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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Perampanel in routine clinical use across Europe: Pooled, multicenter, observational data

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Summary

Objective: To pool observational data on the routine use of perampanel to obtain information on real-world outcomes and data in populations typically underrepresented in clinical trials.

Methods: Individual-level data of people with epilepsy treated with perampanel at 45 European centers were merged into a single dataset. Prespecified outcomes were: 1-year retention rate, 1-year seizure freedom rate (duration ≥6 months), and incidence of treatment-emergent adverse events (TEAEs). In addition, relationships were explored with logistic regression analyses.

Results: The full analysis set comprised 2396 people: 95% had focal seizures; median epilepsy duration was 27 years; median number of concomitant antiepileptic drugs (AEDs) was 2; and median prior AEDs was 6. One-year retention rate was 48% (1117/2332; 95% confidence interval [CI] 46-50%), and 1-year seizure-free rate (≥6-month duration) was 9.2% (74/803; 95% CI 7-11%). Median treatment duration was 11.3 months (1832 patient-years); median dose was 8 mg. In 388 individuals with available data at 3, 6, and 12 months, responder rates were 42%, 46%, and 39%, respectively. During the first year, TEAEs were reported in 68% of participants (1317/1497; 95% CI 66-70%). Logistic regression found higher age at perampanel initiation was associated with higher seizure-free rate, and higher number of prior AEDs with lower seizure-free rate and lower rates of somatic TEAEs. In 135 individuals aged ≥65 years, 1-year retention rate was 48% and seizure-free rate was 28%.

Significance: Across a large, treatment-resistant population, add-on perampanel was retained for ≥1 year by 48% of individuals, and 9% were seizure-free for ≥6 months. TEAEs were in line with previous reports in routine clinical use, and less frequent than in the clinical trial setting. No new or unexpected TEAEs were seen. Despite the limitations of observational studies, our data indicate that some individuals may derive a marked benefit from the use of perampanel.

KEYWORDS
antiepileptic drug, elderly, pharmacotherapy, real-world evidence, seizure freedom

1 | INTRODUCTION

1.1 | Background and rationale

Clinical trials provide data for regulatory approval of antiepileptic dugs (AEDs) but do not provide all the information required by prescribers to guide best use in clinical practice.[1] Limited populations, rapid titration, and strict dosing criteria do not reflect real-life use of antiepileptic dugs (AEDs), and hence, clinical trials of AEDs have limited external validity. People included in trials usually have more severe epilepsy than seen in routine practice[1]; certain populations are underrepresented in trials (eg, the elderly and those with intellectual impairment); and doses and

Key Points

- Perampanel, added to current AEDs, was continued for at least a year in 48% of people
- The median dose used was 8 mg (or 6 mg in people aged ≥65 years)
- The chance of seizure freedom increased with increasing age and decreased with increasing number of previous AEDs
- 1 year after starting perampanel, 9% of people were seizure-free (for at least 6 months), and 28% of people aged ≥65 were seizure-free

titration regimens in real-life settings are often different than in trials.[2] Real-world evidence, therefore, is important,[3] and evidence of effectiveness in the "usual circumstances of healthcare practice" is increasingly vital in health policy decision making.[4] To improve the quality of observational study design and reporting, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) have recently published recommendations.[3]

Perampanel is approved for add-on treatment of people aged ≥12 years with refractory focal seizures[5] and with primary generalized tonic–clonic seizures in idiopathic generalized epilepsy.[6] To assess the effectiveness of perampanel, many centers have collected and published data from clinical records of people prescribed perampanel in routine practice (Table S1).

Some case series have also been published on the use of perampanel in specific situations—seizure associated with glioma,[7,8] progressive myoclonus epilepsies,[9–12] other myoclonus,[13–15] and status epilepticus[16–18]—and case reports of adverse events (Table S2).

1.2 | Objectives

Our objectives were to provide a large dataset reflecting perampanel routine clinical use over the past 4 years; to provide data on subpopulations who are typically not included in trials; and to provide preliminary information on clinical characteristics that may be associated with greater likelihood of seizure freedom, retention, or treatment-emergent adverse events (TEAEs) on perampanel.

2 | METHODS

2.1 | Study design, setting, and patients

This was a pooled, individual-level analysis of observational studies of perampanel in routine clinical practice in specialized centers across Europe. Investigators who had already gathered data were identified and invited to participate, with the aim of obtaining a full analysis set (FAS) of at least 2000 people. Some centers included here had previously published results.[19–25] Appropriate ethics committee approvals and informed consent were obtained by centers for the original data acquisition and for incorporating data into this analysis, as required. This was an exploratory study; the protocol and analysis plan are available on request; we have stated in this report where we deviated from the original analysis plan; and the authors are prepared to address methodological criticisms of the study (as per ISPOR-ISPE recommendations).

Data were received from 47 centers in Spain, Italy, Germany, the UK, France, Austria, and Sweden, and data from 45 were included (Table S3). Perampanel treatment started between June 2009 and July 2016. Individual centers and investigators set their own inclusion criteria: in general, only individuals who started perampanel and had a follow-up visit were included. The decision to prescribe perampanel was made by the treating physician based on clinical need and suitability. Some centers included only individuals with focal seizures and some only included people aged ≥18 years.

2.2 | Data sources

Anonymized, individual-level data were merged into a single dataset and translated or transformed as necessary for consistency. Data from specific centers were excluded if the nature or format was inconsistent or incompatible. Data points missing because of differences in recording format were manually explored and replaced where possible; no imputations were made for remaining missing values.

The FAS comprised all individuals who took at least 1 dose of perampanel. Not all sites recorded the same information for every individual and therefore sites had different amounts of missing data, which could not be assumed to indicate lack of a particular event (eg, lack of adequate data to determine seizure freedom could not be assumed to indicate lack of seizure freedom). We therefore defined evaluable populations for each outcome we analyzed. The evaluable population for retention comprised all those from the FAS without missing retention data. The evaluable population for seizure freedom: participants who could be determined as seizure-free or not (freedom from all seizures at 12 months and for ≥6 months). The evaluable population for TEAEs: all participants except those with missing data on the "*Adverse event yes/no*" variable (ie, missing data were not assumed to indicate no TEAE). A subpopulation of this was used to examine the frequency of individual TEAEs: all individuals in the evaluable population for TEAEs, excluding any who were recorded as having an AE but who had no individual AE specified (this avoided underestimating the frequency of individual TEAEs, which would have been a consequence of using the overall TEAE population as a denominator).

2.3 | Outcome measures

Time points were defined as the clinic visit closest to 3 months (ie, from 0 to 4.5 months), 6 months (4.5-9 months), and 12 months (9-15 months) after initiation of perampanel. The main outcome measure was predefined as the 1-year retention rate (proportion remaining on

perampanel at 1 year), in the evaluable population for retention. Reasons for discontinuation were reported as given by investigators.

Three secondary outcome measures were predefined: (1) Seizure freedom rate at 1 year, defined as the proportion of people free of seizures for ≥6 months at 1 year, in the evaluable population for seizure freedom. Post hoc, we also calculated pragmatic seizure freedom, using the same numerator but as a proportion of the FAS. (2) TEAE rate at 1 year, defined as the proportion with ≥1 TEAE reported during the first year after initiating perampanel in the evaluable population for TEAEs. (3) Rate of individual TEAEs, defined as the proportion reporting specific TEAEs in the evaluable population for individual TEAEs.

Perampanel levels can be affected by strong enzyme inducers or inhibitors. For our analysis, carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, and primidone were categorized as enzyme-inducing AEDs (EIAEDs).

2.4 | Data analysis and statistics

All statistical analyses followed a prespecified plan, to avoid potential post hoc bias. Baseline characteristics of the FAS, the 3 evaluable populations, and key outcomes were summarized descriptively. Statistical comparisons between groups or to baseline were not attempted. Instead, rates and confidence intervals were calculated for the key outcomes measures.

Changes in seizure frequency at 3, 6, and 12 months relative to baseline were categorized as seizure frequency increased, no change, <50% improvement (reduction), and ≥50% improvement (reduction) in seizure frequency, according to information provided by investigators (which included both subjective and objective judgment of frequency change).

TEAEs were collected as reported. To handle text variation and different languages, the original terms were converted into predefined, standardized collective terms, and also grouped into categories (Table S4). After reviewing the dataset, some additional collective terms were added post hoc.

Time-to-event analysis explored retention over time and the impact of baseline characteristics on probability of retention, by calculating the Kaplan-Meier estimates of the respective retention curves. We explored the following characteristics: ≤3 versus >3 concomitant AEDs at baseline; early (≤2 prior AEDs) versus late (>2 prior) add-on of perampanel; fast titration (dose increases at intervals of ≤2 weeks) versus slow (intervals of >2 weeks); and by mechanism of action (MOAs) of concomitant AED (Table S5 for MOA categories).

Regression analyses were used in an exploratory way to provide preliminary information on associations between preselected explanatory variables (Table S6) and seizure freedom, and for selected TEAE categories (cognitive, psychiatric, somatic, weight gain/loss).

Because of the relatively small number of participants with 12-month seizure freedom data, not all variables could be included in one single regression model.[26] Instead, we selected 7 variables as the maximum number to be included at any one time for the seizure freedom outcome, and repeatedly conducted regression analyses using all possible combinations of 7 variables from the prespecified list (Table S6). This gave 792 models. Results were summarized by showing the median and 95% confidence intervals (CIs) for all 792 regression coefficients, and the proportion of P values that were ≤0.05. Fewer variables were explored for the TEAEs of interest (Table S6). For the TEAE category "Weight gain," only one single regression model was conducted, because the ratio of the number of events and the number of variables was sufficiently large, thus not requiring any subset selection.

3 | RESULTS

3.1 | Patients

Individual-level data from 45 study sites (Table S3) were included: data on 1457 individuals have been published previously,[19–25] and data on 909 individuals are new to the literature. The FAS comprised 2396 individuals; the evaluable population for retention 2332; the evaluable population for TEAEs 1947; and the evaluable population for seizure freedom 803. Key characteristics are shown in Table 1—no differences were apparent between the populations. The most common concomitant AEDs at baseline were levetiracetam (taken by 873/2343 patients with available data, 37.3%), lamotrigine (669/2343; 28.6%), lacosamide (614/2343, 26.2%), and carbamazepine (551/2343, 23.5%). Twelve percent (281/2343) were taking 1 concomitant AED at baseline; 38.0% were taking 2 (890/2343); 32.7% were taking 3 (766/2343); and 14.0% were taking 4 or more (328/2343).

Of the FAS, 78.5% of patients had a history of focal seizures (1753/2233); a minority (5.1%, n = 114) had generalized seizures only; and 16.4% (n = 366) had both seizure types.

Where data were available, 58% had "symptomatic" etiology (1248/2140) and 34% unknown (726/2140). A history of psychiatric disorders was recorded in 30% (586/1936); 29.8% (264/885) had current psychiatric comorbidities; and 7.4% (165/2229) had a nonprogressive neurological deficit. The majority (91%, 1982/2170) were aged 18-64; 5 were aged <12 years; and 134 were aged ≥65 years (Table S7 for full demographics).

TABLE 1 Key demographic characteristics of the 4 analysis populations

	Full analysis set[a] (N = 2396)	Evaluable population for retention[b] (N = 2332)	Evaluable population for seizure freedom[c] (N = 803)	Evaluable population for TEAEs[d] (N = 1947)
Female gender, n (%)	1235 (51.6%)	1203 (51.6%)	419 (52.2%)	1020 (52.4%)
Evaluable population	N = 2394	N = 2330	N = 803	N = 1945
Median age at PER initiation, years (IQR)	40 (30-50)	40 (30-51)	39 (30-50)	40 (30-50)
Evaluable population	N = 2218	N = 2170	N = 803	N = 1840
Age ≥65 at PER initiation, n (%)	135 (6.1%)	134 (6.2%)	46 (5.7%)	107 (5.8%)
Evaluable population	N = 2218	N = 2170	N = 803	N = 1840
Median duration of epilepsy, years (IQR)	27 (17-39)	27 (17-39)	30 (19-41)	28.3 (18-30)
Evaluable population	N = 2215	N = 2153	N = 800	N = 1853
Median number of previous AEDs (IQR)	6 (4-9)	6 (4-9)	6 (3-9)	6 (4-9)
Evaluable population	N = 2229	N = 2174	N = 747	N = 1833
Median number of concomitant AEDs (IQR)	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)
Evaluable population	N = 2343	N = 2286	N = 803	N = 1894
Taking an EIAED, n (%)	1315 (56.1%)	1282 (65.1%)	519 (64.6%)	1130 (59.7%)
Evaluable population	N = 2343	N = 2286	N = 803	N = 1894
Median PER dose at 12 months, mg (IQR)	8 (6-8)	8 (6-8)	8 (6-8)	8 (6-8)
Evaluable population	N = 993	N = 993	N = 727	N = 897
Median time on PER, months (IQR)	11.3 (5.4-12.8)	11.4 (5.4-12.8)	12.0 (11.4-12.5)	11.2 (5.0-12.5)
Evaluable population	N = 1987	N = 1956	N = 718	N = 1729

AED, antiepileptic drug; EIAED, enzyme-inducing AED (carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, and primidone); FAS, full analysis set; IQR, interquartile range; PER, perampanel; TEAE, treatment-emergent adverse event.

[a]FAS: All patients included in the dataset.

[b]All patients from the FAS whose PER status was known at 12 months (±3 months); that is, either ongoing on PER or had a PER stop date at or prior to 12 months.

[c]All patients from the FAS who could be determined as either seizure-free or not seizure-free at 12 months, using a definition of freedom from all seizures for ≥6 months.

[d]All patients except those with no information provided on the "*Adverse event yes/no*" variable.

3.2 | Perampanel exposure

The total exposure to perampanel was 1832 person-years. In the FAS and the evaluable populations for retention rate, TEAEs, and seizure freedom, the median perampanel starting dose was 2 mg and the median dose at 12 months was 8 mg. In the FAS, few people were on doses below 4 mg (n = 23) or higher than 12 mg (n = 5). Of those with data available, most (87.2%, 945/1084) were titrated in 2 mg increments at intervals of ≤2 weeks ("fast" titration); and 12.8% (139/1084) were titrated slower (intervals of >2 weeks). The proportion of people with fast titration was similar among those on EIAEDs (85.9%; 512/596) and no EIAEDs (88.7%; 433/488). The median time on perampanel was 11.3 months (interquartile range [IQR] 5-13 months) in the FAS, with minimal variation across the other evaluation populations (Table 1).

Most individuals (84%) took perampanel as late add-on after >2 prior AEDs (1881/2227); 10% took perampanel as early add-on (≤2 prior AEDs; 214/2227); 54 took perampanel as part of de novo polytherapy; and 78 as monotherapy (Table S8).

3.3 | Retention

3.3.1 | Retention at 12 months

At 12 months, 47.9% of the evaluable population for retention was still taking perampanel (1117/2332; 95% CI 45.9-49.9); 16% had discontinued due to intolerability (380/2332), 11% due to lack of efficacy (250/2332), 6% due to both (129/2332), 2% due to seizure worsening (45/2332), and other reasons, or not specified, in 411 patients (Figure S1).

3.3.2 | Retention in subpopulations

The retention rate at 12 months in people with only focal seizures was 49.5% (856/1728; 95% CI 47.2-51.9); in those with only generalized seizures was 57.0% (61/107;

95% CI 47.6-66.4); and in those with a nonprogressive neurologic deficit was 39.0% (62/159; 95% CI 31.4-46.6; Table S8).

3.3.3 | Retention over time

Confidence bands on retention curves overlapped for all subgroups examined, but areas of separation were apparent between some subgroups, suggesting a trend toward improved retention with slow versus fast titration (Figure 1A), early versus late add-on (Figure 1B), concomitant AED(s) including a sodium-channel blocker mode of action (versus no sodium-channel blocker, Figure 1C), and concomitant AED(s) including a potassium-channel mode of action (versus no potassium channel, Figure 1D). The overall retention curve and other subgroups are shown in Figure S2. The retention did not appear to be different between patients taking 1-3 concomitant AEDs (N = 1667) and those taking ≥4 AEDs (N = 307) at baseline (Figure S2B).

3.4 | Seizure freedom

One year after initiating perampanel, 9.2% of the evaluable population had been seizure-free for ≥6 months (74/803; 95% CI 7.2-11.2). The pragmatic seizure-free rate (intent-to-treat) was 3.1% (74/2396). The seizure-free rate among people with focal seizures only was 9.3% (72/773; 95% CI 7.3-11.4) and in those with a nonprogressive neurologic deficit was 13.2% (5/38; 95% CI 2.4-23.9; Table S9). Too few had only primary generalized seizures (N = 18) to allow seizure freedom estimations in this group.

3.5 | Tolerability

Overall, 67.6% of the evaluable population (1317/1947; 95% CI 65.6-69.7) reported TEAEs up to 12 months. Frequency was similar in patients with focal seizures only (65.0%; 950/1462). Individuals with no data recorded for TEAEs were excluded from the analysis and only those with a definitive "no," or a TEAE recorded, were evaluated. We therefore expect this to be an overestimation of the TEAE frequency, as investigators are more likely to document nothing when adverse events are absent than when they are present.

The incidence of TEAEs appeared to be similar among those with slow titration (80.2%; 105/131; 95% CI 73.3-87.0) and fast titration (77.7%; 585/753; 95% CI 74.7-80.7), and confidence intervals overlapped. The most common types of TEAEs were dizziness/vertigo, behavioral psychiatric TEAEs, and somnolence/sleepiness (Table 2). When TEAEs were grouped into broader categories, 26% of patients had at least 1 psychiatric TEAE; 22% had at least 1 cognitive; and 28% had at least 1 somatic TEAE.

3.6 | Seizure frequency

For a small subset of individuals, seizure frequency change relative to pre-perampanel baseline was categorized at all time-points (3, 6, and 12 months: N = 388). At 3 months after initiating perampanel, 42% had ≥50% reduction in seizure frequency. By 12 months, the proportion responding was 38.9%, there was no change or <50% improvement in 51%, and 40 patients had increased/worse seizures than baseline (Figure 2).

3.7 | Relationships between variables and outcomes

3.7.1 | Logistic regression: Seizure freedom

Seven hundred ninety-two models were generated for each explanatory variable. Age at perampanel initiation and number of previously failed AEDs were the only variables that were significantly associated with seizure freedom in all models (Table 3). Higher age was associated with higher chance of seizure freedom (median regression coefficient 0.035; and the minimum and maximum regression coefficients were all above zero [range 0.03-0.045]), and higher number of previously failed AEDs at baseline was associated with a lower chance of seizure freedom (−0.215; −0.259 to −0.184). Weaker associations were also found: a lower chance of seizure freedom was associated with use of EIAEDs (in 75% of models) and with late (versus early) add-on of perampanel (in 58%); and a higher chance of seizure freedom was associated with use of an SV2A-modulating concomitant AED (ie, levetiracetam or brivaracetam), in 60% of models.

3.7.2 | Logistic regression: Adverse events

No variables (Table S6) were found to be associated with occurrence of psychiatric TEAEs, cognitive TEAEs, or weight/appetite change. However, higher number of prior AEDs was associated with a lower chance of somatic/type-A TEAEs (regression coefficient −0.067; Table S10).

3.8 | Elderly subpopulation

3.8.1 | Clinical characteristics

At perampanel initiation, 135 patients were aged ≥65 years. Fewer people in this group (43.6%) were taking EIAEDs than in the overall population (56.1%). Other

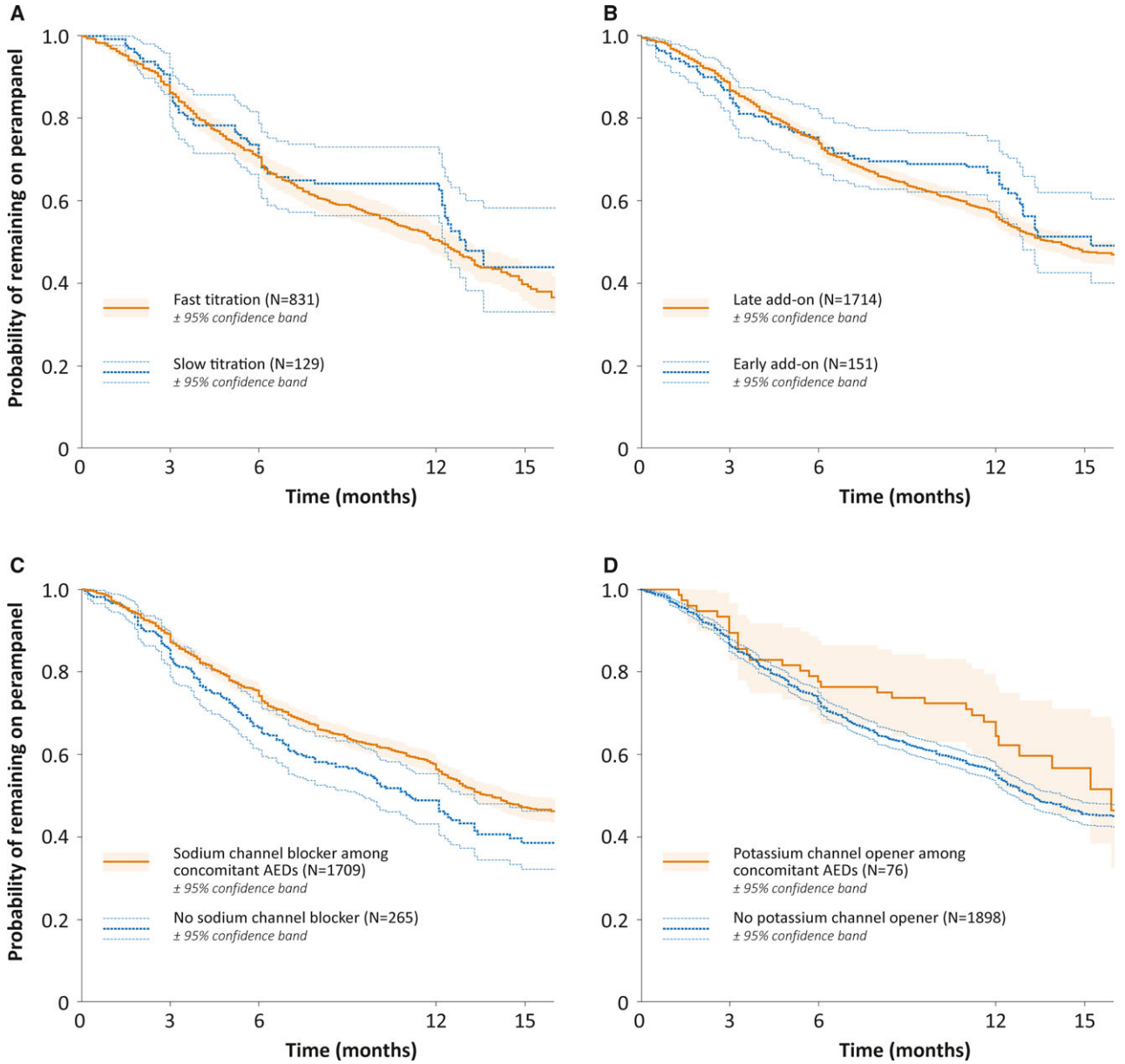

FIGURE 1 Kaplan-Meier retention curves by patient subgroups. Proportion of patients continuing on perampanel over time. A, Individuals with fast titration (dose increases at intervals of ≤2 weeks) versus slow titration (intervals of >2 weeks). B, Individuals with early add-on perampanel (with ≤2 prior AEDs) versus late add-on (>2 prior AEDs). C, Individuals taking concomitant AED(s) that included a sodium-channel blocker versus no sodium-channel blocker. D, Individuals taking concomitant AED(s) that included a potassium-channel opener (ie, retigabine/ezogabine), versus no potassium-channel opener

characteristics were similar to the overall population: the majority had focal seizures, unknown (cryptogenic) or symptomatic etiology, had taken a median of 5 previous AEDs, and were taking 2 concomitant AEDs at baseline (Table 4).

3.8.2 | Perampanel exposure

Perampanel starting dose was 2 mg, and the median dose at 12 months was 6 mg, which was lower than the overall population (8 mg). Median time on perampanel was similar to that of the overall population (Table 1 and 4).

3.8.3 | Retention

At 12 months, 64 of 134 participants aged ≥65 years with evaluable data remained on perampanel (47.8%; 95% CI 39.3-56.2). Discontinuation was due to intolerability in 23.9% (n = 32), lack of efficacy in 6% (n = 8), both intolerability and lack of efficacy in 3.0% (n = 4), other reasons in 3% (n = 4), and was not specified in 15.7% (n = 21).

TABLE 2 Treatment-emergent adverse events (TEAEs) reported in the first year of perampanel exposure in the evaluable population for individual TEAEs (N = 1824) and the subset of this population who were aged ≥65 years (N = 97)

	Overall (N = 1824)		Age ≥65 (N = 97)	
TEAE type	**n**	**%**	**n**	**%**
Dizziness/vertigo/ataxia	375	20.6%	24	24.7%
Behavioral psychiatric TEAE[a]	348	19.1%	16	16.5%
Somnolence/sleepiness	273	15.0%	16	16.5%
Falls/unsteadiness/ataxia	100	5.5%	8	8.2%
Fatigue	93	5.1%	8	8.2%
Depressed mood and mood disorders	88	4.8%	5	5.2%
Weight gain	63	3.5%	3	3.1%
Other TEAE	56[b]	3.1%	3[c]	3.1%
Mental confusion/slowing/ psychomotor retardation	42	2.3%	7	7.2%
Headache	41	2.2%	0	
Nausea/vomiting/GI problems	37	2.0%	1	1.0%
Psychosis/hallucination/delusion	32	1.8%	1	1.0%
Anxiety	30	1.6%	0	
Sleep disturbance[d]	28	1.5%	2	2.1%
Diplopia or other visual disturbance	26	1.4%	2	2.1%
Memory problems[d]	23	1.3%	2	2.1%
Seizures increased/worsening[d,e]	23	1.3%	1	1.0%
Speech problems/slurred speech	16	0.9%	2	2.1%
Other psychiatric TEAE	15[f]	0.8%	0	
Suicidal thoughts/ideation[d]	14	0.8%	1	1.0%
Weight loss	14	0.8%	0	
Back pain/arthralgia[d]	9	0.5%	0	
Rash/skin-related problems	9	0.5%	1	1.0%
General/unspecified CNS side effects	4	0.2%	1	1.0%
Increased appetite	4	0.2%	0	
Decreased appetite	2	0.1%	0	
Tremor[d]	2	0.1%	1	1.0%

[a]Such as anger, aggression, irritability.

[b]Other TEAEs: unspecified (n = 28); paresthesia/dysesthesia (n = 4); drop attacks (n = 3); cough (n = 2), and remainder (n = 19) occurred in 1 patient each (alopecia, ankle edema, clumsiness, constipation, cramps, dyspnea, erectile dysfunction, euphoria, hair loss, hypersalivation, hypothyroidism, photophobia, pneumonia, reduction/loss of libido, snoring, sweating, tachycardia, transient thrush, and urinary urgency).

[c]Other TEAEs in ≥65: Other TEAEs were not specified (n = 2) and pneumonia (n = 1).

[d]TEAE term added post hoc, after review of data.

[e]TEAEs of seizures increased/worsening were not based on any specific criteria or cutoff.

[f]Other psychiatric TEAEs: unspecified (n = 7); apathy (n = 3) psychogenic nonepileptic seizure (n = 2); emotional instability (n = 1); inappropriate laughter (n = 1); and self-injury (n = 1).

3.8.4 | Seizure freedom

At 12 months, 13 of the 46 patients aged ≥65 with evaluable data were seizure-free for at least 6 months (28.3%; 95% CI 15.2-41.3). The pragmatic seizure-free rate was 9.7% (13/134).

3.8.5 | Tolerability

Of 107 elders with evaluable data, 85 reported TEAEs (79.4%; 95% CI 71.8-87.1). Individual TEAEs are shown in Table 2. When TEAEs were grouped into broader categories, 23.7% of patients had ≥1 psychiatric TEAE; 33.0% had ≥1 cognitive TEAE; 34.0% had ≥1 somatic TEAE; and 3.1% had TEAEs related to weight/appetite change.

4 | DISCUSSION

The main strengths of our analysis are in looking for broad patterns in a large, diverse population and in hypothesis generation. In over 2000 people with epilepsy—from individuals late in the treatment pathway with refractory epilepsy and other comorbidities, to people just starting polytherapy for the first time—half persisted with perampanel for a year, and 9% achieved seizure freedom. TEAEs were reported in 68% and no new, idiosyncratic reactions were documented in 1832 patient-years.

We identified some interesting trends that merit further research. First, the likelihood of seizure freedom increased with increasing age. This is consistent with another report[24] and may be related to the inherent neurobiology and seizure etiology in these people, as that report also found a higher chance of seizure freedom in people with a vascular etiology.[24]

Second, a higher number of previous AEDs (ie, use of perampanel as late add-on) were associated with a lower chance of seizure freedom. This is consistent with other reports,[24,27] and a higher number of prior AEDs are generally considered a proxy for more severe, refractory epilepsy, which is harder to treat. An alternative possibility is that failure of multiple AEDs can indicate suboptimal adherence and pseudo-refractory epilepsy.[28]

Third, that use of EIAEDs was weakly associated with lower chance of seizure freedom. This is consistent with other reports[24] and is likely to be caused by lower perampanel levels due to enzyme induction.[29]

There was a weak association suggesting a higher chance of seizure freedom among patients whose concomitant AEDs included an SV2A modulator (ie, levetiracetam or brivaracetam) than those with no SV2A modulator. Of interest, retention rates did not differ between these 2

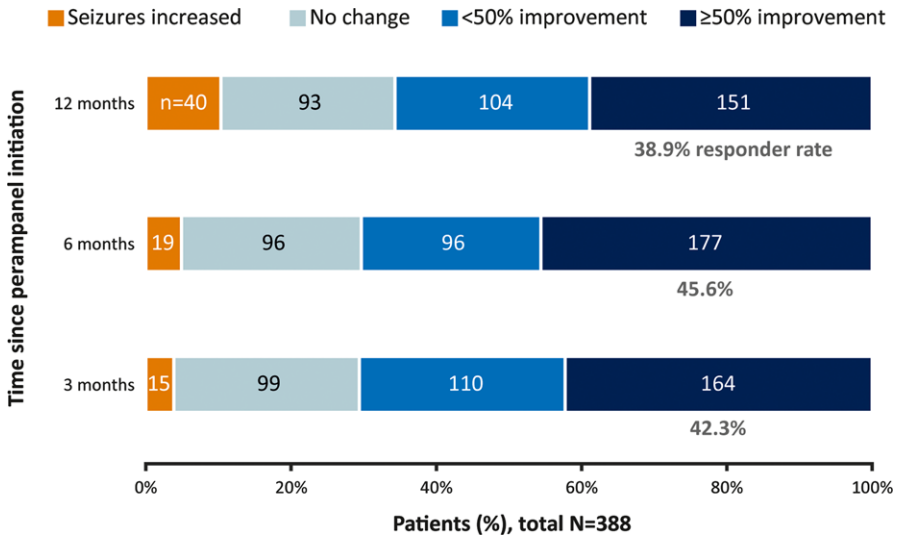

FIGURE 2 Seizure frequency change relative to baseline. Seizure frequency change relative to baseline in the 388 patients who had evaluable seizure frequency data at baseline 3, 6, and 12 months

populations (Figure S2), but there was a possible trend toward increased retention in those using concomitant sodium-channel blockers (versus no sodium-channel blockers) and concomitant retigabine versus no retigabine (although the populations were uneven and small, with only 76 patients taking retigabine, and only 265 patients taking no concomitant sodium-channel-blocking drugs at baseline). No other clear associations between the mechanism of action of concomitant AEDs and seizure freedom or retention were found. The possible synergistic efficacy of different AED combinations is an interesting topic that deserves further examination in future studies. Our ability to explore this further is limited by lack of detail on the exact timings of concomitant AED use.

Of interest, retention appeared similar between people taking ≤3 concomitant AEDs and those taking ≥4 (Figure S2B), and only small differences were seen between those with ≤2 and >2 prior AEDs (Figure 1B). So although an increasing number of prior AEDs does affect the chance of seizure freedom, the addition of perampanel still benefitted some patients with multiple failed AEDs and those with heavy concomitant AED load. This suggests that the 0% seizure-free rate previously reported in people with 6-7 prior AEDs[30] is an overly negative view of the true pattern of seizure response and remission.[31,32]

Our data cannot be compared directly with other real-world evidence and with clinical studies, mainly because of the diversity of real-world populations; however, all aspects of our data were broadly in line with other similarly designed studies. Our 1-year retention rate (48%) is in line with other reports with perampanel (46%,[33] 48%,[34,35] 55%,[36,37]). Retention is an important measure of overall effectiveness not just AEDs but also other drugs, in a naturalistic setting, as it reflects the combined impact of a drug's effectiveness and its tolerability.[38]

Seizure freedom rates vary widely in observational studies with perampanel and will be influenced heavily by patient populations and by the exact definition of seizure freedom and the calculation method. Our figure of 9% (seizure-free at 1 year and for ≥6 months) is lower than some reports that use similar definitions (14%[39]), higher than others (0%,[34,37,40,41] 4%,[33] 6%[35,42]), and higher than in the phase III clinical trials (~4% seizure-free over a 13-week maintenance period).[5] We also calculated the pragmatic seizure freedom rate (3.1%)—the number seizure-free expressed as a proportion of the FAS (n = 2396). This avoids any bias from excluding people who cannot continue on the drug for 12 months, but in a population like ours, the pragmatic method underestimates the true rate, as many patients who were actually seizure-free have to be excluded because definitions or data collection is not exactly consistent. Our 50% responder rate was 39% at 1 year, which is similar to rates in the clinical trials after 19 weeks of exposure but could be calculated for only relatively few people, as seizure frequency was rarely recorded in a format we could use in our analysis.[5,43]

It is important to note that we did not see any previously unknown adverse reactions, and our overall adverse event rates were consistent with previous reports. Between 50 and 70% of participants reported at least 1 adverse event during perampanel treatment in most observational studies,[35,39–42,44] and up to 81% in a refractory population with intellectual disability.[34] Dizziness is reported at a consistent rate of 14-18%[34–36,39,41,42,44] which is much lower than in clinical trials (32% with 8 mg perampanel).[5] This is probably due to slower titration in routine use than the 2 mg

TABLE 3 Logistic regression of variables and seizure freedom

Variable	Regression coefficient			Significant results, n (%)[d]		Non-sig. results, n (%)
	Median	Minimum	Maximum	>0	<0	
Age at PER start	0.035	0.034	0.045	**792 (100%)**	0	0
Number of previous AEDs	−0.215	−0.259	−0.185	0	**792 (100%)**	0
Use of EIAED(s)[a]	−756	−1.014	−0.415	0	*594 (75%)*	198 (25%)
MOA: SV2A[b]	0.668	0.423	0.997	*476 (60%)*	0	316 (40%)
PER late add-on[c]	−0.796	−1.06	0.394	0	*459 (58%)*	333 (42%)
MOA: Sodium-channel[b]	−0.728	−1.17	−0.272	0	310 (39%)	482 (61%)
MOA: GABA[b]	−0.579	−0.851	−0.323	0	70 (8.8%)	722 (91.2%)
MOA: Mixed[b]	−0.255	−0.695	0.172	0	2 (0.3%)	790 (99.7%)
Duration of epilepsy	0.004	−0.017	0.015	0	0	792 (100%)
Symptomatic etiology	0.203	−0.007	0.448	0	0	792 (100%)
MOA: Calcium-channel[b]	−0.249	−0.63	0.141	0	0	792 (100%)
MOA: Potassium-channel[b]	−1.25	−1.549	−0.977	0	0	792 (100%)
TEAEs in first 12 months	0.008	−0.191	0.295	0	0	792 (100%)

AED, antiepileptic drugs; EIAED, enzyme-inducing AED; GABA, γ-aminobutyric acid; MOA, mechanism of action; PER, perampanel; SV2A, synaptic vesicle protein 2A; TEAE, treatment-emergent adverse event.

Bold indicates variables with strong associations with seizure freedom. *Italics* indicate variables with weaker associations with seizure freedom.

[a]Defined as carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, and primidone.

[b]For AEDs in each MOA category see Table S5.

[c]Previously failed >2 AEDs.

[d]Significant results with a regression coefficient >0 indicate positive correlation; <0 indicates a negative correlation.

every week used in the trials. Slow titration in our dataset (increases at intervals of >2 weeks) was, however, not associated with fewer total AEs than fast titration, which is inconsistent with clinical experience and with other reports with perampanel.[24,35,45]

Behavioral reactions can be problematic with some AEDs.[46] In our population, behavioral TEAEs (including aggression, anger, and irritability) were documented in 19% of people, depression in 4.8%, and suicidal ideation in 0.8%. The rate of behavioral TEAEs was slightly lower in our elderly population (16.5%) than overall (19%). Our grouping of "behavioral TEAEs" does not correspond directly with any TEAE groupings reported from the phase III trials, so comparisons are difficult. The closest match would be TEAEs broadly related to aggression or hostility, which occurred in 12% (8 mg) and 20% (12 mg) of those in the clinical trials.[47] Our overall rate of psychiatric TEAEs (25.7%) was slightly higher than reported in the phase III trials (17%, 8 mg; 22%, 12 mg),[47] which is not surprising as the trials excluded patients with significant psychiatric conditions.[48]

Perampanel doses of 6-8 mg are most common in studies of routine clinical use,[24,35,45] and slightly lower doses may be effective in some populations such as older people and those with intellectual disability. For example, people with epilepsy and profound intellectual disability were maintained on a lower perampanel dose (median 4 mg) than people with mild or no intellectual disability (median 6 mg).[23] Our subpopulation of people aged ≥65 used a lower median dose (6 mg) than the overall population (8 mg).

Limitations of this study include the retrospective rather than prospective data collection; the lack of control group and blinding; the wide variation in populations, settings, and standard practice that comes from multicenter and cross-country pooling of data; and the nonoverlapping and missing data that result from different data collection practices in the contributing centers. The retrospective nature means that statistically rigorous exploration of associations between variables and outcomes was not possible; however, we felt that the large numbers did justify attempts at retention survival curves, and the logistic regression analyses to identify predictors of seizure freedom, which could provide helpful guidance for future detailed study.

The benefits of collecting such a wide spectrum of data include the generalizability of the results to routine clinical practice; the ability to explore subpopulations that have small numbers in individual centers; the power of large numbers to detect idiosyncratic reactions; and the ability to construct meaningful survival curves for retention.

In conclusion, perampanel was effective in routine clinical use in a wide variety of people with epilepsy, which was usually refractory. No unexpected patterns of adverse events were detected. We recommend consistent bedtime

TABLE 4 Characteristics and perampanel exposure, patients aged ≥65 years

	Patients aged ≥65 years (N = 135)
Female gender, n (%)	68 (50.4%)
Evaluable population	N = 135
Median age at PER initiation, years (IQR)	69 (67-74)
Evaluable population	N = 135
Median duration of epilepsy, years (IQR)	45 (17.4-65.5)
Evaluable population	N = 124
Etiology evaluable population, n (%)	N = 128
Symptomatic	92 (71.9%)
Unknown[a]	35 (27.3%)
Other	1 (0.8%)
Median number of previously failed AEDs (IQR)	5 (2-8)
Evaluable population	N = 131
Number of concomitant AEDs at PER initiation (IQR)	2 (1-3)
Evaluable population	N = 133
Taking EIAEDs[b] at PER initiation, n (%)	58 (43.6%)
Evaluable population	N = 133
Median PER dose at 12 months	6 (4-8)
Evaluable population	N = 56
Median time on PER, months (IQR)	11.4 (4.9-12.9)
Evaluable population	N = 99

[a]Previously "cryptogenic."
[b]Defined as carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, and primidone.

dosing and slow titration (increasing every 2-4 weeks) to 6-8 mg. Data from our analysis, and others,[24,35,45] also suggest that perampanel can be considered as an early add-on option. An interesting observation is that perampanel seemed to be very effective in older people in this cohort, but this remains to be confirmed in clinical trials.

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DISCLOSURE OF CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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

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