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ORIGINAL RESEARCH

Lacosamide is Associated with a Higher Treatment Persistence at 12 Months than Brivaracetam and Perampanel Despite Similar Efficacy

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ABSTRACT

Introduction: Evidence directly comparing newer antiseizure medications (ASMs) is limited but crucial for guiding treatment decisions. This study compared the real-world effectiveness and tolerability of brivaracetam (BRV), lacosamide (LCM) and perampanel (PER) as add-on therapy

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in adults with epilepsy, applying a causal–inference extension of the COMPARE study. The aim of this approach was to overcome the limitations of standard multivariable analyses, better approximate causal effects, and reinforce the credibility of the results.

Methods: Data were retrospectively collected in the Italian multicentre COMPARE study. To emulate a randomized setting, we estimated multinomial propensity scores and applied stabilized inverse probability weights. The primary analysis used a log-logistic accelerated failure time model to estimate time-to-treatment discontinuation, adjusting for adverse events (AEs), clinical response and follow-up duration. Secondary analyses evaluated changes in total and concomitant drug load and tolerability over time.

Results: Among the 850 subjects included in this analysis (259, 240 and 351 receiving LCM, BRV and PER, respectively; 53.4% female; median age 43 years), the estimated probability of 12-month retention was highest for LCM (86.1%), followed by BRV (79.1%) and PER (75.4%). Long-term trends suggested convergence of PER and LCM retention, whereas BRV discontinuation remained higher. In the adjusted analyses, BRV and PER were associated with shorter time-to-treatment discontinuation than LCM, but this negative effect decreased over time, while the beneficial effect of clinical response strengthened. Total drug load increased across all groups but remained lowest for LCM; concomitant ASM load decreased, particularly among responders. AEs were mostly mild, with

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dizziness, irritability and somnolence the most common AEs. AE rates were initially higher for PER and BRV, but differences diminished over time.

Conclusion: Treatment discontinuation in epilepsy emerges as a dynamic process shaped by both tolerability and clinical response. Early persistence was higher for LCM, whereas long-term retention was improved for BRV and PER. These results support a personalized approach to ASM selection that integrates early tolerability with sustained effectiveness.

Keywords: Antiseizure medications; Comparative analysis; Drug load; Epilepsy; Real world study; Retention rate; Safety

Key Summary Points

Why carry out this study?
There is a lack of evidence comparing the use of antiseizure medication (ASMs)
Applying causal–inference methods via propensity score estimation to real-world data can improve our understanding of ASM use
Using this approach, we explored potential differences in the clinical effectiveness and tolerability of brivaracetam, lacosamide and perampanel as add-on therapy in adults with epilepsy
What was learned from the study?
Lacosamide had a higher retention rate than perampanel and brivaracetam that was not only justified by its efficacy and tolerability
After 12 months of treatment, there was no difference among the three drugs in terms of efficacy, tolerability and retention rate
Total and concomitant medication load changed over time, reflecting the complexity of treatment, rather than directly indicating drug effectiveness

INTRODUCTION

Epilepsy is a common and diverse group of neurological disorders, defined by a persistent predisposition to generate epileptic seizures, which significantly impair the quality of life for an estimated 70 million people globally [1–4]. Pharmacological management with antiseizure medications (ASMs), either as monotherapy or in combination with other therapies, remains the cornerstone of treatment for people with epilepsy (PWE) [5–7]. However, unmet therapeutic needs persist, not only for drug-resistant PWE, who require more effective and targeted therapies, but also for treatment-responsive individuals, who often struggle with issues of tolerability and adherence [5, 8–11].

Over recent decades, the number of ASMs available has steadily increased, with newer agents offering improved or novel mechanisms of action. Compared to first-generation ASMs, many of these newer drugs demonstrate more favourable pharmacokinetic properties and reduced potential for drug–drug interactions [5, 6]. Despite these advances, their efficacy profiles have not shown substantial improvements, and the overall prevalence of drug-resistant epilepsy has remained largely unchanged [10]. Additionally, clinicians are frequently faced with the challenge of selecting the most appropriate ASM from a range of options with overlapping indications, often without robust comparative evidence to guide individualized treatment decisions.

Randomized controlled trials (RCTs) are considered the gold standard for evaluating the efficacy and safety of new treatments, and these trials remain critical in informing clinical guidelines. However, the generalizability of RCT findings to real-world populations is limited. Regulatory approval of ASMs typically requires only the demonstration of superiority to placebo in reducing seizure frequency, without a mandate for direct comparison with existing therapies. As a result, head-to-head RCTs between ASMs are rare. For some drugs, such trials are conducted only years after market approval, if at all.

In the absence of direct comparative trials, indirect methods, such as network meta-analyses

and, increasingly, real-world evidence (RWE) studies serve as alternative approaches to assess the relative effectiveness and safety of ASMs (especially for third-generation drugs), which lack both head-to-head comparisons and long-term safety data [12–16]. In this context, RWE can play a pivotal role in informing clinical decision-making by reflecting treatment outcomes in broader, more heterogeneous populations.

In an attempt to explore and compare the effectiveness of brivaracetam (BRV), eslicarbazepine acetate (ESL), lacosamide (LCM) and perampanel (PER) in PWE, we have previously published the results of the "COMPARE" study, which analysed data on 960 patients from 22 epilepsy centres in Italy [17]. The initial findings of this investigation pointed to some differences among these drugs and indicated some useful aspects that could be applied in epilepsy clinical management [17, 18]. However, in the COMPARE study, differences among newer ASMs were evaluated using standard multivariable statistical techniques. While informative, such approaches are limited in their ability to adequately adjust for baseline imbalances and cannot reliably support causal interpretations, particularly in the absence of randomization.

To address these limitations, in the present study we employed a causal–inference framework using stabilized inverse probability of treatment weights derived from propensity score estimation. This approach allows for the construction of a pseudo-randomized comparison, improving covariate balance across treatment groups and enabling the estimation of marginal (population-average) effects, which are more applicable to clinical and policy decision-making. By reducing confounding and selection bias, propensity score weighting enhances the credibility of RWE and approximates the causal inferences typically derived from RCTs.

Building on this framework, in the current study we aimed to compare treatment retention at 6 and 12 months among patients initiating add-on therapy with BRV, LCM or PER. This analysis represents a causal–inference extension of the COMPARE study, with ESL excluded from the analysis to improve model stability and ensure adequate covariate balance. In addition, we investigated the potential mediating and modifying role of the two main reasons for treatment discontinuation, namely, lack of clinical efficacy and the occurrence of adverse events (AEs). These factors were modelled not only as main effects but also in interaction with time (on the log scale), with the aim to assess how their impact on treatment retention may vary over the treatment course. Finally, we explored how the introduction of these ASMs into the therapeutic regimen may influence broader pharmacological management. Specifically, we assessed changes in overall drug load and the use of concomitant ASMs to understand whether and how the study drugs may reshape pharmacological treatment strategies. We also considered longitudinal aspects of tolerability in order to capture how AEs and treatment sustainability evolve over time.

METHODS

Participants, Data Collected and Outcome Measures

The raw data analysed in this study were derived from the previously published article reporting on the real-world study "COMPARE" [17]. Briefly, our previous study was a multicentre observational study, following STROBE guidelines, which retrospectively collected data from 22 Italian hospitals/epilepsy centres between January 2018 and October 2021. It included adult outpatients (≥18 years) with a confirmed diagnosis of epilepsy, who began treatment with one of four ASMs (BRV, ESL, LCM or PER) as add-on therapy in routine clinical practice. Patients with changes in ASM therapy during the previous 3 months, substance abuse, pregnancy, psychogenic seizures or treatment for status epilepticus were excluded from the study.

The overall, anonymized 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. As the study was based on retrospective and fully anonymized data, written informed consent was not required.

Baseline information included demographics, seizure characteristics, epilepsy aetiology, prior and concomitant treatments and seizure frequency. Seizure frequency was categorized as daily, weekly or monthly based on the 3 months prior to treatment. Follow-up data at 6, 12, 24 and 36 months after treatment initiation included treatment retention, efficacy, AEs and reasons for ASM discontinuation. The primary endpoint was treatment persistence, assessed via the retention rate, which is considered to be a global measure of ASM effectiveness. Secondary outcomes included efficacy (measured as ≥ 50% seizure reduction or seizure freedom) and safety, assessed by the proportion of patients with ≥ 1 AE. AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA) system. Data quality was monitored locally and by the national coordinating group.

In the present study, we expanded the methodological approach of the "COMPARE" study and provided further information on changes in drug burden and tolerability over time. Total drug load was quantified as the sum of the ratios between the prescribed daily dose (mg) and the defined daily dose (mg) as provided by the Collaborating Centre for Drug Statistics Methodology of the World Health Organization, for each ASM included in the individual regimen [19]. Concomitant ASMs were categorized according to their main mechanism of action (MoA) and their ability to strongly induce enzyme metabolism. Specifically, ASMs were grouped into sodium channel blockers (SCBs; carbamazepine, eslicarbazepine acetate, lacosamide, lamotrigine, oxcarbazepine, phenytoin, rufinamide) versus all other MoAs, and into strong enzyme inducers (EIs; carbamazepine, phenobarbital, phenytoin, primidone) versus non-enzyme inducers (nEIs).

Statistical Analysis

Continuous variables were described by mean and standard deviation if the data were normally distributed or by the median and interquartile range (IQR) in case of skewed data. Counts and percentages were used for categorical variables. Between-group differences were assessed using the chi-squared test for categorical variables and the Kruskal–Wallis test for continuous variables. Propensity scores were estimated by using a multinomial model, following the framework proposed by Garrido et al. [20, 21]. Covariates were selected based on theoretical considerations, including those expected to influence both treatment assignment and outcome, as well as those related only to the outcome. Variables that were only related to treatment assignment, those only affected by treatment (i.e. post-treatment) or those that perfectly predicted treatment allocation were excluded. In addition to main effects, candidate interactions among covariates were systematically tested and retained if they improved model fit and covariate balance. The final model was selected based on standardized mean differences (SMDs), visual inspection of the overlap in propensity score distributions across treatment groups and model fit assessed using the Akaike (AIC) and Bayesian (BIC) information criteria. Stabilized inverse probability weights were computed to reduce variance and improve the precision of the estimates, as suggested by Chesnaye et al. [22]. These weights were applied in all subsequent analyses to estimate marginal (population-average) effects. Propensity score overlap was visually inspected, and SMDs were reassessed after weighting to ensure adequate covariate balance across treatment groups.

As a primary analysis, we fitted a log-logistic accelerated failure time (AFT) model to evaluate the association between each ASM and time-to-treatment discontinuation. The AFT framework was preferred over the Cox proportional hazards model based on both theoretical and empirical considerations. Theoretically, the AFT model directly estimates the effect of covariates on the timing of the event, providing time ratios that are more interpretable in the context of treatment duration. Empirically, visual inspection of Kaplan–Meier curves and smoothed hazard estimates revealed non-proportional hazards with a non-monotonic pattern (i.e. hazard rates increasing and then decreasing over time), violating the proportional hazards assumption and supporting the use of a parametric distribution such as the log-logistic. The log-logistic distribution was selected based on superior model fit compared to alternative parametric

specifications (Weibull, log-normal, gamma), as indicated by lower values of AIC and BIC criteria, and a better distribution of Cox–Snell residuals.

To explore the contribution of AEs and clinical response to treatment discontinuation, and to assess whether their effects varied over time, we included these variables along with their interactions with the logarithm of follow-up time.

To evaluate the robustness of our findings, we performed sensitivity analyses using cluster-robust standard errors to account for intra-cluster correlation and a symmetric trimming procedure, by excluding the 10% of observations with the lowest and highest propensity scores, following the approach recommended by Crump et al. [23].

As secondary exploratory analyses, we assessed changes in drug load and tolerability over time. Drug burden was analysed both including and excluding the study ASMs in order to quantify the overall drug load and that of all the concomitant ASMs. Exploratory analyses were also performed based on clinical response (defined as a ≥ 50% reduction in seizure frequency from baseline) and on subgroups stratified according to the MoAs and EI profile of ASMs. Descriptive paired comparisons, such as 12-month drug load versus baseline, were conducted using either the paired t-test or the Wilcoxon signed-rank test, depending on data distribution and number of observations. For comparisons involving > 2 time points, repeated-measures one-way analysis of variance (ANOVA) or the Friedman test was applied, as appropriate based on data normality. Post-hoc analyses were performed using the Bonferroni correction (for ANOVA) or Dunn's test (for the Friedman test). Between-group differences (e.g. in total drug load between responders and non-responders or in the proportion of patients experiencing AEs) were assessed using the Chi-squared test for categorical variables and the Welch's t-test, the Mann–Whitney *U* test or the Kruskal–Wallis test for continuous variables, as appropriate based on data distribution and number of groups.

RESULTS

Sample Description

A total of 850 patients were included in the study, of whom 259 (30.5%) received LCM, 240 (28.2%) received BRV and 351 (41.3%) received PER (Table 1). The cohort consisted of 454 women (53.4%) and 396 men (46.6%), with no significant differences in sex distribution between treatment groups ($p = 0.609$). The overall median age was 43 (IQR 28–55) years, with similar values ($p = 0.191$) across treatment arms: mean age of 44 (IQR 27–59) years for patients receiving LCM; 44.5 (IQR 31.5–53.5) years for BRV; and 40 (IQR 27–54) years for PER. Median duration since epilepsy diagnosis varied between treatment groups ($p < 0.001$): 130 (IQR 36–274) months for patients receiving LCM; 270 (IQR 144–432) months for those receiving BRV; and 216 (IQR 96–364) months for those receiving PER.

Pharmacoresistance, defined as prior use of > 2 ASMs, was differently distributed ($p < 0.001$), with higher frequency in the BRV (73.8%) and PER (64.4%) groups than in the LCM group (37.1%). Most patients had focal seizures (69.3% overall), particularly in the LCM (74.1%) and BRV (72.1%) groups, compared with the PER group (63.8%). Generalized seizures were rare overall (5.1%) and more frequent in the PER group (8.0%) than in the LCM (3.15%) and BRV (3.0%) groups. Both focal and generalized seizures were present in 23.4% of the cohort, ranging from 18.9% in the LCM group to 25.9% in the PER group. The distribution of seizure types differed significantly across treatment arms ($p = 0.001$).

Seizure frequency at baseline also showed significant differences ($p = 0.003$). Daily seizures were more frequently reported in the BRV (24.2%) and PER (23.9%) groups compared with the LCM group (13.5%); weekly seizures were reported in approximately one third of patients across all groups (34.6% BRV, 31.7% LCM, 32.5% PER); and monthly seizures were more common in the LCM group (52.9%) compared with the BRV (39.2%) and PER groups (42.2%).

Table 1 Baseline characteristics of the study cohort

Characteristics	Overall cohort ($N = 850$)	Brivaracetam ($N = 240$)	Lacosamide ($N = 259$)	Perampanel ($N = 351$)	p
Female sex, *n* (%)	454 (53.4)	128 (53.3)	136 (52.5)	190 (54.1)	0.609
Age in years, median (IQR)	43 (28–55)	44.5 (31.5–53.5)	44 (27–59)	40 (27–54)	0.191
Disease duration in months, median (IQR)	204 (84–372)	270 (144–432)	130 (36–274)	216 (96–364)	< 0.001
Seizure type, n (%)					
Focal	589 (69.3)	173 (72.1)	192 (74.1)	224 (63.8)	0.001
Generalized	43 (5.1)	7 (3.0)	8 (3.15)	28 (8.0)	
Focal and generalized	199 (23.4)	59 (24.6)	49 (18.9)	91 (25.9)	
Unknown	19 (2.2)	1 (0.4)	10 (3.9)	8 (2.3)	
Aetiology, n (%)					
Structural	442 (52.0)	121 (50.4)	142 (54.8)	179 (51.0)	0.882
Genetic	67 (7.8)	22 (9.2)	21 (8.1)	24 (6.8)	
Immune	12 (1.4)	4 (1.7)	3 (1.2)	5 (1.5)	
Infectious	8 (0.9)	3 (1.3)	1 (0.4)	4 (1.1)	
Unknown	321 (37.8)	90 (37.5)	92 (35.5)	139 (39.6)	
Seizure frequency, n (%)					
Daily	177 (20.8)	58 (24.2)	35 (13.5)	84 (23.9)	0.003
Weekly	279 (32.8)	83 (34.6)	82 (31.7)	114 (32.5)	
Monthly	379 (44.6)	94 (39.2)	137 (52.9)	148 (42.2)	
na	15 (1.8)	5 (2.1)	5 (1.9)	5 (1.4)	
Epilepsy surgery, n (%)					
Not indicated	700 (82.4)	188 (78.3)	220 (84.9)	292 (83.2)	0.184
Performed	64 (7.5)	24 (10.0)	15 (5.8)	25 (7.1)	
Indicated but not still performed	72 (8.5)	25 (10.4)	22 (8.5)	25 (7.1)	
na	14 (1.7)	3 (1.3)	2 (0.8)	9 (2.6)	
Number of previous ASMs > 2, *n* (%)	499 (58.7)	177 (73.8)	96 (37.1)	226 (64.4)	< 0.001

Table 1 continued

Characteristics	Overall cohort ($N=850$)	Brivaracetam ($N=240$)	Lacosamide ($N=259$)	Perampanel ($N=351$)	p
Concomitant ASMs, n (%)					
1	370 (43.5)	89 (37.1)	158 (61.0)	123 (35.0)	< 0.001
2	323 (38.0)	90 (37.5)	71 (27.4)	162 (46.1)	
3	152 (17.8)	60 (25.0)	26 (10.0)	66 (18.8)	
na	5 (0.6)	1 (0.4)	4 (1.5)	0 (0.0)	

Statistical significance was assessed by the Kruskal–Wallis (continuous variables) or Chi-squared (categorical variables) tests

ASMs Antiseizure medications, *IQR* interquartile range, *na* not available data

Regarding epilepsy aetiology, structural causes were the most frequent (52.0% overall), with similar proportions in the three treatment groups: 54.8% in the LCM group, 50.4% in the BRV group and 51.0% in the PER group. Other aetiologies included unknown (37.8% overall; 35.5% in the LCM group, 37.5% in the BRV group and 39.6% in the PER group), genetic (7.8% overall; 8.1%, 9.2% and 6.8%, respectively), immune (1.4% overall; 1.2%, 1.7% and 1.5%, respectively) and infectious (0.9% overall; 0.4%, 1.3% and 1.1%, respectively). No significant differences were observed in aetiology distribution across groups ($p=0.882$).

Finally, concomitant ASM use differed significantly across groups ($p<0.001$). Overall, 43.5% of subjects were on monotherapy, with the highest proportion in the LCM group (61.0%), followed by the BRV group (37.1%) and the PER group (35.0%). Use of two ASMs was more frequent in the PER group (46.1%) compared with the BRV (37.5%) and LCM groups (27.4%), while the proportion of patients receiving ≥ 3 ASMs was highest in the BRV group (25.0%).

Retention

Time-to-Event Analysis

Visual inspection of the Kaplan–Meier curves (Fig. 1) revealed a marked difference in treatment retention during the first 12 months, with LCM showing the most favourable profile compared with BRV and PER.

At 12 months, the estimated probability of remaining on treatment was 86.1% for the LCM group, 79.1% for the BRV group and 75.4% for the PER group. Beyond the first year, the curve of the PER group tended to run approximately parallel with that of the LCM group, suggesting both groups had similar long-term discontinuation rates, while drug discontinuation continued to be more pronounced in the BRV group compared with the groups receiving the other two drugs. Over the full 36-month follow-up, the estimated probability of remaining on treatment was 83.4% for the LCM group, 69.0% for the PER group and 66.4% for the BRV group.

Propensity scores multinomial model included age, sex, time since epilepsy diagnosis, epilepsy aetiology, prior exposure to ASMs, surgery for epilepsy, seizure type and concomitant ASMs at baseline. Visual inspection of the propensity score distributions (Fig. 2) revealed

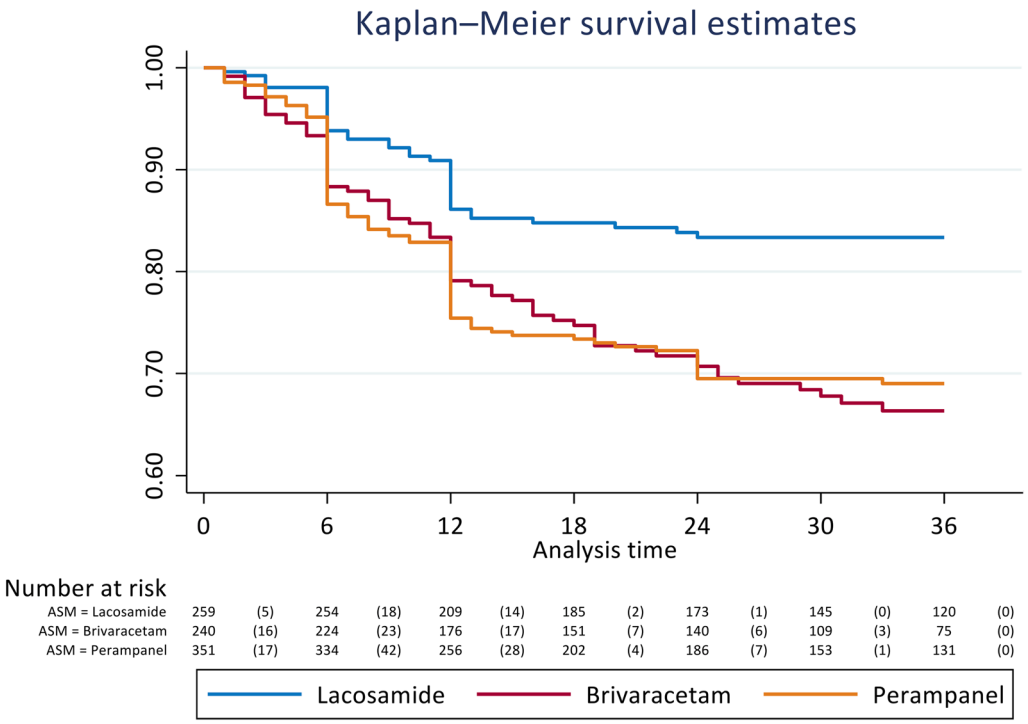


Fig. 1 Kaplan–Meier estimates of treatment retention over time by antiseizure medication. The survival curves represent time-to-treatment discontinuation for patients treated with lacosamide (blue), brivaracetam (red) and perampanel (orange). *ASM* Antiseizure medication

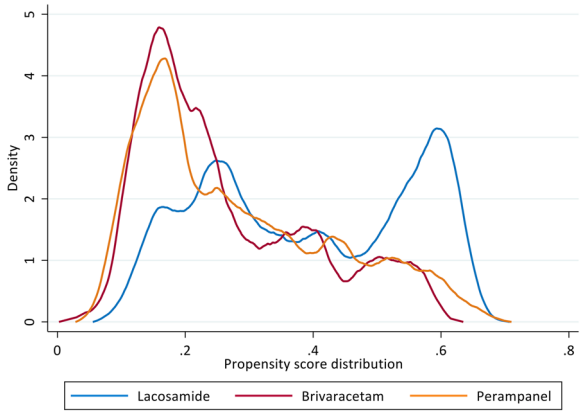


Fig. 2 Distribution of estimated propensity scores across treatment groups. Kernel density estimates show the distribution of propensity scores for patients treated with lacosamide (blue), brivaracetam (red), and perampanel (orange). Propensity scores were estimated by multinomial regression model

adequate overlap among the three treatment groups, although some regions exhibited lower density in the tails. Despite this, the common support was sufficient to proceed with inverse probability weighting. Furthermore, following weighting, covariate balance across treatment groups was generally good, with all SMDs $< \pm 0.1$, except for the "Focal/Generalized" seizure type. This variable showed a modest imbalance in two pairwise comparisons: – 0.125 for BRV versus PER, and – 0.102 for BRV versus LCM. Despite this, the values remained $< \pm 0.2$, a threshold still considered acceptable [24]. Multinomial propensity model details and full balance diagnostics are reported in Electronic Supplementary Material (ESM) Tables S1–S3.

Log-Logistic Modelling

When BRV and PER were compared with LCM in an unadjusted generalized gamma AFT model reflecting their total effect, including all potential mediating mechanisms, both drugs were associated with significantly shorter times to treatment discontinuation. The time ratio (TR) for BRV and PER was 0.47 (95% confidence interval [CI] 0.27, 0.84) and 0.46 (95% CI 0.27, 0.78), respectively, indicating a higher risk of earlier discontinuation relative to LCM.

After adjustment with AEs, clinical efficacy and the interaction terms with time, significant time-dependent effects were observed (Table 2). Indeed, for both BRV and PER, the interaction terms with log-time (TR 2.50 and 2.60, respectively) suggested that the negative impact on retention decreased over time, when compared to LCM. Similarly, the interaction between AEs and log-time (TR 1.26, 95% CI 1.02, 1.54) indicated that the detrimental effect of AEs also diminished with time. Conversely, the interaction between clinical response and log-time (TR 1.51, 95% CI 1.21, 1.89) suggested that the beneficial effect of clinical efficacy on retention strengthened over time.

Model Fit and Sensitivity Analyses

The Cox–Snell residual plot (ESM Figure S1) showed a reasonably good fit, with the Nelson–Aalen cumulative hazard closely following the reference line $y = x$. This suggests that the model performs adequately overall. Some mild divergence in the upper tail may indicate a slight overestimation of survival at longer follow-up times, but this deviation does not appear to compromise the overall validity of the model. Notably, the results proved robust across different sensitivity checks. Trimming of extreme weights and the use of cluster-robust standard errors (accounting for clustering by centre) did not materially affect the treatment effect estimates, which remained consistent in terms of direction, size, and statistical significance.

Secondary, Explorative Analyses

Drug Load Modifications over Time

Data on the dosages of concomitant ASMs were collected in the study Case Report Form at baseline and from 12 months of treatment onward. Among subjects still on treatment at 12 months, complete dose information for both study and

Table 2 Log-logistic accelerated failure time regression model for time-to-treatment discontinuation

Time-to-treatment discontinuation	Time ratio[a]	95% Lower confidence interval	95% Upper confidence interval	*p*
Brivaracetam (vs. lacosamide)	0.32	0.22	0.47	< 0.001
Perampanel (vs. lacosamide)	0.31	0.22	0.45	< 0.001
Adverse events (yes vs. no)	0.70	0.57	0.86	0.001
Clinical response (yes vs. no)	1.16	1.01	1.33	0.036
Brivaracetam × log-time (vs. lacosamide)	2.50	2.21	2.83	< 0.001
Perampanel × log-time (vs. lacosamide)	2.60	2.34	2.88	< 0.001
Adverse events × log-time	1.26	1.02	1.54	0.028
Clinical response × log-time	1.51	1.21	1.89	< 0.001

Model includes treatment group, adverse events, clinical response and their interactions with log-time. Estimates are weighted by inverse probability of treatment assignment (IPTW). *n*: 779. Ln-gamma: − 1.29 (95% confidence interval − 1.60, − 0.98)

[a]Time ratios (TR) < 1 indicate shorter time-to-event (earlier discontinuation); TR > 1 indicate longer time-to-event

concomitant ASMs was available for 217, 184 and 149 patients treated with PER, LCM and BRV, respectively.

At baseline, subjects in the LCM group had a significantly lower total drug load (median 1.33, IQR 0.67–2.00) than those in the BRV (median 1.80, IQR 1.15–2.75; $p=0.002$) and PER (median 2.00, IQR 1.2–2.69; $p<0.0001$) groups. No significant difference was observed between the BRV and PER groups ($p>0.9999$).

After 1 year of treatment, total drug load increased significantly in all groups compared with baseline ($p<0.0001$). Median total drug load at 12 months was 3.50 (IQR 2.40–4.50) for subjects treated with BRV, 1.85 (IQR 1.17–2.67) for those treated with LCM and 2.33 (IQR 1.74–3.23) for those on PER; this corresponds to a median percentage increase of 85.71% (IQR 50.00–148.10%), 33.33% (IQR 0.00–67.98%) and 33.33% (IQR 12.25–56.25%), respectively. At this time point, total drug load remained significantly lower in the LCM group compared with both the BRV ($p<0.0001$) and PER ($p=0.0001$) groups, and was significantly higher in the BRV group compared with the PER ($p<0.0001$) group.

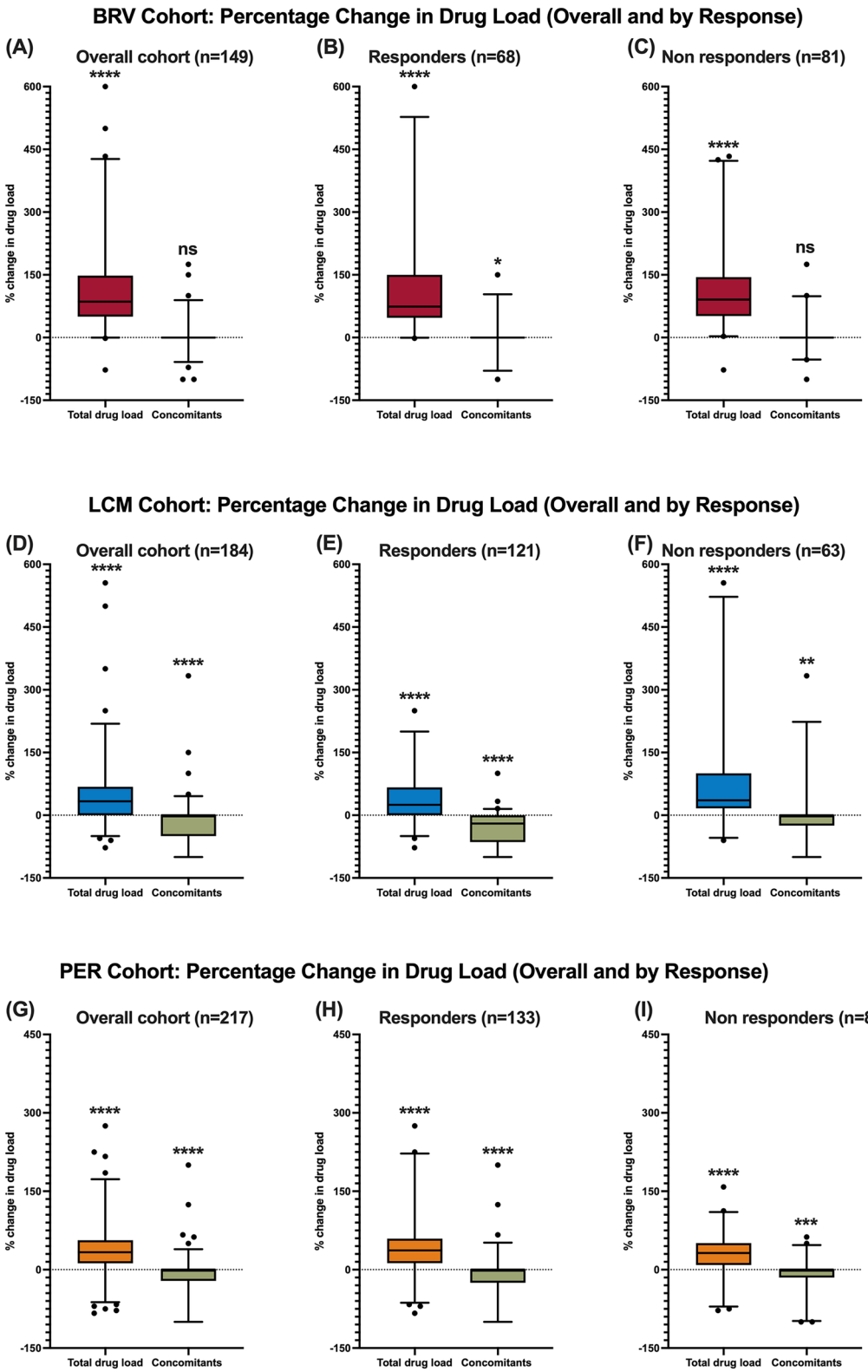
Compared with baseline, the 12-month load of concomitant ASMs decreased significantly in the LCM group (median 1.00 [IQR 0.50–2.00]; $p<0.0001$), with a median percentage change of 0.00% (IQR – 50 to 333.33%). A significant reduction was also observed in the PER group (median 1.67 [IQR 1.00–2.52]; $p<0.0001$; median percentage change 0.00% [IQR – 21.38 to 0.00%]), whereas in the BRV group, the reduction was not statistically significant (median 1.67 [IQR 1.00–2.70]; $p=0.419$; median percentage change 0.00%, [IQR: 0.00–0.00%]).

Stratification by clinical response showed significantly higher 12-month total drug load in non-responders compared with responders across all treatment groups: BRV (3.80 [IQR 3.16–4.79] vs. 2.67 [IQR: 2.06–4.00]; $p<0.0001$), LCM (2.33 [IQR 1.75–3.50] vs. 1.67 [IQR 1.00–2.33]; $p<0.0001$) and PER (2.72 [IQR 1.83–3.64] vs. 2.17 [IQR 1.50–3.02]; $p=0.007$). This difference was already present at baseline, with non-responders starting with a higher total drug load (BRV: 2.07 [IQR 1.33–3.07] vs. 1.5 [IQR 1.00–2.37]; $p=0.003$; LCM: 1.83 [IQR 1.00–2.83] vs. 1.33 [IQR 0.67–2.00]; $p=0.004$; PER: 2.00 [IQR 1.40–3.08] vs. 1.80 [IQR 1.00–2.67]; $p=0.005$) (ESM Figs. S2–S4). Compared with responders, median percentage changes from baseline to 12 months were 90.91% (IQR 51.32–144.5%) versus 73.87% (IQR: 47.27–150%) in the BRV group; 35.71% (IQR 16.49–100%) versus 25% (IQR 0.00–66.67%) in the LCM group; and 31.81% (IQR 8.95–50.86%) versus 36.84% (IQR 12.50–59.41%) in the PER group.

Notably, a significant reduction in median concomitant ASM load at 12 months emerged in the BRV group only among responders (baseline: 1.50 [IQR 1.00–2.37] vs. 1.40 [IQR 0.93–2.24]; $p=0.019$), whereas the reduction remained non-significant among non-responders (baseline: 2.07 [IQR: 1.33–3.07] vs. 2.00 [IQR: 1.37–2.91]; $p=0.544$). Although the median percentage change remained 0.00% in both BRV subgroups, the trend toward a greater reduction in concomitant load among responders became more evident in the LCM (– 20% [IQR – 64.11 to 0.00] vs. 0.00% [IQR – 25 to 0.00%]) and PER (0.00% [IQR – 25 to 0.00%] vs. 0.00% [IQR – 15.06 to 0.00%]) groups (Fig. 3).

When ASMs were stratified by MoA and EI features, significant increases in drug load were observed in the BRV group only in the subgroups classified as MoAs other than SCBs (from a median of 0.75 [IQR 0.00–1.50] to 2.10 [IQR 1.50–3.34]; $p<0.0001$) and as nEIs (from a median of 1.33 [IQR 0.67–2.29] to 3.00 [IQR 2.00–4.02]; $p<0.0001$)—and only when BRV itself was included in these categories. In contrast, in the LCM and PER groups, the only subgroup in which drug load did not significantly change was that of strong EIs, already minimally used at baseline (median and IQR 0.00), and further reduced over time. Although total drug load within SCBs and nEIs (for LCM), and within other MoAs and nEIs (for PER) increased due to the addition of the study drugs, the load of co-prescribed ASMs within these same categories decreased significantly (Figs. 4, 5, 6).

In terms of the percentage contribution to total drug load after 1 year of treatment, BRV accounted for 44.8%, LCM for 37.5% and PER for 29.3%. A detailed overview of how pharmacological burden redistributed across MoAs and EI properties is provided in ESM Figs. S5 and S6.


BRV Cohort: Percentage Change in Drug Load (Overall and by Response)
(A)
Overall cohort (n=149)
(B)
Responders (n=68)
(C)
Non responders (n=81)
LCM Cohort: Percentage Change in Drug Load (Overall and by Response)
(D)
Overall cohort (n=184)
(E)
Responders (n=121)
(F)
Non responders (n=63)
PER Cohort: Percentage Change in Drug Load (Overall and by Response)
(G)
Overall cohort (n=217)
(H)
Responders (n=133)
(I)
Non responders (n=84)
% change in drug load
Total drug load
Concomitants
ns
*
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◂**Fig. 3** Percentage change in drug load from baseline to 12 months, shown as percentage changes in drug load across the three treatment groups, both in the overall cohort and stratified by clinical response (defined as a ≥ 50% reduction in seizure frequency from baseline). **a** Percentage change from baseline to 12 months in total drug load and in the load of all concomitant ASMs in the overall cohort treated with BRV ($n = 149$). **b** Percentage change from baseline to 12 months in total drug load and in the load of all concomitant ASMs in responders treated with BRV ($n = 68$). **c** Percentage change from baseline to 12 months in total drug load and in the load of all concomitant ASMs in non-responders treated with BRV ($n = 81$). **d** Percentage change from baseline to 12 months in total drug load and in the load of all concomitant ASMs in the overall cohort treated with LCM ($n = 184$). **e** Percentage change from baseline to 12 months in total drug load and in the load of all concomitant ASMs in responders treated with LCM ($n = 121$). **f** Percentage change from baseline to 12 months in total drug load and in the load of all concomitant ASMs in non-responders treated with LCM ($n = 63$). **g** Percentage change from baseline to 12 months in total drug load and in the load of all concomitant ASMs in the overall cohort treated with PER ($n = 217$). **h** Percentage change from baseline to 12 months in total drug load and in the load of all concomitant ASMs in responders treated with PER ($n = 133$). **i** Percentage change from baseline to 12 months in total drug load and in the load of all concomitant ASMs in non-responders treated with PER ($n = 84$). Box limits indicate the first (Q1) and third (Q3) quartiles, with the central line representing the median. Whiskers extend to show the 2.5th and 97.5th percentile interval, while individual points represent values outside this range. In panels **g**, **h**, one data point falls above the upper axis limit and is not shown to improve graph readability (the change from a drug load of 0.06 to 0.75 corresponds to an increase of 1100%, although the clinical significance of such a percentage change is less relevant). Asterisks indicate significance at $^{*}p \le 0.05$, $^{**}p \le 0.01$, $^{***}p \le 0.001$ and $^{****}p \le 0.0001$ from the Wilcoxon matched-pairs signed-rank test comparing absolute values at 12 months to baseline (see Figs. 4a, b, 5a, b, 6a, b and ESM Figs. S2–S4). *ASMs* Antiseizure medications, *BRV* brivaracetam, *LCM* lacosamide, *PER* perampanel, *ns* not significant

Finally, dosage data were sufficiently complete to perform a 24-month analysis in a subset of subjects who remained on treatment. In detail, data were available for 104 patients in the LCM group, 94 in the PER group and 73 in the BRV group. In this subcohort, no significant changes in both total and stratified drug load were observed between 12 and 24 months. A detailed overview is provided in ESM Figs. S7–S9.

Adverse Events over Time

After 6 months of treatment, 19.52% of patients on PER, 14.16% of those on BRV and 12.94% of those on LCM experienced at least one AE, with no significant differences among groups ($p = 0.071$). During this period, a total of 220 AEs were reported, with the most common being dizziness (35/220, 15.91%), irritability (33/220, 15.00%) and somnolence (32/220, 14.55%). When stratified by treatment group, dizziness accounted for 7.50%, 12.64% and 22.58% of AEs in patients receiving BRV, LCM and PER, respectively; irritability accounted for 20.0%, 5.75% and 21.51%, respectively; and somnolence accounted for 20.0%, 12.64% and 13.98%, respectively. Only the distribution of irritability differed significantly among these subgroups ($p = 0.005$).

Between 6 and 12 months, the proportion of subjects experiencing at least one AE differed significantly across treatment groups ($p < 0.0001$): 3.96% in the LCM group, 12.65% in the BRV group and 18.18% in the PER group. A total of 88 AEs were recorded, with irritability (23/88, 26.14%) and dizziness (17/88, 19.32%) being the most frequently reported during this time period. No significant differences among groups emerged for either irritability ($p = 0.616$) or dizziness ($p = 0.123$).

In the 12- to 24-month interval, AE rates remained significantly different across groups ($p = 0.003$), with 2.73% of patients receiving LCM, 13.25% of patients receiving BRV and 14.71% of patients receiving PER reporting at least one AE. Among the 34 AEs recorded, the most frequently reported were irritability and dizziness (each 7/34, 20.59%). Irritability accounted for 23.08% of AEs in the BRV group and 22.22% of AEs in the PER group, and was not reported in the LCM group. Dizziness was reported in 66.67% and 27.78% of AEs in the LCM and PER groups, respectively, and was not reported in the BRV group.

In the final year of observation (24–36 months), the proportion of patients

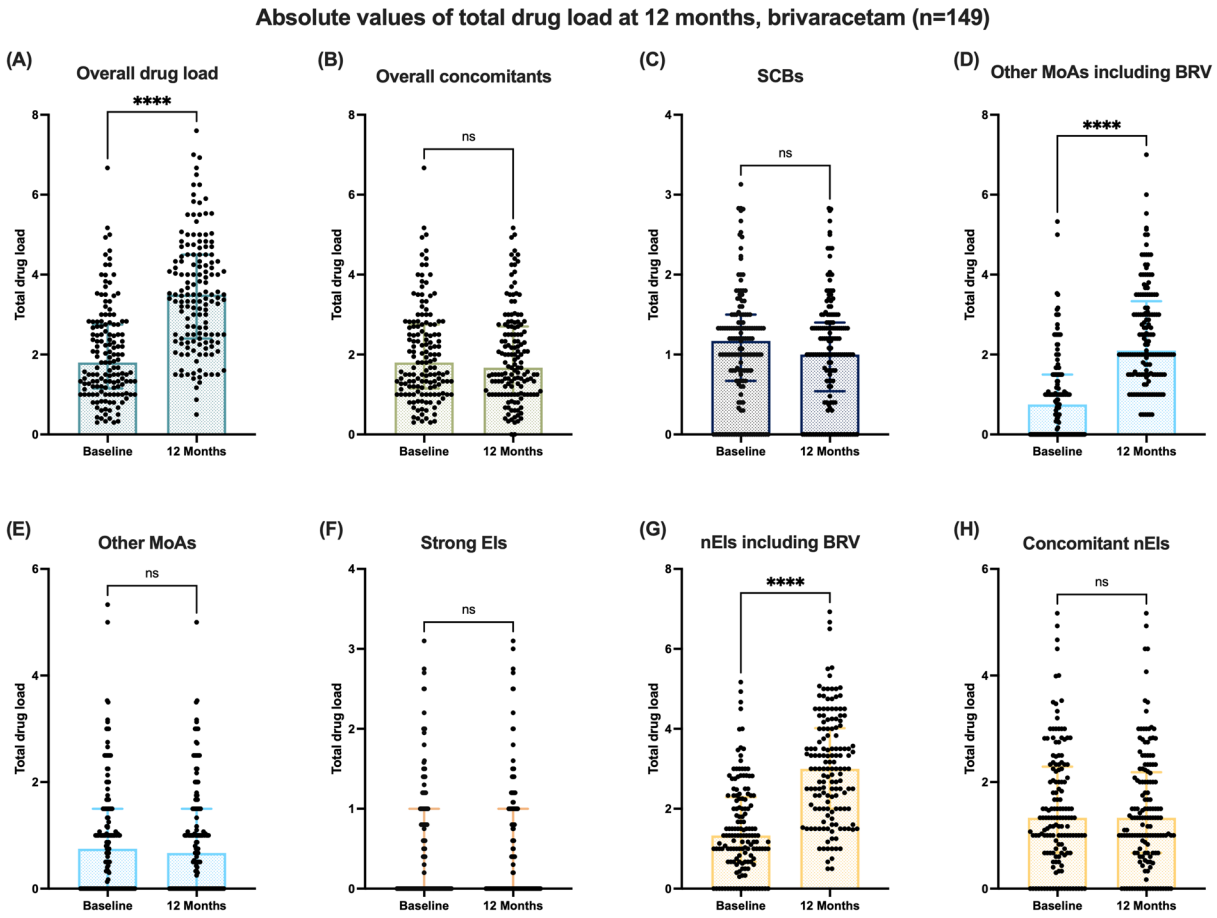

Fig. 4 Changes in total and stratified drug load (absolute values) from baseline to 12 months in the BRV group. Graphs illustrate scatter plots with bars showing the median and interquartile range of absolute ASM load values in the cohort treated with BRV ($n = 149$), including total ASM load and ASM load stratified by mechanism of action (MoA) and enzyme-inducing properties. Asterisks indicate significance at $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$ and $^{****}p \leq 0.0001$ from the Wilcoxon matched-pairs signed-rank tests comparing 12-month values with baseline for: **a** Total ASM load (including BRV), **b** load of all concomitant ASMs (excluding BRV), **c** load of SCBs (carbamazepine, eslicarbazepine acetate, lacosamide, lamotrigine, oxcarbazepine, phenytoin, rufinamide), **d** ASMs with MoAs other than SCBs (including BRV), **e** ASMs with MoAs other than SCBs (excluding BRV), **f** strong EIs (carbamazepine, phenobarbital, phenytoin, primidone), **g** nEIs (including BRV), **h** nEIs (excluding BRV). *ASMs* Antiseizure medications, *BRV* brivaracetam, *EIs* strong enzyme inducers, *nEIs* non-enzyme inducers, *ns* not significant, *SCBs* sodium channel blockers

experiencing at least one AE no longer differed significantly across treatment groups ($p = 0.102$): 1.79% in the LCM group, 9.52% in the BRV group and 12.50% in the PER group. Only nine AEs were reported overall, including three cases of irritability (1 in the BRV group, 2 in the PER group) and two cases of headache (both in the PER group).

The proportion of subjects experiencing AEs within each observation time interval, along with the temporal trend in the absolute number of the most frequently reported AEs, is illustrated in Fig. 7, whereas a comprehensive overview of all AEs reported across intervals is provided in ESM Table S3.

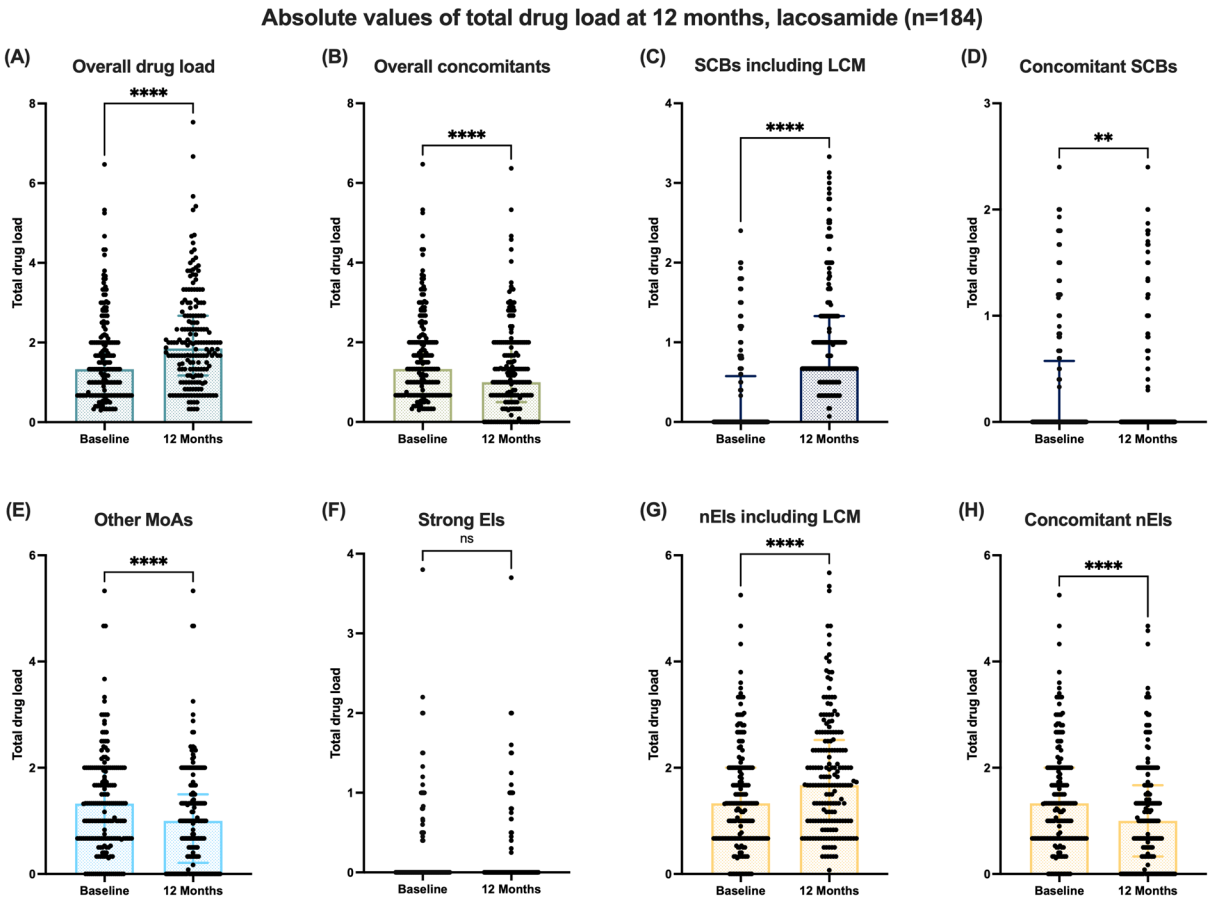

Fig. 5 Changes in total and stratified drug load (absolute values) from baseline to 12 months in the LCM group. Graphs illustrate scatter plots with bars showing the median and interquartile range of absolute ASM load values in the cohort treated with LCM ($n = 184$), including total ASM load and ASM load stratified by mechanism of action (MoA) and enzyme-inducing properties. Asterisks indicate significance at $^{*}p \le 0.05$, $^{**}p \le 0.01$, $^{***}p \le 0.001$ and $^{****}p \le 0.0001$ from the Wilcoxon matched-pairs signed-rank tests comparing 12-month values with baseline for: **a** Total ASM load (including LCM), **b** load of all concomitant ASMs (excluding LCM), **c** load of SCBs (carbamazepine, eslicarbazepine acetate, lacosamide, lamotrigine, oxcarbazepine, phenytoin, rufinamide), **d** SCBs (excluding LCM), **e** ASMs with MoAs other than SCBs, **f** strong EIs (carbamazepine, phenobarbital, phenytoin, primidone), **g** nEIs (including LCM), **h** nEIs (excluding LCM). *ASMs* Antiseizure medications, *EIs* strong enzyme inducers, *LCM* lacosamide, *nEIs* non-enzyme inducers, *ns* not significant, *SCBs* sodium channel blockers

DISCUSSION

The primary aim of this study was to compare the real-world time-to-treatment discontinuation of three commonly prescribed ASMs, namely BRV, LCM and PER, and also to explore their impact on overall drug load and longitudinal tolerability when used as add-on treatments. Using a flexible modelling strategy based on generalized gamma AFT models, weighted by inverse probability of treatment, we observed that treatment discontinuation dynamics varied meaningfully across these three medications and over time.

In our previous study, treatment retention, efficacy and AEs were analysed using separate multivariable models, including survival models for retention and logistic regression for efficacy and safety outcomes. The main reasons for applying a different statistical approach in the present study were to overcome the

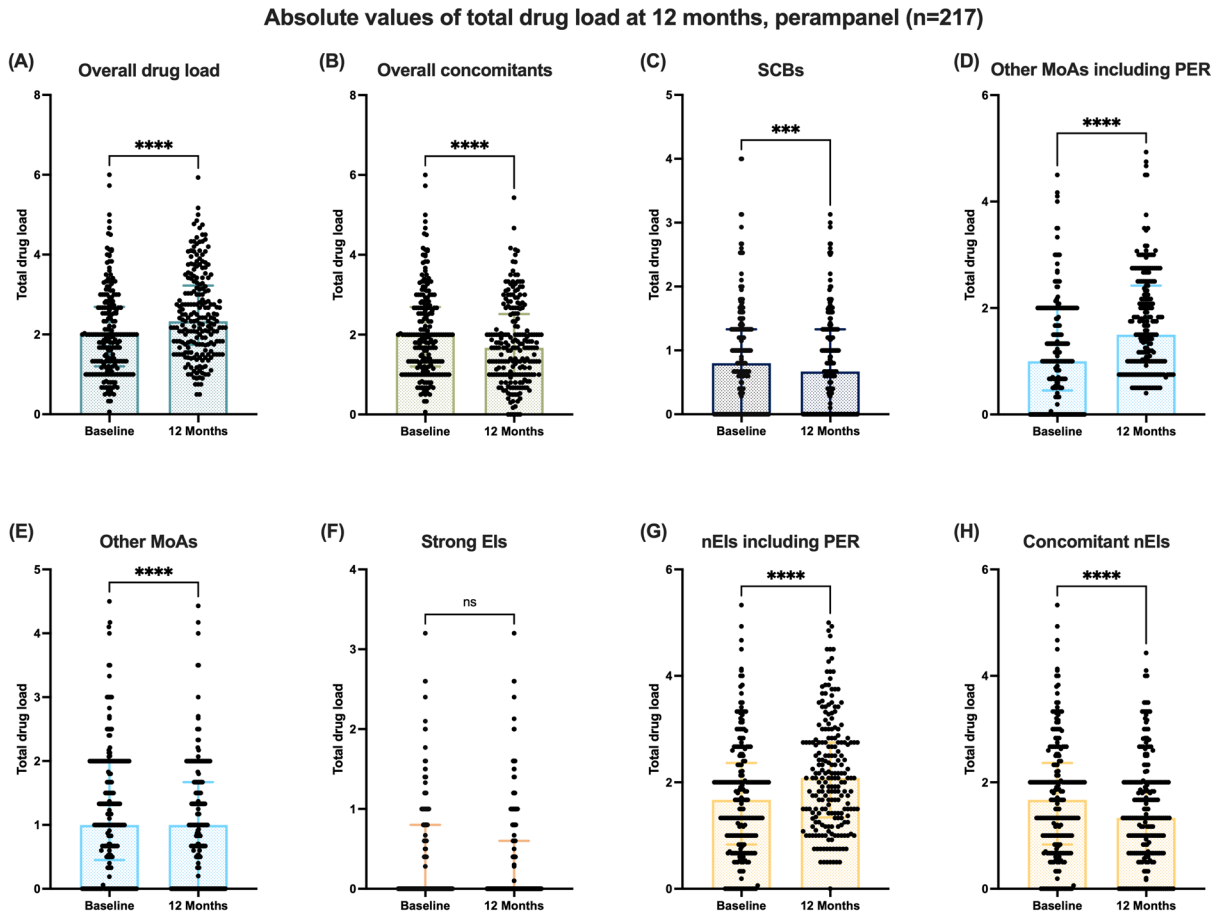

Fig. 6 Changes in total and stratified drug load (absolute values) from baseline to 12 months in the PER group. Graphs illustrate scatter plots with bars showing the median and interquartile range of absolute ASM load values in the cohort treated with PER ($n = 149$), including total ASM load and ASM load stratified by mechanism of action (MoA) and enzyme-inducing properties. Asterisks indicate significance at $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$ and $^{****}p \leq 0.0001$ from the Wilcoxon matched-pairs signed-rank tests comparing 12-month values with baseline for: **a** Total ASM load (including PER), **b** load of all concomitant ASMs (excluding PER), **c** load of SCBs (carbamazepine, eslicarbazepine acetate, lacosamide, lamotrigine, oxcarbazepine, phenytoin, rufinamide), **d** ASMs with MoAs other than SCBs (including PER), **e** ASMs with MoAs other than SCBs (excluding PER), **f** strong EIs (carbamazepine, phenobarbital, phenytoin, primidone), **g** nEIs (including PER), **h** nEIs (excluding PER). *ASMs* Antiseizure medications, *EIs* strong enzyme inducers, *nEIs* non-enzyme inducers, *ns* not significant, *PER* perampanel, *SCBs* sodium channel blockers

limitations of the standard multivariable analyses used previously, by improving covariate balance through propensity score weighting and capturing time-varying treatment persistence attributable to AEs and clinical efficacy, thereby better approximating causal effects and addressing residual confounding. This methodological extension complements and reinforces the robustness and credibility of the previously observed treatment patterns, consistently highlighting higher retention with LCM.

In the unadjusted model, both BRV and PER were associated with a significantly shorter time (about 30% shorter for both) to treatment discontinuation compared with LCM, suggesting lower overall persistence. However, when clinical response and AEs were accounted for, the strength of this association diminished,

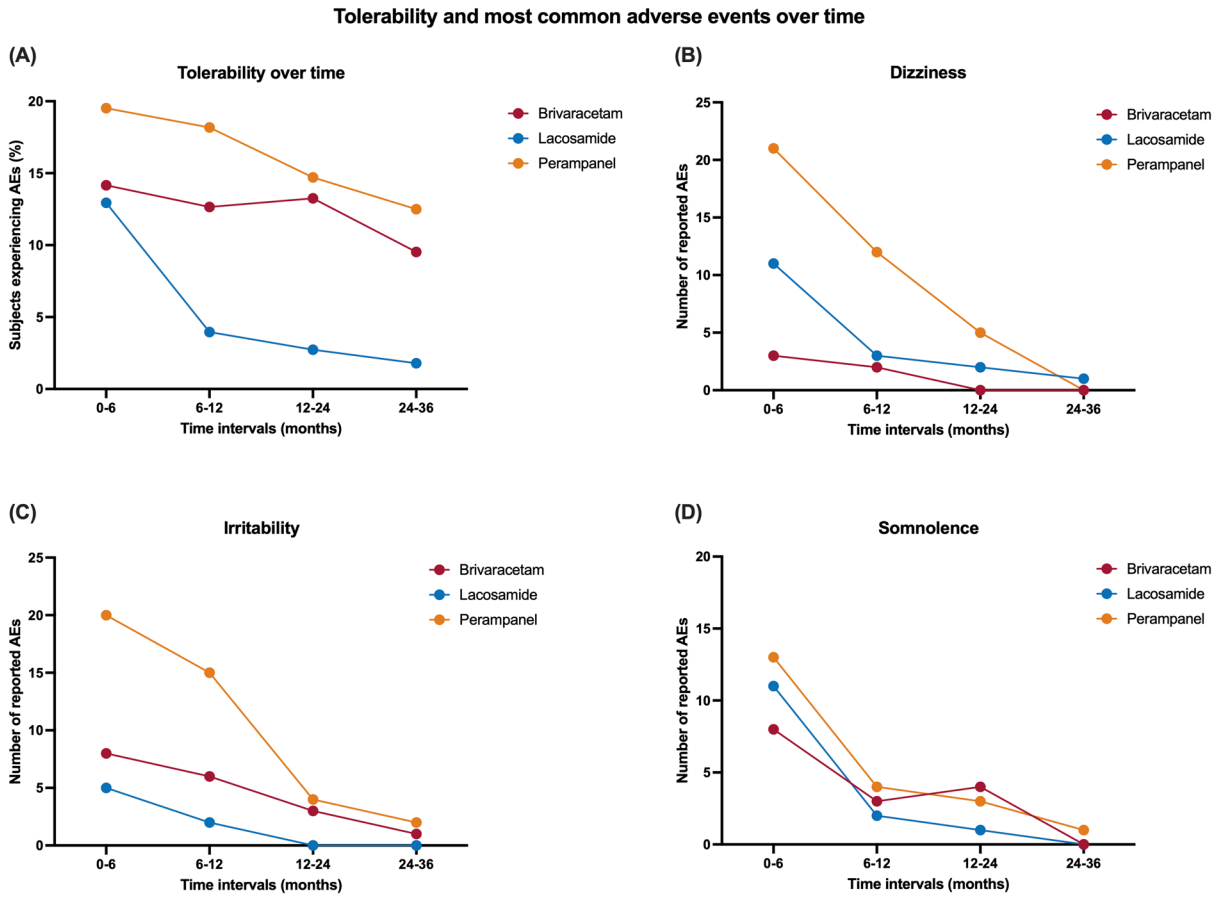

Fig. 7 Tolerability and most common adverse events over time. **a** Proportion of subjects experiencing AEs within each observation interval (0–6, 6–12, 12–24 and 24–36 months). **b** Temporal trend in the absolute number of dizziness reports. **c** Temporal trend in the absolute number of irritability reports. **d** Temporal trend in the absolute number of somnolence reports. *AE* Adverse event

indicating a possible mediating role of these patient-level variables. This result is in line with our previous study and observations and clearly visible in the Kaplan–Meier curve reported in this study [17]. Furthermore, it is clinically meaningful to consider that a drug would be withdrawn after a reasonable time if deemed ineffective or being not tolerated.

The final model, which incorporated time-by-covariate interactions, provided the best fit to the observed data and revealed a more nuanced dynamic, with better persistence found for LCM early in the treatment course, but with this advantage declining over time. Indeed, both BRV and PER showed a progressively improved time to discontinuation as time passed. This pattern is likely driven by early AEs (mainly for PER) or lack of initial efficacy (mainly for BRV) leading to discontinuation. This initial phase is followed by a stabilization of tolerability and efficacy among patients who will then remain on treatment. In other words, while there is initially a higher early discontinuation rate for BRV and PER compared to LCM, after a certain period of time these have a lower discontinuation rate than LCM; this latter drug has a stable discontinuation rate over time.

Clinical response emerged as a strong predictor of treatment persistence throughout follow-up. Subjects who experienced meaningful

clinical benefit, as defined by clinicians, were substantially more likely to remain on treatment, and this effect became stronger over time.

Conversely, the impact of AEs on discontinuation was most pronounced early in the treatment course and gradually waned, consistent with a habituation effect or clinical strategies for managing tolerability issues. Considering the distribution and type of AEs, it can be hypothesized that this result is based on the selection of PWE, with a higher acceptance of the single AE. In clinical practice, it is well known that some individuals will not complain about side effects, thereby permitting the use of high drug doses, while other individuals will just stop a drug after a couple of weeks at the most due to unbearable side effects. Our study shows that among the three drugs, PER is the least tolerated, as also supported by other studies [12, 14, 15].

A unique outcome of our analysis is that the higher persistence for LCM treatment observed in our study is not completely justified by efficacy and tolerability. It would appear that some other factors may justify clinical use up to at least 12 months when the discontinuation rate became more similar among the three drugs. However, within the framework of our study, we were unable to identify any other specific factor (at least collected in the database) justifying this clinical behaviour.

Finally, the observed trends in total and concomitant drug load suggest that both clinical efficacy and tolerability shape broader treatment strategies. Over the 12-month period, total drug load increased across all treatment groups, with greater percentage changes from baseline observed in non-responders. Notably, non-responders already exhibited a higher total drug load at baseline across all groups, possibly reflecting greater clinical complexity. An exception to this trend was seen in the PER group, where a slightly higher median percentage change was observed among responders. This finding was likely driven by a single outlier: one subject experienced an extreme relative increase in drug load (from 0.06 to 0.75) due to a very low baseline dose, an effect that was clinically marginal but had a statistically significant impact.

Overall, the increase in total drug load largely reflected the introduction or up-titration of the study drug. However, when focusing specifically on concomitant ASMs, a significant reduction in burden was observed in the LCM and PER groups, particularly among responders. In the BRV group, this reduction did not reach significance in the overall cohort but became significant when focusing exclusively on responders. These findings suggest that achieving seizure control facilitates treatment streamlining, offering an opportunity to reassess and potentially reduce background therapy. Nonetheless, tolerability likely plays an independent and complementary role in guiding treatment adjustments. This is particularly evident when drug load was stratified by MoA and EI properties. For example, in the LCM group, the burden of SCBs significantly declined, potentially reflecting efforts to minimize cumulative side effects from overlapping mechanisms. In contrast, in the BRV group, total drug load increased without a corresponding reduction in concomitant therapy. This pattern may indicate a tendency to preserve existing regimens when the added medication, such as BRV, has a favourable tolerability and interaction profile, reducing the need for dose adjustments.

Between 12 and 24 months, total drug load remained stable across groups, suggesting that most therapeutic fine-tuning occurs within the first year. This plateau likely marks a critical phase for balancing efficacy and tolerability, although the absence of further change may also be influenced by selection bias, as only clinically stable patients were retained in long-term follow-up.

Strengths and Limitations

This study benefits from a robust methodological framework that integrates causal inference techniques (through propensity score weighting) and flexible survival modelling with time-varying effects to reflect the complexity of clinical decision-making and patient experience. The analysis focused on patients initiating add-on therapy, ensuring comparable treatment

settings across groups while acknowledging that the clinical spectrum of indications (e.g. focal vs. generalized seizure types) differs among drugs and was therefore accounted for in the propensity model. However, limitations include the observational design, which precludes definitive causal conclusions despite adjustment strategies, and potential residual confounding by unmeasured variables. The chosen log-logistic AFT model showed good fit to the data, as evidenced by the Cox–Snell residual plot, and model performance was also tested against alternative hazard specifications (e.g. Weibull, log-normal), with the log-logistic consistently providing the best fit.

The sample size was adequate, with the number of events per covariate exceeding the commonly accepted rule-of-thumb of at least ten events per variable, thus ensuring sufficient statistical power and stability of estimates.

However, some limitations should be acknowledged. Approximately 9% of patients were excluded from the multivariable model due to missing data on key variables. Nevertheless, we have no theoretical reason to believe that the missingness in these variables was not at random (MNAR), which reduces the risk of systematic bias. Secondly, although the overlap in propensity score distributions was acceptable, the possibility of unmeasured baseline and unmeasured post-treatment confounders cannot be excluded. These factors might explain at least part of the differences in treatment retention observed between the three drugs.

Clinical Implications

Our findings confirm once more the efficacy of these ASMs in a real-world setting, implying a thoughtful choice based on evidence, personal knowledge and experience. As indicated by experts consensus articles [25, 26], the choice of an ASM from the second onward must be based on several aspects, among which quality of life and tolerability must be considered and somewhat outweigh efficacy [27–29]. Additionally, this study underscores the importance of monitoring and managing early tolerability to improve treatment persistence. Clinicians may consider LCM when tolerability is a primary concern in the initial weeks, while recognizing that BRV and PER may achieve similar long-term adherence in patients who tolerate the early phase. The strong influence of clinical response highlights the need for early identification of treatment benefit and for strategies that optimize patient-reported outcomes.

CONCLUSIONS

Treatment discontinuation in epilepsy is a dynamic process shaped by both tolerability and efficacy. While LCM is associated with better early persistence, BRV and PER demonstrate improved retention over time, particularly among responders. Interestingly, drug load represents a clinical parameter that is difficult to consider; as expected, we found that the drug load of concomitant drugs was meaningfully reduced in responders, but it was also reduced in non-responders, possibly to counterbalance the increase in total drug load caused by the addition of a new drug. Overall, drug load and modulation of therapy may not be considered an efficacy parameter. These results support a personalized approach to ASM selection, integrating early tolerability and long-term effectiveness in the decision-making that guides clinical choices.

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

Declarations

Conflict of Interest. Roberta Roberti has received speaker's or consultancy fees from Eisai, UCB Pharma and Jazz Pharmaceuticals. Francesca Anzellotti has received travel support from Eisai, UCB and Angelini Pharma; and has speaker honoraria from Eisai and Angelini Pharma. Giovanni Boero has received speaker's or consultancy fees from Eisai, Angelini Pharma and UCB Pharma. Paolo Bonanni has received speaker's or consultancy fees from Bial, Eisai, GW, LivaNova, Lusofarmaco, Proveca and Roche. Laura Canafoglia has participated in pharmaceutical industry-sponsored clinical trials for UCB Pharma and other pharmaceutical industries; and has received speaker honoraria from Eisai. Alfredo D'Aniello has participated in pharmaceutical industry-sponsored clinical trials for UCB Pharma; has received speaker honoraria and consultancy fees from Eisai, UCB Pharma, Angelini Pharma and Neuraxpharm; and has served on advisory boards for Angelini Pharma. Filippo Dainese has received speaker's or consultancy fees from UCB Pharma, Eisai and Bial. Giancarlo Di Gennaro has received speaker honoraria from UCB Pharma, Eisai, Lusofarmaco, Livanova, Angelini Pharma and Jazz Pharmaceuticals; and has served on advisory board for Bial, Arvelle, Angelini Pharma, Livanova, Neuraxpharma and UCB Pharma. Fedele Dono has received travel support from Eisai, UCB Pharma and Angelini Pharma; and has received speaker honoraria from Eisai. Giovanni Falcicchio has received speaker fees from Angelini Pharma. Edoardo Ferlazzo has received speaker honoraria from UCB Pharma, Eisai and Angelini Pharma. Antonio Gambardella has received speaker honoraria from UCB Pharma, Eisai, Angelini Pharma, Jazz, Bial and Zambon. Angela La Neve has received speaker's or consultancy fees from Eisai, Mylan, Sanofi, Bial, GW, Arvelle, Angelini Pharma and UCB Pharma; and has served on scientific advisory boards for GW Pharma, Jazz Pharmaceuticals and Angelini Pharma. Simona Lattanzi has received speaker's or consultancy fees from Angelini Pharma, Eisai, GW Pharmaceuticals, Medscape and UCB Pharma; and has served on advisory boards for Angelini Pharma, Arvelle Therapeutics, BIAL, Eisai and GW Pharmaceuticals outside the submitted work. Simona Lattanzi received research grant support from the Ministry of Health and the Ministry of University and Research outside the submitted work. Pietro Mattioli has received speaker honoraria from Angelini Pharma. Emilio Russo has received speaker fees or funding from and has participated on advisory boards for Angelini Pharma, Eisai, Ethypharm, GW Pharmaceuticals, Jazz Pharmaceuticals, Kolfarma and UCB Pharma. Simona Lattanzi is an Editorial Board member of *Neurology and Therapy*, but was not involved in the selection of peer reviewers for the manuscript or in any of the subsequent editorial decisions. Cristina Politi, Vincenzo Belcastro, Simone Beretta, Carmen De Caro, Roberta Di Giacomo, Jacopo C DiFrancesco, Nicoletta Foschi, Alfonso Giordano, Angelo Labate, Ugo Leggio, Claudio Liguori, Marta Maschio, Annacarmen Nilo, Francesca Felicia Operto, Angelo Pascarella, Giada Pauletto, Luciano Pellegrino, Rosaria Renna and Gionata Strigaro and Gianfranco Di Gennaro have no conflicts of interest.

Ethical Approval. The overall, anonymized 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. As the study was based on retrospective and fully anonymized data, written informed consent was not required.

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