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RESEARCH ARTICLE

Freedon study: Real-life outcomes of cenobamate in different lines of treatment

Vicente Villanueva[1] | José María Serratosa[2] | Alejandro Fernández-Cabrera[3] | Manuel Toledo[4] | Beatriz González-Giráldez[2] | José C. Estevez[5] | Juan Jesús Rodríguez Uranga[6] | Maria Machio Castelló[2] | Maria Dolores Castro-Vilanova[7] | Juan José Poza[8] | Xiana Rodríguez-Osorio[9] | Kevin G. Hampel[1] | Elena Fonseca[4] | Francisco Javier López-González[9] | Mercedes Garcés[1] | Laura Abraira[4] | Jordi Ciurans[10] | Daniel Campos-Fernández[4] | Estevo Santamarina[4] | Juan María Sanchez-Caro[6] | Lucas Iacampo[11] | Julia Renau[12] | Miguel Ángel García-Quesada[13] | Carla Anciones[14] | María Isabel Chamorro[15] | Iratxe Maestro[6] | Pablo Cabezudo[16] | Raquel Calle[17] | Jesús Macarron[18] | Beatriz Cabezas[19] | María Carrasco[17] | María López[20] | Marta Marín[21] | Rosa Querol[22] | Belén Baena[23] | Vanessa García-Morales[24] | Samuel López-Maza[4] | Álvaro Juiz[9] | Blanca Mercedes-Alvarez[23] | Carla Amarante[2] | Ana del Villar[25] | Ascensión Castillo[26] | Marta Rubio-Roy[27] | Javier Martinez-Poles[28] | Asier Gómez-Ibáñez[21] | Beatriz Parejo-Carbonell[29] | Anabelén Martínez Garcia[30] | Ignacio Carrera[31] | Pablo Iriarte[8] | Fátima Romero-Aguilera[32] | on behalf of the Pharmacological Therapy Working group of the Spanish Epilepsy Society and Freedon Group

Correspondence
José María Serratosa, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain.
Email: joseserratosa@me.com

Funding information
Angelini Pharma; Sociedad Española de Epilepsia

Abstract

Objectives: Cenobamate is an antiseizure medication (ASM) with proven effectiveness in individuals with highly refractory epilepsy. This study investigated the effectiveness and tolerability of cenobamate in different treatment lines and a less refractory setting.

Methods: This was a multicenter, retrospective, observational study. Adults with focal epilepsy, 2–6 prior ASMs, and ≥12 months between cenobamate initiation and database closure were included. Data from patients' charts were collected and included in the Drug-Resistant Epilepsy Registry of the Spanish Epilepsy Society using Research Electronic Data Capture. Primary effectiveness endpoints included changes in seizure frequency at 3, 6, and 12 months after cenobamate

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initiation according to different treatment lines. Primary safety endpoints included the percentage of patients with adverse events (AEs).

Results: In total, 486 patients were included (mean age 42.8 years). The mean number of prior ASMs was 4.4 (2–6); the mean number of concomitant ASMs at cenobamate initiation was 2.5 (1–5). At 12 months, treatment retention was 92% and median dose was 200 mg. One-year seizure-freedom rates were 32.5%, 33.3%, 21.4%, 24.2%, and 11.4% in those treated with 2–6 prior ASMs, respectively. The proportions of patients achieving ≥50%, ≥75%, ≥90%, and 100% reductions in seizure frequency at 12 months were significantly higher in patients with 2–3 (earlier treatment lines) vs 4–6 prior ASMs (later treatment lines; $p \leq .004$). Improvements in seizure severity were reported in 71.9% of patients during follow-up (82.5% and 62.1% in those with 2 and 6 prior ASMs, respectively). At 12 months, 56.4% of patients had reported AEs, with somnolence the most frequent, and 4.9% had AEs requiring cenobamate discontinuation.

Significance: Cenobamate was effective and well tolerated in patients who had tried 2–6 prior ASMs in a real-world setting. High effectiveness was confirmed at 1 year, with better outcomes in earlier users.

KEYWORDS

antiseizure medication, epilepsy, seizures

1 | INTRODUCTION

Many factors affect quality of life (QoL) in individuals with epilepsy, most notably the duration of epilepsy, the number of prescribed antiseizure medications (ASMs), associated comorbidities, and impacts on employment.[1] For affected individuals, achieving seizure freedom is an important milestone, since ongoing seizures can impact daily activities, including working life and ability to drive.[2,3]

Although the majority of patients are able to achieve seizure freedom after treatment with their first or second ASM,[4] a significant proportion remain suboptimally controlled and spend a considerable amount of time transitioning to subsequent lines of treatment. A Spanish study of over 5000 patients with epilepsy reported that those not achieving satisfactory control of seizures took 4 years to reach the fourth line of their treatment; furthermore, the progression across subsequent treatment lines was associated with a high burden of comorbidities and high cost.[5] Therefore, early and satisfactory seizure control is crucial for patients with epilepsy.

Cenobamate (CNB) is a relatively new ASM with a novel, dual mechanism of action. It blocks persistent sodium currents by promoting the inactivated state of voltage-gated sodium channels while also acting as a positive allosteric modulator of γ-aminobutyric acid A ($GABA_A$) receptors.[6] CNB is approved in Europe as adjunctive treatment for focal seizures, with or without secondary generalization, in adult patients who have not achieved adequate seizure control after at least two ASMs.[7] Similarly, CNB is approved in the United States for the treatment of focal seizures in adult patients.[8]

Key points

- Cenobamate was effective in reducing seizures in patients with epilepsy across different treatment lines.
- Responder and seizure-freedom rates were highest when cenobamate was introduced in early lines of treatment (after 2–3 prior antiseizure medications).
- Cenobamate treatment also reduced the severity of seizures and the number of concomitant antiseizure medications.
- Earlier use of cenobamate may improve seizure control in patients with focal seizures.

In two randomized controlled trials (RCTs), CNB has demonstrated high seizure-freedom rates,[9,10] and long-term effectiveness and tolerability have been demonstrated in additional open-label studies.[11–13]

In recent years, several real-world studies have demonstrated the efficacy of CNB in patients with highly

refractory drug-resistant epilepsy (DRE).[14–18] These studies reported seizure-freedom rates of up to 20% in individuals who had previously tried an average of 7–12 antiseizure medications (ASMs), suggesting a potential advantage over other ASMs. However, outcomes with CNB in earlier lines of treatment (e.g., after two failed prior ASMs) have not been reported extensively, especially with regard to long-term outcomes.[19–22]

In prior publications, early use of CNB is defined as treatment with fewer than 6 prior ASMs,[19] whereas absolute drug resistance has been defined as failure of 6 or more ASMs (based on a cohort of 478 patients from a single center).[23] Therefore, the aim of this study was to assess the 1-year effectiveness and tolerability of CNB in a large population of patients with epilepsy who received CNB in different lines of treatment within clinical practice. We specifically focused on a less refractory population (defined as individuals with 2–6 prior ASMs) to provide real-world outcomes data for this underrepresented group.

2 | METHODS

2.1 | Study design

This was a multicenter, retrospective, observational study assessing the effectiveness and safety of CNB in different lines of treatment within a real-world setting. Epilepsy specialists from 32 Spanish hospitals took part in the study. The study protocol followed the code of ethics set out in the 1964 Declaration of Helsinki (and later amendments) and was approved by the Ethics Committee at the Hospital Universitario y Politécnico La Fe. The study was conducted by members of the Pharmacological Therapy Working Group of the Spanish Epilepsy Society (SEEP), using data from the Drug-Resistant Epilepsy Registry.

Inclusion criteria included age ≥18 years, a diagnosis of focal seizures, treatment with 2–6 prior ASMs (including concomitant ASMs at baseline), initiation of CNB treatment ≥1 year before database closure (June 2025), and written informed consent from patients or their legal representatives according to the study protocol. Exclusion criteria included inaccurate or unreliable clinical records according to participating physicians, and participation of patients in a Spanish Expanded Access Program (EAP).[14]

2.2 | Study outcomes

The effectiveness population comprised patients who met the inclusion and exclusion criteria and had one or more efficacy assessment. The safety population included all patients who met the inclusion and exclusion criteria and received ≥1 dose of CNB.

Primary effectiveness endpoints included: (1) seizure freedom at 3, 6, and 12 months (defined as no seizures since the prior visit) for different lines of CNB treatment; (2) ≥90%, ≥75%, and ≥50% seizure reduction from baseline for different lines of CNB treatment; (3) worsening of seizure frequency (i.e., the proportion of patients with an increase in seizure frequency at each timepoint); and (4) mean and median changes in seizure frequency from baseline for different lines of CNB treatment. Secondary effectiveness endpoints included the CNB retention rate at each timepoint and the evaluation of the severity of seizures. A post hoc analysis assessed the proportion of patients achieving seizure freedom over the last 9 or 12 months of treatment.

The primary safety endpoint was the proportion of patients experiencing adverse events (AEs) at each timepoint. Secondary endpoints assessed the proportion of patients who discontinued treatment due to AEs. Data on AEs were obtained from clinical records and classified by investigators as mild (i.e., no impact on daily activities), moderate (i.e., interfering with daily activities), or severe (i.e., preventing daily activities). Only AEs judged by treating physicians to be related to CNB were included in the analysis. For cumulative reporting, AEs were aggregated across the entire study population at each timepoint.

2.3 | Data collection

Patients' clinical charts were reviewed by participating physicians and data were collected according to usual clinical practice for each center. Each time a new ASM was initiated, visits were conducted at baseline and at 3, 6, and 12 months following treatment initiation according to usual practice.

Data were collected through the SEEP Drug-Resistant Epilepsy registry and managed using Research Electronic Data Capture (REDCap).[24,25]

Patient demographic and clinical characteristics were collected at baseline, including age, gender, time since diagnosis, epilepsy etiology, seizure frequency (i.e., mean number of seizures per month during the 3-month period preceding CNB initiation), prior and concomitant ASM use, prior epilepsy surgery (including vagus nerve stimulation [VNS]), and comorbidities.

For each visit, the following information was extracted from clinical charts: CNB dose, seizure frequency, change in seizure severity (i.e., improvement, no change, or worsening since the last visit), change in concomitant ASM use, and AEs. During the observation period, one or more blood test (a complete blood count and biochemistry) was

usually conducted for each patient and recorded in the clinical chart. The CNB titration schedule and target dose were selected according to physicians' choice.

Patients were stratified into earlier (i.e., 2–3 prior ASMs) and later (i.e., 4–6 prior ASMs) treatment groups.

A post hoc analysis assessed the proportion of patients achieving continuous seizure freedom for the whole 12-month period or the last 9 months of treatment.

2.4 | Statistical analysis

The log-rank test was used to compare time-to-event variables between groups. The Mann–Whitney test was used to compare median reductions in seizure frequency between groups and differences in CNB dose according to treatment response. Treatment response (i.e., 100%, ≥90%, ≥75%, and ≥50% reduction in seizure frequency) was compared between groups using the chi-square test. Continuous related variables were analyzed using Wilcoxon's test. AEs were recorded as frequency and percentages. Comparisons of safety endpoints between groups were performed using the chi-square test. IBM SPSS Statistics 28.0 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses and the threshold for statistical significance was 5% ($p < .05$).

3 | RESULTS

3.1 | Patient baseline characteristics and disposition

A total of 573 patients were entered into the study database; 486 patients were eligible for final analysis as they fulfilled the inclusion/exclusion criteria and received ≥1 dose of CNB. All 87 patients who were excluded from the study had received >6 prior ASMs. Patient and disease characteristics at baseline are shown in Table 1. The mean age of patients was 42.8 years and 53.9% were male. The median time since epilepsy diagnosis increased according to the number of prior ASMs (6.1, 7.2, 13.3, 19.8, and 19.7 years in patients with 2–6 prior ASMs, respectively). The most frequent etiology was structural (57%).

The mean number of prior ASMs was 4.4 (range 2–6). Overall, 127 patients had received 2–3 prior ASMs (i.e., earlier treatment lines) and 358 patients had received 4–6 prior ASMs (i.e., later treatment lines).

The most frequently used prior ASMs overall were levetiracetam (69.8%), lacosamide (58.2%), and perampanel (42.4%). In the earlier treatment group, levetiracetam (42.5%), lacosamide (36.2%), and eslicarbazepine (33.1%) were the most frequently used, whereas in the later

TABLE 1 Patient demographics and disease characteristics at baseline.

Characteristic	All patients (*N* = 486)
Male sex, *n* (%)	262 (53.9)
Mean age, years (range)	42.8 (18–88)
Median time since epilepsy diagnosis, years (IQR)	14.5 (6–25)
Seizure frequency/28 days	
Mean (SD)	11.6 (21)
Median (IQR)	3.7 (1.3–10.3)
Etiology, *n* (%)	
Structural	279 (57)
Cortical developmental malformation	64 (13)
Mesial temporal sclerosis	62 (13)
Vascular	38 (8)
Tumor	38 (8)
Traumatic	14 (3)
Cavernoma	10 (2)
Perinatal hypoxia	6 (4)
TSC	2 (.4)
Genetic	29 (6)
Autoimmune	17 (3.5)
Infectious	10 (2)
Other	45 (9)
Unknown	166 (34)
Number of prior ASMs, *n* (%)	
2	40 (8.2)
3	87 (17.9)
4	113 (23.3)
5	132 (27.7)
6	114 (23.5)
Mean (range)	4.4 (2–6)
Median (IQR)	5 (3–5)
Number of concomitant ASMs	
Mean (range)	2.5 (1–5)
Median (IQR)	3 (2–3)
Seizure frequency/28 days	
Mean (SD)	11.6 (21)
Median (IQR)	3.7 (1.3–10.3)
Psychiatric comorbidity, *n* (%)	154 (31.8)
Intellectual disability, *n* (%)	90 (18.9)
Prior treatment, *n* (%)	
Resective surgery	30 (6.2)
Neurostimulation	14 (2.9)
Invasive electrodes	12 (2.5)

Abbreviations: ASMs, antiseizure medications; IQR, interquartile range; SD, standard deviation; TSC, tuberous sclerosis complex.

treatment group this was lacosamide (44.3%), brivaracetam (31.2%), and perampanel (29.8%).

At baseline, patients were taking an average of 2.5 concomitant ASMs (range 1–5). The number of concomitant ASMs at baseline increased with increasing number of prior ASMs (the number of concomitant ASMs was 1.7, 2.3, 2.3, 2.7, and 2.9 in patients with 2, 3, 4, 5, and 6 prior ASMs, respectively; $p < .001$). The most frequently used ASMs at baseline were lacosamide (42.2%), levetiracetam (29.8%), brivaracetam (29.2%), and perampanel (27.2%).

3.2 | Interval between patient visits

Although patient visits were scheduled for 3, 6, and 12 months after CNB initiation, timings differed slightly between patients, reflecting real-world clinical practice. Mean and median times between visits are shown in Table S1.

3.3 | Treatment retention

Patient disposition is shown in Figure S1. Treatment retention rates for CNB were 97.5% (474/486) at 3 months, 95.1% (462/486) at 6 months, and 92% (447/486) at 12 months. The 12-month retention rate was similar regardless of the CNB treatment line (90%, 94.3%, 94.7%, 90.2%, and 90.4% in patients with 2, 3, 4, 5, and 6 prior ASMs). The mean time on treatment was 13.2 months (range .1–13.9). There were no significant differences in the time on treatment between patients receiving CNB in different treatment lines ($p = .55$; log-rank test), or between those receiving CNB in earlier (2–3 prior ASMs) vs later (4–6 prior ASMs) treatment lines ($p = .66$; log-rank test) (Figure S2).

3.4 | Cenobamate dosage

The mean daily CNB dose was 121 mg (range 12.5–300) at 3 months, 174.3 mg (25–400) at 6 months, and 215 mg (25–500) at 12 months; median doses were 100 mg, 200 mg, and 200 mg at 3, 6 and 12 months, respectively. The median CNB dosage at 12 months was 200 mg for all treatment lines; there were no statistically significant differences in CNB dosage at 3, 6 and 12 months across treatment lines or for earlier versus later treatment. CNB titration was slower than recommended in the label. During titration, CNB dose was compared for responders versus non-responders. At 3 months, there was a significantly higher dose of CNB among responders than non-responders at the ≥50% and ≥75% levels; no other comparisons reached statistical significance at 3 or 6 months (Table S2).

3.5 | Concomitant ASMs

There was a statistically significant reduction in concomitant ASM use during CNB treatment ($p < .001$; Wilcoxon test) (Figure 1). A reduction in either the dose or number of concomitant ASMs occurred in 82.2% of patients (61.3% at 0–3 months, 55.7% at 3–6 months, and 50.9% at 6–12 months).

The most common concomitant ASMs at 12 months of CNB treatment were brivaracetam (28.2%), lacosamide (25.1%), levetiracetam (24.9%), and perampanel (21.2%); the most common in patients receiving CNB in earlier lines of treatment (2–3 prior ASMs) were levetiracetam (31.5%), brivaracetam (22.8%), perampanel (20.5%), and clobazam (8.7%), whereas the most common in those receiving CNB in later lines were brivaracetam (30.1%), lacosamide (27.9%), levetiracetam (22.6%), and perampanel (21.4%). Sodium channel blockers were the most

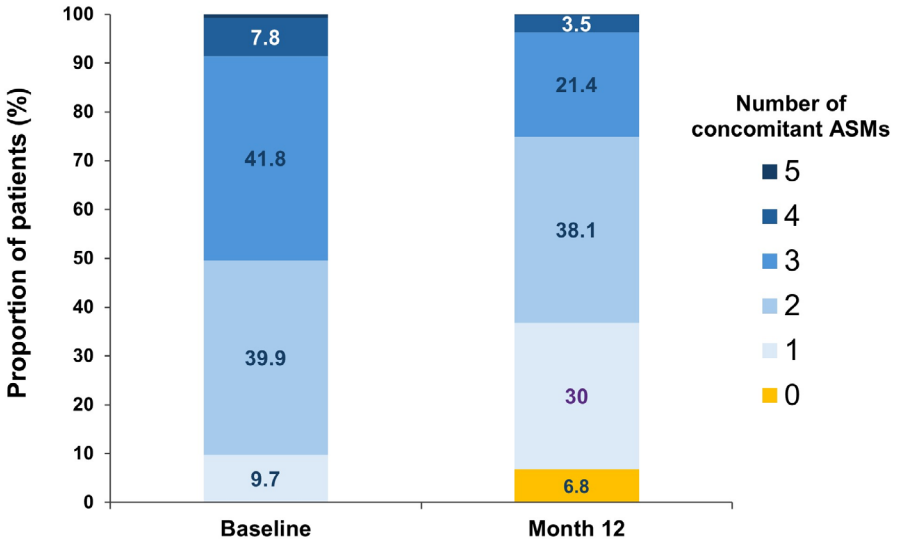

FIGURE 1 Number of concomitant ASMs at baseline and 12 months after cenobamate initiation. ASMs, antiseizure medications.

frequently reduced concomitant ASMs at the 1-year follow-up.

3.6 | Effectiveness

There was a progressive reduction in seizure frequency with CNB treatment, which became more pronounced over the course of follow-up. The median percentage reduction in seizure frequency was 45.6% at 3 months, 60% at 6 months, and 77.3% at 12 months. At 12 months, the median percentage reduction in seizure frequency differed significantly according to treatment line; among patients with 2, 3, 4, 5, and 6 prior ASMs, the median reduction with CNB was 87.5%, 89.5%, 78.2%, 70%, and 71.6%, respectively ($p = .009$). Patients with 2–3 prior ASMs experienced a significantly greater median reduction in seizure frequency between baseline and 12 months compared with those with 4–6 prior ASMs (87.5% vs 74.1%; $p = .001$; Mann–Whitney test).

The proportions of patients with ≥50%, ≥75%, and ≥90% reductions in seizure frequency were 49%, 29.7%, and 20.2% at 3 months; 57.8%, 40.2%, and 26% at 6 months; and 71.1%, 52.8%, and 35.3% at 12 months (Figure 2). Seizure-freedom rates also increased progressively during follow-up, from 16.2% at 3 months to 21% at 6 months and 22.9% at 12 months (Figure 2). For patients with focal-to-bilateral tonic–clonic seizures, seizure-freedom rates were 53.8% at 3 months, 64.2% at 6 months, and 66.4% at 12 months. At 3, 6, and 12 months after CNB initiation, the proportions of patients experiencing a worsening of seizure frequency were 12.1%, 14.8%, and 10.1%, respectively.

The proportion of patients with ≥50%, ≥75%, ≥90%, and 100% reductions in seizure frequency at 12 months decreased significantly with increasing treatment line (Table 2; for the ≥50% responder category, the difference between 2 and 6 prior ASMs was not significant [$p = .053$] but the difference between 2–3 and 4–6 prior ASMs was significant [$p = .001$]). Seizure-freedom at 1 year was 32.5%, 33.3%, 21.4%, 24.2%, and 11.4% in those treated with 2, 3, 4, 5, and 6 prior ASMs, respectively. At 12 months, the proportion of patients with a worsening in seizure frequency was not significantly different between early and late lines of treatment (7.9% with 2–3 prior ASMs vs 10.9% with 4–6 prior ASMs; $p = .33$), although this was numerically higher in those receiving CNB in later lines.

In the post hoc analysis, 10.1% of patients achieved continuous seizure freedom from treatment onset to 12 months (16.5% in those with 2–3 prior ASMs vs 7.8% with 4–6 prior ASMs; $p = .005$); 15.3% achieved continuous seizure freedom between Months 3 and 12 (21.3% with 2–3 prior ASMs vs 13.1% with 4–6 prior ASMs; $p = .029$).

Overall, 71.9% of patients reported an improvement in seizure severity during CNB treatment and 7.5% reported a worsening (Figure 3). The proportion of patients reporting improvements in seizure severity decreased with increasing lines of treatment; improvements were reported by 82.5% of those with two prior ASMs and 62.1% with six prior ASMs (Figure 3).

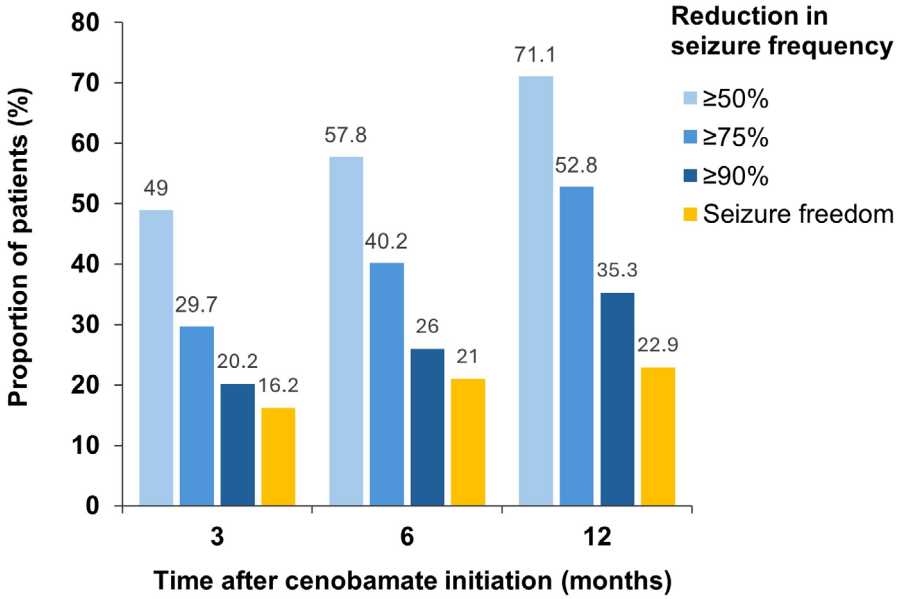

FIGURE 2 Proportion of patients with a reduction in seizure frequency following cenobamate initiation. Bars show ≥50, ≥75%, ≥90%, and 100% reductions in seizure frequency at 3, 6, and 12 months after cenobamate initiation.

3.7 | Safety

The cumulative percentage of patients with AEs was 41.8% (194/464) at 3 months, 51.4% (250/486) at 6 months, and 56.4% (274/486) at 12 months (Table 3). At 12 months, 27.4% (133/486) of patients had mild AEs, 24.9% (121/486) had moderate AEs, and 4.1% (20/486) had severe AEs. The most common AEs were somnolence (147/486; 32.3%), dizziness (91/486; 18.7%), mental slowness (28/486; 5,8%), and fatigue (24/486; 4.9%) (Table S3).

The percentage of patients with AEs at 3, 6, and 12 months increased broadly with the number of prior ASMs, although this increase was only significant for the 3-month time point (Table 3; $p = .024$ at 3 months; chi-square test). Individual AEs by line of treatment are reported in Table S3.

The cumulative percentage of patients with AEs leading to treatment discontinuation over 12 months of CNB treatment was 4.9% (24/486; Table 3). The most frequent AEs leading to treatment discontinuation were somnolence (1.9%), dizziness (1.6%), skin rashes (1%), and headache (1%). No cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) were reported. No association between the percentage of patients with AEs leading to treatment discontinuation and line of treatment was observed (Table 3).

TABLE 2 Proportion of patients with ≥50%, ≥75%, ≥90%, and 100% reductions in seizure frequency at 12 months according to the number of prior ASMs.

	Number of prior ASMs								
	2 (*n* = 40)	3 (*n* = 87)	4 (*n* = 112)	5 (*n* = 132)	6 (*n* = 114)	*p* value[a]	2–3 (*n* = 127)	4–6 (*n* = 358)	*p* value[b]
Responder status									
≥50%, *n* (%)	32 (80)	70 (80.5)	82 (73.2)	86 (65.2)	75 (65.8)	.053	102 (80.3)	243 (67.9)	.001
≥75%, *n* (%)	28 (70)	53 (60.9)	60 (53.6)	60 (45.5)	55 (48.2)	.028	81 (63.8)	175 (48.9)	.004
≥90%, *n* (%)	19 (47.5)	43 (49.4)	39 (34.8)	43 (32.6)	27 (23.7)	.02	62 (48.8)	109 (30.4)	.001
100%[c], *n* (%)	13 (32.5)	29 (33.3)	24 (21.4)	32 (24.2)	13 (11.4)	.03	42 (33.1)	69 (19.3)	.001

Abbreviation: ASMs, antiseizure medications.

[a]Difference across 2–6 ASMs (chi-square test).

[b]2–3 vs 4–6 prior ASMs (chi-square test).

[c]Seizure freedom.

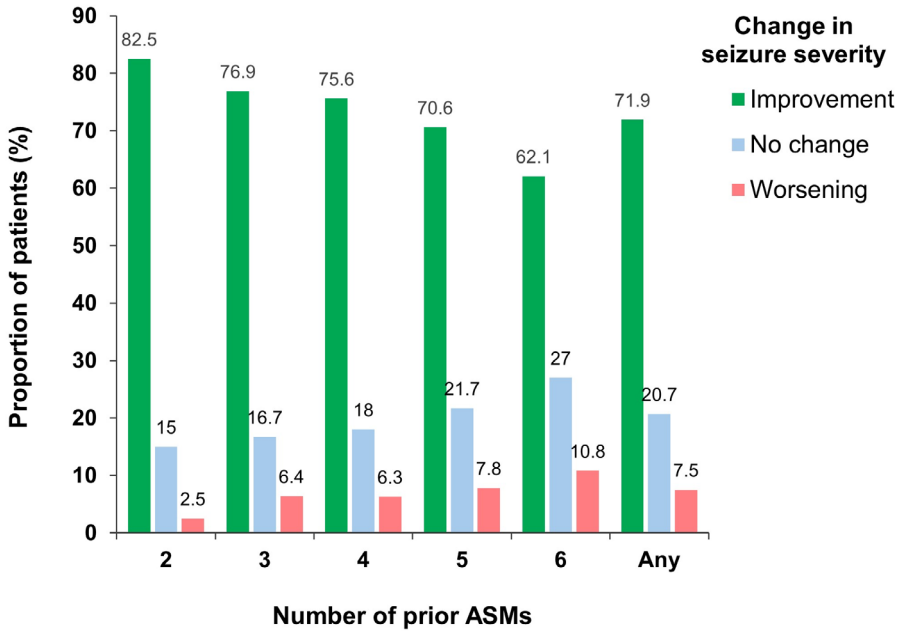

FIGURE 3 Change in seizure severity according to the number of prior ASMs. Bars show improvement, no change or worsening of seizure severity in patients with 2, 3, 4, 5, 6 or any prior ASMs. ASMs, antiseizure medications.

TABLE 3 Cumulative percentage of adverse events.

	3 months ($n = 464$)[a]	6 months ($n = 486$)[a]	12 months ($n = 486$)[a]
AE, *n* (%)			
Any	194 (41.8)	250 (51.4)	274 (56.4)
Mild	NR	NR	133 (27.4)
Moderate	NR	NR	121 (24.9)
Severe	NR	NR	20 (4.1)
AE by treatment line, *n*/*N* (%)			
2 prior ASMs	12/39 (30.8)	16/40 (40)	18/40 (45)
3 prior ASMs	37/86 (43)	43/87 (49.4)	47/87 (54)
4 prior ASMs	35/110 (31.8)	54/113 (47.8)	60/113 (53.1)
5 prior ASMs	63/123 (51.2)	72/132 (54.5)	78/132 (59.1)
6 prior ASMs	47/106 (44.3)	65/114 (57)	71/114 (62.3)
AE leading to treatment withdrawal, *n* (%)	NR	NR	24 (4.9)
AE leading to treatment withdrawal by treatment line, %			
2 prior ASMs	NR	NR	4/40 (10)
3 prior ASMs	NR	NR	3/87 (3.4)
4 prior ASMs	NR	NR	2/113 (1.8)
5 prior ASMs	NR	NR	8/132 (6.1)
6 prior ASMs	NR	NR	7/114 (6.1)

Abbreviations: AE, adverse events; ASMs, antiseizure medications; NR, not reported.

[a]Unless otherwise indicated.

Laboratory disturbances were reported in two patients. One patient already receiving valproic acid (VPA) had a mild liver enzyme increase (aspartate aminotransferase 78 U/L [0–34] and gamma-glutamyl transferase 165 U/L [10–49]) after CNB was added; liver enzymes normalized after reduction of concomitant VPA. Another patient had hyponatremia (127 mEq/L [136–45]), which returned to normal after discontinuing concomitant eslicarbazepine acetate. Both patients continued treatment with CNB without reduction of the dose.

4 | DISCUSSION

This study offers real-world evidence supporting the long-term effectiveness and tolerability of CNB in a large series of patients when used in different, and especially early, treatment lines. Results were generally in line with those from the controlled regulatory trials and the prospective open-label safety trial.[9,10,13]

Since its approval in 2021 for the treatment of uncontrolled focal seizures,[7] CNB has garnered significant attention owing to its high seizure-freedom rates, meaningful reductions in seizure frequency, and predictable tolerability profile.[9,10,26] EAPs have highlighted robust efficacy in individuals with highly refractory DRE (mean of 7–12 prior ASMs) in real-world settings.[14–16,18] These outcomes align with results from a single-center study of patients with DRE, which reported 61% responder and 14% seizure-freedom rates at 12 months. Our study focused on individuals with 2–6 prior ASMs before starting CNB, a setting where results are not reported extensively. Notably, the 12-month rates of seizure freedom (22.9%) and ≥90% seizure reduction (35.3%) compare favorably with those observed in ultra-refractory patients.[14–16,18] We observed significant improvements in efficacy in those who had received 2–3 vs 4–6 prior ASMs. These results represent a marked improvement over historical data, which showed unchanging seizure-freedom rates after failure of two ASMs across three decades, despite the introduction of new ASMs over this time.[4] In our study, 10.1% of patients achieved continuous seizure freedom for the full 12 months of treatment and 15.3% for the final 9 months of treatment. These outcomes were highly encouraging, especially as patients had failed at least two prior ASMs and underwent a gradual titration within the treatment period to achieve the effective dose (i.e., 200 mg, as defined in clinical trials).[27]

Our results, based on a large patient cohort with a 1-year follow-up, are consistent with data from other real-world studies exploring the efficacy of CNB in early treatment lines. The BLESS study analyzed early

adjunctive treatments in patients who had received 2–3 prior ASMs reporting a 71% responder rate and a 20% seizure-freedom rate with CNB,[20] strikingly similar to our outcomes. Notably, these rates were higher than with other ASMs, including lacosamide, levetiracetam, valproate, and topiramate, when used in early treatment lines by the same group.[20] A retrospective analysis of 475 patients treated with CNB reported seizure-freedom rates of 24.4%, 21.8%, and 7.7% in patients with 1–3, 4–7, and >7 prior ASMs, respectively, although only 41 patients were included in the earliest-line group.[22] Similarly, a retrospective study of 20 patients receiving CNB observed seizure-freedom rates of 38% in those with <6 prior ASMs compared with 14% in those with >10 prior ASMs.[19] Finally, in the BLESS study involving 388 patients treated with CNB, 22% of those with 2–3 prior ASMs had sustained seizure freedom for 24 weeks compared with 9% of those with >3 prior ASMs.[21] Together, these results suggest that CNB is most effective when given in earlier lines of treatment.

Most patients (71.9%) in our study reported an improvement in seizure severity during CNB treatment, and this proportion decreased with increasing lines of treatment. Consistent with this observation, a study of patients with highly refractory focal seizures (median 10 prior ASMs) found that CNB reduced seizure intensity in 51% of patients.[28] Increased seizure severity is associated with lower QoL and more seizure-related injuries among individuals with epilepsy.[29–31]

In our study, reductions in seizure frequency increased with longer treatment duration. This probably reflects a gradual increase in CNB dose over time, as titration was performed more slowly than the 11 weeks recommended in the label. The usual effective daily dose of 200 mg was achieved at 6 months, corresponding with the progressive improvement in seizures. It can therefore be speculated that a faster titration, following on-label recommendations, may have achieved better early outcomes.

In our series, the median CNB dose at 12 months was the same across treatment lines. In a retrospective study, higher seizure-freedom rates were observed in patients with <6 versus >10 prior ASMs, despite a lower median daily dose of CNB in the earlier vs later treatment lines (250 vs 300 mg). This suggests that CNB dose could be tailored to the degree of epilepsy refractoriness based on the prior number of ASMs. Nevertheless, a minimum effective dose of 200 mg has been consistently reported across all studies, regardless of lifetime ASM history.[19] Moreover, based on findings from previous studies, increasing the CNB of dose could be related to better outcomes, particularly in later lines of treatment,[16] and in patients reporting focal seizures evolving to bilateral tonic–clonic seizures.[32] Under-dosing in our study, therefore, may have limited treatment efficacy, particularly in the later lines. It could be speculated that optimizing treatment to maximally tolerated, Summary of Product Characteristics (SmPC) recommended doses could have achieved better outcomes.

CNB retention in our study was high (92% at 12 months), consistent with early adjunctive use and surpassing other ASMs in early treatment lines.[20] A 1-year CNB retention rate of 93% was recently reported in patients with ≥2 ASM failures, higher than for than brivaracetam (73%) and lamotrigine (68%).[33] These findings align with pooled analyses from three trials showing an 80% 1-year CNB retention rate, exceeding historical ASM benchmarks.[34]

The tolerability profile of CNB in the current series was similar to that reported in previous studies assessing its use in early treatment lines.[19,22] Although we observed a numerical increase in AEs among patients with a higher number of prior ASMs, this was only significant at 3 months, possibly reflecting the usual CNB titration period and the higher baseline number of concomitant ASMs in patients with more extensive treatment histories. The reduction of concomitant ASMs appears to be central to the improvement in tolerability during titration, particularly in heavily medicated patients.[35] In support of these findings, a single-center study involving 34 patients reported a decrease in the mean number of concomitant ASMs from 2.9 at baseline to 1.6 at the end of follow up.[36] In line with our findings, a lower AE rate with CNB was reported by Martinez-Lizana et al. in those with <6 vs >10 previous ASMs (55% vs 75%, respectively).[19] Similarly, Lattanzi et al. observed higher AE rates when CNB was used in later lines of treatment, with 23.4% of late users vs 5.3% of early users reporting AEs at 24 weeks.[21]

The most frequent AEs in our study (somnolence and dizziness) were consistent with those described previously, including the largest study conducted with an open-label design.[37] AEs were independent of treatment line and occurred mainly during the titration phase, suggesting a favorable long-term tolerability profile.[38,39] Despite previous concerns regarding the appearance of skin rash, this AE was rare in our series, as in the open-label study,[37] and no cases of DRESS were reported. In a recent study including 332 patients, 27.8% experienced ≥10% weight loss during CNB treatment.[40] Consistent with data from larger series,[21] weight loss was not observed in our study, although there was no systematic monitoring of vital signs. Laboratory abnormalities were infrequent in our series, in line with previous reports.[21]

Considering concomitant ASMs, the most frequently used at 12 months were levetiracetam in early treatment lines and brivaracetam in later lines. This underscores the benefit of combining ASMs with different mechanisms of action—the combination of a synaptic vesicle glycoprotein 2A (SV2A) ligand and a sodium channel blocker has been

identified as particularly effective.[41,42] Therefore, exploring new synergistic combinations with CNB, beyond the already reported favorable interaction with clobazam,[43] may further enhance therapeutic outcomes and deserves further investigation.

As with all retrospective, observational studies, our analysis is limited by potential selection bias and confounding variables. Differences in CNB doses and concomitant ASM use between patients may have impacted effectiveness and tolerability outcomes. In addition, vital signs were not systematically assessed. Furthermore, fewer patients received CNB in earlier vs later treatment lines, potentially limiting the generalizability of findings regarding early use. Nonetheless, our study is the largest real-world series to date assessing CNB use across early treatment lines, and offers valuable insights into the effectiveness and tolerability of CNB when introduced early in patients with epilepsy.

5 | CONCLUSION

In conclusion, the results of this study suggest that CNB may be most effective when introduced early in the treatment pathway for epilepsy, leading to improved seizure control, reduced seizure severity, and concomitant ASM simplification, all of which are associated with better QoL. Therefore, early use of CNB could be an important strategy to optimize outcomes and may be considered a potential modifier of the course of focal epilepsy after the failure of 2 ASMs. Further studies are required to support these findings and to provide additional data on its effectiveness and safety during early use, especially in unexplored populations.

AFFILIATIONS

[1]Department of Neurology, Member of ERN EPICARE, Hospital Universitario y Politécnico La Fe, Valencia, Spain
[2]Department of Neurology and Instituto de Investigación Sanitaria-Fundación Jiménez Díaz, Hospital Universitario Fundación Jiménez Díaz, Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain
[3]Department of Neurology, Hospital Universitario Lucus Augusti, Lugo, Spain
[4]Department of Neurology, Vall d'Hebron University Hospital and Vall d'Hebron Research Institute (VHIR), Barcelona, Spain
[5]Department of Neurology, Hospital Universitario Reina Sofía, Córdoba, Spain
[6]Department of Neurology, Centro de Neurología Avanzada Sevilla, Sevilla, Spain
[7]Department of Neurology, Hospital Álvaro Cunqueiro de Vigo, Vigo, Spain
[8]Department of Neurology, Hospital Universitario de Donostia, Donostia, Spain
[9]Department of Neurology, Complexo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain
[10]Department of Neurology, Hospital General de Granollers, Granollers, Spain
[11]Department of Neurology, Hospital Universitario de Canarias, La Laguna, Spain
[12]Department of Neurology, Hospital General Universitario Castellón, Castelló, Spain
[13]Department of Neurology, Hospital General Universitario de Elche, Elche, Spain
[14]Department of Neurology, Hospital Nuestra Señora del Rosario y Sanitas La Zarzuela, Madrid, Spain
[15]Department of Neurology, Hospital Universitario Virgen de la Victoria, Málaga, Spain
[16]Department of Neurology, Hospital Regional Universitario de Málaga and Instituto de Investigación Biomédica de Málaga, Málaga, Spain
[17]Department of Neurology, Hospital Universitario Clínico San Cecilio, Granada, Spain
[18]Department of Neurology, Hospital Universitario de Burgos, Burgos, Spain
[19]Department of Neurology, Hospital Universitario de León, León, Spain
[20]Department of Neurology, Hospital General Universitario Santa Lucía, Cartagena, Spain
[21]Department of Neurology, Clínica Universitaria de Navarra, Pamplona, Spain
[22]Department of Neurology, Hospital Universitario de Badajoz, Badajoz, Spain
[23]Department of Neurology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[24]Department of Neurology, Hospital Universitario de Álava, Vitoria, Spain
[25]Department of Neurology, Consorcio Hospitalario Provincial de Castellón, Castelló de la Plana, Spain
[26]Department of Neurology, Hospital General de Valencia, Valencia, Spain
[27]Department of Neurology, Hospital Universitario Parc Taulí, Sabadell, Spain
[28]Department of Neurology, Hospital Universitario Rey Juan Carlos, Móstoles, Spain
[29]Department of Neurology, Hospital Universitario Clínico San Carlos, Madrid, Spain
[30]Department of Neurology, Hospital Universitario Son Espases, Palma, Spain
[31]Department of Neurology, Hospital Universitario Nuestra Señora de Valme, Sevilla, Spain
[32]Spanish Epilepsy Society, Madrid, Spain

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

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. The study protocol was approved by the hospital's ethics committee and was in accordance with the code of ethics set out in the 1964 Declaration of Helsinki and its later amendments.

CONSENT TO PARTICIPATE

For all patients participating in the study, written informed consent was obtained from the patient or their legal representative according to the study protocol.

ORCID

Alejandro Fernández-Cabrera https://orcid.org/0000-0002-8383-163X
José C. Estevez https://orcid.org/0000-0001-5960-8457
Juan Jesús Rodríguez Uranga https://orcid.org/0009-0007-5354-1256
Kevin G. Hampel https://orcid.org/0000-0003-3582-060X
Elena Fonseca https://orcid.org/0000-0002-3895-1237
Laura Abraira https://orcid.org/0000-0002-5119-7929
Estevo Santamarina https://orcid.org/0009-0006-3940-8953
Pablo Cabezudo https://orcid.org/0000-0002-6421-5348
Beatriz Cabezas https://orcid.org/0000-0001-6653-3027
Marta Marín https://orcid.org/0000-0001-6839-7751

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SUPPORTING INFORMATION

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

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