Received: 31 July 2023 | Revised: 22 November 2023 | Accepted: 30 November 2023

DOI: 10.1111/epi.17843

Epilepsia®

RESEARCH ARTICLE

A real-world comparison among third-generation antiseizure medications: Results from the COMPARE study

Roberta Roberti[1] | Gianfranco Di Gennaro[1] | Francesca Anzellotti[2] | Dario Arnaldi[3,4] | Vincenzo Belcastro[5] | Simone Beretta[6] | Giovanni Boero[7] | Paolo Bonanni[8] | Laura Canafoglia[9] | Alfredo D'Aniello[10] | Filippo Dainese[11] | Carmen De Caro[1] | Giancarlo Di Gennaro[10] | Roberta Di Giacomo[12] | Jacopo C. DiFrancesco[6] | Fedele Dono[2,13] | Giovanni Falcicchio[14] | Edoardo Ferlazzo[15,16] | Nicoletta Foschi[17] | Silvia Franciotta[11] | Antonio Gambardella[18] | Alfonso Giordano[19] | Luigi Francesco Iannone[20] | Angelo Labate[21] | Angela La Neve[14] | Simona Lattanzi[17] | Ugo Leggio[22] | Claudio Liguori[23,24] | Marta Maschio[25] | Annacarmen Nilo[26] | Francesca Felicia Operto[27] | Angelo Pascarella[15,16] | Giada Pauletto[28] | Rosaria Renna[29] | Gionata Strigaro[30,31] | COMPARE Study Group† | Emilio Russo[1]

Correspondence
Emilio Russo, Science of Health Department, School of Medicine, University Magna Græcia of Catanzaro, Via T. Campanella, 115, Catanzaro 88100, Italy.
Email: erusso@unicz.it

Abstract

Objective: There are few comparative data on the third-generation antiseizure medications (ASMs). We aimed to assess and compare the effectiveness of brivaracetam (BRV), eslicarbazepine acetate (ESL), lacosamide (LCM), and perampanel (PER) in people with epilepsy (PWE). Efficacy and tolerability were compared as secondary objectives.

Methods: This multicenter, retrospective study collected data from 22 Italian neurology/epilepsy centers. All adult PWE who started add-on treatment with one of the studied ASMs between January 2018 and October 2021 were included. Retention rate was established as effectiveness measure and described using Kaplan–Meier curves and the best fitting survival model. The responder status and the occurrence of adverse events (AEs) were used to evaluate efficacy and

Abbrevations: AORN, Azienda Ospedaliera di rilievo nazionale; ASST, Azienda socio sanitaria territoriale; DiBraiN, Dipartimento di biomedicina traslazionale e neuroscienze; DIDAS, Dipartimento didattico-scientifico-assistenziale; IRCCS, Istituto di ricovero e cura a carattere scientifico; SS, santissima; UOSD, Unità Operativa Semplice Dipartimentale

Roberta Roberti and Gianfranco Di Gennaro contributed equally to this work.

†COMPARE Study Group members are given in Appendix 1.

For Affiliation refer page on 469

safety, respectively. The odds of AEs and drug efficacy were estimated by two multilevel logistic models.

Results: A total of 960 patients (52.92% females, median age = 43 years) met the inclusion criteria. They mainly suffered from structural epilepsy (52.29%) with monthly (46.2%) focal seizures (69.58%). Compared with LCM, all the studied ASMs had a higher dropout risk, statistically significant in the BRV levetiracetam (LEV)-naïve (hazard ratio [HR] = 1.97, 95% confidence interval [CI] = 1.17–3.29) and PER groups (HR = 1.64, 95% CI = 1.06–2.55). Women were at higher risk of discontinuing ESL (HR = 5.33, 95% CI = 1.71–16.61), as well as PER-treated patients with unknown epilepsy etiology versus those with structural etiology (HR = 1.74, 95% CI = 1.05–2.88). BRV with prior LEV therapy showed lower odds of efficacy (odds ratio [OR] = .08, 95% CI = .01–.48) versus LCM, whereas a higher efficacy was observed in women treated with BRV and LEV-naïve (OR = 10.32, 95% CI = 1.55–68.78) versus men. PER (OR = 6.93, 95% CI = 3.32–14.44) and BRV in LEV-naïve patients (OR = 6.80, 95% CI = 2.64–17.52) had a higher chance of AEs than LCM.

Significance: Comparative evidence from real-world studies may help clinicians to tailor treatments according to patients' demographic and clinical characteristics.

KEYWORDS

brivaracetam, comparative study, eslicarbazepine acetate, lacosamide, perampanel

1 | INTRODUCTION

Epilepsies are common and heterogeneous neurological disorders, characterized by an enduring predisposition to generate epileptic seizures,[1] which significantly affect the quality of life of approximately 70 million people worldwide.[2,3]

Symptomatic pharmacological treatment with antiseizure medications (ASMs) by different monotherapies or combinations remains the mainstay for people with epilepsy (PWE), but there are still unmet needs for both the treatment-responsive population (facing tolerability and adherence issues) and treatment-resistant patients (needing better or more targeted efficacy).[4]

Over the past decades, the number of available ASMs has progressively increased, and new drugs with either improved or new mechanisms of action have been marketed.[5,6] Compared with first-generation ASMs, most of them are characterized by more favorable pharmacokinetics and drug interaction profiles. Nevertheless, efficacy profiles do not seem to be improved, and so far, little has changed in the incidence of drug-resistant epilepsy.[7] Furthermore, to optimize and tailor treatments, clinicians have to choose among ASMs that often have overlapping indications, and selecting the most appropriate drug for each patient may be difficult.[8] Comparative evidence of the effectiveness and safety of each ASM is crucial to developing treatment guidelines supporting clinical decisions.[9] The best source of evidence comes from randomized controlled trials (RCTs), but it is well recognized that their results may not accurately reflect the effectiveness of therapies in real-life settings.[10,11] Additionally, to be approved, new ASMs only have to demonstrate reducing seizure frequency more effectively than placebo, without undue side effects.[10,12] Because regulatory bodies do not require direct comparisons between ASMs, few head-to-head RCTs have been conducted[13,14]; for some ASMs, comparative effectiveness trials may not be conducted for a long time after marketing, and for other ones, they may

Key Points

- This study supports the long-term effectiveness and tolerability of BRV, ESL, LCM, and PER
- LCM had the highest retention rate throughout the 3-year study period
- Age, sex, and etiology of epilepsy are potential outcome predictors deserving further investigation

never be conducted at all.[10,11] In the absence of head-to-head RCTs, as an alternative source of comparative evidence both indirect comparisons between ASMs through network meta-analyses and real-world evidence (RWE) studies may be used, preferably the latter.[11]

To date, there are no head-to-head studies performed to directly compare the efficacy and safety of third-generation ASMs.[15] Furthermore, being recently marketed, there is little information on long-term safety profiles. In this scenario, data from RWE studies can be useful to address the question of which could be the best (or the most suitable) ASM for each patient.

Herein, we report the results from COMPARE, a multicenter, observational, retrospective study aimed at assessing and comparing the retention rate, efficacy, and tolerability of the third-generation ASMs, approved for focal epilepsy, brivaracetam (BRV), eslicarbazepine acetate (ESL), lacosamide (LCM), and perampanel (PER) when used as add-on treatment in PWE.

2 | MATERIALS AND METHODS

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Guidelines[16] were followed to report this multicenter observational study, which collected data from 22 Italian hospitals/epilepsy centers between January 2018 and October 2021. Adult (age ≥ 18 years) outpatients with an established diagnosis of epilepsy according to the International League Against Epilepsy classification,[17] who started treatment with one ASM among BRV, ESL, LCM, and PER as part of routine clinical practice, at licensed doses and indications, were retrospectively identified. To make the study cohort more homogenous, we only included patients starting one of the drugs as an add-on therapy. Exclusion criteria were status epilepticus as a reason for administration of one of the studied ASMs, documented changes in antiseizure therapy (either dose or type of ASM) during the previous 3 months, history of substance abuse during the previous 2 years, pregnancy and/or breastfeeding, and psychogenic nonepileptic seizures. The overall data collection was approved by the ethics committee of Calabria Region, Italy (protocol number 115/19) and conducted in accordance with the Declaration of Helsinki and center-specific institutional requirements. Because data collection was retrospective and anonymized, written informed consent was not required.

2.1 | Data collection

Demographics and clinical data collected at baseline included age, sex, disease duration, seizure type, epilepsy etiology, history of febrile seizures and epilepsy surgery, number of therapeutic attempts before inclusion, concomitant ASMs, and seizure frequency. The latter was defined as the mean monthly seizure frequency in the 3 months before starting study treatments and classified as daily (≥1 seizure per day), weekly (≥1 seizure per week), or monthly (<1 seizure per week). Patient seizure diaries and medical records of routine follow-up visits were reviewed to collect data on retention, clinical response, and occurrence of adverse events (AEs) after 6, 12, 24, and 36 months of therapy, according to the different duration of patients' follow-up. Data on ASM discontinuation and its causes were also reported. For patients lost at follow-up, we did not assume that they could continue at another prescriber.

The principal investigator at each center checked individual patient data on a regular basis to handle errors or inconsistencies; a further check of data quality and completeness was carried out by the national coordinator group of the study.

2.2 | Outcome measures

The percentage of patients still on therapy (retention rate) over time was established as primary endpoint, because retention data represents a global indicator of a drug's clinical effectiveness recommended by the European Medicines Agency.[18]

Two secondary outcomes were also established to assess and compare the efficacy and safety of the studied ASMs. The efficacy outcome was evaluated using the responder status, defined as the responder rate (≥50% reduction in monthly seizure frequency compared with baseline) plus the seizure-free rate (no seizures since the last study time point), whereas the percentage of patients who experienced ≥1 AE was assumed as safety outcome. AEs were also detailed and classified using the Medical Dictionary for Regulatory Activities (version 22.0).

2.3 | Statistical analysis

Gaussian continuous variables were described by mean and SD. Median and interquartile range were used in case of skewness. Counts and percentages were used for categorical variables. Normality distribution of continuous variables was verified by the Shapiro–Wilk test.

Five treatment subgroups were considered, as patients treated with BRV were divided into two groups, depending on whether they were naïve to levetiracetam (LEV) treatment.

Kaplan–Meier curves were used to investigate the overall between-drug differences in retention time

(which describes how long the patients remain on therapy, and as a consequence, the retention rate at a specific time point), and the best fitting survival model was used to estimate the role of the following potential predictors: sex, age, epilepsy etiology, number of previously used ASMs (two or less, more than two), disease duration (months from diagnosis), responder status, and occurrence of AEs. Within-hospital correlation was accounted by entering a shared frailty term in the model. Model selection was performed by comparing the semiparametric Cox model and the most common (Weibull, exponential, Gompertz) parametric models. Comparison was carried out by using Akaike information criterion and analyzing the Cox–Snell residuals. The proportional hazards assumption was assessed by analyzing the Schoenfeld residuals.

The odds of AEs and drug efficacy were estimated by two multilevel logistic models in which clustering within patients and within hospitals was accounted. Estimates were adjusted for the previously listed covariates and for the follow-up time. Model adequacy was assessed by investigating Pearson residuals, goodness of fit test, and specification link test for single-equation models.

Both the survival and the logistic models described above were also run separately for each drug to compare how patient characteristics affect retention, responder status, and AEs.

The analysis had exploratory and hypothesis-generating aims. No formal power analysis was performed. Missing data were treated by listwise deletion. Efficacy and safety data on patients who dropped out were imputed using the last observation carried forward.

Statistical significance was set at 5%. All statistical analyses were conducted with the statistical package Stata 16.0.

3 | RESULTS

3.1 | Baseline demographic and clinical characteristics

Baseline demographic and clinical characteristics of the overall cohort are summarized in Table 1, which also shows patients' stratification by treatment subgroup. All patients had at least one concomitant ASM, as detailed in Table S1 (percentages of <1% in the overall cohort were not reported).

At the cutoff date of October 2021, 960 patients (52.92% females, median age = 43 years) met the inclusion criteria. Perampanel was the most commonly prescribed ASM (355, 37%), followed by LCM (263, 27.4%), BRV (242, 25.2%), and ESL (100, 19.4%).

One hundred sixty-five patients treated with BRV were naïve to LEV, whereas 77 patients had a history of prior LEV therapy.

The majority of patients had only focal seizures (69.58%), 5.21% had only generalized seizures, and for 2.19% onset was unknown; the remaining patients experienced both seizure types. More than half of the overall cohort suffered from structural epilepsy (52.29%). At baseline, the median disease duration was 204 months (Q_1-Q_3 = 80–372), and seizure frequency was mainly monthly (46.2%). The overall cohort had a history of a median of 3 ($Q1$-Q_3 = 2–4) previous therapeutic attempts. The studied ASMs were administered concomitantly with a median number of 2 (Q_1-Q_3 = 1–2) ASMs, mainly LEV (32.8%), valproic acid (21.6%), and carbamazepine (21.1%).

3.2 | Follow-up data

Treatment duration ranged from 1 to 36 months. Follow-up visits were on average quarterly during the first year of treatment and half-yearly thereafter. Of 960 patients, 904 underwent a visit after 6 months of treatment; longer term follow-up data, at 12, 24, and 36 months, were available for 718, 562, and 375 patients, respectively.

The median daily dose remained stable over time in patients treated with BRV who had a history of prior LEV therapy, as well as in patients who started LCM, whereas it increased progressively in the remaining treatment subgroups (Table S2).

3.3 | Outcome measures

3.3.1 | Retention rate

Overall, 197 patients (20.5%) discontinued treatment, mainly due to lack of efficacy (121, 61.4%), followed by intolerable AEs (74, 37.6%). Fifty-three (5.5%) patients were lost to follow-up, and two women (.8%) withdrew from treatment because they had planned a pregnancy. Patients lost to follow-up, dropout rates, and related causes in the overall cohort and stratified per drug are summarized in Table S3.

According to Kaplan–Meier analysis (Figure 1), BRV in LEV-naïve patients had the lowest retention and LCM had the highest. An exponential parametric frailty model was selected using Akaike information criterion and Cox–Snell residual analysis, as reported in Table 2. According to the model, the dropout hazard was doubled in BRV patients naïve to LEV (hazard ratio [HR] = 1.97, 95% confidence interval [CI] = 1.17–3.29) and PER showed a 64% increased risk (HR = 1.64, 95%

TABLE 1 Baseline characteristics of the study cohort.

Characteristic	Overall patients, $n = 960$	Brivaracetam, LEV-naïve, $n = 165$	Brivaracetam, prior LEV, $n = 77$	Eslicarbazepine acetate, $n = 100$	Lacosamide, $n = 263$	Perampanel, $n = 355$
Female sex, *n* (%)	508 (52.92)	87 (52.7)	41 (53.2)	48 (48)	140 (53.2)	192 (54.1)
Age, years, median (Q_1–Q_3)	43 (29–56)	43 (30–53.5)	47 (33.5–54)	45 (31–58)	44 (27–59)	40 (27–54)
Disease duration, months, median (Q_1–Q_3) [$n = 947$]	204 (80–372)	270 (149.3–429)	324 (132.5–474)	180 (72–300)	130 (36–268.5)	216 (96–372)
Seizure type, *n* (%)						
Focal	668 (69.58)	114 (69.1)	59 (76.6)	72 (72)	195 (74.2)	228 (64.2)
Generalized	50 (5.21)	6 (3.6)	2 (2.6)	6 (6)	8 (3)	28 (7.9)
Focal and generalized	221 (23.02)	44 (26.7)	16 (20.8)	20 (20)	50 (19)	91 (25.6)
Unknown	21 (2.19)	1 (.6)	0	2 (2)	10 (3.8)	8 (2.3)
Febrile convulsions, *n* (%) [$n = 919$]	65 (7.1)	9 (5.8)	8 (10.8)	7 (7)	14 (5.4)	27 (8.1)
Etiology, *n* (%)						
Structural	502 (52.29)	84 (50.9)	37 (48.1)	57 (57)	144 (54.8)	180 (50.7)
Unknown	361 (37.61)	60 (36.4)	32 (41.5)	35 (35)	94 (35.7)	140 (39.5)
Genetic	72 (7.50)	15 (9.1)	7 (9.1)	3 (3)	21 (8)	26 (7.3)
Immune	13 (1.35)	3 (1.8)	1 (1.3)	1 (1)	3 (1.1)	5 (1.4)
Infectious	12 (1.25)	3 (1.8)	0	4 (4)	1 (.4)	4 (1.1)
Seizure frequency, *n* (%) [$n = 940$]						
Daily	198 (21)	42 (26.1)	17 (22.4)	16 (16.8)	37 (14.3)	86 (24.6)
Weekly	308 (32.8)	65 (40.4)	18 (23.7)	28 (29.5)	83 (32.2)	114 (32.6)
Monthly	434 (46.2)	54 (33.5)	41 (53.9)	51 (53.7)	138 (53.5)	150 (42.8)
Epilepsy surgery, *n* (%) [$n = 946$]						
Not indicated	795 (84)	131 (80.4)	58 (76.3)	87 (87)	224 (85.8)	295 (85.3)
Performed	73 (7.7)	15 (9.2)	10 (13.2)	8 (8)	15 (5.8)	25 (7.2)
Indicated but not performed	78 (8.3)	17 (10.4)	8 (10.5)	5 (5)	22 (8.4)	26 (7.5)
ASMs before inclusion, median (Q_1–Q_3) [$n = 941$]	3 (2–4)	4 (3–5)	4 (2–5)	3 (2–4)	2 (1–3)	3 (2–4)
Concomitant ASMs, median, (Q_1–Q_3) [$n = 944$]	2 (1–2)	2 (1–3)	1.5 (1–2)	1 (1–2)	1 (1–2)	2 (1–2)

Note: Numbers in brackets represent number of patients for whom data were available.

Abbreviations: ASM, antiseizure medication; LEV, levetiracetam.

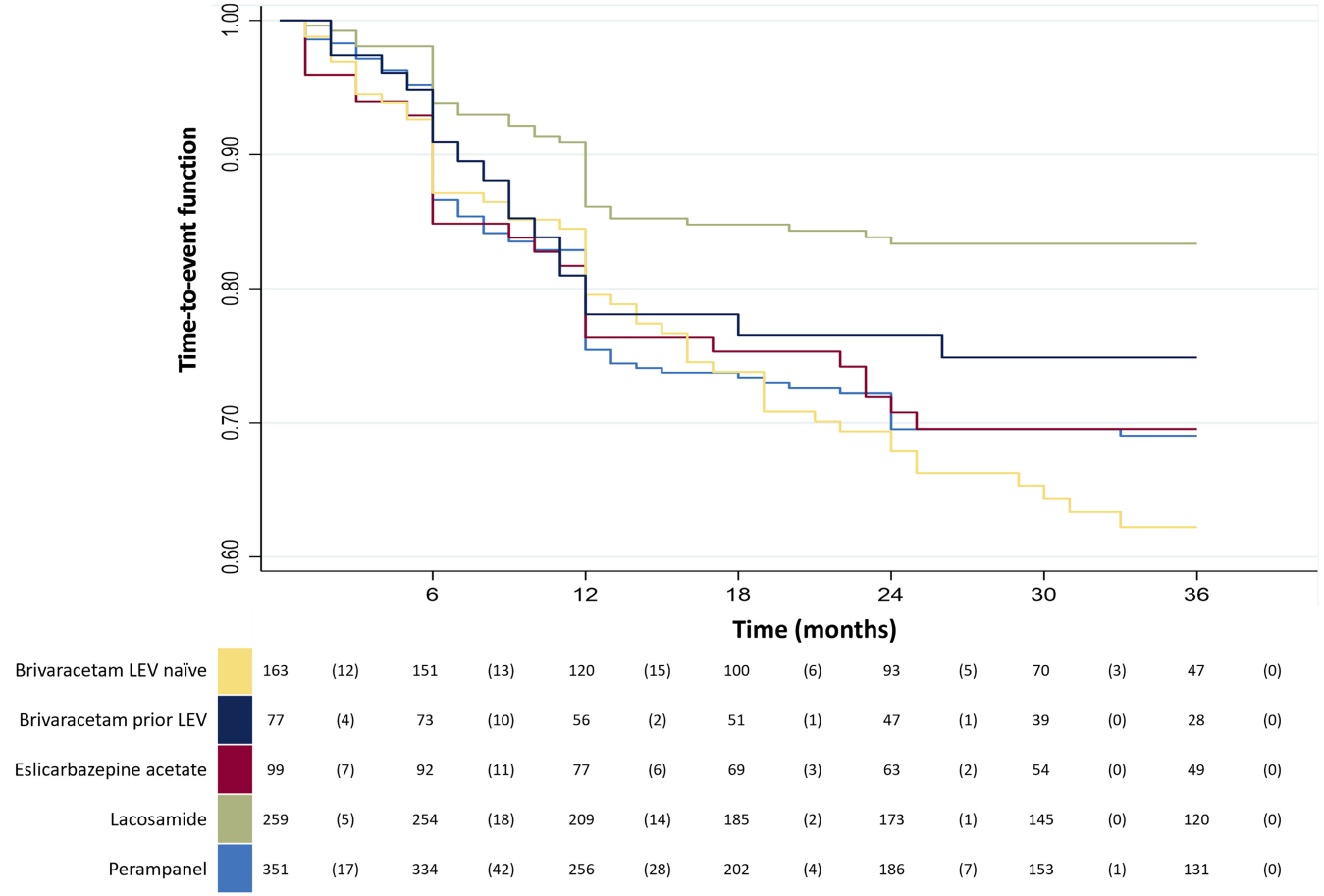

FIGURE 1 Retention rates of the studied drugs according to Kaplan–Meier analysis. LEV, levetiracetam.

CI = 1.06–2.55) when compared to LCM (reference category). As expected, drug efficacy was significantly associated with a lower dropout hazard (HR = .19, 95% CI = .13–.27) and the presence of AEs was associated with a higher risk (HR = 2.09, 95% CI = 1.50–2.93). Sex, age, epilepsy etiology, number of previously used ASMs, and disease duration showed no statistically significant effect on the overall retention time. The clustering of patients in the different hospitals/epilepsy centers showed a significant effect, as demonstrated by the likelihood-ratio test of the shared frailty ($p < .001$), and Schoenfeld residuals-based test ($p = .069$) assured the proportionality of hazard assumption.

When the effect of patient characteristics was investigated considering the drugs individually, age did not appear as a significant predictor of retention time. Only in patients treated with LCM, a 3% reduction in hazard of dropout was associated with increasing age of 1 year (HR = .97, 95% CI = .94–.99). Regarding sex-related differences, female patients were found to be at higher risk of abandoning ESL (HR = 5.33, 95% CI = 1.71–16.61) and when treated with BRV, without prior LEV use, they showed an almost statistically significant increased risk of dropout (HR = 1.86, 95% CI = 1.00–3.46). Interestingly, PER-treated patients with unknown epilepsy etiology showed a higher dropout risk (HR = 1.74, 95% CI = 1.05–2.88) than those with structural etiology (reference category). Occurrence of AEs more than doubled the risk of discontinuation in patients treated with PER (HR = 2.39, 95% CI = 1.48–3.87) and LCM (HR = 2.82, 95% CI = 1.15–6.92), whereas the responder status significantly protected against dropout regardless of the drug, with the higher hazard reduction observed in the patients treated with LCM (HR = .08, 95% CI = .03–.23). Finally, the disease duration and the number of ASMs taken previously were not associated with the discontinuation of any of the drugs under examination.

3.3.2 | Efficacy

LCM showed the highest rate of responder status after 6 months of treatment (64.3%) and maintained percentages of ~60% over time; 1 year after starting therapy, the proportion of responder plus seizure-free patients with ESL was the largest reported throughout the study (67.1%), but this percentage markedly reduced thereafter. The responder plus seizure-free rates with PER increased up to

TABLE 2 Hazard of dropout: Comparative and per drug estimates.

		Brivaracetam LEV-naïve	Brivaracetam prior LEV	Eslicarbazepine acetate	Lacosamide	Perampanel
Comparative estimates		**1.97 (1.17–3.29)**, p = .010*	**1.12 (.57–2.21), *p* = .740**	**1.68 (.95–2.96), *p* = .076**	**Reference category**	**1.64 (1.06–2.55)**, p = .028*
Characteristic						
Age	.99 (.98–1.01), *p* = .395	.98 (.95–1.01), *p* = .157	.99 (.95–1.05), *p* = .856	1.01 (.98–1.03), *p* = .542	.97 (.94–.99), ***p* = .018***	.99 (.98–1.01), *p* = .308
Female sex	1.24 (.93–1.65), *p* = .143	1.86 (1.00–3.46), *p* = .051	1.31 (.39–4.43), *p* = .668	5.33 (1.71–16.61), ***p* = .004****	.71 (.34–1.46), *p* = .346	.94 (.6–1.48), *p* = .792
Disease duration	1.00 (.99–1.00), *p* = .407	1.00 (.99–1.00), *p* = .057	1.00 (.99–1.01), *p* = .333	1.00 (.99–1.01), *p* = .263	1.00 (.99–1.00), *p* = .279	.99 (.99–1.00), *p* = .548
Number of previous ASMs > 2	.89 (.63–1.24), *p* = .487	.81 (.34–1.91), *p* = .623	.5 (.13–1.98), *p* = .325	1.11 (.39–3.17), *p* = .850	.57 (.28–1.19), *p* = .137	1.12 (.65–1.93), *p* = .672
Responder status	.19 (.13–.27), ***p* < .001*****	.24 (.11–.51), ***p* < .001*****	.17 (.03–.83), ***p* = .028***	.11 (.03–.37), ***p* < .001*****	.08 (.03–.23), ***p* < .001*****	.17 (.1–.31), ***p* < .001*****
AE occurrence	2.09 (1.50–2.93), ***p* < .001*****	1.06 (.48–2.36), *p* = .883	.59 (.07–5.22), *p* = .635	2.45 (.75–7.99), *p* = .136	2.82 (1.15–6.92), ***p* = .023***	2.39 (1.48–3.87), ***p* < .001*****
Cause of epilepsy[a]						
Unknown etiology	1.09 (.8–1.47), *p* = .598	1.09 (.57–2.11), *p* = .791	1.31 (.42–4.12), *p* = .645	.91 (.33–2.49), *p* = .858	1.03 (.47–2.26), *p* = .936	1.74 (1.05–2.88), ***p* = .030***
Other etiologies[b]	.75 (.41–1.39), *p* = .360	.55 (.18–1.7), *p* = .299	2.7 (.45–16.05), *p* = .276	.4 (.04–3.51), *p* = .405	.55 (.11–2.67), *p* = .458	.54 (.18–1.63), *p* = .276

Note: Results are reported as hazard ratio (95% confidence interval), *p*-value. Bold font indicates statistical significance.

Abbreviations: AE, adverse event; ASM, antiseizure medication; LEV, levetiracetam.

[a]Cause of epilepsy reference category: structural etiology.

[b]Other etiologies: genetic, immune, infectious. *$p < .05$, **$p < .01$, ***$p < .001$.

66.7% after 2 years of treatment. Finally, the responder status of patients treated with BRV and naïve to LEV rose from 41.8% (at 6 months) to 61.6% (36 months), whereas that of BRV patients previously treated with LEV was the lowest observed in the whole cohort, reaching 50% only after 3 years of treatment (Figures 2, S1, and S2).

In the overall logistic model (Table 3), BRV with prior LEV therapy showed lower odds of efficacy (odds ratio [OR] = .08, 95% CI = .01–.48) when compared with LCM (reference category). Perampanel (OR = .52, 95% CI = .17–1.64), ESL (OR = .45, 95% CI = .09–2.12), and BRV in LEV-naïve patients (OR = .41, 95% CI = .10–1.62) also appeared less effective than LCM, although the difference was not statistically significant. Furthermore, patients who had taken more than two other ASMs in the past had a lower probability of drug efficacy (OR = .05, 95% CI = .02–.12). Conversely, increased efficacy was observed with increasing follow-up duration (OR = 1.02, 95% CI = 1.00–1.04).

When the effect of patients' characteristics was assessed by stratifying the analysis for each drug (Table 3), patients who were previously treated with more than two ASMs had a lower probability of efficacy in the ESL (OR = .03, 95% CI = .003–.36), LCM (OR = .05, 95% CI = .01–.31), PER (OR = .06, 95% CI = .01–.39), and BRV-LEV-naïve (OR = .06, 95% CI = .01–.60) groups. In contrast, the difference was not statistically significant in the BRV group with a previous history of LEV therapy (OR = .08, 95% CI = .003–1.99).

A higher efficacy at longer follow-up time points was statistically significant only in patients treated with PER (OR = 1.03, 95% CI = 1.00–1.06). Finally, a higher efficacy was shown in women treated with BRV and naïve to LEV (OR = 10.32, 95% CI = 1.55–68.78) when compared with men.

3.3.3 | Safety

In the entire cohort, 189 of 960 (19.7%) patients experienced at least one AE; in detail, 92 of 355 (25.9%) were treated with PER, 40 of 263 (15.2%) with LCM, 28 of 165

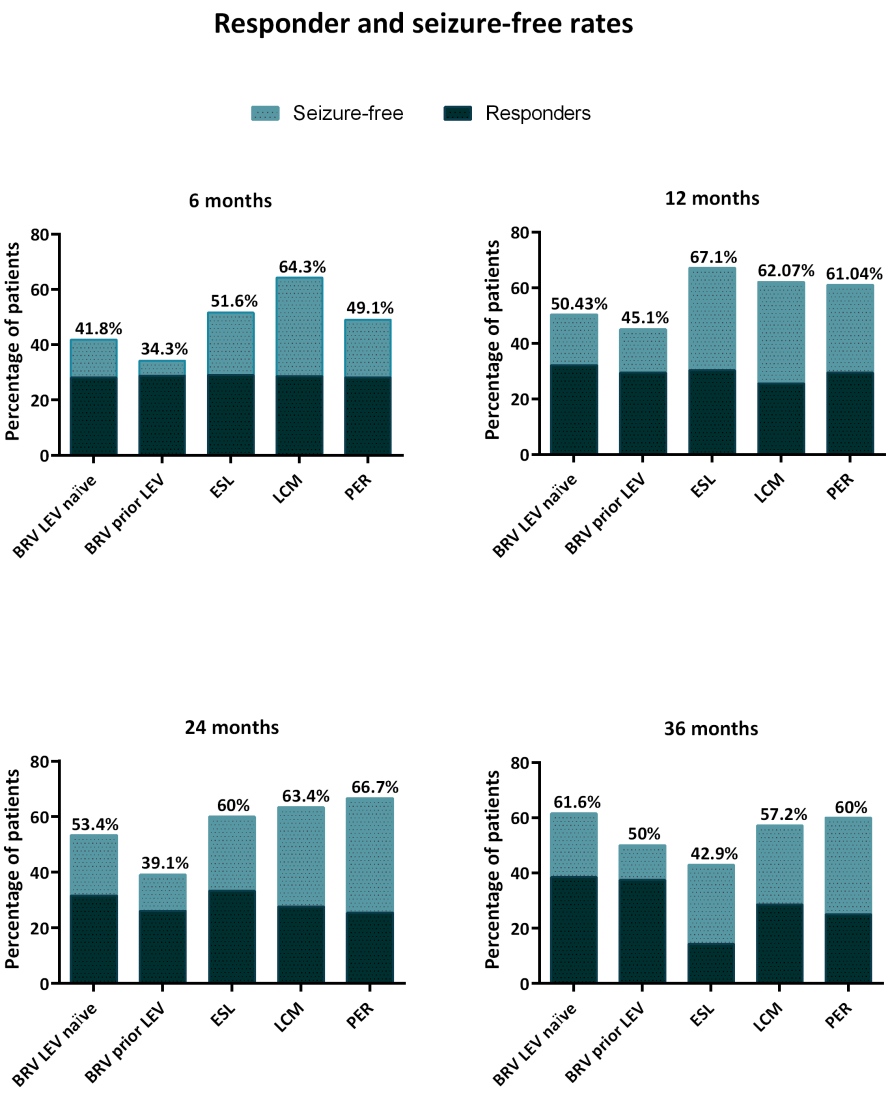

FIGURE 2 Responder and seizure-free rates at each study time point. BRV, brivaracetam; ESL, eslicarbazepine acetate; LCM, lacosamide; LEV, levetiracetam; PER, perampanel.

(16.7%) with BRV and without prior LEV, 18 of 100 (18.0%) with ESL, and 11 of 77 (14.3%) with BRV and prior LEV. Seventy-four of 189 (39.2%) discontinued treatment due to AEs that were not tolerable. However, there were no serious AEs. The overall number of AEs reported throughout the study period was 372 (see Table 4), and consisted mainly of dizziness (17.7%), irritability (17.7%), and somnolence (14.2%).

When the five drugs were compared for safety (Table 5), PER (OR = 6.93, 95% CI = 3.32–14.44) and BRV in LEV-naïve patients (OR = 6.80, 95% CI = 2.64–17.52) showed a higher chance of AEs than LCM (reference category). Conversely, in patients treated with ESL (OR = 1.47, 95% CI = .52–4.12) and BRV with prior LEV (OR = .89, 95% CI = .30–2.59), no statistically significant differences emerged. A higher frequency of AEs was observed with increasing age (OR = 1.03, 95% CI = 1.01–1.05). Interestingly, with increasing follow-up duration, the probability of AEs decreased (OR = .96, 95% CI = .94–.97).

When the five groups were analyzed separately, older patients showed a higher risk of AEs when treated with ESL (OR = 1.21, 95% CI = 1.05–1.39), LCM (OR = 1.09, 95% CI = 1.03–1.14), and with BRV without previous LEV therapy (OR = 1.06, 95% CI = 1.01–1.12). Contrariwise, a reduced chance of AE occurrence was associated with longer follow-up duration in patients treated with PER (OR = .97, 95% CI = .94–1.00), ESL (OR = .70, 95% CI = .54–.91), and LCM (OR = .95, 95% CI = .91–.99), and with increasing months since epilepsy diagnosis in the ESL (OR = .98, 95% CI = .97–1.00) and in the BRV with prior LEV (OR = .97, 95% CI = .94–1.00) groups. The effect of the disease duration was opposite in the BRV group naïve to LEV (OR = 1.01, 95% CI = 1.00–1.01).

Among patients treated with ESL (OR = 23.44, 95% CI = 1.19–462.91) and with LCM (OR = 7.90, 95% CI = 1.41–44.25), those who were treated with more than two previous ASMs were significantly more at risk of AEs. Moreover, female subjects treated with BRV and LEV-naïve had a higher risk of AEs (OR = 5.36, 95% CI = 1.23–23.36). Finally, compared with patients suffering from structural epilepsy, those with unknown etiology treated with BRV and naïve to LEV had a lower chance of AEs (OR = .13, 95% CI = .03–.62), whereas those treated with ESL reported AEs more frequently (OR = 77.68, 95% CI = 2.93–2062.34).

4 | DISCUSSION

This multicenter, retrospective study provides real-world data on the effectiveness and safety of four among the newest ASMs in PWE. Our cohort consisted of 960 adult patients from 22 Italian centers, mainly refractory to pharmacological treatment. After the start of one of the studied ASMs as part of routine clinical practice, patients showed high retention rates, albeit with increasing differences over time. At 1 year of follow-up, all the ASMs had retention rates of at least 75%, in line with previous real-life studies.[19–21] The only exception was LCM, whose retention rate was >80%, as already reported by a retrospective, early add-on study,[22] but maintained through the study period. The retention rate of the remaining ASMs progressively reduced; as a consequence, the gap between the percentages shown by the survival curves after 3 years of follow-up ranged from >80% (LCM) to >50% (BRV in patients naïve to LEV). Consistently, an overall retention rate of 50.8% was observed in long-term follow-up data on patients treated with BRV in clinical practice.[23]

Compared with LCM, all the studied ASMs had a higher risk of treatment withdrawal, statistically significant in the BRV LEV-naïve and PER groups, which also were associated with the highest odds of AE occurrence. Furthermore, patients treated with LCM had higher odds of achieving responder status, although statistical significance was reached only in comparison with the BRV group with a history of prior LEV therapy.

Responder status and AE occurrence significantly affected the hazard of dropout in the overall logistic model (albeit in opposite directions), highlighting how the decision to continue a therapy is the result of a complex benefit–risk balance. In this light, retention rates are confirmed as good indicators of clinical efficacy, tolerability, safety, and adherence over a specified time frame.[24]

Age and sex emerged as potential predictors of treatment discontinuation in the per drug stratified analysis, suggesting a reduced risk with increasing age in patients taking LCM, whereas female sex might predict an increased risk of discontinuing ESL. Limited data exist on the use of LCM in elderly patients[25]; single-center, real-life experiences showed a favorable tolerability profile.[26,27] However, elderly patients may be at increased risk of cardiac disorders and falls, and the special warnings for cardiac rhythm and conduction problems, as well as for dizziness, reported by the LCM summary of product characteristics (SmPC), should be kept in mind. Women treated with ESL had a five times greater dropout risk compared with men, and a similar (but not statistically significant) trend was observed in women naïve to LEV who were taking BRV. It is noteworthy that in the logistic models assessing the effects of patients' characteristics for each drug, female patients treated with BRV and naïve to LEV also were 10 times more

TABLE 3 Efficacy outcome (responder status): Comparative and per drug estimates.

		Brivaracetam LEV-naïve	Brivaracetam prior LEV	Eslicarbazepine acetate	Lacosamide	Perampanel
Comparative estimates		**.41 (.10–1.62), *p* = .202**	**.08 (.01–.48)**, p = .006**	**.45 (.09–2.12), *p* = .309**	**Reference category**	**.52 (.17–1.64), *p* = .266**
Characteristic						
Age	1.02 (.99–1.04), *p* = .272	1.02 (.96–1.09), *p* = .459	.98 (.88–1.09), *p* = .680	1.04 (.98–1.11), *p* = .206	.98 (.93–1.04), *p* = .544	1.03 (.98–1.08), *p* = .275
Female sex	1.16 (.51–2.65), *p* = .716	10.32 (1.55–68.78), ***p* = .016***	1.07 (.04–25.65), *p* = .967	.26 (.03–2.25), *p* = .223	1.06 (.21–5.34), *p* = .947	.47 (.10–2.12), *p* = .325
Disease duration	.99 (.99–1.00), *p* = .064	.99 (.99–1.00), *p* = .775	.99 (.99–1.00), *p* = .906	.99 (.99–1.00), *p* = .385	.99 (.99–1.00), *p* = .527	.99 (.99–1.00), *p* = .121
Number of previous ASMs > 2	.05 (.02–.12), ***p* < .001*****	.06 (.01–.60), ***p* = .017***	.08 (.003–1.99), *p* = .122	.03 (.003–.36), ***p* = .005****	.05 (.01–.31), ***p* = .002****	.06 (.01–.39), ***p* = .003****
Follow-up duration	1.02 (1.00–1.04), ***p* = .010***	1.02 (.98–1.05), *p* = .368	1.05 (.99–1.11), *p* = .082	.99 (.95–1.04), *p* = .725	1.02 (.99–1.05), *p* = .153	1.03 (1.00–1.06), ***p* = .050***
Cause of epilepsy[a]						
Unknown etiology	1.37 (.55–3.43), *p* = .499	5.96 (.77–46.42), *p* = .088	.93 (.04–22.49), *p* = .965	1.73 (.18–16.23), *p* = .631	1.73 (.28–10.76), *p* = .557	.36 (.07–1.90), *p* = .227
Other etiologies[b]	.57 (.13–2.51), *p* = .454	.23 (.01–4.58), *p* = .337	16.69 (.04–7021.05), *p* = .361	.38 (.01–14.76), *p* = .604	.20 (.01–4.35), *p* = .308	.52 (.03–8.00), *p* = .638

Note: Results are reported as odds ratio (95% confidence interval), *p*-value. Bold font indicates statistical significance.

Abbreviations: ASM, antiseizure medication; LEV, levetiracetam.

[a]Cause of epilepsy reference category: structural etiology.

[b]Other etiologies: genetic, immune, infectious. *$p < .05$, **$p < .01$, ***$p < .001$.

TABLE 4 Number of treatment emergent adverse events reported throughout the study period.[a]

Adverse event	Overall, $N=372$	Brivaracetam LEV-naïve, $n=54$	Brivaracetam prior LEV, $n=28$	Eslicarbazepine acetate, $n=21$	Lacosamide, $n=102$	Perampanel, $n=167$
Dizziness	66 (17.7)	3 (5.6)	2 (7.1)	6 (28.6)	17 (16.7)	38 (22.8)
Irritability	66 (17.7)	11 (20.4)	7 (25)	0	7 (6.9)	41 (24.6)
Somnolence	53 (14.2)	11 (20.4)	4 (14.3)	3 (14.3)	14 (13.7)	21 (12.6)
Agitation	27 (7.3)	7 (13.0)	5 (17.9)	0	6 (5.9)	9 (5.4)
Aggression	23 (6.2)	3 (5.6)	4 (14.3)	1 (4.8)	4 (3.9)	11 (6.6)
Headache	18 (4.8)	0	0	1 (4.8)	6 (5.9)	11 (6.6)
Fatigue	17 (4.6)	4 (7.4)	0	0	6 (5.9)	7 (4.2)
Depression	11 (3.0)	3 (5.6)	0	0	5 (4.9)	3 (1.8)
Memory impairment	7 (1.9)	1 (1.9)	1 (3.6)	1 (4.8)	3 (2.9)	1 (.6)
Psychomotor retardation	7 (1.9)	0	1 (3.6)	0	3 (2.9)	3 (1.8)
Tremor	7 (1.9)	3 (5.6)	0	0	3 (2.9)	1 (.6)
Gastrointestinal disorders	7 (1.9)	0	0	1 (4.8)	4 (3.9)	2 (1.2)
Insomnia	6 (1.6)	1 (1.9)	0	0	3 (2.9)	2 (1.2)
Anxiety	5 (1.3)	2 (3.7)	0	2 (9.5)	1 (1.0)	0
Disturbance in attention	5 (1.3)	0	0	1	3 (2.9)	1 (.6)
Confusional state	5 (1.3)	2 (3.7)	1 (3.6)	0	0	2 (1.2)
Nausea	5 (1.3)	1 (1.9)	0	0	3 (2.9)	1 (.6)
Weight increased	5 (1.3)	1 (1.9)	0	1 (4.8)	3 (2.9)	0
Weight decreased	5 (1.3)	1 (1.9)	2 (7.1)	0	2 (2.0)	0

Note: Data are presented as *n* (%).

Abbreviation: LEV, levetiracetam.

[a]Percentages < 1% in the overall cohort were not reported.

likely to respond to treatment and five times more likely to experience AEs than males. The relatively higher chance of treatment response than AE occurrence allows us to speculate about a potential greater impact of tolerability profile on the risk of withdrawing treatment for women taking BRV and LEV-naïve, but not for those taking ESL. According to this hypothesis, female individuals with newly diagnosed epilepsy had higher rates of intolerable AEs than males in a large, longitudinal cohort study.[28] Moreover, both ESL and BRV have no sex-related pharmacokinetic differences that might explain different tolerability profiles. In general, there are few known sex-related differences in pharmacokinetics or in response to ASMs.[29] Recently, a retrospective population-based cohort study reported lower effectiveness of LEV in women compared with men, pointing out the existence of well-known, innate, sex-related differences in comorbidity patterns (and related, concomitant therapies).[30]

In the comparisons for efficacy, patients treated with BRV and previously with LEV had the lowest likelihood of being responders, but they also were the only ones to show a lower (albeit not statistically significant) risk of AE occurrence than the LCM group. Of note, the BRV group with a history of prior LEV therapy showed responder plus seizure-free rates higher than those reported in a pooled analysis of BRV RCTs (up to 50% in our cohort vs. up to 39.5%),[31] in line with real-life experiences.[19,32,33] In these studies, contrasting results were observed about the impact of the previous use of LEV on efficacy outcome.

A longer follow-up duration was associated with increased efficacy in the overall logistic model and in patients treated with PER in the stratified analysis. These data could be explained by a progressive optimization of ASM therapeutic doses, or by the selection of a responders' population over time.

Moreover, the number of previous therapeutic attempts significantly affected the efficacy outcome, and it is well known that the chance of controlling seizures with subsequent treatments decreases after each failed intervention.[34,35]

In the safety analysis, PER and BRV in LEV-naïve patients showed a more than six times greater risk of AE occurrence compared with LCM. In contrast, BRV was

TABLE 5 Safety outcome (adverse event occurrence): Comparative and per drug estimates.

		Brivaracetam LEV-naïve	Brivaracetam prior LEV	Eslicarbazepine acetate	Lacosamide	Perampanel
Comparative estimates		**6.80 (2.64–17.52), p < .001*****	**.89 (.30–2.59), *p* = .826**	**1.47 (.52–4.12), *p* = .466**	**Reference category**	**6.93 (3.32–14.44),** p < .001***
Age	1.03 (1.01–1.05), ***p* = .001****	1.06 (1.01–1.12), ***p* = .023***	2.01 (.88–4.61), *p* = .099	1.21 (1.05–1.39), ***p* = .009****	1.09 (1.03–1.14), ***p* = .001****	.99 (.96–1.02), *p* = .547
Female sex	.65 (.35–1.23), *p* = .186	5.36 (1.23–23.36), ***p* = .025***	62.24 (.01–472 353.8), *p* = .365	4.61 (.47–44.91), *p* = .188	3.76 (.69–20.61), *p* = .127	.39 (.12–1.21), *p* = .102
Disease duration	.998 (.996–.999), ***p* = .035***	1.01 (1.00–1.01), ***p* = .001****	.97 (.94–1.00), ***p* = .041***	.98 (.97–1.00), ***p* = .010***	.99 (.99–1.00), *p* = .141	1.00 (.99–1.00), *p* = .887
Number of previous ASMs > 2	1.24 (.65–2.38), *p* = .517	.96 (.18–4.99), *p* = .959	1.79×10^{16} ($.001–2.60 \times 10^{35}$), *p* = .096	23.44 (1.19–462.91), ***p* = .038***	7.90 (1.41–44.25), ***p* = .019***	.30 (.09–1.06), *p* = .061
Follow-up duration	.96 (.94–.97), ***p* < .001*****	.97 (.92–1.02), *p* = .275	.81 (.63–1.03), *p* = .091	.70 (.54–.91), ***p* = .007****	.95 (.91–.99), ***p* = .018***	.97 (.94–1.00), ***p* = .037***
Cause of epilepsy[a]						
Unknown etiology	.64 (.35–1.17), *p* = .148	.13 (.03–.62), ***p* = .010***	3.06×10^{-11} (1.69×10^{-23}–55.38), *p* = .093	77.68 (2.93–2062.34), ***p* = .009****	.48 (.12–1.93), *p* = .302	.92 (.40–2.12), *p* = .845
Other etiologies[b]	3.62 (1.42–9.21), ***p* = .007****	.0001 (1.07×10^{-6}–.01), ***p* < .001*****	.87 (.0001–13 068.12), *p* = .978	4.19 (.06–304.87), *p* = .513	2.19 (.22–22.12), *p* = .507	3 013 034 (1.52×10^{-27}–5.97×10^{39}), *p* = .703

Note: Results are reported as odds ratio (95% confidence interval), *p*-value. Bold font indicates statistical significance.

Abbreviations: ASM, antiseizure medication; LEV, levetiracetam.

[a]Cause of epilepsy reference category: structural etiology.

[b]Other etiologies: genetic, immune, infectious. *$p < .05$, **$p < .01$, ***$p < .001$.

the best tolerated option in an indirect comparison of data from the pivotal RCTs of the four studied ASMs.[36] Likewise, in a subsequent network metanalysis that also included data on the newer ASM cenobamate, BRV and LCM seemed to have the best tolerability profile, whereas cenobamate resulted as the most effective drug. In detail, BRV and LCM were associated with a lower percentage of patients experiencing AEs than ESL, and PER was associated with a higher risk of AEs than BRV.[37] Therefore, the higher risk of AEs in patients treated with PER over the other comparators is in line with literature findings, but the percentages of AE occurrence in our cohort (25.9%) were lower than those reported in RCTs (up to 86.8%)[38] and in a pooled analysis of data from real-world studies (49.9%).[39] Furthermore, the AEs experienced with PER were tolerated in approximately two thirds of the patients, and the good tolerability profile is supported by the high retention rates shown in real-life settings.[40]

A higher frequency of AEs was observed with increasing age. In elderly patients, the presence of a large number of comorbidities and the subsequent polytherapy may reduce adherence to treatments and increase the risk of drug–drug interactions and AEs.[41,42] Additionally, ASM tolerability may be significantly affected by frailty (which represents the most problematic expression of aging[43]), as suggested by a statistically and clinically significant association between the increases in the Edmonton Frailty Score and those in the Liverpool Adverse Events Profile in older PWE.[44]

In the overall logistic model and in the ESL, LCM, and PER groups, longer follow-up was associated with a reduced risk of AE occurrence. All the AEs reported were mild or moderate in severity. They were mainly related to the central nervous system and the gastrointestinal system and did not differ from those reported as common in the SmPCs and in the literature.[19–21,45] It is well known that AEs due to ASMs mostly appear during initiation and early treatment and some of them tend to regress spontaneously thereafter. Therefore, a reduction in AE occurrence at increasing follow-up duration was expected. Additionally, it may be hypothesized that patients who experienced improvements in epileptic symptoms may have been more prone to tolerate AEs and progressively reduced their reporting to the clinician. Likewise, patients with longer disease duration may have tried a greater

number of ASMs and have more experience with potential AEs, underreporting them.

Finally, etiology-related differences in tolerability emerged in the per drug analyses, suggesting that unknown etiology might be associated with a better tolerability profile in patients treated with BRV and naïve to LEV, but it was also a predictor of AE occurrence in patients treated with ESL. Despite the difference in the probability of AE occurrence, epilepsy type does not seem to affect the risk of withdrawal owing to AEs.[28]

Among the major strengths of our study are the real-life setting, which allows data collection in daily clinical practice scenarios nonreplicable by RCTs (also adding information on groups of patients usually excluded by clinical trials), and the analysis method. Generally, RWE studies do not perform adjustments for baseline differences between comparator groups and provide only nominal comparative evidence for ASM treatments.[11] Furthermore, results from indirect comparisons between studies should be interpreted with caution, owing to differences in the studied populations, in the choice of the outcome measured, and in the outcome definition. In this study, different treatment groups were compared using the same outcome definition; we also tried to overcome the selection bias, accounting for cluster differences in the studied population. We did not perform an adjustment for a propensity score of treatment, but there were no a priori assumptions justifying this practice.

Additionally, the large sample size allowed us to perform explorative subgroup analyses, which suggested further investigation on the following findings: (1) the reduced risk of treatment discontinuation as the patients' age increased in the LCM group; (2) sex-related differences in the hazard of dropout in the ESL group, and in treatment response and AE occurrence risk in the LEV-naïve BRV group; and (3) etiology-related differences in the likelihood of AE occurrence according to the type of ASM.

The foremost limitations of the study are due to the retrospective design, the recruitment of patients at different times, and the use of an outcome measure (i.e., the ≥50% reduction in baseline seizure frequency), which should be overcome. Self-reported seizure counting may be an unreliable measure,[46] which also lacks important information on the impact of treatments on patients' quality of life (e.g., it does not explain why some non-responders and/or patients with AEs do not discontinue therapy). In this light, assessing at least the changes in seizure frequency by seizure type could be more informative, but this was not possible. Regarding this latter point, as in RCTs, we cannot exclude diagnostic mistakes, which may also be suspected by the high percentage in this sample of patients with both focal and generalized seizures. However, when analyzing patients with only focal seizures, the results of the study do not change (see Figure S3). This being a real-world study, any mistake will correctly influence patient outcomes better representing clinical practice than in RCTs. Along this line, a similar consideration may be applied to ASM titration and maximum dose used. In the real-world setting, both will be optimized for each patient and therefore would account as a key factor determining the outcome. Clearly, any mistake would influence the outcomes, although the results obtained here indicate that all drugs had a high retention rate and on average the doses used were in line with the current clinical use. Furthermore, there being many missing data on the doses of concomitant ASMs did not allow us to evaluate the effect of cotreatments and drug–drug interactions on outcome measures or the impact of the studied ASMs on patients' total drug load. Finally, in our study, we did not exclude patients naïve to every ASM under examination; therefore, a single patient might have failed one of the others before receiving the ASM considered in the analysis.

In conclusion, our data support the long-term effectiveness and tolerability of the four third-generation ASMs in a large cohort of PWE in a real-life setting. Patients treated with LCM showed the highest retention rate throughout the analysis time. Compared with LCM, BRV with prior LEV use was associated with a lower likelihood of achieving seizure response, whereas PER and BRV without prior LEV use was associated with a higher probability of AE occurrence. Moreover, the number of previous therapeutic attempts and the follow-up duration significantly affected the efficacy outcome; age, disease duration, follow-up duration, and epilepsy etiology were found to be risk predictors of AE occurrence. The inclusion of the newest ASMs in the comparative assessment is mandatory, as well as further investigations on subgroup analysis results regarding differences per age, sex, and etiology of epilepsy. A deeper understanding of how some demographic and clinical characteristics may affect drugs' safety and efficacy profile could help clinicians to identify the most appropriate drug for each patient, taking another step toward precision medicine.

AUTHOR CONTRIBUTIONS

Roberta Roberti, Gianfranco Di Gennaro, Emilio Russo: Conception and design of the study; acquisition and analysis of data; drafting a significant portion of the manuscript and figures; final revision of the manuscript. **Carmen De Caro:** Interpretation of data; drafting a significant portion of the manuscript. **Luigi Francesco Iannone:** Conception and design of the study; acquisition and analysis of data. **Francesca Anzellotti, Dario Arnaldi,**

Vincenzo Belcastro, Simone Beretta, Giovanni Boero, Paolo Bonanni, Laura Canafoglia, Alfredo D'Aniello, Fedele Dono, Giancarlo Di Gennaro, Roberta Di Giacomo, Jacopo C. DiFrancesco, Filippo Dainese, Giovanni Falcicchio, Edoardo Ferlazzo, Nicoletta Foschi, Silvia Franciotta, Antonio Gambardella, Alfonso Giordano, Angelo Labate, Angela La Neve, Simona Lattanzi, Ugo Leggio, Claudio Liguori, Marta Maschio, Annacarmen Nilo, Francesca Felicia Operto, Angelo Pascarella, Giada Pauletto, Rosaria Renna, Gionata Strigaro: Acquisition of data; critical revision of the manuscript. **COMPARE Study Group:** Significant contribution to data acquisition.

AFFILIATIONS

[1]Science of Health Department, School of Medicine, Magna Græcia University of Catanzaro, Catanzaro, Italy
[2]Department of Neurology, Epilepsy Center, SS Annunziata Hospital, Chieti, Italy
[3]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Clinical Neurology, University of Genoa, Genoa, Italy
[4]IRCSS Ospedale Policlinico San Martino, Genoa, Italy
[5]Neurology Unit, Maggiore Hospital, ASST Lodi, Lodi, Italy
[6]Department of Neurology, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy
[7]Complex Structure of Neurology, SS Annunziata Hospital, Taranto, Italy
[8]Epilepsy and Clinical Neurophysiology Unit, Scientific Institute, IRCCS Eugenio Medea, Conegliano, Treviso, Italy
[9]Integrated Diagnostics for Epilepsy, Fondazione IRCCS Istituto Neurologico Besta, Milan, Italy
[10]IRCCS Neuromed, Pozzilli, Italy
[11]Clinical Neurophysiology Unit, Clinical Neurology, DIDAS Department, Padua, Italy
[12]Epilepsy Unit, Fondazione IRCCS Istituto Neurologico Besta, Milan, Italy
[13]Department of Neuroscience, Imaging and Clinical Science, D'Annunzio University of Chieti-Pescara, Chieti, Italy
[14]DiBraiN Department, University of Bari Aldo Moro, Bari, Italy
[15]Department of Medical and Surgical Sciences, Magna Græcia University of Catanzaro, Catanzaro, Italy
[16]Regional Epilepsy Center, Bianchi-Melacrino-Morelli Great Metropolitan Hospital, Reggio Calabria, Italy
[17]Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy
[18]Department of Medical and Surgical Sciences, Institute of Neurology, Magna Græcia University of Catanzaro, Catanzaro, Italy
[19]Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy
[20]Section of Clinical Pharmacology and Oncology, Department of Health Sciences, University of Florence, Florence, Italy
[21]Neurophysiopathology and Movement Disorders Clinic, University of Messina, Messina, Italy
[22]Unit of Neurophysiopathology, ASST Spedali Civili, Brescia, Italy
[23]Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
[24]Neurology Unit, Epilepsy Center, University Hospital Tor Vergata, Rome, Italy
[25]Center for Tumor-Related Epilepsy, UOSD Neuro-Oncology, IRCCS Regina Elena National Cancer Institute, Rome, Italy
[26]Clinical Neurology Unit, Department of Head, Neck, and Neurosciences, Santa Maria della Misericordia University Hospital, Udine, Italy
[27]Child and Adolescent Neuropsychiatry Unit, Department of Medicine, Surgery, and Dentistry, University of Salerno, Fisciano, Italy
[28]Neurology Unit, Department of Head, Neck, and Neurosciences, Santa Maria della Misericordia University Hospital, Udine, Italy
[29]Neurology and Stroke Unit, Department of Emergency and Acceptance, AORN Antonio Cardarelli Hospital, Naples, Italy
[30]Neurology Unit, Department of Translational Medicine, Epilepsy Center, University of Piemonte Orientale, Novara, Italy
[31]Maggiore della Carità University Hospital, Novara, Italy

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST STATEMENT

F.A. has received travel support from Eisai, UCB, and Angelini Pharma and speaker honoraria from Eisai and Angelini Pharma. G.B. has received speaker or consultancy fees from Eisai, Angelini Pharma, and UCB Pharma. P.B. has received speaker or consultancy fees from BIAL, Eisai, GW Pharmaceuticals, LivaNova, Lusofarmaco, Proveca, and Roche. L.C. has participated in pharmaceutical industry-sponsored clinical trials for UCB Pharma and other pharmaceutical industries, and has received speaker honoraria from Eisai. A.D. has participated in pharmaceutical industry-sponsored clinical trials for UCB Pharma, has received speaker honoraria from Eisai, UCB, Angelini Pharma, and Neuraxpharm, and has served on advisory boards for Angelini Pharma. F.D. has received speaker or consultancy fees from UCB, Eisai, and BIAL. Gianf.D.G. has participated on advisory boards and pharmaceutical industry-sponsored symposia for UCB Pharma, Eisai, BIAL, Lusofarmaco, LivaNova, Arvelle, and Angelini Pharma. F.D. has received travel support from Eisai, UCB, and Angelini Pharma and speaker honoraria from Eisai. G.F. has received speaker fees from Angelini Pharma. E.F. has received speaker honoraria from UCB, Eisai, and Angelini Pharma. A.Ga. has received speaker honoraria from UCB, Eisai, Angelini Pharma, Jazz, BIAL, and Zambon. L.F.I. has received personal fees or travel grants from Eli Lilly, Teva, and Lundbeck. A.L.N. has received speaker or consultancy fees from Eisai, Mylan, Sanofi, BIAL, GW Pharmaceuticals, Arvelle, Angelini Pharma, and UCB Pharma and has served on scientific advisory boards for GW Pharmaceuticals, Jazz Pharmaceuticals, and Angelini Pharma. S.L. has received speaker or consultancy fees from Angelini Pharma, Eisai, GW Pharmaceuticals, and UCB Pharma and has served on advisory boards for

Angelini Pharma, Arvelle Therapeutics, BIAL, Eisai, and GW Pharmaceuticals. C.L. has participated on advisory boards for and has received research support from Eisai. M.M. has received travel support from Eisai. G.P. has received speaker's or consultancy fees from Eisai, Angelini Pharma, LivaNova, Lusofarmaco, and UCB Pharma. E.R. has received speaker fees or funding from and has participated on advisory boards for Arvelle Therapeutics, Angelini Pharma, Eisai, Pfizer, GW Pharmaceuticals, Jazz Pharmaceuticals, UCB, and Lundbeck. G.S. has received speaker and consultancy fees from Eisai and Angelini Pharma. All other authors report no conflicts of interest.

ORCID

Francesca Anzellotti https://orcid.org/0000-0003-0808-3042
Laura Canafoglia https://orcid.org/0000-0002-5385-761X
Roberta Di Giacomo https://orcid.org/0000-0003-4202-955X
Jacopo C. DiFrancesco https://orcid.org/0000-0002-4102-1188
Fedele Dono https://orcid.org/0000-0003-3575-2942
Giovanni Falcicchio https://orcid.org/0000-0003-0745-5246
Antonio Gambardella https://orcid.org/0000-0001-7384-3074
Angelo Labate https://orcid.org/0000-0002-8827-7324
Simona Lattanzi https://orcid.org/0000-0001-8748-0083
Claudio Liguori https://orcid.org/0000-0003-2845-1332
Annacarmen Nilo https://orcid.org/0000-0001-9827-8059
Francesca Felicia Operto https://orcid.org/0000-0002-2444-8761
Angelo Pascarella https://orcid.org/0000-0002-0085-9494
Emilio Russo https://orcid.org/0000-0002-1279-8123

REFERENCES

1. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475–82.
2. Beghi E. The epidemiology of epilepsy. Neuroepidemiology. 2020;54:185–91.
3. Fattorusso A, Matricardi S, Mencaroni E, Dell'Isola GB, Di Cara G, Striano P, et al. The pharmacoresistant epilepsy: an overview on existant and new emerging therapies. Front Neurol. 2021;22:12.
4. Steriade C, French J. Tackling the unmet therapeutic needs in nonsurgical treatments for epilepsy. JAMA Neurol. 2022;79(12):1223–4.
5. Löscher W, Klein P. The pharmacology and clinical efficacy of antiseizure medications: from bromide salts to cenobamate and beyond. CNS Drugs. 2021;35(9):935–63.
6. Chen Z, Brodie MJ, Kwan P. What has been the impact of new drug treatments on epilepsy? Curr Opin Neurol. 2020;33(2):185–90.
7. Perucca E, Brodie MJ, Kwan P, Tomson T. 30 years of second-generation antiseizure medications: impact and future perspectives. Lancet Neurol. 2020;19(6):544–56.
8. Perucca E, Wiebe S. Not all that glitters is gold: a guide to the critical interpretation of drug trials in epilepsy. Epilepsia Open. 2016;1(1–2):9–21.
9. Kanner AM, Ashman E, Gloss D, Harden C, Bourgeois B, Bautista JF, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy. Neurology. 2018;91(2):82–90.
10. Perucca E. From clinical trials of antiepileptic drugs to treatment. Epilepsia Open. 2018;3:220–30.
11. Thieffry S, Klein P, Baulac M, Plumb J, Pelgrims B, Steeves S, et al. Understanding the challenge of comparative effectiveness research in focal epilepsy: a review of network meta-analyses and real-world evidence on antiepileptic drugs. Epilepsia. 2020;61(4):595–609.
12. French J. What is a fair comparison in head-to-head trials of antiepileptic drugs? Lancet Neurol. 2011;10(10):866–7.
13. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet. 2007;369(9566):1016–26.
14. Marson A, Burnside G, Appleton R, Smith D, Leach JP, Sills G, et al. The SANAD II study of the effectiveness and cost-effectiveness of valproate versus levetiracetam for newly diagnosed generalised and unclassifiable epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. Lancet. 2021;397(10282):1375–86.
15. Kwok CS, Johnson EL, Krauss GL. Comparing safety and efficacy of "third-generation" antiepileptic drugs: long-term extension and post-marketing treatment. CNS Drugs. 2017;31:959–74.
16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453–7.
17. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512–21.
18. European Medicines Agency. *Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders* [Internet]. 2018. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-clinical-investigation-medicinal-products-treatment-epileptic-disorders-revision-3_en.pdf
19. Lattanzi S, Canafoglia L, Canevini MP, Casciato S, Chiesa V, Dainese F, et al. Adjunctive Brivaracetam in focal epilepsy: real-world evidence from the BRIVAracetam add-on first Italian netwoRk STudy (BRIVAFIRST). CNS Drugs. 2021;35(12):1289–301.
20. Villanueva V, Holtkamp M, Delanty N, Rodriguez-Uranga J, McMurray R, Santagueda P. Euro-Esli: a European audit of real-world use of eslicarbazepine acetate as a treatment for partial-onset seizures. J Neurol. 2017;264(11):2232–48.
21. Rodríguez-Osorio X, Lema-Facal T, Rubio-Nazábal E, Castro-Vilanova MD, Pato-Pato A, Abella-Corral J, et al.

Perampanel effectiveness and safety as early add-on treatment for focal-onset seizures: PEREAGAL study. Epilepsy Res. 2021;172:106570.
22. Villanueva V, Garcés M, López-Gomáriz E, Serratosa JM, González-Giráldez B, Parra J, et al. Early add-on Lacosamide in a real-life setting: results of the REALLY study. Clin Drug Investig. 2015;35(2):121–31.
23. Strzelczyk A, Zaveta C, Podewils F, Möddel G, Langenbruch L, Kovac S, et al. Long-term efficacy, tolerability, and retention of brivaracetam in epilepsy treatment: a longitudinal multicenter study with up to 5 years of follow-up. Epilepsia. 2021;62(12):2994–3004.
24. Chung S, Wang N, Hank N. Comparative retention rates and long-term tolerability of new antiepileptic drugs. Seizure. 2007;16(4):296–304.
25. Lezaic N, Gore G, Josephson CB, Wiebe S, Jetté N, Keezer MR. The medical treatment of epilepsy in the elderly: a systematic review and meta-analysis. Epilepsia. 2019;60(7):1325–40.
26. Rainesalo S, Mäkinen J, Raitanen J, Peltola J. Clinical management of elderly patients with epilepsy; the use of lacosamide in a single center setting. Epilepsy Behav. 2017;75:86–9.
27. Del Bianco C, Placidi F, Liguori C, Mari L, Ulivi M, Ornello R, et al. Long-term efficacy and safety of lacosamide and levetiracetam monotherapy in elderly patients with focal epilepsy: a retrospective study. Epilepsy Behav. 2019;94:178–82.
28. Alsfouk BAA, Brodie MJ, Walters M, Kwan P, Chen Z. Tolerability of antiseizure medications in individuals with newly diagnosed epilepsy. JAMA Neurol. 2020;77(5):574–81.
29. Perucca E, Battino D, Tomson T. Gender issues in antiepileptic drug treatment. Neurobiol Dis. 2014;72:217–23.
30. Cepeda MS, Teneralli RE, Kern DM, Novak G. Differences between men and women in response to antiseizure medication use and the likelihood of developing treatment resistant epilepsy. Epilepsia Open. 2022;7(4):598–607.
31. Ben-Menachem E, Mameniškienė R, Quarato PP, Klein P, Gamage J, Schiemann J, et al. Efficacy and safety of brivaracetam for partial-onset seizures in 3 pooled clinical studies. Neurology. 2016;87(3):314–23.
32. O'Brien TJ, Borghs S, He QJ, Schulz A, Yates S, Biton V. Long-term safety, efficacy, and quality of life outcomes with adjunctive brivaracetam treatment at individualized doses in patients with epilepsy: an up to 11-year, open-label, follow-up trial. Epilepsia. 2020;61(4):636–46.
33. Adewusi J, Burness C, Ellawela S, Emsley H, Hughes R, Lawthom C, et al. Brivaracetam efficacy and tolerability in clinical practice: a UK-based retrospective multicenter service evaluation. Epilepsy Behav. 2020;106:106967.
34. Schiller Y, Najjar Y. Quantifying the response to antiepileptic drugs: effect of past treatment history. Neurology. 2008;70(1):54–65.
35. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs a 30-year longitudinal cohort study. JAMA Neurol. 2018;75:279–86.
36. Li-na Z, Deng C, Hai-jiao W, Da X, Ge T, Ling L. Indirect comparison of third-generation antiepileptic drugs as adjunctive treatment for uncontrolled focal epilepsy. Epilepsy Res. 2018;139:60–72.
37. Lattanzi S, Trinka E, Zaccara G, Striano P, Russo E, Del Giovane C, et al. Third-generation Antiseizure medications for adjunctive treatment of focal-onset seizures in adults: a systematic review and network meta-analysis. Drugs. 2022;82(2):199–218.
38. French JA, Krauss GL, Steinhoff BJ, Squillacote D, Yang H, Kumar D, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. Epilepsia. 2013;54(1):117–25.
39. Villanueva V, D'Souza W, Goji H, Kim DW, Liguori C, McMurray R, et al. PERMIT study: a global pooled analysis study of the effectiveness and tolerability of perampanel in routine clinical practice. J Neurol. 2022;269(4):1957–77.
40. Gasparini S, Ferlazzo E, Neri S, Cianci V, Iudice A, Bisulli F, et al. Effectiveness of perampanel as the only add-on: retrospective, multicenter, observational real-life study on epilepsy patients. Epilepsia Open. 2022;7:687–96.
41. Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. Lancet. 2007;370(9582):185–91.
42. Roberti R, Palleria C, Nesci V, Tallarico M, Di Bonaventura C, Cerulli Irelli E, et al. Pharmacokinetic considerations about antiseizure medications in the elderly. Expert Opin Drug Metab Toxicol. 2020;16(10):983–95.
43. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752–62.
44. Vary-O'Neal A, Miranzadeh S, Husein N, Holroyd-Leduc J, Sajobi TT, Wiebe S, et al. Association between frailty and Antiseizure medication tolerability in older adults with epilepsy. Neurology. 2022;100:e1135–47. https://doi.org/10.1212/WNL.0000000000201701
45. Yang C, Peng Y, Zhang L, Zhao L. Safety and tolerability of lacosamide in patients with epilepsy: a systematic review and meta-analysis. Front Pharmacol. 2021;12:694381.
46. Fisher RS, Blum DE, DiVentura B, Vannest J, Hixson JD, Moss R, et al. Seizure diaries for clinical research and practice: limitations and future prospects. Epilepsy Behav. 2012;24(3):304–10.

SUPPORTING INFORMATION

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

How to cite this article: Roberti R, Di Gennaro G, Anzellotti F, Arnaldi D, Belcastro V, Beretta S, et al. A real-world comparison among third-generation antiseizure medications: Results from the COMPARE study. Epilepsia. 2024;65:456–472. https://doi.org/10.1111/epi.17843

APPENDIX 1

COMPARE STUDY GROUP

Vincenzo Andreone: Neurology and Stroke Unit, Department of Emergency and Acceptance, AORN Antonio Cardarelli Hospital, Naples, Italy. Valeria Badioni: Neurology Unit, Maggiore Hospital, ASST Lodi, Lodi, Italy. Chiara Bedetti: Istituto Serafico di Assisi, Perugia, Italy; Department of Neurology, Città di Castello Hospital, Italy. Lara Buttarelli: Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy. Claudia Cagnetti: Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy. Roberto Cantello: Epilepsy Center, Neurology Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; Maggiore della Carità University Hospital, Novara, Italy. Vittoria Cianci: Regional Epilepsy Center, Bianchi-Melacrino-Morelli Great Metropolitan Hospital, Reggio Calabria, Italy. Alberto Danieli: Epilepsy and Clinical Neurophysiology Unit, Scientific Institute, IRCCS Eugenio Medea, Conegliano, Treviso, Italy. Francesco Deleo: Epilepsy Unit, Fondazione IRCCS Istituto Neurologico Besta, Milan, Italy. Eugenio Donato di Paola: Science of Health Department, School of Medicine, Magna Græcia University of Catanzaro, Catanzaro, Italy. Andrea Donniaquio: Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Clinical Neurology, University of Genoa, Genoa, Italy. Giacomo Evangelista: Department of Neurology, Epilepsy Center, SS Annunziata Hospital, Chieti, Italy; Department of Neuroscience, Imaging and Clinical Science, D'Annunzio University of Chieti-Pescara, Chieti, Italy. Mariana Fernandes: Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy. Francesco Fortunato: Institute of Neurology, Department of Medical and Surgical Sciences, Magna Græcia University of Catanzaro, Catanzaro, Italy. Sara Gasparini: Department of Medical and Surgical Sciences, Magna Græcia University of Catanzaro, Catanzaro, Italy; Regional Epilepsy Center, Bianchi-Melacrino-Morelli Great Metropolitan Hospital, Reggio Calabria, Italy. Santo Gratteri: Department of Medical and Surgical Sciences, Magna Græcia University of Catanzaro, Catanzaro, Italy. Matilde Lazzari: Epilepsy Center, Neurology Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; Maggiore della Carità University Hospital, Novara, Italy. Andrea Maialetti: Center for Tumor-Related Epilepsy, UOSD Neuro-Oncology, IRCCS Regina Elena National Cancer Institute, Rome, Italy. Pietro Mattioli: Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Clinical Neurology, University of Genoa, Genoa, Italy. Nicola Biagio Mercuri: Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy. Miriam Olivieri: Child and Adolescent Neuropsychiatry Unit, Department of Medicine, Surgery, and Dentistry, University of Salerno, Fisciano, Italy. Elisa Osanni: Epilepsy and Clinical Neurophysiology Unit, Scientific Institute, IRCCS Eugenio Medea, Conegliano, Treviso, Italy. Maria Grazia Pascarella: Neurology Unit, Maggiore Hospital, ASST Lodi, Lodi, Italy. Chiara Pastori: Epilepsy Unit, Fondazione IRCCS Istituto Neurologico Besta, Milan, Italy. Luciano Pellegrino: Clinical Neurophysiology Unit, Clinical Neurology, DIDAS Department, Padua, Italy. Stefano L. Sensi: Department of Neuroscience, Imaging and Clinical Science, D'Annunzio University of Chieti-Pescara, Chieti, Italy. Payam Tabaee Damavandi: Department of Neurology, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy. Lorenzo Tinti: Department of Neurology, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy. Lorenzo Verriello: Neurology Unit, Department of Head, Neck, and Neurosciences, Santa Maria della Misericordia University Hospital, Udine, Italy. Pio Zoleo: Institute of Neurology, Department of Medical and Surgical Sciences, Magna Græcia University of Catanzaro, Catanzaro, Italy.