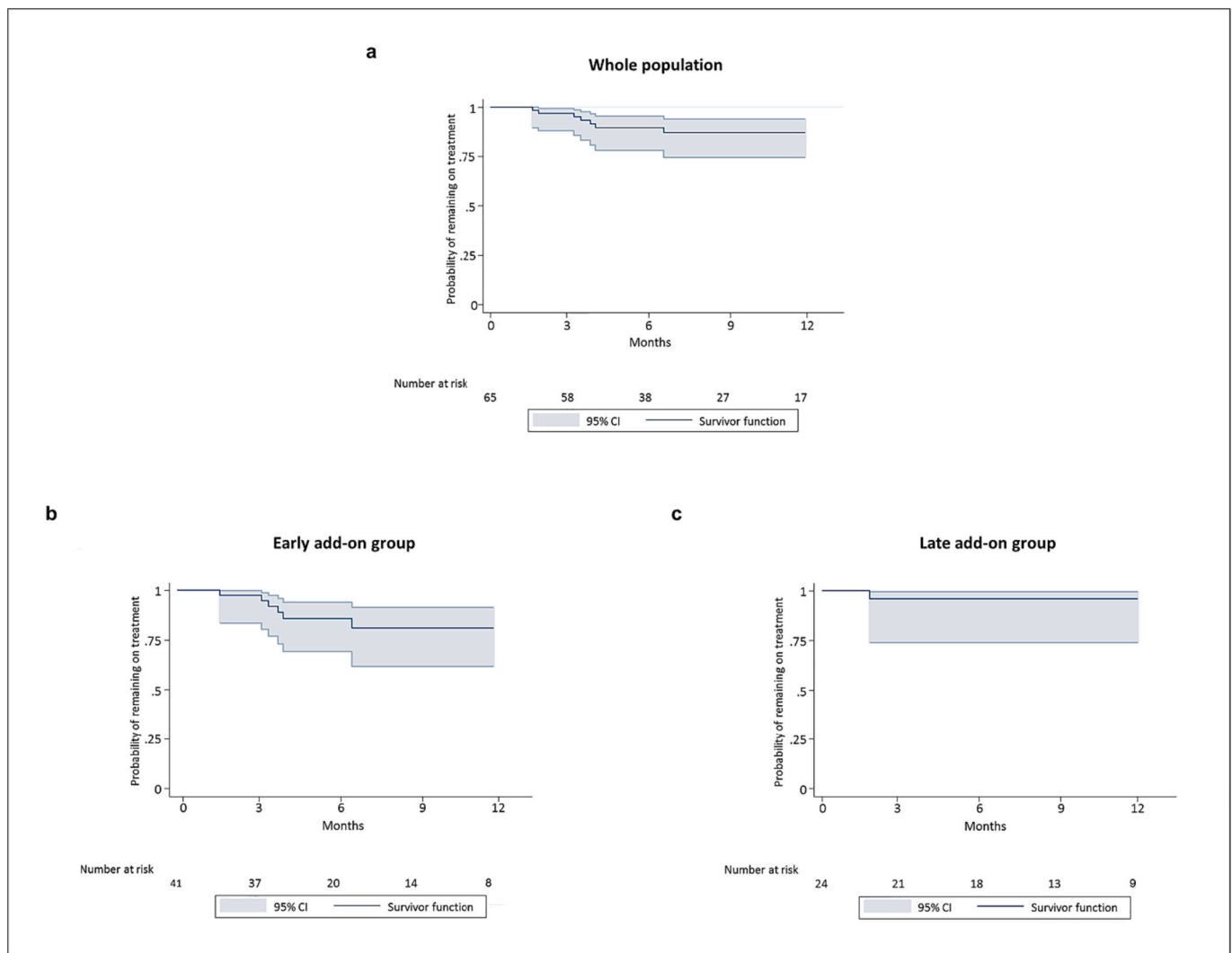


Fig. 1. Kaplan–Meier retention curves over 12 months of the whole cohort and by patient subgroups. The figure shows the proportion of patients continuing on perampanel over time in the whole population (a), and in the early (b) and late add-on (c) subgroups.

88.6% and 89.7%). The proportion of individuals remaining seizure-free from all seizure types was 59.5%, 63.6% and 72.4%, at 3, 6 and 12 months, respectively (Fig. 3a).

Safety data were available for 63 patients during the overall period of observation (41 patients at visit 1, 40 patients at visit 2, and 25 patients at visit 3). Adverse events were reported by 22 out of 63 patients (34.9%). Specifically, AEs were reported in 16/41 (39.0%), 5/40 (12.5%), and 6/25 (24%) patients, at visits 1, 2, and 3, respectively. Most discontinuations due to AEs were registered before visit 1 (4 out of 7). Serious AEs were very rare: only two events (behavioral problem and dizziness) occurred, without reported deaths. The details about the type of AEs are reported in Table 2.

No major differences among patients grouped according to the concomitant ASM mechanism of action were observed neither in the outcomes or safety measures (all  $p > 0.05$ ). Similarly, all endpoints' measures were not statistically different in the group taking an EiASM and a non-EiASM (all  $p > 0.05$ ).

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

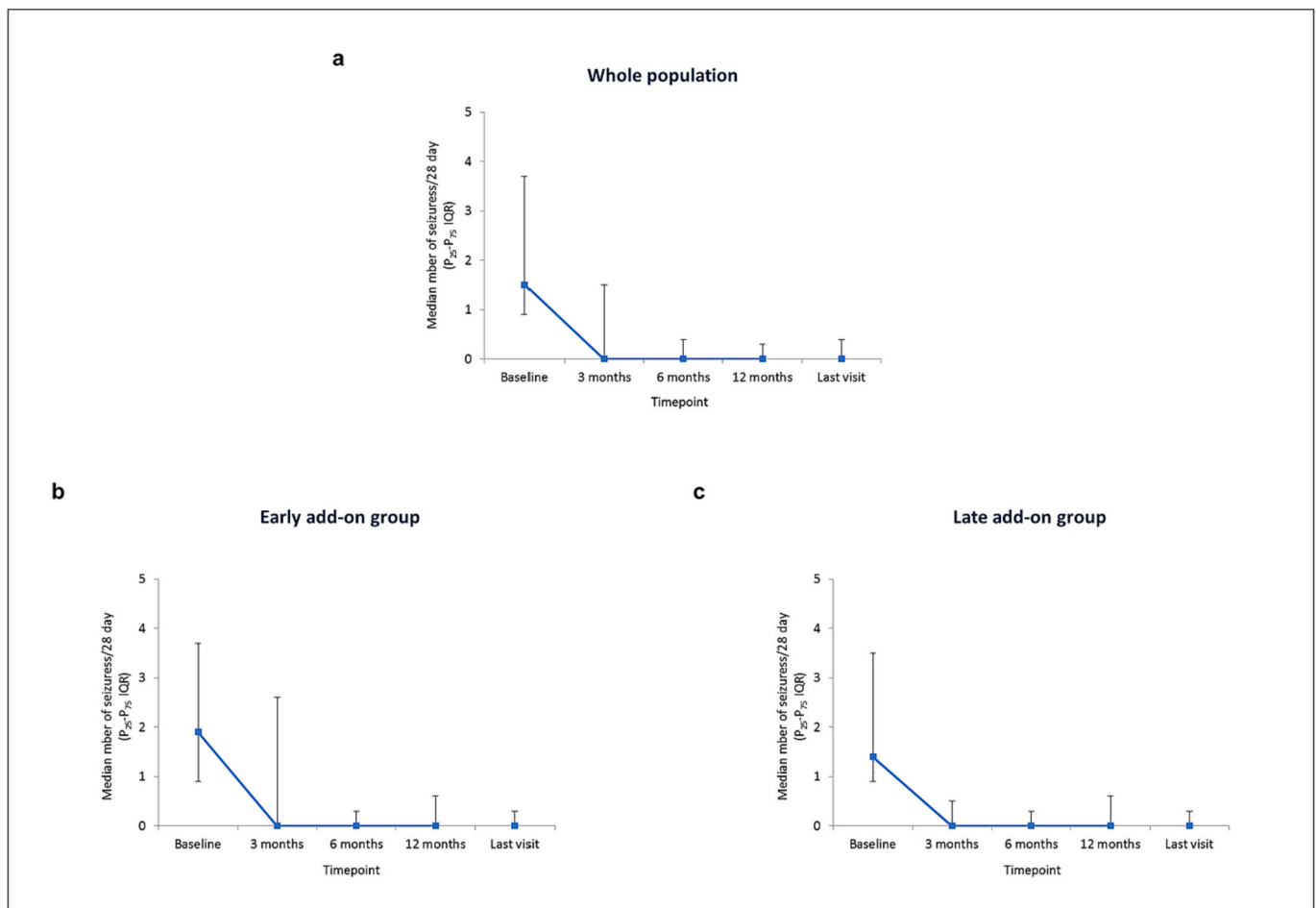
A total of 41 subjects (mean age  $75.5 \pm 7.2$  years) had received none or one add-on ASM before PER (early add-on group, Table 1). Almost 25% of these subjects received PER as their first add-on ASM. At the last visit, the mean PER dose was  $4.3 \pm 1.4$  mg/day (range: 2–10). Visit 1

was performed by 25 subjects, visit 2 was performed by 27 subjects, and visit 3 by 16 subjects. The mean daily dose of PER was  $4.5 \pm 1.5$  mg at 3 months,  $4.6 \pm 1.6$  mg at 6 months and  $4.6 \pm 1.5$  mg at 12 months.

Retention rates were 88% (22/25 evaluable patients), 86.7% (26/30) and 70% (14/20) at 3-, 6- and 12-month follow-up visits. The cumulative probability to remain on treatment was 0.96 at 12 months (Kaplan–Meier curve in Fig. 1b). Treatment withdrawal occurred in 6 patients because of poor tolerability (4 subjects, 71.4%) or both insufficient efficacy and poor tolerability (2 subjects, 28.6%).

The total seizure frequency normalized per 28 days decreased from a median of 1.9 (IQR 0.9–3.4; range 0.3–46.7) at baseline to 0 (IQR 0–0.3; range 0–7) at the last visit (Fig. 2b). The seizure median number lowered to 0 (IQR 0–2.6; range 0–36.2) at visit 1 (–100%), to 0 (IQR 0–0.3; range 0–5.6) at visit 2 (–100%) and to 0.1 (IQR 0–0.6; range 0–7) at visit 3 (–100%). Number of seizures significantly decreased from baseline for visit 1 ( $p < 0.001$ ), visit 2 ( $p < 0.001$ ) and visit 3 ( $P = 0.001$ ). The difference between visit 2 and visit 1 and between visit 3 and visit 2 were not significant.

The responders' rate was 90.2% considering the last visit, with a percentage of seizure-free subjects of 70.7%. Responders' rate was also persistently high compared with baseline at visits 1, 2 and 3 (72%, 92.6% and 93.8%, respectively). The proportion of individuals remaining seizure-free from all seizure types was 56%, 66.7% and 75%, at 3, 6 and 12 months, respectively (Fig. 3b).



**Fig. 2.** Median 28 days normalized seizure frequencies (with P25 and P75 IQR) at baseline, 3-, 6-, 12-months and last follow-up visit. The baseline median 28 days normalized seizure frequencies of the whole population (a), as well as of early add-on group (b) and late add-on group (c), significantly decreased at the 3-, 6-, 12-months and last visit.

Data about AEs were available for 39 patients. Specifically, AEs occurred in 9/24 (37.5%) at visit 1, in 3/23 (13%) at visit 2 and 6/12 (50%) at visit 3. Adverse events caused PER discontinuation in 6 patients (3 at visit 1, 1 at visit 2 and 2 at visit 3) and two of them were categorized as serious.

As regards the late add-on group, visit 1 was performed by 17 subjects, visit 2 was performed by 17 subjects, and visit 3 by 13 subjects. The mean daily dose of PER was  $4.1 \pm 1.3$  mg at 3 months,  $4.7 \pm 1.7$  mg at 6 months and  $4.8 \pm 1.5$  mg at 12 months. Considering the last available visit, the mean PER dose was  $4.5 \pm 1.5$  mg/day (range: 2–10). In this group, retention rates were 94.1%, 94.4% and 92.8% at visit 1, visit 2, and visit 3, respectively. Complete adjunctive details about demographical, clinical, efficacy outcome and safety data are reported in Tables 1 and 2, and in Fig. 1c, 2c and 3c.

We compared the early add-on and late add-on groups. The two groups did not differ for age, sex, age of epilepsy onset, types of epilepsy, etiology and mean PER dose (at both last visit and each follow-up visit). The two groups significantly differed for the concomitant ASM at baseline ( $\chi^2 = 19.956$ ,  $p = 0.018$ ), as levetiracetam was used most frequently in the early add-on group (22/41, 53.7%) compared to late add-on group (5/24, 20.8%, 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 and seizure-free subjects resulted higher in the early add-on group at the 6- and 12-month visit, even if without statistically significant differences (all  $p > 0.05$ , Fig. 3). Likewise, no significant difference was found for AEs incidence between the two groups ( $p > 0.05$ );

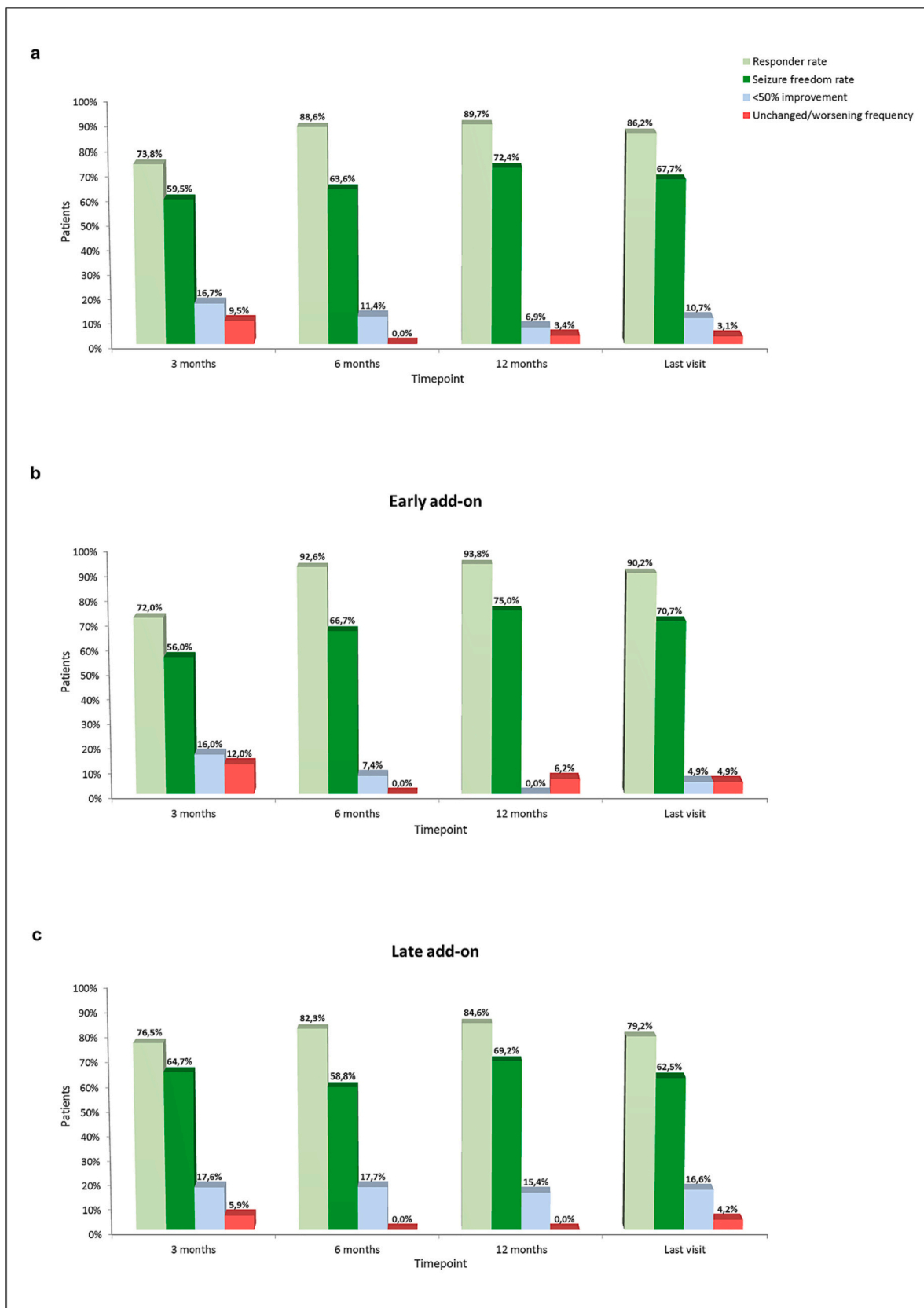
however, considering each follow-up reports, AEs rate at visit 3 was significantly higher ( $p = 0.005$ ) in early add-on group as no events were reported in the late add-on one. Nevertheless, no differences in discontinuation rates due to AEs were found at all follow-up visits.

#### 4. Discussion

This study investigated the tolerability and effectiveness of PER as the only concomitant add-on ASM for the treatment of epilepsy (both focal and generalized seizures) in patients aged  $\geq 65$  years in a real-world context. To date, clinical data on PER in elderly patients with epilepsy are limited (Table 3) [35–41] with none of them designed to evaluate PER as only add-on ASMs.

The present subanalysis of the PEROC study [34] comprised 65 elderly patients with predominantly focal onset seizures, of whom about two-thirds received PER as an early add-on ASM.

In the current study, all efficacy measures confirmed the usefulness of PER as a single add-on treatment in elderly patients. First, we found high retention rates at each established time point, proving that treatment with PER was both effective and well tolerated. Indeed, about 80% of patients remained on PER treatment at 12 months after drug introduction. Treatment withdrawal was mainly due to poor tolerability; concomitant lack of efficacy caused PER discontinuation only in two out of seven cases. The retention rate observed in our population was quite similar to that found by Lattanzi and colleagues in a real-world multicenter study, showing that 78.3% of enrolled subjects were still on PER after 12 months, with the greater amount of treatment discontinuation



**Fig. 3.** Clinical response to adjunctive perampanel. The figure shows the responder rate, seizure freedom rate, and the proportions of elderly patients with <50% improvement in seizure frequency and unchanged/worsening seizure frequency at 3, 6, and 12 months and the last visit in the whole cohort (a) and 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.	63	39	24
Subjects with any adverse events, n (%)	22 (34.9)	14 (33.3)	8 (33.3)
Serious adverse events	2 (3.2)	2 (5.1)	0
Withdrawal due to adverse events	7 (11.1)	6 (15.4)	1 (4.2)
Type of adverse event, n (%)			
Dizziness/Vertigo	7 (11.1)	6 (15.4)	1 (5)
Irritability/Nervousness	5 (7.9)	3 (7.7)	2 (8.3)
Instability/Ataxia	3 (4.8)	3 (7.7)	0
Drowsiness	2 (3.2)	1 (2.6)	1 (4.2)
Behavioral disorders	2 (3.2)	0	2 (8.3)
Memory disturbances	1 (1.6)	1 (2.6)	1 (4.2)
Other	4 (6.3)	2 (5.1%)	2 (8.3)

due to poor tolerability [39]. Similarly, in the recent pooled analysis of data from two previous large clinical practice multicenter studies, including 343 patients aged  $\geq 65$  years, discontinuation in the elderly subgroup was mainly due to AEs [40]; nevertheless, a relatively high retention rate (61.5%) was found [39]. This study included data from a previously published pooled, multicenter, individual-level analysis of observational studies in the clinical practice setting reporting PER retention  $< 50\%$  after 12 months [37]. Lastly, data from a long-term (57 months) prospective audit demonstrated a retention rate of 75% [36]. The higher retention rate observed in our population compared to most other reports may be due to the higher number of concomitant ASMs in the other study populations as compared to our cohort, in which PER was the only concomitant ASM. Indeed, our result is in line with other studies that used PER as an add-on to monotherapy [31,32].

Another favourable factor may be the mean low PER dose (about 4 mg along the overall period of observation) intake of our population. Elderly individuals often require lower doses of ASMs due to age-related changes in pharmacokinetics, such as reduced renal clearance or slower drug metabolism [4]. However, the different study designs and study populations (e.g., focal epilepsies only vs. the inclusion of generalized epilepsies, the higher number of concomitant and previous ASMs) make comparison difficult. Our study also demonstrated a high retention rate in patients aged  $\geq 65$  years when PER was used as the first option in patients who failed the first ASM. In line with the result of the previous PEROC study [33], the retention rate was similar in the early add-on and late add-on groups. A higher retention rate when PER is used as an early add-on in adult epileptic patients has been reported [18,27–29,32,33,42].

Analysis of specific efficacy outcomes further highlighted the usefulness of PER as a single add-on treatment in elderly patients. Median seizure number reduction, responders' rate and proportion of seizure-free subjects resulted very high: at the 12-month follow-up visit, the

median seizure number was significantly lower than baseline, with a responders' rate of about 90%, and more than two-third of seizure-free individuals. These percentages are higher than previous studies on elderly patients, reporting a responder rate and a seizure freedom rate at 12 months ranging from 57.6% to 73.7% and from 23.9% to 40.1%, respectively [37–40]. However, these data are hard to compare, due to heterogeneity in study design, inclusion criteria, characteristics, and number of patients. Inconsistency may be partially explained by differences in the study population: indeed, our cohort could comprise a small amount of drug-resistant epilepsy, as about two thirds of patients were taking PER as the first or second add-on ASMs and the mean number of previous ASMs was lower than other studies [37,39,40].

In this sub-analysis we found a higher rate of responders and seizure freedom at all time points, as compared to the results of the main study [34]. These results are in line with Wheless et al., which demonstrated the greatest effectiveness of PER in patients aged  $> 65$  years in comparison with other age categories [40]. Noteworthy, we observed good seizure response both in the early and late add-on groups, with slightly better responder and seizure-free rates in the early compared with late add-on patients at the 6- and 12-month visits. Better seizure control when PER is administered as an early add-on treatment is known [18,27–33,42]. Moreover, despite the limited sample size (10 patients), Liguori et al. reported a higher seizure freedom rate in people with epilepsy with  $\geq 60$  years taking PER as first than as second add-on ASM [42]. Our findings further support the use of PER as an early option and unique add-on in patients failing to control seizure after one ASM and provide evidence of PER efficacy in the elderly population.

Adverse events were reported in about one-third of patients, occurring frequently within the first three months after PER introduction. These data are consistent with the two previous real-life studies, reporting AEs in 34.8% and 35% of their sample, respectively [36,39], whereas a higher incidence was found in the two large pooled real-world studies [37,40], reporting a rate of AEs of 55% and nearly 80%. Our finding is in obvious contrast with the RCTs sub-analysis study in elderly patients, reporting a rate of 85% [35], but the difference may be easily explained by the dissimilar characteristic of studies (e.g. the potential recall bias in retrospective study design, lower PER doses and the slow, customized titration, as well as the overall lower drug load in our cohort). Noteworthy, the rate of AEs in this subgroup analysis was higher than that found in the previous PEROC analysis on the overall cohort (34.9% vs. 20%) [34]. This finding was consistent with Wheless et al. that the incidence of AEs in people treated with PER increased with age category [40] and, more broadly, with the evidence indicating older individuals treated with ASMs are more likely to experience side effects than younger ones [4]. The decline in homeostatic mechanisms due to aging, which is responsible for the delayed pharmacodynamics adaptation to drugs, may also account for the higher occurrence of AEs in the first few months after PER introduction [4].

According to the literature [36,37,39,40,43,44], dizziness and

**Table 3**  
Available literature data on the use of perampanel in elderly.

Study	Design	Follow-up duration	N° of patients	Retention Rate	Responder rate	Seizure freedom	Adverse events
Leppik et al., 2015 [35]	Pooled subanalysis of three phase III trials	23 weeks	20	n.a.	28.6% (8/28)	n.a.	85.0%
Trinka et al., 2016 [36]	Review article including prospective audit data	57 months	20	75% (15/20)	40% (8/20)	35% (7/20)	35% (7/20)
Rohracher et al., 2019 [37]	Pooled individual analysis of real-world studies	12 months	135	47.8% (64/134)	n.a.	28.3 (13/46)	79.4% (85/107)
Liguori et al., 2020 [38]	Retrospective study	12 months	10	70% (7/10)	60% (6/10)	40% (4/10)	n.a.
Lattanzi et al., 2021 [39]	Retrospective study	12 months	92	78.3% (72/92)	57.6% (53/92)	23.9% (22/92)	34.8% (32/92)
Wheless et al., 2023 [40]	Pooled individual analysis of real-world studies	12 months	394	61.5% (211/343)	73.7% (129/175)	40.1% (77/192)	55.0% (193/351)

n.a.: not available.

irritability were the most common reported side effects. Importantly, cognitive side effects (e.g. drowsiness, memory and attention disturbances) were very uncommon, hence suggesting a favourable tolerability profile of PER regarding cognitive effects, which represent a main concern in the management of epilepsy in the older population. The rate and type of AEs did not differ in function of the mechanism of action of the concomitant ASMs (EiASM vs non-EiASM) as well as between early and late add-on groups. No new or unexpected safety concerns emerged, confirming the relatively good safety profile of PER in the elderly.

The effectiveness and safety profile of PER in elderly proved highly favourable when compared to other third generation ASMs. Retention-rate, responder-rate and seizure-freedom rate in our study were superior to those reported by brivaracetam in the elderly in Lattanzi et al.'s study [45]. The safety profile of PER appears to be rather positive even when compared to eslicarbazepine, which was associated with AEs in 77.5% of patients with focal seizures [46]. Of course, making direct comparisons among ASM is challenging due to the different nature of these studies.

The main strengths of this study are the use of PER in combination with a single ASM (thus limiting drug interactions), the recruitment across multiple sites located in different regional territories and the real-world setting, which best reflects the real treatment approach employed in the everyday circumstances of clinical practice and allow the findings to be generalized the broader population of elderly epileptic patients.

The main limitation of this study is the open-label and retrospective design of the study, which might have introduced potential sources of biases. Another limitation due to the retrospective nature of the study is the unavailability of complete data for all enrolled subjects at all time points and the exclusion of individuals with incomplete data or with follow-up visits not respecting the established schedule. These concerns may limit the generalizability of the results. Moreover, there was no control group permitting the assessment of the effects of PER vs. placebo or being treated with other drugs, hence information about the comparative efficacy and safety of PER and other ASMs were not achievable. Lastly, AEs might be underreported as they were collected through open/general questions during clinical visits rather than by standardized questionnaires.

## 5. Conclusions

We demonstrated the good effectiveness and safety of adjunctive PER as the only concomitant add-on ASM in older patients in real-life conditions. Treatment with PER was maintained by most patients until 12 months follow-up and showed good efficacy, with a high seizure freedom rate. Tolerability was good, with a low rate of PER-related AEs and without clinically relevant drug–drug interactions. Finally, PER demonstrated effective and well tolerated regardless of whether used as early add-on or late add-on treatment, supporting the use of PER as a broad-spectrum, early add-on therapy.

## 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. Informed consent was obtained from all individual participants or legal representatives included in the study.

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