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Comparative Effectiveness of Brivaracetam, Cenobamate, Lacosamide, and Perampanel in Focal Epilepsy

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IMPORTANCE Treatment decisions in drug-resistant focal epilepsy remain largely empirical, as direct comparative evidence among newer antiseizure medications (ASMs) is limited. Real-world data can complement randomized clinical trials by providing insights into long-term effectiveness and safety across diverse populations.

OBJECTIVE To compare effectiveness and safety of brivaracetam, cenobamate, lacosamide, and perampanel as adjunctive therapies in adults with drug-resistant focal epilepsy.

DESIGN, SETTING, AND PARTICIPANTS This was a multicenter pooled analysis of 4 previously conducted retrospective real-world medical record–review studies (January 2017-January 2024). Included were adult patients (aged ≥16 years) with drug-resistant focal epilepsy, as defined by the International League Against Epilepsy. Participants were recruited from 71 epilepsy centers.

EXPOSURES Add-on treatment with brivaracetam, cenobamate, lacosamide, or perampanel.

MAIN OUTCOMES AND MEASURES The primary outcome was the responder rate at 6 months, defined as greater than or equal to 50% seizure frequency reduction from baseline. Secondary outcomes included 12-month responder rate, seizure freedom (≥3 months at 6 months and ≥6 months at 12 months), and 12-month ASM retention. Safety was assessed by incidence of adverse effects. Generalized linear mixed models adjusted for demographic and clinical covariates were used to compare treatment outcomes, with cenobamate as reference ASM.

RESULTS Of 2386 ASM prescriptions screened, 1993 prescriptions from 1949 patients (1036 of 1947 female [53.2%]; sex information was missing in 0.1% of prescriptions) with a median (IQR) age of 42 (29-55) years at ASM prescription, met inclusion criteria and were included in the pooled analysis. Brivaracetam accounted for 953 prescriptions (47.8%), followed by perampanel (607 [30.5%]), lacosamide (241 [12.1%]), and cenobamate (192 [9.6%]). After adjustment, cenobamate demonstrated significantly higher odds of 50% or greater response at 6 months compared with brivaracetam (odds ratio [OR], 0.18; 95% CI, 0.12-0.28; $P < .001$), perampanel (OR, 0.26; 95% CI, 0.16-0.42; $P < .001$), and lacosamide (OR, 0.29; 95% CI, 0.17-0.49; $P < .001$). Results were consistent for secondary effectiveness outcomes at 12 months, with cenobamate outperforming other ASMs in terms of 50% or greater response and seizure freedom. Cenobamate was associated with the highest rate of adverse effects during follow-up (111 [57.8%]), and lacosamide was associated with the lowest (35 [14.8%]). Cenobamate was associated with a higher likelihood of treatment retention at 12 months compared with brivaracetam (OR, 0.43; 95% CI, 0.26-0.69; $P < .001$) and perampanel (OR, 0.56; 95% CI, 0.32-0.99; $P = .047$), with no significant difference vs lacosamide (OR, 0.81; 95% CI, 0.41-1.59; $P = .53$).

CONCLUSIONS AND RELEVANCE These study findings suggest superior effectiveness of cenobamate over brivaracetam, lacosamide, and perampanel in adults with drug-resistant focal epilepsy in a large real-world setting.

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Multimedia

Supplemental content

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Focal epilepsy represents the most common form of epilepsy in adults and encompasses a clinically and etiologically heterogeneous group of disorders.[1] Seizure control remains suboptimal for a substantial proportion of patients, contributing to reduced quality of life, increased health care burden, and higher risks of injury and sudden unexpected death in epilepsy.[2,3]

Despite the expanding arsenal of antiseizure medications (ASMs), treatment decisions in focal epilepsy remain largely empirical. In clinical practice, the selection of an ASM is frequently guided by expert opinion, historical precedent, tolerability profiles, or regulatory approval, rather than by direct comparative evidence of effectiveness.[4] Although randomized clinical trials (RCTs) have established the efficacy of individual ASMs vs placebo, they rarely provide head-to-head comparisons and typically involve highly selected patient populations, with limited follow-up duration.[5] Consequently, long-term effectiveness and tolerability in real-world populations remain insufficiently characterized.

In this context, real-world data have emerged as a valuable complement to traditional RCTs, capturing outcomes in broader and diverse populations.[6-8] However, real-world comparative effectiveness studies in epilepsy remain relatively scarce, often limited by small sample sizes, heterogeneity in methodology, and inadequate adjustment for confounding variables.[8]

Brivaracetam, cenobamate, lacosamide, and perampanel are among the most widely used newer-generation ASMs for focal epilepsy. Although these drugs have demonstrated efficacy in RCTs as adjunctive therapies,[9] their comparative effectiveness and long-term tolerability remain poorly delineated.

In this pooled analysis of harmonized retrospective real-world medical record-review studies, we investigated the comparative effectiveness and safety of brivaracetam, cenobamate, lacosamide, and perampanel in adults with drug-resistant focal epilepsy.

Key Points

Question What is the comparative effectiveness and safety of brivaracetam, cenobamate, lacosamide, and perampanel as adjunctive therapies in adults with drug-resistant focal epilepsy?

Findings In this pooled analysis of real-world medical record–review studies of 1949 patients with drug-resistant focal epilepsy, cenobamate was associated with higher responder rates and seizure freedom at 6 and 12 months compared with brivaracetam, lacosamide, and perampanel, albeit with a higher incidence of adverse effects.

Meaning These results suggest that cenobamate offers superior long-term effectiveness over other newer ASMs in drug-resistant focal epilepsy, although its increased risk of adverse effects should be carefully weighed in clinical decision-making.

Methods

Participants

This multicenter pooled analysis of previously conducted retrospective real-world medical record-review studies adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) reporting guidelines.[10,11] For each of the studies included in the pooled analysis, approval was obtained from the relevant ethics committees, and written informed consent was obtained from all participants.

This article reports a pooled analysis of harmonized retrospective medical record-review datasets including patients with epilepsy treated at 71 epilepsy centers (primary, secondary, and tertiary care) between January 1, 2017, and January 31, 2024. All patients included in this analysis had been previously enrolled in 1 of 4 investigator-initiated retrospective real-world studies: the Brivaracetam Add-On First Italian Network Study (BRIVAFIRST) study, the Perampanel as Only Concomitant Antiseizure Medication (PEROC) study, the COMPARE study, and the Cenobamate Expanded Access Program, conducted within nationwide collaborative networks that ensured a standardized methodological framework (eTable 1 in Supplement 1 contains details on these studies).[12-15]

For the present study, individual-level clinical data from retrospective medical record-reviews were pooled and harmonized to ensure consistency in outcome definitions and variable structures. Baseline variables common to all datasets and included in this analysis were demographic characteristics, age at seizure onset, epilepsy etiology, number of previously tried ASMs, number of concomitant ASMs at baseline, and seizure frequency during the 12-week period before ASM initiation, categorized as daily (≥1/day), weekly (≥1/week but <1/day), or monthly (<1/week) (eMethods in Supplement 1). Participant race and ethnicity were not systematically collected in the original medical record-review studies and, therefore, not included in the pooled analysis.

From the original datasets, patients were included in the present analysis if they met the following criteria: initiation of brivaracetam, cenobamate, lacosamide, or perampanel as adjunctive therapy for drug-resistant focal epilepsy—defined in accordance with the International League Against Epilepsy as failure to achieve sustained seizure freedom despite adequate trials of at least two appropriately chosen and dosed ASMs[16]; age 16 years or older at the time of ASM prescription; and a minimum follow-up of 6 months after ASM initiation, unless treatment was discontinued earlier due to inefficacy or adverse effects. Patients were excluded if they had a history of generalized seizure types, a diagnosis of combined generalized and focal epilepsy, or developmental and epileptic encephalopathies (DEEs).

Data quality in the final dataset was ensured through a multistep verification process (eMethods in Supplement 1).

Outcome Measures

The primary outcome of the study was the responder rate at 6 months, defined as a reduction of at least 50% in seizure frequency compared with the baseline observation period. Secondary outcomes included the responder rate at 12 months and

seizure freedom at 6 and 12 months. Seizure freedom was defined as the absence of seizures since at least the previous follow-up visit—that is, for a minimum of 3 months at the 6-month assessment and 6 months at the 12-month follow-up (eMethods in Supplement 1). For patients who discontinued the prescribed ASM due to ongoing seizures or adverse effects, treatment was considered ineffective from the time of discontinuation onward for all outcome analyses. As a measure of tolerability, we assessed treatment retention rate at 12 months.

Safety was evaluated by recording the occurrence of adverse effects during follow-up, which were categorized into somnolence or fatigue; central nervous system symptoms such as headache, tremor, tics, diplopia, or ataxia; vertigo or dizziness; behavioral adverse effects including irritability, aggressiveness, or new-onset or worsening mood disorders; gastrointestinal symptoms such as nausea, vomiting, anorexia, diarrhea or constipation; dermatological manifestations including rash or hair loss; and hyponatremia.

Statistical Analysis

Given that the proportion of missing data was below 5% for all baseline variables and primary outcome (eFigure 1 in Supplement 1), a complete case analysis was performed. The prespecified primary analysis assessed the comparative effectiveness of brivaracetam, cenobamate, lacosamide, and perampanel using a generalized linear mixed model (GLMM) with a logit link and binomial distribution. The primary outcome (ie, responder rate at 6 months) was modeled as the dependent variable, with ASM type included as a fixed effect. Cenobamate was used as reference category, and comparative effectiveness data were reported as odds ratios (ORs) with 95% CIs.

The model was adjusted for the following covariates: age at ASM initiation, age at epilepsy onset, sex, number of previously tried ASMs, number of concomitant ASMs, epilepsy etiology (with structural etiology as reference category), and baseline seizure frequency (with monthly frequency as reference). Each ASM exposure was treated as a separate observation; therefore, patients who received more than 1 of the studied ASMs contributed multiple entries. To account for within-patient clustering and between-center variability, crossed random effects for individual patients and recruiting centers were included.

The same prespecified GLMM framework was applied to secondary outcomes: seizure freedom at 12 months, responder rate at 12 months, seizure freedom at 6 months, and ASM retention at 12 months. To visualize treatment effects adjusted for confounding, estimated marginal means of predicted probabilities and corresponding 95% CIs were calculated for responder and seizure freedom rates for each ASM.

As sensitivity analyses, GLMMs were performed for both primary and secondary outcomes, after imputing missing data using multiple imputation by chained equations.[17] In addition to these prespecified analyses, an additional sensitivity analysis excluding the PEROC cohort was performed to account for heterogeneity in original follow-up visit definitions in the PEROC dataset.

Finally, the proportions of patients reporting adverse effects across treatment groups were compared using the χ^2 test. All statistical analyses were conducted using R, version 3.5.1 (R Foundation for Statistical Computing). All P values were 2-sided, and P <.05 was considered statistically significant.

Results

Clinical Characteristics of Patients

Between January 1, 2017, and January 31, 2024, a total of 2386 ASM prescriptions involving brivaracetam, cenobamate, lacosamide, and perampanel were identified. Of these, 393 (16.5%) were excluded: 73 (3.1%) due to duplication, 46 (1.9%) for age younger than 16 years, 37 (1.6%) for not meeting criteria for drug-resistant epilepsy, 155 (6.5%) due to ineligible epilepsy syndromes (generalized, combined, or DEE), and 82 (3.4%) for insufficient follow-up.

The final cohort included 1993 distinct ASM prescriptions from 1949 patients (1036 of 1947 female [53.2%]; 911 of 1947 male [46.8%]; sex information was missing in 0.1% of prescriptions). Median (IQR) age at prescription was 42 (29-55) years. Brivaracetam accounted for 953 prescriptions (47.8%), followed by perampanel (607 [30.5%]), lacosamide (241 [12.1%]), and cenobamate (192 [9.6%]) (eFigure 2 in Supplement 1).

Patients prescribed cenobamate had the highest rate of daily (31.8%) and weekly (54.7%) seizures at baseline, number of concomitant ASMs (median [IQR], 3 [2-4]), and prior treatment exposures (median [IQR], 10 [8-13]), whereas those taking lacosamide had the lowest. Detailed baseline characteristics are reported in **Table 1**.

Comparative Effectiveness at 6 Months

The unadjusted 50% or greater responder rates at 6 months were as follows: lacosamide 63.3% (n = 152), perampanel 58.9% (n = 327), cenobamate 52.1% (n = 100), and brivaracetam 41.1% (n = 375).

After GLMM adjustment, cenobamate was associated with significantly higher odds of response compared with all other treatments: brivaracetam (OR, 0.18; 95% CI, 0.12-0.28; P < .001), perampanel (OR, 0.26; 95% CI, 0.16-0.42; P < .001), and lacosamide (OR, 0.29; 95% CI, 0.17-0.49; P < .001) (**Figure 1**A). Full model results are detailed in **Table 2**. The predicted probabilities of achieving 50% or greater seizure reduction were cenobamate 0.82 (95% CI, 0.73-0.88), lacosamide 0.57 (95% CI, 0.45-0.67), perampanel 0.54 (95% CI, 0.45-0.63), and brivaracetam 0.45 (95% CI, 0.37-0.54) (Figure 1B).

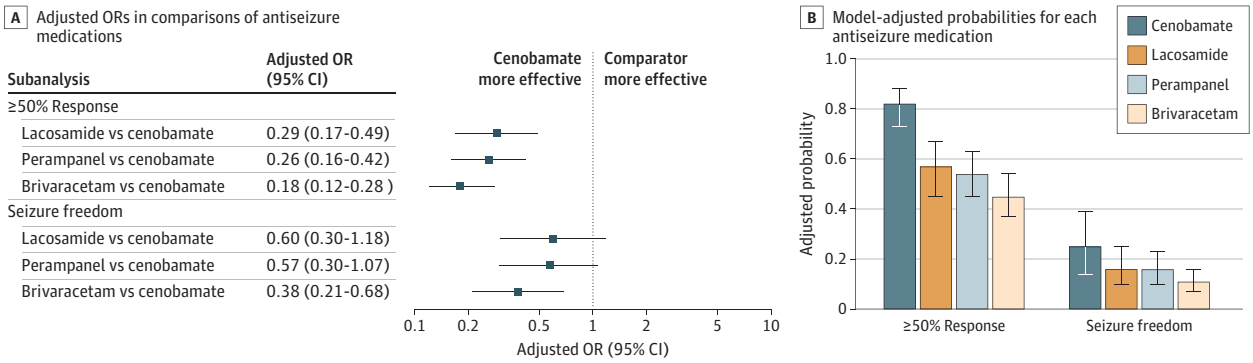
At the 6-month follow-up, unadjusted greater than or equal to 3-month seizure freedom rates were as follows: lacosamide 35.0% (n = 84), perampanel 26.8% (n = 149), brivaracetam 15.4% (n = 140) and cenobamate 12.0% (n = 23). In the adjusted model, cenobamate showed a significantly higher likelihood of greater than or equal to 3-month seizure freedom at 6 months only compared with brivaracetam (OR 0.38; 95% CI, 0.21-0.68; P = .001), with no significant differences vs lacosamide (OR, 0.60; 95% CI, 0.30-1.18; P = .14) or perampanel (OR, 0.57; 95% CI, 0.30-1.07; P = .08) (Figure 1A). eTable 2

Table 1. Comparison of Baseline Characteristics Across Different Antiseizure Medications (ASMs)

Variable	BRV	CNB	LCM	PER	*P* value
Female sex, No. (%)	500 (52.5)	107 (55.7)	128 (53.1)	340 (56.2)	.50
Male sex, No. (%)	453 (47.5)	85 (44.3)	113 (46.9)	265 (43.8)	
Age at prescription, median (IQR), y	45.0 (33.0-56.0)	38.0 (27.7-49.2)	44.0 (27.0-59.0)	39.0 (24.0-53.0)	<.001
Age at seizure onset, median (IQR), y	13.0 (5.3-25.0)	10.0 (4.0-15.7)	26.4 (11.3-45.6)	16.0 (8.0-36.4)	<.001
Prior ASM attempts, median (IQR), No.	6 (3-8)	10 (8-13)	3 (2-5)	4 (2-6)	<.001
Concurrent ASMs, median (IQR), No.	2 (1-3)	3 (2-4)	1 (1-2)	1 (1-2)	<.001
Etiology, No. (%)					
Structural	507 (53.2)	97 (50.5)	135 (56)	344 (57.3)	.002
Genetic/presumed genetic	38 (4)	6 (3.1)	20 (8.3)	42 (7)	
Autoimmune	9 (0.9)	4 (2.1)	3 (1.2)	3 (0.5)	
Infectious	26 (2.7)	8 (4.2)	1 (0.4)	10 (1.7)	
Unknown	373 (39.1)	77 (40.1)	82 (34.0)	201 (33.5)	
Seizure frequency, No. (%)					
Monthly	314 (32.9)	26 (13.5)	126 (52.9)	184 (30.3)	<.001
Weekly	450 (47.2)	105 (54.7)	79 (33.2)	265 (43.7)	
Daily	189 (19.8)	61 (31.8)	33 (13.9)	158 (26.0)	

Abbreviations: BRV, brivaracetam; CNB, cenobamate; LCM, lacosamide; PER, perampanel.

Figure 1. Adjusted Odds Ratios (ORs) and Probabilities of 50% or Greater Response and Greater Than or Equal to 3-Month Seizure Freedom at 6-Month Follow-Up



A, Shows adjusted ORs and 95% CIs of brivaracetam (BRV), lacosamide (LCM), and perampanel (PER) vs cenobamate (CNB). OR values less than 1 indicate superior effectiveness of CNB over comparators. B, Shows model-adjusted probabilities for each antiseizure medication (ASM). Models were adjusted for age at ASM initiation, age at epilepsy onset, sex, number of previously tried ASMs, number of concomitant ASMs, epilepsy etiology (structural as reference category), and baseline seizure frequency (monthly frequency as reference category).

in Supplement 1 displays full model results. Predicted probabilities of greater than or equal to 3-month seizure freedom were as follows: cenobamate, 0.25 (95% CI, 0.14-0.39), perampanel, 0.16 (95% CI, 0.10-0.23), lacosamide, 0.16 (95% CI, 0.10-0.25), and brivaracetam, 0.11 (95% CI, 0.07-0.16) (Figure 1B).

Comparative Effectiveness at 12 Months

Among the 1742 prescriptions with 12-month follow-up data, unadjusted 50% or greater responder rates were as follows: perampanel 59.5% (n = 269), cenobamate 58.4% (n = 94), lacosamide 56.0% (n = 117), and brivaracetam 41.4% (n = 381). In adjusted analyses, cenobamate was associated with significantly higher odds of response than brivaracetam (OR, 0.16; 95% CI, 0.10-0.25; $P < .001$), lacosamide (OR, 0.21; 95% CI, 0.12-0.37; $P < .001$), and perampanel (OR, 0.24; 95% CI, 0.14-0.41; $P < .001$) (**Figure 2**A). Full model results are shown in eTable 3 in Supplement 1. Predicted probabilities were cenobamate, 0.84 (95% CI, 0.75-0.90), perampanel, 0.56 (95% CI, 0.46-0.65), lacosamide, 0.52 (95% CI, 0.40-0.64), and brivaracetam, 0.45 (95% CI, 0.36-0.54) (Figure 2B).

Unadjusted greater than or equal to 6-month seizure freedom rates at 12 months were as follows: lacosamide 33.5% (n = 70), perampanel 28.3% (n = 128), brivaracetam 15.3% (n = 141), and cenobamate 14.3% (n = 23). Adjusted models confirmed a significantly higher probability of greater than or equal to 6-month seizure freedom at 12 months with cenobamate vs brivaracetam (OR, 0.26; 95% CI, 0.14-0.50; $P < .001$), peram-

Table 2. Generalized Linear Mixed Model of ≥50% Responder Rate at the 6-Month Follow-Up[a]

Variable	OR (95% CI)	*P* value
Prescribed ASM (cenobamate as reference)		
Brivaracetam	0.18 (0.12-0.28)	<.001
Lacosamide	0.29 (0.17-0.49)	<.001
Perampanel	0.26 (0.16-0.42)	<.001
Age at prescription, y	1.002 (0.99-1.01)	.72
Age at seizure onset, y	1.01 (1.001-1.02)	.02
Female sex	0.90 (0.73-1.10)	.30
Etiology (structural as reference)		
Genetic/presumed genetic	1.08 (0.67-1.75)	.75
Autoimmune	0.80 (0.29-2.22)	.67
Infectious	1.59 (0.78-3.23)	.29
Unknown	1.01 (0.81-1.25)	.95
Prior ASM attempts	0.89 (0.85-0.93)	<.001
Concomitant ASMs	0.75 (0.65-0.86)	<.001
Seizure frequency (monthly as reference)		
Weekly	0.70 (0.55-0.89)	.004
Daily	0.54 (0.40-0.73)	<.001

Abbreviations: ASM, antiseizure medication; OR, odds ratio.

[a] Model adjusted for age at ASM initiation, age at epilepsy onset, sex, number of previously tried ASMs, number of concomitant ASMs, epilepsy etiology, and baseline seizure frequency, with random intercepts for patients and recruiting centers to account for within-patient clustering and between-center variability.

panel (OR, 0.41; 95% CI, 0.21-0.82; *P* = .01), and lacosamide (OR, 0.43; 95% CI, 0.21-0.90; *P* = .02) (Figure 2A). Full model results are fully summarized in eTable 4 in Supplement 1. Predicted probabilities were cenobamate, 0.32 (95% CI, 0.19-0.49), lacosamide, 0.17 (95% CI, 0.10-0.27), perampanel, 0.16 (95% CI, 0.10-0.25), and brivaracetam, 0.11 (95% CI, 0.07-0.17) (Figure 2B).

Tolerability and Adverse Effects

At 12 months, the unadjusted retention rates were lacosamide 84.7% (n = 177), perampanel 79.4% (n = 362), cenobamate 77.6% (n = 125), and brivaracetam 71.7% (n = 660). GLMM showed that cenobamate had significantly higher retention than brivaracetam (OR, 0.43; 95% CI, 0.26-0.69; *P* < .001) and perampanel (OR, 0.56; 95% CI, 0.32-0.99; *P* = .047), with no significant difference vs lacosamide (OR, 0.81; 95% CI, 0.41-1.59; *P* = .53) (Figure 2A and eTable 5 in Supplement 1). Predicted probabilities of ASM retention are displayed in Figure 2B.

Cenobamate was associated with the highest rate of adverse effects during follow-up (111 [57.8%]), followed by perampanel (187 [31.7%]), brivaracetam (251 [30.5%]), and lacosamide (35 [14.8%]). Adverse effect subtypes by ASM are detailed in **Table 3**.

Sensitivity Analysis

Sensitivity analysis of the primary outcome using multiple imputation yielded consistent results as follows: cenobamate vs brivaracetam (OR, 0.18; 95% CI, 0.12-0.28; *P* < .001), cenobamate vs perampanel (OR, 0.27; 95% CI, 0.17-0.43; *P* < .001), and cenobamate vs lacosamide (OR, 0.30; 95% CI, 0.17-0.50; *P* < .001). Consistent findings were confirmed also for secondary outcomes (eTable 6 in Supplement 1). The additional sensitivity analysis excluding the PEROC cohort yielded results consistent with the primary analyses (eTable 7 in Supplement 1).

Discussion

This comparative effectiveness pooled analysis of harmonized retrospective medical record–review studies sought to provide real-world evidence on the effectiveness and tolerability of 4 newer-generation ASMs—brivaracetam, cenobamate, lacosamide, and perampanel—in adults with drug-resistant focal epilepsy. Our results reveal robust, adjusted estimates of treatment outcomes in a real-world setting, demonstrating that cenobamate was associated with significantly higher responder rates at both 6 and 12 months and a greater likelihood of seizure freedom at 12 months compared with the other agents studied. These findings remained consistent across primary and sensitivity analyses after adjusting for established clinical confounders.[18,19]

Specifically, although cenobamate showed unadjusted 6- and 12-month responder rates comparable with the other analyzed ASMs, the adjusted models revealed a markedly superior effectiveness of cenobamate. This high efficacy profile is consistent with findings from open-label extension studies and real-world observational data, which have highlighted the therapeutic potential of cenobamate in refractory focal epilepsy.[20,21] Moreover, our results align with prior network meta-analyses of RCTs, which have similarly demonstrated greater effectiveness of cenobamate compared with other newer-generation ASMs.[22,23] Consistent conclusions have also emerged from smaller real-world comparative studies, further supporting the superior clinical effectiveness of cenobamate compared with other ASMs.[24,25] A comparative effectiveness analysis of ASMs in emulated trials using information from electronic health records through an informatics-based framework also identified cenobamate among the third-line ASMs with the highest rates of retention over 5 years of follow-up in focal epilepsies.[26]

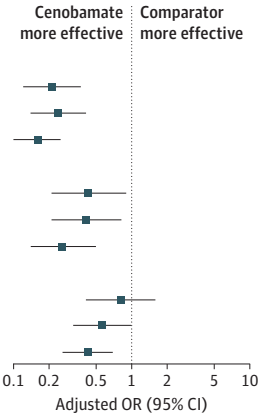
Lacosamide and perampanel showed intermediate effectiveness, with GLMM-adjusted responder rates ranging between 52% and 57% and adjusted seizure freedom probabilities of 16% to 17% at 12 months. Interestingly, both agents were associated with higher unadjusted seizure freedom rates compared with cenobamate at 6 and 12 months, whereas the adjusted models highlighted a superior effectiveness of cenobamate at both time points. This discrepancy underscores the critical importance of accounting for confounding factors when interpreting observational data and reinforces the value of comparative effectiveness studies in epilepsy research.[10]

Brivaracetam demonstrated a trend toward lower efficacy across all end points, with GLMM-adjusted responder rates below 50% and greater than or equal to 6-month seizure freedom rates near 11% at 12 months. Although brivaracetam is

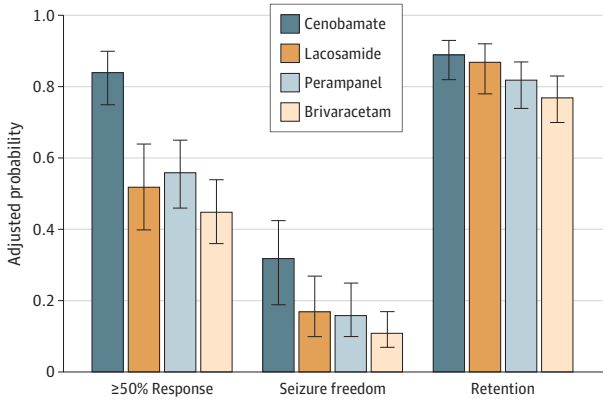
Figure 2. Adjusted Odds Ratios (ORs) and Probabilities of 50% or Greater Response, Greater Than or Equal to 6-Month Seizure Freedom, and Antiseizure Medication (ASM) Retention at 12-Month Follow-Up

A Adjusted ORs in comparisons of antiseizure medications

Subanalysis	Adjusted OR (95% CI)
≥50% Response	
Lacosamide vs cenobamate	0.21 (0.12-0.37)
Perampanel vs cenobamate	0.24 (0.14-0.41)
Brivaracetam vs cenobamate	0.16 (0.10-0.25)
Seizure freedom	
Lacosamide vs cenobamate	0.43 (0.21-0.90)
Perampanel vs cenobamate	0.41 (0.21-0.82)
Brivaracetam vs cenobamate	0.26 (0.14-0.50)
Retention	
Lacosamide vs cenobamate	0.81 (0.41-1.59)
Perampanel vs cenobamate	0.56 (0.32-0.99)
Brivaracetam vs cenobamate	0.43 (0.26-0.69)



B Model-adjusted probabilities for each antiseizure medication



A, Shows adjusted ORs and 95% CIs of brivaracetam (BRV), lacosamide (LCM), and perampanel (PER) vs cenobamate (CNB). OR values less than 1 indicate superior effectiveness of CNB over comparators. B, Shows model-adjusted probabilities for each ASM. Models adjusted for age at ASM initiation, age at epilepsy onset, sex, number of previously tried ASMs, number of concomitant ASMs, epilepsy etiology (structural as reference category), and baseline seizure frequency (monthly frequency as reference category).

Table 3. Adverse Effects Profile[a]

Adverse effect	No. (%) BRV (n = 823)	CNB (n = 192)	LCM (n = 237)	PER (n = 589)	*P* value
Any	251 (30.5)	111 (57.8)	35 (14.8)	187 (31.7)	<.001
Behavioral	86 (10.4)	9 (4.7)	11 (4.6)	87 (14.8)	<.001
CNS	57 (6.9)	40 (20.8)	13 (5.5)	25 (4.2)	<.001
Gastrointestinal disorders	17 (2.1)	3 (1.6)	8 (3.4)	12 (2.0)	.56
Hyponatremia	0 (0)	3 (1.6)	0 (0.0)	0 (0.0)	<.001
Skin disorders	6 (0.7)	0 (0)	2 (0.8)	0 (0)	.11
Somnolence/fatigue	86 (10.4)	54 (28.1)	13 (5.5)	42 (7.1)	<.001
Vertigo/dizziness	45 (5.3)	41 (20.3)	7 (3.0)	64 (10.9)	<.001

Abbreviations: BRV, brivaracetam; CNB, cenobamate; CNS, central nervous system; LCM, lacosamide; PER, perampanel.

[a] Numerators per antiseizure medication and percentages refer to the number of prescriptions with available adverse effect data.

often chosen for its favorable tolerability and titration profile,[27] its modest effectiveness in this cohort may reflect the underlying characteristics of the treated population. Specifically, patients prescribed brivaracetam had epilepsy that was more difficult to treat compared with those receiving lacosamide or perampanel, including a greater number of previously failed ASMs and a higher polytherapy burden. Consequently, the reduced effectiveness observed with brivaracetam compared with perampanel and lacosamide may partly reflect unmeasured residual confounding related to disease severity at the time of prescription.

Tolerability profiles varied significantly among analyzed ASMs. Cenobamate was associated with the highest incidence of adverse effects, most commonly somnolence, dizziness, and other central nervous system symptoms, in line with previous findings.[22,28] The higher rate of adverse effects observed with cenobamate may partly reflect the greater concomitant ASM load in this subgroup, which could have increased susceptibility to pharmacokinetic or pharmacodynamic interactions. Nevertheless, this higher rate of adverse effects did not translate into lower treatment retention, which remained high in both unadjusted and adjusted analyses. Cenobamate demonstrated a higher adjusted probability of 12-month retention compared with brivaracetam and perampanel, with similar rates to lacosamide. This suggests that the adverse effects of cenobamate may be considered acceptable in light of its substantial efficacy. Alternatively, the high retention observed may reflect use of cenobamate within an early access program, where clinicians—viewing cenobamate as a last-resort option for patients with few remaining alternatives—may have been more inclined to manage adverse effects by adjusting concomitant ASMs rather than discontinuing cenobamate. In contrast, lacosamide was associated with the lowest incidence of adverse effects and the highest unadjusted retention rate. This may partly reflect the lower burden of concomitant ASMs in patients prescribed lacosamide and aligns with prior findings from network meta-analyses.[22,29] Brivaracetam and perampanel were also associated with lower overall adverse effect rates than cenobamate, although behavioral adverse effects were more frequently reported with these agents than with sodium channel blockers such as lacosamide and cenobamate.

Additional consideration arises from the pharmacokinetic profile of cenobamate, a potent inhibitor of cytochrome P2C19 (CYP2C19) and inducer of CYP3A4 and CYP2B6.[30] These characteristics may increase the risk of clinically significant drug-drug interactions, especially in patients receiving multiple ASMs or other medications metabolized via these pathways.[31] Moreover, strong CYP3A4 induction has been associated with an increased risk of cardiovascular events and possible bone mineral density reduction, with evidence suggesting increased bone turnover after 1 year of treatment with cenobamate.[32-36] These considerations should be taken into account when selecting ASMs, as other analyzed newer-generation ASMs lack these substantial pharmacokinetics interactions and may represent suitable options for frailer patients or those with less complicated epilepsy courses, where efficacy could still be obtained along with optimal tolerability.

Finally, this pooled analysis contributes to characterizing baseline patient features associated with treatment response at the time of adjunctive ASM prescription in individuals with drug-resistant focal epilepsy. Beyond the well-recognized influence of prior ASM exposures and concomitant ASM burden on medication response,[18] this study highlights higher baseline seizure frequency as significantly associated with lower treatment response across all outcome measures. Although baseline seizure frequency has previously been linked to the probability of developing drug resistance,[2] its impact on the likelihood of response to adjunctive therapy in drug-resistant patients has remained insufficiently clarified.

Strengths and Limitations

A key strength of this study lies in its large-scale real-world comparative effectiveness analysis of third-generation ASMs in drug-resistant focal epilepsy, encompassing over 1900 evaluable prescriptions from diverse clinical settings and incorporating rigorous adjustment for potential confounding factors.

Nonetheless, certain limitations should be acknowledged. The retrospective nature of the study introduces the possibility of residual confounding despite statistical adjustments. Although data quality was improved through harmonization and internal cross-checks, the datasets derive from retrospective medical record reviews, and we did not perform an independent source-level audit. As a result, ascertainment and reporting of seizure frequency and adverse events may be less complete or consistent than in prospectively conducted trials. Additionally, selection bias may also be present, especially regarding cenobamate, which was often prescribed to patients with more refractory epilepsy or within specialized centers included in early access programs. However, adjustments for baseline differences and inclusion of recruiting center as a random effect likely mitigated this bias. Seizure frequency, a relevant variable in our models, was analyzed as a categorical variable to ensure methodological consistency across original datasets, although this approach may have reduced the level of detail captured. Finally, adverse effects were reported using unadjusted rates, which may be influenced by differences in concomitant ASMs load across treatment groups.

Conclusions

Among the evaluated newer-generation ASMs, cenobamate was associated with the highest likelihood of achieving treatment response and seizure freedom in adults with drug-resistant focal epilepsy, albeit with a higher incidence of adverse effects. Further prospective studies and pragmatic head-to-head trials are warranted to confirm these findings, define optimal treatment sequencing, and best ASM combination strategies.

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