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RESEARCH ARTICLE

Characteristics, therapeutic pathway and the economic burden of patients with drug-resistant epilepsy: A real-world analysis following the introduction of cenobamate in Italy

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Abstract

Objectives: Drug-resistant epilepsy (DRE) remains a major clinical challenge, affecting approximately one-third of patients with epilepsy. Cenobamate, a novel antiseizure medication (ASM) approved in Italy in 2022, has shown promise in clinical trials. However, real-world data on its use, especially economic evaluations, remain limited. This analysis assessed the impact of cenobamate in Italian clinical practice, focusing on demographics, clinical traits, treatment patterns, health care use, and costs among patients with focal epilepsy treated or potentially eligible for cenobamate.

Methods: A retrospective observational study was conducted using administrative health care databases covering ~12 million individuals. Adult patients with focal epilepsy were identified and stratified into three groups: (1) overall focal epilepsy population, (2) DRE patients treated with cenobamate, and (3) DRE patients potentially eligible but untreated with cenobamate. Data on demographics, comorbidities, drug utilization, health care resource use, and direct costs were analyzed. Generalized linear models (GLMs) were used to identify predictors of health care and hospitalization costs.

For affiliations refer to page 12.

Results: Among 3950 patients with focal epilepsy, 1577 (41%) had DRE. Cenobamate-treated patients were younger (mean age 42.6 vs 52.8 years) and had fewer comorbidities. Early adoption trends showed patients starting cenobamate after fewer previous treatments. Cenobamate was associated with a reduction in polypharmacy and lower hospitalization rates and specialist visits. Treatment persistence at 12 months was higher in the cenobamate group (69.6% vs 49.3%). Despite slightly higher overall health care costs (+€916, $p < .05$), cenobamate significantly reduced hospitalization costs (−€679, $p < .05$).

Significance: This real-world study highlights a progressively earlier adoption of cenobamate in Italy over the last few years, with patients starting after fewer prior treatments. Compared to patients potentially eligible but untreated with cenobamate, those receiving cenobamate showed greater treatment persistence, reduced polypharmacy, fewer hospitalizations, and fewer neurological visits. Despite higher drug costs, overall health care efficiency improved, supporting its potential as an effective earlier-line option.

KEYWORDS

cenobamate, drug-resistant epilepsy, health care costs, lines of therapy, real-world evidence

1 | INTRODUCTION

Epilepsy is one of the most common chronic neurological diseases worldwide, affecting people of all ages. The World Health Organization (WHO) estimates currently that ~50 million people live with epilepsy globally,[1] although this may underrate those with active epilepsy who could benefit from treatment.[2,3]

Focal epilepsy, the most frequent form in both pediatric and adult populations,[4] may arise from a variety of structural, genetic, infectious, metabolic, immune, or unknown causes.[5] Common etiologies include cortical dysplasia, hippocampal sclerosis, prior brain injuries, and neurodevelopmental disorders. These underlying pathologies contribute to the heterogeneity of focal epilepsy presentation and treatment response, reinforcing the importance of personalized management strategies.[3–6] Epilepsy strongly affects patient's independence and psychological health, leading to important repercussions on all aspects of health-related quality of life.[6] Epilepsy requires long-term treatment, leading to significant economic burden for National Health Systems (NHS) through direct health care costs and substantial social costs due to reduced work capacity.[7,8]

Epilepsy is typically treated with chronic use of antiseizure medications (ASMs),[9] but about one-third of patients develop drug-resistant epilepsy (DRE), defined as failure to control seizures with two well-tolerated ASMs[10–12]; in such cases, the effectiveness of further monotherapies declines, making combination therapies—sometimes involving three drugs—essential for improved seizure control.[13]

Key points

- Drug-resistant epilepsy (DRE) affects over 40% of patients with focal epilepsy in Italy and drives a high clinical and economic burden, especially through hospitalizations.
- Cenobamate, approved in 2022, is being prescribed earlier in treatment, particularly in younger patients with fewer comorbidities.
- Compared with eligible but untreated patients, cenobamate users had higher treatment persistence, reduced polypharmacy, and fewer hospitalizations and neurological visits.
- Overall health care costs were slightly higher due to drug expenses, but hospitalization costs dropped, indicating greater healthcare value.

Previous data by our research group, derived from a setting of real clinical practice in Italy, showed that 25% of the patients with focal epilepsy were resistant to ASMs, resulting in substantial health care expenditures driven mainly by costs of hospitalization and therapies.[7]

In the last few years, the introduction of cenobamate has represented an important addition to the expanding range of therapeutic options for adult DRE, particularly those who had previously undergone treatment with at least two different ASMs without achieving adequate seizure control.[14,15] Cenobamate was approved based

on randomized, double-blind, placebo-controlled trials showing that daily doses of 100–400 mg significantly reduced seizure frequency in patients with longstanding focal seizures and a median baseline of 8.5 seizures per 28 days.[16] These positive outcomes led to cenobamate approval in the United States in November 2019,[17] and in the European Union in March 2021.[18] In Italy, cenobamate was approved for reimbursement by the Italian Medicines Agency (AIFA) on May 9, 2022, as adjunctive therapy for focal seizures in adults with epilepsy who failed to achieve adequate seizure control despite a history of treatment with at least two ASMs.[19]

The present analysis was undertaken to evaluate the effects following cenobamate advent in the Italian clinical practice. Specifically, the main goals were to describe patients with focal epilepsy treated with cenobamate and those potentially eligible but untreated with cenobamate, focusing on the demographic and clinical characteristics, drug utilization (switch, add-on, treatment persistence), health care resource use (HCRU), and direct costs for the Italian NHS.

2 | PATIENTS AND METHODS

2.1 | Data source

A retrospective analysis was carried out by integrating the administrative databases of a pool of Italian entities, with data available from January 2009 to May 2024, covering about 12 million health-assisted individuals. The analysis used the following databases: demographic database for patient demographic data; pharmaceutical database for reimbursed drugs, including the Anatomical-Therapeutic Chemical (ATC) code and prescription date; hospitalization database for discharge diagnoses, classified by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), and diagnosis dates; outpatient database for dates and types of diagnostic tests and specialist visits; and exemption database for waiver payment codes indicating diagnosis-based exemptions from healthcare service costs.

Approval has been obtained from the ethics committees of the involved health care entities. The dataset used consists solely of anonymized data.

2.2 | Study population and design

According to a previously described methodology,[20,21] adult patients with focal epilepsy were screened within the study sample by the presence of all the following criteria: (i) at least one hospitalization discharge diagnosis at primary or secondary level for focal epilepsy (ICD-9-CM codes as diagnosis proxies listed in Table S1) from January 2010 to December 2019; (ii) at least one prescription for an ASM (ATC codes: N03A, N05BA09), with the first as monotherapy and at least 60-day supply from January 2010 to May 2023; (iii) at least one electroencephalography study (EEG; ICD-9-CM procedure code 89.14), searched throughout the time of data availability from January 2009 to May 2024; OR at least one prescription of cenobamate (ATC code N03AX25), from June 2022 to May 2024, after its approval in Italy.[19] Patients <18 years of age were excluded.

The analyses were performed on the following groups: (i) total patients with focal epilepsy diagnosis; (ii) patients treated with cenobamate (herein termed "cenobamate-treated"); (iii) patients potentially eligible but untreated with cenobamate (herein termed "cenobamate-eligible/untreated"), defined through a diagnosis of focal epilepsy with at least two failed ASMs and current therapy with a third ASM without a cenobamate prescription.

The index date was defined during the inclusion period as: (i) the date of the first prescription of (monotherapy with at least 60-day supply) for patients with focal epilepsy diagnosis, or (ii) the date of the first prescription of a third line for cenobamate-treated patients, or (iii) the date of the first prescription of a third line for cenobamate-eligible/untreated patients.

All the patients were investigated 12 months prior to the index date (characterization period) and were observed for at least 12 months after (follow-up period).

2.3 | Baseline characteristics

For all patients included in the study, demographic characteristics, that is, age and sex distribution, were collected at the index date. Each patient's clinical status was evaluated during the characterization period searching for the following comorbidities (identified by the codes listed in Table S2), commonly associated with epilepsy[22]: dementia, migraine, hypertension, previous cardiovascular events, tumors, peptic ulcer, and arthritis.

Finally, data on the 10 most frequent hospitalizations, grouped by Major Diagnostic Categories (MDC) and 10 most frequent drugs, grouped by second level ATC code, were also collected.

2.4 | Drug utilization and disease progression

Previous treatments were investigated in terms of the number of previous treatments during the

characterization period. A switch to a different drug from the one currently prescribed, or the addition of a new drug to the existing regimen, marks the start of a new treatment line during follow-up. Persistence with the index drug was estimated considering the presence of at least one prescription of index-molecule during the last 3 months of the 12-month follow-up. Finally, the use of other drugs was determined as the average number of other drugs different from the one prescribed at index date. Disease progression was assessed through the time to reach DRE status, namely the estimated average time in months for a patient from the first prescription encountered in the database to the identification of DRE status. Then, the time (in months) from the first ASM prescription to the first cenobamate prescription was also calculated.

To better understand the trends in early adoption of cenobamate over time, treatment patterns were analyzed within four cohorts, defined according to the inclusion criteria and corresponding timeframes used to capture patient histories. The proportion of patients with cenobamate monotherapy and those with 1, 2, 3, and 4 add-on therapies was calculated across four cohorts: *Cohort 1*, cenobamate-treated included between January 2010 and March 2022; *Cohort 2*, cenobamate-treated included between January 2010 and May 2023; *Cohort 3*, naïve users starting cenobamate in September 2023; and *Cohort 4*, naïve users starting cenobamate between June 2022 and September 2024. For *Cohorts 1* and *2*, patients were identified based on inclusion criteria such as hospitalization discharge diagnoses for focal epilepsy, prior ASM prescriptions, or EEG records, and the longer timeframes before May 2022 were used to capture previous treatment histories, as cenobamate itself only became available in Italy after its approval in May 2022. Then, a focus analysis on a subset of patients with at least 12 months of data availability before and after cenobamate therapy initiation was carried out to assess the average number of treatments before and after starting cenobamate.

Finally, prescription patterns and treatment sequencing of three ASMs, brivaracetam (ATC code N03AX23), perampanel (ATC code N03AX22), and lacosamide (ATC code N03AX18), were analyzed within the total DRE population and the subgroup of cenobamate-treated patients. The rationale for selecting these three drugs was that they were among the most commonly prescribed newer-generation ASMs available and reimbursed in Italy during the inclusion period; moreover, these agents are used widely in clinical practice for drug-resistant focal epilepsy. Although other ASMs were prescribed in some patients, these three were chosen to provide a consistent and clinically relevant illustration of treatment patterns. For each of the three medications, patients with at least one prescription during the observation period were identified in both groups. Within the cenobamate-treated group, further evaluation was carried out to determine the position of each drug in the treatment sequence, considering up to the fourth used. Patients whose exposure to a given medication occurred as the fifth or later in sequence were not detailed in the treatment sequencing tables but were included in overall counts.

2.5 | Health care resource consumption and related direct costs for the Italian NHS

The analysis of HCRU (drugs, hospitalizations, and outpatient specialist services) per alive patient was evaluated at 12 months of follow-up in total patients with focal epilepsy, cenobamate-treated patients, and cenobamate-eligible/untreated patients.

The average medical costs (€) were calculated during the first 12 months of follow-up (outliers and deaths excluded) as total expenses per patient for each of the following items: all-cause hospitalizations (determined using the diagnosis-related group [DRG] tariffs) and epilepsy-related hospitalizations (considering ICD-9-CM codes 345.90; 345.91), all drug costs and ASM costs (evaluated using the NHS purchase price), outpatient specialist service costs (according to regional tariffs), and electroencephalography costs. Costs were reported for cenobamate-treated patients and cenobamate-eligible/untreated patients.

2.6 | Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD), and categorical data as counts and percentages. Subgroup comparisons used the Student *t* test and chi-square test, as appropriate. Results for subgroups with fewer than three patients were not reported (NI) per European Union (EU) anonymization guidelines. Predictors of treatment persistence were analyzed via logistic regression with covariates including age, sex, comorbidities, and treatment status. Odds ratios (ORs) and 95% confidence intervals (CI) were reported. Generalized linear models (GLMs) with a gamma distribution assessed total and hospitalization costs over 12 months, excluding deceased patients, with adjustments for confounders. Outliers (>3 SD from the mean) were excluded from cost analysis. Significance was set at $p < .05$ and statistical analyses used STATA SE 17.0.

3 | RESULTS

3.1 | Demographic and clinical variables

From a sample of 12 million citizens, 3950 patients with a diagnosis of focal epilepsy were identified, of whom 3849 (97.4%) had at least 12 months of available follow-up. Among them, 1577 patients (41%) were identified as DRE, 545 (34.6%) were cenobamate-treated and 1032 (65.4%) were cenobamate-eligible/untreated.

As Table 1A shows, cenobamate-treated patients were on average younger than cenobamate-eligible/untreated ones (45.7 vs 52.8 years, respectively), and sex distribution was similar.

Cenobamate-treated patients showed a generally milder comorbidity profile (Table 1B). Specifically, hypertension was found in 18.7% of cenobamate-treated and 50.8% of cenobamate-eligible/untreated patients. Likewise, peptic ulcer was found in 25.9% of cenobamate-treated and 59.8% of cenobamate-eligible/untreated patients; previous cardiovascular events were experienced by 1.3% and 19.8% of the cenobamate-treated and untreated patients, respectively.

In both groups, disorders of the nervous system were largely the most common cause of hospital admission, and systemic antibacterials, drugs for acid-related disorders, and ASMs were the most frequently prescribed drugs. Specifically, cenobamate-treated compared to cenobamate-eligible/untreated patients showed markedly lower proportions of prescriptions for drugs for acid-related disorders (28.3% and 60.9%, respectively), agents acting on the renin–angiotensin system (13.0% and 37.6%), and corticosteroids for systemic use (16.5% and 26.2%).

TABLE 1 Demographic characteristics (A) and comorbidity profile (B) of the overall patients with focal epilepsy and patients with DRE divided into cenobamate-treated and cenobamate-eligible/untreated patients.

	Cenobamate-treated patients ($N=545$)	Cenobamate-eligible/untreated patients ($N=1032$)
(A) Demographics		
Age, mean (±SD)	42.6 (±14.6)	52.8 (±18.4)
Age range, *n* (%)		
18–24 years	74 (13.6%)	97 (9.4%)
25–34 years	106 (19.4%)	102 (9.9%)
35–44 years	117 (21.5%)	152 (14.7%)
45–54 years	116 (21.3%)	180 (17.4%)
55–64 years	98 (18.0%)	167 (16.2%)
65–74 years	25 (4.6%)	188 (18.2%)
75–84 years	8 (1.5%)	133 (12.9%)
>84 years	NI	13 (1.3%)
Male, *n* (%)	249 (45.7%)	461 (44.7%)
(B) Comorbidities, *n* (%)		
Hypertension	102 (18.7%)	524 (50.8%)
Peptic ulcer[a]	141 (25.9%)	617 (59.8%)
Cardiovascular disease	7 (1.3%)	200 (19.4%)
Tumors	NI	55 (5.3%)
Dementia	0 (.0%)	17 (1.6%)
Migraine	5 (.9%)	14 (1.4%)
Arthritis	NI	11 (1.1%)

Abbreviation: NI, not issuable for data privacy (<4 patients); SD, standard deviation.

[a]Proxy: prescription of gastric secretion inhibitors.

3.2 | Drug utilization

The estimated median time for a patient from first ASM prescription encountered in the database and the identification of DRE status was 53.2 (±38.6) months. In addition, the average time from the first ASM prescription to the first cenobamate prescription was 117.5 (±47.6) months.

Persistence was evaluated in alive patients with at least 12 months of follow-up, considering the overall focal epilepsy population ($N=3773$), DRE cenobamate-treated patients ($N=135$), and cenobamate-eligible/untreated ones ($N=882$).

As shown in Figure 1, the proportion of persistent patients was significantly higher in the cenobamate-treated compared to the eligible but untreated (69.6% vs 49.3%, $p<.001$). In the logistic regression model evaluating predictors of treatment persistence, treatment with cenobamate was significantly associated with higher persistence (OR 2.270, 95% CI: 1.516–3.399; $p<.001$). The presence of peptic ulcer was also associated with higher odds of treatment persistence (OR 1.341, 95% CI: 1.003–1.794; $p<.05$). No significant associations were found for age, sex, migraine, hypertension, or cardiovascular disease (all p's $>.05$) (Table S3).

The initiation of treatment with cenobamate occurred progressively earlier in the disease course across successive cohorts of patients with DRE. In the first cohort (inclusion: January 2010 to March 2022), patients had undergone an average of eight prior ASMs, which decreased slightly to 7.6 in the second cohort (inclusion: January 2010 to May 2023). A more pronounced decline was observed in the third cohort (naïve users as of September 2023), with six average prior ASMs. The fourth cohort (naïve users between June 2022 and September 2024) demonstrated the most significant reduction, with only 4.6 prior ASMs before starting cenobamate (Table S4).

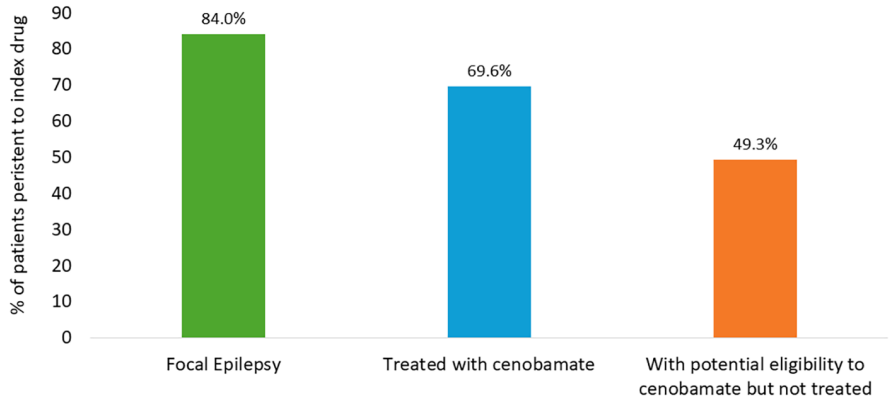

FIGURE 1 Proportion of patients persistent to index therapy in the group with focal epilepsy and that with drug-resistant epilepsy (DRE) divided into treated with cenobamate and potentially eligible but not treated.

The analysis of a subset of 135 patients with at least 12 months of data both before and after the initiation of cenobamate therapy during the whole study period showed a reduction in the average number of simultaneously prescribed treatments, from 3.0 ± 1.1 to 2.6 ± 1.0 in the 12-month window before and after cenobamate initiation, respectively. One year after starting cenobamate, 37.8% of patients were taking on average two other ASMs, so cenobamate was used as the third add-on therapy; 33.3% of patients were taking on average three other ASMs, so cenobamate was used as the fourth add-on therapy; 11.1% of patients were taking on average one other ASM, so cenobamate was used as the second add-on therapy; and 1.5% patients used cenobamate as entry monotherapy (Figure 2A).

The same analysis was replicated in Cohort 4 consisting of the cenobamate-naïve patients who received cenobamate between June 2022 and September 2024. Considering a subset of 152 patients with at least 12 months of data both before and after the initiation of cenobamate therapy, the average number of simultaneously prescribed treatments dropped from 2.8 ± 1.2 to 2.5 ± 1.1 in the 12-month window before and after cenobamate initiation, respectively. In this group, 1 year after starting cenobamate, 40.8% of patients were taking on average two other ASMs, so cenobamate was used as the third add-on therapy; 29.6% of patients were taking on average three other ASMs, so cenobamate was used as the fourth add-on therapy; 11.2% of patients were taking on average one other ASM, so cenobamate was used as the second add-on therapy; and 3.3% patients used cenobamate as entry monotherapy (Figure 2B).

The analyses of the prescription patterns and treatment sequencing of brivaracetam, perampanel, and lacosamide across the observation period, revealed that 10% of patients in the DRE group ($N = 882$) received at least one prescription of perampanel, 4.8% were prescribed brivaracetam, and 38% received lacosamide. Among cenobamate-treated patients ($N = 135$), these proportions were notably higher: 60% had at least one prescription for perampanel, 48.1% at least one for brivaracetam, and 65.2% at least one for lacosamide.

Focusing on treatment sequences within the cenobamate group (Table 2), fewer than patients received perampanel as a first-line drug, followed by 1.5% as second-line, 1.3% as third-line, and 6.2% as fourth-line. For brivaracetam, 1.8% received it as first-line, 2.8% as second-line, 8.8% as third-line, and 11.2% as fourth-line therapy. Lacosamide was prescribed as first line in 5.1% of cases, second line in 8.3%, third line in 14.1%, and fourth line in 13.4%. The remaining patients received these drugs beyond the fourth position in their treatment sequence.

3.3 | HCRU and direct health care costs

The analysis of HCRU revealed that at 12-month follow-up, cenobamate-treated patients had a significantly lower number of hospitalizations (both all-cause and epilepsy-related) and provisions of outpatient specialist services (both all-cause and epilepsy-related) as compared to cenobamate-eligible/untreated patients (Table 3).

The details on the provision of specialist visits and neurological visits at 12-month follow-up in DRE cenobamate-treated patients and cenobamate-eligible/untreated patients are reported in Table S5. DRE cenobamate-treated patients showed fewer specialist visits compared to cenobamate-eligible/untreated patients. Specifically, the cenobamate-treated group had a mean of 3.9 specialist visits, whereas the non-treated group had on average 6.2 visits. The difference was even more pronounced when focusing on neurological visits, as cenobamate-treated patients averaged 2.2 visits over the year, in contrast to 4.3 visits among the cenobamate-eligible/untreated.

At 12-month follow-up, cenobamate-treated patients incurred a total mean health care cost per patient of €4520, with €3515 of this amount related specifically to epilepsy. Cenobamate-eligible/untreated patients had total health care costs of €4369, with epilepsy-related costs of €1604. The costs for drug costs in

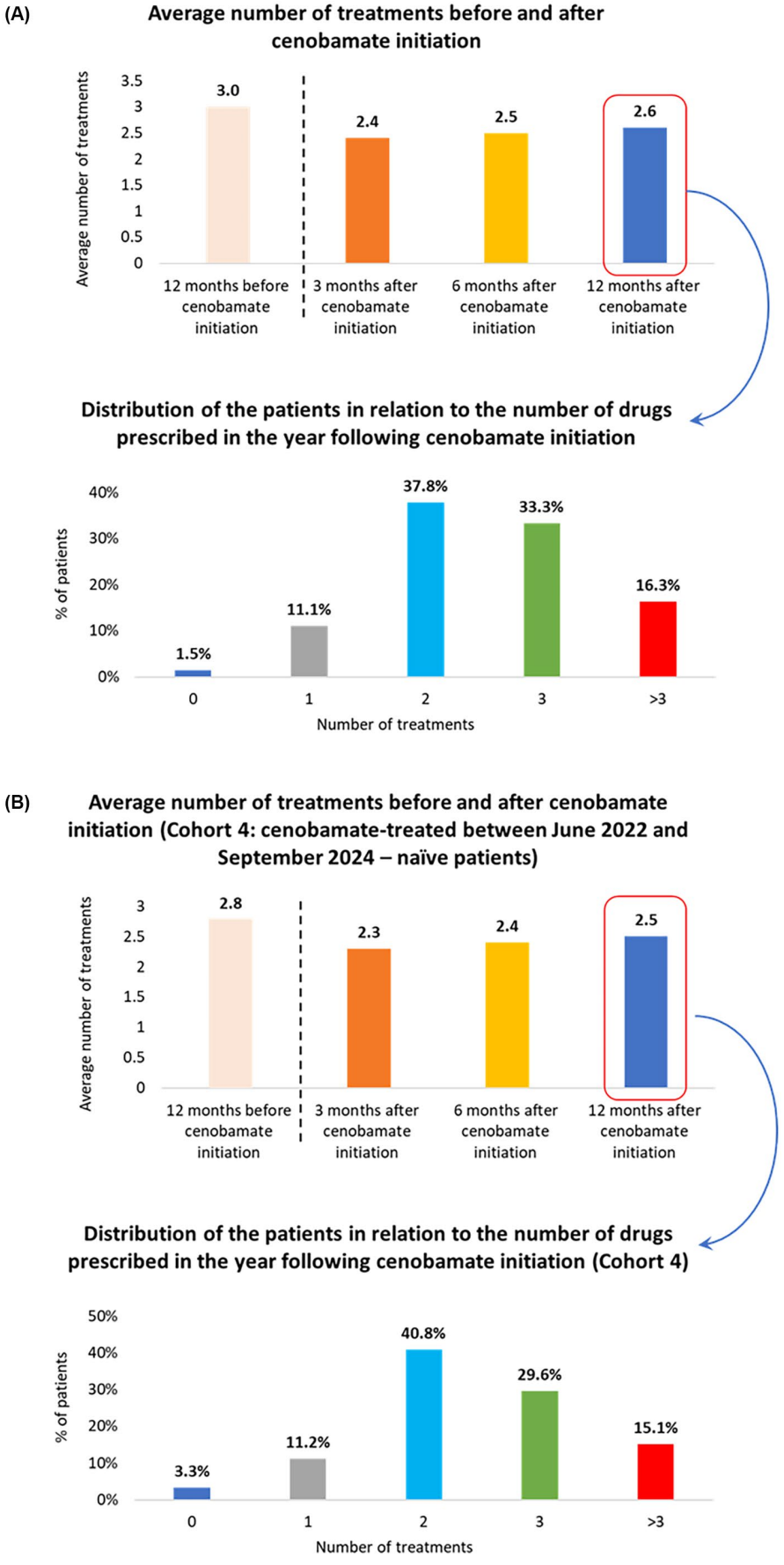

FIGURE 2 Average number of treatments before and after cenobamate initiation and focus on patients' distribution according to the number of drugs prescribed in the year after cenobamate initiation (A) in the total 135 cenobamate-treated patients and (B) in cenobamate-naïve patients who received cenobamate between June 2022 and September 2024 (Cohort 4).

cenobamate-treated patients were €3719, of which €3341 was epilepsy related. In addition, all drug costs were €1924 for cenobamate-eligible/untreated patients, €1074 due to epilepsy-related drugs. Hospitalization costs were markedly lower in the cenobamate-treated group, totaling €465 for all causes and €165 for epilepsy-related hospitalizations, whereas the cenobamate-eligible/untreated patients incurred €1861 in total hospitalization costs and €518 for epilepsy-related hospitalizations. The costs for outpatient specialist services were €336 in total and €8 related to epilepsy in cenobamate-treated, whereas these costs were €585 overall and €12 for epilepsy-specific services in cenobamate-eligible/untreated patients (Figure 3).

TABLE 2 Positioning in line of treatment lines (up to the fourth) of brivaracetam, perampanel, and lacosamide among cenobamate-treated patients ($N = 545$) across the observation period.

Medication	Cenobamate-treated patients ($N = 545$)
Brivaracetam	
I drug	<4
II drug	8 (1.5%)
III drug	7 (1.3%)
IV drug	34 (6.2%)
Perampanel	
I drug	10 (1.8%)
II drug	15 (2.8%)
III drug	48 (8.8%)
IV drug	61 (11.2%)
Lacosamide	
I drug	28 (5.1%)
II drug	45 (8.3%)
III drug	77 (14.1%)
IV drug	73 (13.4%)

Note: Data are *n* (%).

The GLMs for total health care costs identified hypertension (coefficient €1109, 95% CI: €476–€1742; $p = .001$), cardiovascular disease (coefficient €972, 95% CI: €113–€1831; $p < .05$), and peptic ulcer (coefficient €1047, 95% CI: €481–€1612; $p < .001$) as significant predictors of higher total costs. Treatment with cenobamate also resulted in increased total health care costs (coefficient €916, 95% CI: €118–€1713; $p < .05$) compared to cenobamate-eligible/untreated patients. Age, sex, and migraine were not significantly associated with total health care costs (all p's $> .05$) (Table S6A). In the GLM analysis of hospitalization costs, treatment with cenobamate was associated with significantly lower hospitalization costs (coefficient −€1290, 95% CI: −€1996 to −€583; $p < .001$) compared to cenobamate-eligible/untreated ones. The presence of other covariates, including age and sex, did not show significant associations with hospitalization costs (all p's $> .05$) (Table S6B).

4 | DISCUSSION

This analysis, based on 20% of the Italian population, examined patients with focal epilepsy, highlighting demographics, comorbidities, treatment patterns, and NHS-related costs. Among 4000 individuals, 41% had DRE. Of them, 34.6% received cenobamate, whereas 65.4% were potentially eligible but remained untreated; notably, despite the proven efficacy of cenobamate in trials such as the Italian BLESS ("Cenobamate in Adults With Focal-Onset Seizures") study,[22] a substantial 65% of eligible patients did not receive this therapy. This gap underscores the underuse of cenobamate and suggests that expanding

TABLE 3 Health care resource use during the first 12 months of follow-up (data are reported as mean ± SD of prescription/delivery per alive patient).

	Patients with focal epilepsy ($N = 3950$)	Cenobamate-treated patients ($N = 545$)	Cenobamate-eligible/untreated patients ($N = 1032$)	p
Drugs (prescriptions)	19.5 (±11.8)	27.7 (±12.9)	26.1 (±14.4)	.223
Hospitalizations	.7 (±1.1)	.2 (±.7)	.8 (±1.3)	**< .001**
Outpatient specialist services (provisions)	7.4 (±8.7)	6.5 (±6.9)	8.9 (±9.2)	**< .01**
Detail on epilepsy-related				
Drugs, epilepsy-related (prescriptions)	9.8 (±4.6)	23.3 (±9.0)	15.1 (±7.8)	**< .001**
Hospitalizations, epilepsy-related	.3 (±.5)	.0 (±.2)	.3 (±.6)	**< .001**
Outpatient specialist services, epilepsy-related (provisions)	.6 (±.8)	.3 (±.8)	.5 (±.8)	**< .01**

Note: Significant *p* values are highlighted in bold.

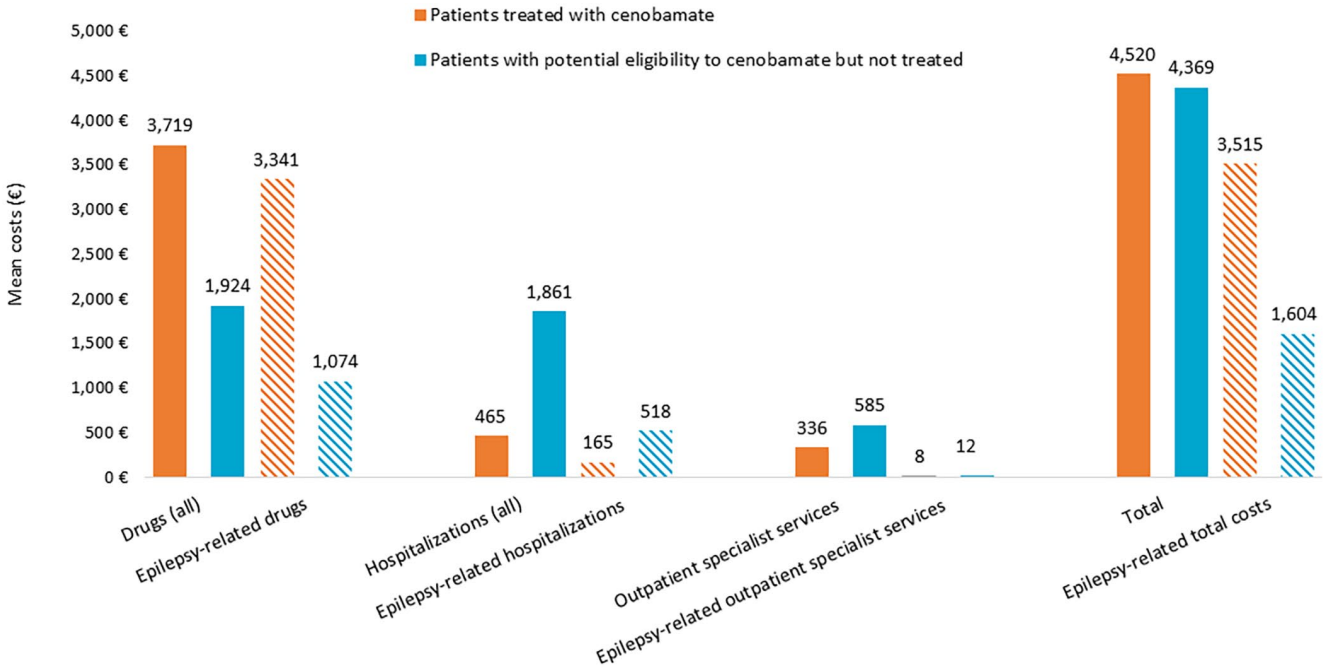

FIGURE 3 Overall and epilepsy-related direct health care costs (€) during the first 12 months of follow-up in DRE cenobamate-treated patients and cenobamate-eligible/untreated patients (outliers and deaths excluded).

its use in clinical practice could enhance outcomes for patients with DRE.

Among DRE patients, cenobamate-treated patients were ~10 year younger than cenobamate-eligible/untreated patients (42.6 vs 52.8 years, respectively), and this might partly explicate their milder comorbidity profile, especially regarding hypertension. The observed demographic and clinical profile of cenobamate-treated patients, being younger and having fewer comorbidities, may be partly explained by a common pattern in the initial adoption of newly introduced therapies. Physicians often begin prescribing novel medications to patients perceived as lower risk in order to assess tolerability and efficacy in a controlled clinical context, particularly when long-term safety data are still maturing. Consistently, in a retrospective study including 51 patients with highly refractory focal epilepsy, the mean age was 42.6 years and 13.7% had hypertension, reflecting a similar demographic and comorbidity profile to the cenobamate-treated cohort in our analysis.[23] A successive multicenter cohort study including 116 patients reported a mean age of 38.2 years, although comorbidity data such as hypertension were not specifically detailed.[24–26] Taken together, these data suggest an increasing attitude by clinicians to favor the use of cenobamate in younger patients with a low comorbidity burden, particularly those who have not achieved adequate seizure control with older generation ASMs. In this population, cenobamate has demonstrated not only improved seizure control but also a more favorable treatment response, supporting its role as a valuable therapeutic option in appropriately selected patients.

In addition, the analysis revealed that cenobamate was frequently introduced earlier in the treatment sequence, preceding the use of newer agents such as brivaracetam, perampanel, and lacosamide. Although early use of cenobamate was limited primarily to younger patients with fewer comorbidities, data from our analysis show a clear shift over time toward initiating treatment earlier in the therapeutic sequence, with patients receiving cenobamate after fewer prior ASMs. This evolution reflects growing clinical confidence and increasing familiarity with the drug, which may ultimately support its broader adoption, including in older individuals and those with more complex clinical profiles. Recent evidence confirms this approach, highlighting cenobamate robust efficacy, with reported ≥50% seizure reduction in ~64%–80% of patients and notably higher seizure-freedom rates than those of other adjunctive therapies.[25,26]

The early initiation of cenobamate may help achieve rapid and substantial seizure control, thereby reducing the clinical necessity for escalation to other third- or fourth-line agents such as brivaracetam and perampanel. Brivaracetam, although generally better tolerated than levetiracetam, especially regarding behavioral adverse events such as irritability, still carries a risk of such effects, albeit to a lesser extent. Nevertheless, its favorable titration schedule and ease of use continue to support its

inclusion in the treatment pathway for select patients. However, brivaracetam, may have lower seizure freedom rates when compared to cenobamate.[25] Similarly, perampanel clinical use can be limited by dose-related behavioral adverse effects, particularly aggression and irritability, which are of greater concern in vulnerable populations.[27] Furthermore, lacosamide, although a valuable therapeutic option, primarily enhances slow inactivation of sodium channels without the dual mechanism seen with cenobamate, which modulates both sodium channels and γ-aminobutyric acid $(GABA)_A$ receptors, potentially resulting in lower efficacy in highly refractory patients.[28] Therefore, the observed prescribing pattern, characterized by early cenobamate introduction followed by selective use of brivaracetam, perampanel, or lacosamide, represents an evidence-based approach aimed at optimizing seizure outcomes while reducing treatment burden and minimizing polypharmacy risks in patients with DRE.

This analysis also showed that, among patients with at least 12 months of follow-up, treatment persistence was significantly higher in those receiving cenobamate compared to cenobamate-eligible/untreated patients (69.6% vs 49.3%, respectively), suggesting a possible association between cenobamate use and improved long-term drug utilization in patients with DRE. These findings are consistent with a previous real-world evidence analysis, which reported 80.4% of patients with highly refractory focal epilepsy remaining on cenobamate therapy at their last follow-up, indicating strong 12-month treatment persistence.[29] Similarly, pooled long-term data from the cenobamate clinical development program reported that ~80% of patients continued therapy at 1 year and 72% at 2 years, further supporting sustained persistence in clinical practice.[25] These findings suggest that cenobamate-treated patients are more likely to remain on therapy over time compared to cenobamate-eligible/untreated individuals, highlighting a notable difference in treatment persistence.

During the various periods of this analysis, a progressively earlier adoption of cenobamate treatment was observed over time. This trend is supported by a real-world, multicenter, retrospective study in Germany involving adult patients with DRE who initiated cenobamate between March 2021 and September 2022. The authors reported a high retention rate of 92% at 12 months, reflecting increasing clinician confidence in prescribing cenobamate earlier in the treatment course for appropriately selected patients.[15]

The impact of cenobamate therapy on the polypharmacy burden in patients with epilepsy was evaluated in patients from the main study population and then in cenobamate-naïve patients treated between June 2022 and September 2024. In both groups, each with at least 12 months of pre- and post-treatment data, a modest but consistent reduction in the average number of simultaneously prescribed ASMs was observed following the initiation of cenobamate. Reducing the number of comedications is a key consideration in epilepsy management, as polytherapy is often associated with increased side effects and reduced adherence. Previous studies suggested that cenobamate, due to its high efficacy and unique pharmacological profile, may allow for reduction in polypharmacy while maintaining or improving seizure control.[16,26]

The observed reduction in the average number of simultaneously prescribed ASMs after initiating cenobamate aligns with previous evidence from open-label extension trials and real-world studies. The observed decrease in concomitant ASM use with cenobamate is consistent with prior evidence from multiple settings. A post hoc analysis of a Phase 3 open-label extension (OLE) trial reported a mean reduction of ~30% in ASM drug load at 12 months and ~32% at 24 months across all ASM classes, including benzodiazepines (−55%).[30] A separate post hoc analysis showed that patients who remained on cenobamate were more likely to taper or discontinue other ASMs more than those who discontinued treatment.[31] Futher real-world data support this trend: in a multicenter retrospective study, 69.7% of patients reduced or stopped concomitant ASMs after at least 6 months, whereas another real-world effectiveness study observed a 44.7% decrease in simultaneous ASM use.[32] Together, these results indicate that cenobamate can simplify treatment regimens by reducing polypharmacy through improved seizure control.

In this study, cenobamate-treated patients were on average younger than cenobamate-eligible but untreated patients. This likely reflects real-world prescribing behavior in the period immediately following cenobamate reimbursement approval in Italy (May 2022), when clinicians tend to adopt a cautious approach and select patients with fewer comorbidities for a newly available therapy. At the same time, our data show a clear trend toward progressively earlier use of cenobamate across successive cohorts, with patients initiating treatment after fewer prior lines of therapy. Taken together, these findings suggest that although cenobamate is positioned increasingly earlier in the treatment pathway, its initial use in clinical practice has been concentrated among younger patients with a lower comorbidity burden, which should be considered when interpreting the generalizability of our results to older subjects.

The analysis of HCRU at 12-month follow-up revealed that cenobamate-treated patients had a lower frequency of specialist visits compared to the non-treated group. Cenobamate-treated patients required notably fewer neurological visits compared to cenobamate-eligible/untreated individuals, suggesting that cenobamate treatment

may contribute to a more stable clinical course. A recent real-world study in Spain found that 44.7% of patients reduced their concomitant ASMs while on cenobamate, suggesting a potential decrease in the need for frequent specialist consultations.[31] However, it should be noted that the observed lower HCRU in our cenobamate-treated patients might be influenced partly by baseline differences between groups. In particular, those who received cenobamate were on average younger and exhibited a lower comorbidity burden than cenobamate-eligible but untreated patients. Although the multivariate analyses adjusted for several clinical covariates, residual confounding due to age and related factors cannot be fully excluded. This potential confounder should therefore be considered when interpreting the reductions in hospitalizations and specialist visits associated with cenobamate.

Analysis of direct health care costs, in a 12-month follow-up study, showed that cenobamate-treated patients had slightly higher total health care costs, mostly attributable to epilepsy-related expenses. Notably, cenobamate treatment was linked to significantly lower hospitalization costs. This finding was confirmed by the GLM, which indicated that cenobamate use was associated with a significant reduction in hospitalization costs (−€679, $p < .05$), despite an overall increase in health care costs (+€916, $p < .05$). Given that cenobamate has only recently been introduced into clinical practice, comprehensive economic evaluations of its impact on health care resource utilization and costs remain limited. In the GLM analyses, neither age nor overall comorbidity burden showed a significant association with total health care costs or hospitalization costs, indicating that the cost differences observed were not explained solely by the younger age or lower comorbidity profile of the cenobamate-treated patients. Nonetheless, our analysis was limited to variables captured in administrative databases, and unmeasured clinical factors could still play a role. Larger prospective studies with more detailed clinical data are warranted to further investigate potential interactions between patient profiles and cost outcomes.

This study has some limitations stemming from the use of anonymized administrative data, which may be incomplete. Primary care services and full clinical histories of comorbidities were not captured, as diagnoses relied on hospital discharge codes and drug prescriptions. Treatment data came from prescriptions and dispensing records, without insight into reasons for therapy changes. Outpatient EEG evaluations were excluded from analysis. In addition, the study population mainly included hospitalized patients, potentially representing more severe cases of focal seizures. This might be the underlying reason for the smaller proportion of patients with epilepsy than the expected prevalence in the general population. This discrepancy is likely due to the inclusion criteria, which required evidence such as hospitalization discharge diagnoses, ASM prescriptions, or EEG records, and to the inherent limitations of administrative databases that capture only reimbursed health care services. Patients managed exclusively through private practice neurological consultations or private prescriptions are not recorded, which may have led to an underestimation of the true population with epilepsy. Finally, the younger age and lower comorbidity burden observed in cenobamate-treated patients may reflect cautious early adoption patterns, introducing potential selection bias.

5 | CONCLUSIONS

This real-world study shows that earlier use of cenobamate in DRE treatment in Italy is increasing, reflecting clinician confidence. Cenobamate-treated patients had better treatment persistence, less polypharmacy, fewer hospitalizations and neurological visits, and greater disease stability. Although total costs were slightly higher due to drug expenses, hospitalization costs dropped. These findings suggest that earlier cenobamate use may improve outcomes and health care efficiency, although further research is needed to assess its long-term value.

AUTHOR CONTRIBUTIONS

Conceptualization: Valentina Perrone and Luca Degli Esposti; Data curation: Valentina Perrone and Chiara Veronesi; Investigation: Valentina Perrone, Chiara Veronesi, Maria Cappuccilli, Maria Ciappetta. and Domenico Lucatelli; Methodology: Andrea Cinti Luciani, Valentina Perrone, Chiara Veronesi, Maria Cappuccilli, Maria Ciappetta, and Domenico Lucatelli; Resources: Luca Degli Esposti; Software: Chiara Veronesi; Supervision: Andrea Cinti Luciani and Luca Degli Esposti; Validation: Andrea Cinti Luciani, Maria Cappuccilli, and Luca Degli Esposti; Visualization: Andrea Cinti Luciani, Maria Cappuccilli, Maria Ciappetta, Domenico Lucatelli, and Luca Degli Esposti; Writing – original draft: Maria Cappuccilli; and Writing – review and editing: Maria Cappuccilli. The authors Margherita Andretta, Marcello Bacca, Antonietta Barbieri, Fausto Bartolini, Alessandro Brega, Maria Rosaria Cillo, Francesco Colasuonno, Stefania Dell'Orco, Fulvio Ferrante, Stefano Grego, Antonella Lavalle, Daniela Mancini, Maurizio Pastorello, Romina Pagliaro, Cataldo Procacci, Camilla Scandolara, Patrizia Schiavone, Loredana Ubertazzo, Paola Valpondi, Adriano Vercellone, and Alberto Zucchi contributed equally to the investigation, methodology, and data curation. All authors have read and agreed to the submitted version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Maria Ciappetta and Domenico Lucatelli are employees of Angelini Pharma. All the other authors have no competing interests to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this article are available at an aggregated level from the authors upon reasonable request and with permission of the participating health care entities. Requests to access should be directed to the corresponding author.

ETHICS STATEMENT

Approval has been obtained from the ethics committees of the involved health care entities. All the results of the analyses were produced and presented as aggregated summaries. The dataset used consists solely of anonymized data.

INFORMED CONSENT

In line with Article 110 (Processing of personal data for medical, biomedical or epidemiological research purposes) of the Italian Privacy Code, informed consent was waived, as obtaining it was deemed impossible or required a disproportionate effort.

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REFERENCES

1. WHO. World Health Organization (WHO): Epilepsy – Key facts. Available from: https://www.who.int/news-room/fact-sheets/detail/epilepsy. Last Accessed 7 April 2025.
2. Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia. 2010;51:883–90.
3. Kovacs M, Fogarasi A, Hegyi M, Siegler Z, Kelemen A, Mellar M, et al. Multicenter retrospective study of patients with PCDH19-related epilepsy: the first Hungarian cohort. Epileptic Disord. 2024;26(5):685–93. https://doi.org/10.1002/epd2.20264
4. Beghi E. The epidemiology of epilepsy. Neuroepidemiology. 2020;54(2):185–91. https://doi.org/10.1159/000503831
5. Nascimento FA, Friedman D, Peters JM, Bensalem-Owen MK, Cendes F, Rampp S, et al. Focal epilepsies: update on diagnosis and classification. Epileptic Disord. 2023;25(1):1–17. https://doi.org/10.1002/epd2.20045
6. Perrone V, Veronesi C, Dovizio M, Ancona DD, Andretta M, Bartolini F, et al. Analysis of patients with focal epilepsy and drug-resistant epilepsy in Italy: evaluation of their characteristics, therapeutic pathway and the consumption of healthcare resources. Clinicoecon Outcomes Res. 2022;14:513–21. https://doi.org/10.2147/CEOR.S361692

7. Boccaletti S, Lucas E, Nixon A, Boskovic N, Di Dato G. Systematic literature review of the humanistic and economic burden of focal epilepsy and primary generalized tonic-clonic seizures in adults. Epilepsia Open. 2024;9(6):2055–86. https://doi.org/10.1002/epi4.13011
8. Perucca E. Antiepileptic drugs: evolution of our knowledge and changes in drug trials. Epileptic Disord. 2019;21(4):319–29. https://doi.org/10.1684/epd.2019.1083
9. 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. https://doi.org/10.1007/s40263-021-00827-8

Published correction appears in *CNS Drugs*. 2021;35(9):1033–4. https://doi.org/10.1007/s40263-021-00853-6

10. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. N Engl J Med. 2011;365(10):919–26. https://doi.org/10.1056/NEJMra1004418
11. Shankar R, Marston XL, Danielson V, do Rego B, Lasagne R, Williams O, et al. Real-world evidence of epidemiology, patient characteristics, and mortality in people with drug-resistant epilepsy in the United Kingdom, 2011–2021. J Neurol. 2024;271(5):2473–83. https://doi.org/10.1007/s00415-023-12165-4
12. Wu C, Wu H, Zhou Y, Liu X, Huang S, Zhu S. Effectiveness analysis of three-drug combination therapies for refractory focal epilepsy. Neurotherapeutics. 2024;21(3):e00345. https://doi.org/10.1016/j.neurot.2024.e00345
13. Rissardo JP, Fornari Caprara AL. Cenobamate (YKP3089) and drug-resistant epilepsy: a review of the literature. Medicina (Kaunas). 2023;59(8):1389. https://doi.org/10.3390/medicina59081389
14. Winter Y, Abou Dargham R, Patiño Tobón S, Groppa S, Fuest S. Cenobamate as an early adjunctive treatment in drug-resistant focal-onset seizures: an observational cohort study. CNS Drugs. 2024;38(9):733–42. https://doi.org/10.1007/s40263-024-01109-9
15. Krauss GL, Klein P, Brandt C, Lee SK, Milanov I, Milovanovic M, et al. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. Lancet Neurol. 2019;19:38–48.
16. FDA approves new treatment for adults with partial-onset seizures. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/ontozry. Last Accessed 7 April 2025.
17. European Medicines Agency (EMA) – Ontozry (cenobamate). Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-adults-partial-onset-seizures. Last Accessed 7 April 2025.
18. Italian Medicines Agency (AIFA). Determination No. 337/2022 of May 9, 2022. Reimbursement status and pricing of the medicinal product for human use "Ontozry". Available from: https://www.gazzettaufficiale.it/eli/id/2022/05/24/22A03014/sg?utm. Last Accessed 7 April 2025.
19. An S, Malhotra K, Dilley C, Han-Burgess E, Valdez JN, Robertson J, et al. Predicting drug-resistant epilepsy – a machine learning approach based on administrative claims data. Epilepsy Behav. 2018;89:118–25. https://doi.org/10.1016/j.yebeh.2018.10.013
20. Franchi C, Giussani G, Messina P, Montesano M, Romi S, Nobili A, et al. Validation of healthcare administrative data for the diagnosis of epilepsy. J Epidemiol Community Health. 2013;67(12):1019–24. https://doi.org/10.1136/jech-2013-202528
21. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives [published correction appears in *Lancet Neurol*. 2016;15(1):28]. Lancet Neurol. 2016;15(1):106–15. https://doi.org/10.1016/S1474-4422(15)00225-2
22. Lattanzi S, Ranzato F, Di Bonaventura C, et al. Effectiveness and safety of adjunctive Cenobamate in people with focal-onset epilepsy: evidence from the first interim analysis of the BLESS study. Neurol Ther. 2024;13(4):1203–17. https://doi.org/10.1007/s40120-024-00634-5
23. Beltrán-Corbellini Á, Romeral-Jiménez M, Mayo P, Sánchez-Miranda Román I, Iruzubieta P, Chico-García JL, et al. Cenobamate in patients with highly refractory focal epilepsy: a retrospective real-world study. Seizure. 2023;111:71–7. https://doi.org/10.1016/j.seizure.2023.07.026
24. Sander JW, Rosenfeld WE, Halford JJ, Steinhoff BJ, Biton V, Toledo M. Long-term individual retention with cenobamate in adults with focal seizures: pooled data from the clinical development program. Epilepsia. 2022;63(1):139–49. https://doi.org/10.1111/epi.17134
25. Sperling MR, Abou-Khalil B, Aboumatar S, Bhatia P, Biton V, Klein P, et al. Efficacy of cenobamate for uncontrolled focal seizures: post hoc analysis of a phase 3, multicenter, open-label study. Epilepsia. 2021;62(12):3005–15. https://doi.org/10.1111/epi.17091
26. Ettinger AB, LoPresti A, Yang H, Williams B, Zhou S, Fain R, et al. Psychiatric and behavioral adverse events in randomized clinical studies of the noncompetitive AMPA receptor antagonist perampanel. Epilepsia. 2015;56(8):1252–63. https://doi.org/10.1111/epi.13054
27. Jin Y, Zhang R, Jiang J, Liu X. Efficacy and tolerability of lacosamide as adjunctive therapy in patients with focal-onset seizures: an observational, prospective study. Acta Neurol Belg. 2023;123(3):1081–7. https://doi.org/10.1007/s13760-023-02236-8
28. Aboumatar S, Ferrari L, Stern S, Wade CT, Weingarten M, Connor GS, et al. Reductions in concomitant antiseizure medication drug load during adjunctive cenobamate therapy: post-hoc analysis of a subset of patients from a phase 3, multicenter, open-label study. Epilepsy Res. 2024;200:107306. https://doi.org/10.1016/j.eplepsyres.2024.107306
29. Lauxmann S, Heuer D, Heckelmann J, Fischer FP, Schreiber M, Schriewer E, et al. Cenobamate: real-world data from a retrospective multicenter study. J Neurol. 2024;271:6605. https://doi.org/10.1007/s00415-024-12510-1

Published correction appears in *J Neurol*. 2024. https://doi.org/10.1007/s00415-024-12606-8.

30. Rosenfeld WE, Abou-Khalil B, Aboumatar S, Bhatia P, Biton V, Krauss GL, et al. Post hoc analysis of a phase 3, multicenter, open-label study of cenobamate for treatment of uncontrolled focal seizures: effects of dose adjustments of concomitant antiseizure medications. Epilepsia. 2021;62(12):3016–28. https://doi.org/10.1111/epi.17092
31. Bosak M, Podraza H, Włoch-Kopeć D, Rysz A, Wężyk K, Grabska-Radzikowska K, et al. Efficacy and safety of Cenobamate: a multicenter, retrospective evaluation of real-world clinical practice. Seizure. 2025;130:25–31. https://doi.org/10.1016/j.seizure.2025.05.002

32. Villanueva V, Santos-Carrasco D, Cabezudo-García P, Gómez-Ibáñez A, Garcés M, Serrano-Castro P, et al. Real-world safety and effectiveness of cenobamate in patients with focal onset seizures: outcomes from an expanded access program. Epilepsia Open. 2023;8(3):918–29. https://doi.org/10.1002/epi4.12757

SUPPORTING INFORMATION

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