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ORIGINAL ARTICLE

# DECREASE study: A European pool-analysis of patients with significant reductions in concomitant antiseizure medications in cenobamate Early Access Programs

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## Abstract

**Objective:** To evaluate the effectiveness and tolerability of cenobamate in patients with a significant reduction in concomitant antiseizure medication (ASM) in European cenobamate Early Access Programs (EAPs).

**Method:** Anonymized patient data from real-world studies/registries associated with European cenobamate EAPs were pooled. Patients were included if they had significantly reduced their concomitant drug load (i.e., converted to cenobamate monotherapy or reduced from multiple to one concomitant ASM) between baseline and the last visit. Effectiveness, tolerability, and dosage of cenobamate were evaluated. Responses according to therapeutic regimen at last visit were studied.

**Results:** Of 694 patients within cenobamate EAPs, 75 (10.7%) met the inclusion criteria (mean age 39.5 years [range 19–65]). At baseline, the median number of prior ASMs was 10 (interquartile range [IQR] 6–13); 46 patients (61.3%) were taking two, 23 (30.7%) were taking three, and six (8%) were taking four concomitant ASMs at baseline. At the last visit, seven patients (9.3%) were converted to monotherapy and 68 (90.7%) were receiving one concomitant ASM.

For affiliations refer to page 1821.

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The median cenobamate dosage at last visit was 300 mg (IQR 200–350). Median cenobamate follow-up was 22 months; 73 patients (97%) had at least 1 year of follow-up and one discontinued cenobamate at 1 year. Twenty-five patients (33.3%) were seizure-free at last visit; 51 (68%) had a ≥50% reduction in seizure frequency. The seizure-freedom rate was numerically, but not significantly, higher in patients converted to monotherapy (57.1%) versus those receiving one concomitant ASM (30.9%; $p = 0.16$). Cenobamate plus clobazam was the most effective combination. Adverse events (AEs) were reported in 55/75 patients (73.3%); the most common were somnolence (30.7%), dizziness/vertigo (28%), and fatigue (26.7%). No AEs led to treatment discontinuation.

**Significance:** Cenobamate demonstrated good effectiveness and tolerability in a population of patients within European EAPs who achieved a significant reduction of concomitant ASM.

**Plain Language Summary:** People with highly drug-resistant epilepsy often need to take several antiseizure medications at the same time. Combined data from European Early Access Programs show that about 10% of people treated with cenobamate were able to stop all other antiseizure medications or reduce treatment to cenobamate plus one other medication. Despite this simplification of treatment, one-third of these patients became seizure-free and more than two-thirds experienced at least a 50% reduction in seizure frequency. Within this group, no patients stopped cenobamate because of side effects.

**KEYWORDS**

cenobamate monotherapy, dual therapy, real-world evidence

## 1 | INTRODUCTION

The burden of disease in people with epilepsy (PWE) is closely linked to seizure control as well as to comorbidities such as mood disorders, fatigue, and sleep disturbances.[1] However, other factors, including high antiseizure medication (ASM) usage, have been associated with multimorbidity in PWE.[2] Therefore, simplifying ASM regimens is an important objective of treatment, with potential to reduce adverse effects, alleviate fatigue, minimize impacts on mood, and ultimately improve patient quality of life.[2–5]

In this context, real-world evidence plays a key role in understanding treatment optimization strategies for PWE. Data from Early Access Programs (EAPs) have been especially valuable in complementing findings from randomized controlled trials, particularly in difficult-to-treat populations who often initiate new therapies while receiving multiple concomitant ASMs.[6–11] While individual EAP studies are typically limited by small sample sizes and heterogeneous study variables/data collection methods, pooled analyses have successfully examined large patient cohorts,[12–14] providing important insights into populations that may be underrepresented in individual studies.[15]

Cenobamate (CNB) is an ASM with a dual mechanism of action, blocking persistent sodium currents by promoting the inactivated state of voltage-gated sodium channels and acting as a positive allosteric modulator of gamma-aminobutyric acid-A ($GABA_A$) receptors at a non-benzodiazepine binding site.[16] 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.[17] In the United States, CNB is approved for the treatment of focal seizures in adult patients.[18]

The use of CNB has been associated with a reduction in concomitant ASMs in both randomized controlled trials[19] and observational studies.[5,20] Similarly, a retrospective analysis of patients enrolled in EAPs in Germany, France, and the United Kingdom reported a modest decrease in concomitant ASM usage following CNB treatment.[6] In the Italian EAP, a reduction of at least one concomitant ASM was observed in 43% of patients receiving CNB.[10] However, detailed information on patients who achieved meaningful reductions in ASM remains limited.

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The current study evaluated the effectiveness and tolerability of CNB in patients who achieved a significant reduction in concomitant ASM across different European EAPs using a pooled analysis methodology. The key aim of the study was to provide a better understanding and characterization of this population, extracted from a large series of patients with long-term follow-up, and to report clinically relevant insights for routine clinical practice.

## 2 | METHODS

### 2.1 | Study design

The reDuction of antisEizure mediCation thRough EArly AccesS of cEnobamate (DECREASE) study was a pooled analysis of individual patient data from real-world studies or registries involving participants in European CNB EAPs to characterize those patients with a significant reduction in concomitant ASM.

Relevant studies and/or registries were identified via searches of the PubMed literature database and abstracts from key epilepsy congresses. Centers involved in these studies were invited to participate in the pooled analysis; a total of 41 centers around Europe, including Italy ($n = 21$), Spain ($n = 14$), Germany ($n = 3$), Hungary ($n = 1$), Ireland ($n = 1$), and the United Kingdom ($n = 1$), agreed to participate.

The EAPs included adult patients with highly drug-resistant epilepsy and focal seizures who were started on CNB before it was marketed in each country. The EAPs did not allow individuals with severe hepatic impairment or end-stage renal disease to take part in the programs. Patients were included from September 2020 onwards. Of all patients within the EAP registries of participating centers, those included in the DECREASE study were those who achieved a significant reduction in concomitant ASM drug load, defined as conversion from polytherapy to CNB monotherapy or reduction from ≥2 to 1 concomitant ASM, between baseline and the last visit. Exclusion criteria for DECREASE were lack of consent from the Principal Investigator of any individual study to participate in the pooled analysis and unreliability of captured data for an individual registry.

Each study or registry included in DECREASE was approved by its own independent ethics committee (EC), following the code of ethics set out in the Declaration of Helsinki. Local ECs were subsequently informed about the DECREASE pooled analysis, if required by local legislation. Written informed consent from patients or their legal representatives was obtained according to individual study protocols.

**Key points**

- In cenobamate Early Access Programs, ~10% of patients could convert to cenobamate monotherapy or one concomitant antiseizure medication.
- Pooled data from this subset of patients supported the continued effectiveness and manageable tolerability of cenobamate.
- One-third of these patients were seizure-free at the last visit, and 68% had at least a 50% reduction in seizure frequency.
- Cenobamate showed good tolerability, with no adverse events leading to treatment discontinuation.
- In a highly drug-resistant, polymedicated population, cenobamate enables antiseizure medication reduction without impacting effe ctiveness.

### 2.2 | Study outcomes

The effectiveness population included patients who had significantly reduced concomitant ASM usage and had at least one effectiveness measurement available. The safety population included those who had significantly reduced concomitant ASM usage and had data on adverse events (AEs) available.

The primary efficacy endpoints included the 50% responder rate (i.e., the proportion of patients with ≥50% reduction in seizure frequency from baseline) and the seizure-freedom rate (i.e., proportion of patients with no seizures since at least the prior visit) at the last visit. Secondary outcomes included CNB retention. The primary safety endpoint was the percentage of patients with cumulative AEs during follow-up at the last visit.

Exploratory analyses included baseline characteristics, CNB dosage, effectiveness, and safety outcomes according to CNB monotherapy or combination therapy at the last visit. A post hoc analysis was performed to evaluate primary efficacy endpoints in those patients with last available follow-up at 1 year and for those with last available follow-up longer than 1 year.

### 2.3 | Data collection

Anonymized data from individual patients with a significant reduction of concomitant ASM usage in each

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study were pooled together, including demographic/disease characteristics, monthly baseline seizure frequency, prior and concomitant ASMs, CNB dosage, effectiveness, and AEs. These data were pooled at a minimum at baseline and at the last available visit (defined as the last recorded observation for each patient in the study/registry, irrespective of when it occurred).

### 2.4 | Statistical analyses

As there was some heterogeneity in the information that each study/registry reported, the current study tried to combine the reported information in the most complete and harmonized way possible. Missing data were not imputed.

Variables were analyzed descriptively according to their type (quantitative or qualitative). As data were not available for all patients, the number with available data for each variable was reported and used as the denominator for frequency analyses.

Longitudinal comparisons for quantitative and dichotomous variables between baseline and last visit were performed using the Wilcoxon and McNemar's tests, respectively. Comparisons between groups were performed using the Mann–Whitney test or the Kruskal–Wallis test (depending on the number of groups) for quantitative variables and the chi-square test for qualitative variables.

The significance level was set at 5%. The SPSS 28.0 statistical package was used for all analyses.

## 3 | RESULTS

In total, 694 patients from the CNB EAPs had available data within the studies and registries included in the pooled analysis. Of these, 75 (10.7%) had a significant reduction of concomitant ASM usage according to the defined criteria (either conversion to CNB monotherapy or simplification from ≥2 to 1 concomitant ASM), thereby fulfilling the inclusion criteria for DECREASE. Baseline characteristics of included and excluded patients were similar (Table S1), except for a significantly lower mean number of concomitant ASMs in included versus non-included patients (2.5 vs. 3.1, respectively; $p < 0.001$). Patient disposition is shown in Figure S1. Seventy-three of 75 patients (97.3%) had at least 1 year of follow-up since CNB onset (mean 25.6 ± 15.4 months; median 22 months [IQR 12–36]; range 7.1–36 months). Of 75 patients, 2 (2.6%) had the last available follow-up at 6 months, 30 (40%) at 12 months, 41 (54.7%) at 18 months, 36 (48%) at 24 months, 32 (42.7%) at 30 months, 24 (32%) at 36 months, 13 (17.3%) at 42 months, 7 (9.3%) at 48 months, 6 (8%) at 54 months, and 6 (8%) at 60 months. Differences in follow-up reflected differences in the follow-up of the original studies. One patient from this cohort discontinued CNB at 1 year owing to a lack of efficacy.

### 3.1 | Baseline characteristics

The baseline characteristics of the study population are shown in Table 1. The mean age of included patients was 39.5 years (range 19–65); 51% were female. Thirty-five patients (46.6%) had structural etiology and a further 35 (46.6%) had unknown etiology.

The median number of prior ASMs was 10 (IQR 6–13); the most frequent were levetiracetam ($n = 39$; 86.7%), lamotrigine ($n = 34$; 75.6%), and lacosamide ($n = 33$; 73.3%; Table S2).

The median number of concomitant ASMs at baseline was 2 [IQR 2–3] (mean 2.5 ± 0.6; range 2–4); the most frequent were clobazam ($n = 32$; 42.7%), carbamazepine ($n = 20$; 26.7%), and lamotrigine ($n = 19$; 25.3%; Table 2). Forty-six patients (61.3%) were taking two concomitant ASMs at baseline, 23 (30.7%) were taking three, and six (8%) were taking four.

### 3.2 | Concomitant ASM

As per design, the number of concomitant ASMs was significantly reduced from treatment onset to last visit ($p < 0.001$; Wilcoxon test). A descriptive characterization of how ASM simplification occurred in this selected population is shown in Figure 1. At the last visit, seven patients (9.3%) were converted to CNB monotherapy and 68 (90.7%) were taking one concomitant ASM. The most common concomitant ASMs at last visit were clobazam ($n = 13$; 17.3%), lamotrigine ($n = 12$; 16%), and brivaracetam ($n = 11$; 14.7%; Table 2).

There was a statistically significant reduction in the number of patients taking carbamazepine ($p = 0.001$; McNemar test), clobazam ($p < 0.001$), eslicarbazepine ($p < 0.001$), lacosamide ($p < 0.001$), lamotrigine ($p = 0.016$), perampanel ($p = 0.001$), valproic acid ($p = 0.016$), and zonisamide ($p = 0.004$) during follow-up (Table 2). There was a numerical, but not significant, reduction in the proportion of patients using all other ASMs between baseline and the last visit (Table 2). Of 68 patients who maintained one concomitant ASM at the last visit, the dosage of concomitant ASM was known for 42; 19/42 (45%) were taking a reduced dosage of the concomitant ASM. The proportion of patients with a dose reduction of a specific ASM, and the extent of those dose reductions, are shown in Table S3. Of 36 patients with longitudinal information available,

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**TABLE 1** Demographic and disease characteristics at baseline.

| Characteristic | All patients $N=75$[a] |
|---|---|
| Female sex, *n* (%) | 38 (51) |
| Mean age, years (range) | 39.5 (19–65) |
| Median time since epilepsy diagnosis to CNB onset, years (IQR) | 24.5 (14–34) |
| Seizure frequency/28 days prior to CNB onset ($n=43$) | |
| Mean (SD) | 37.7 (85.1) |
| Median (IQR) | 12 (4–30) |
| Etiology, *n* (%) | |
| Structural | 35 (46.6) |
| Cortical developmental malformation | 14 (18.6) |
| Vascular | 5 (6.6) |
| Tumor | 4 (5.3) |
| Mesial temporal sclerosis | 3 (4) |
| Perinatal | 1 (1.3) |
| Cavernoma | 1 (1.3) |
| Other | 7 (9.3) |
| Genetic | 2 (2.6) |
| Autoimmune | 1 (1.3) |
| Infectious | 4 (5.3) |
| Unknown | 33 (44) |
| Number of prior ASMs, *n* (%) ($n=60$) | |
| 2–3 | 4 (6.7) |
| 4–6 | 12 (20) |
| 7–10 | 16 (26.7) |
| ≥11 | 28 (46.5) |
| Mean (range) | 10.1 (2–20) |
| Median (IQR) | 10 (6–13) |
| Number of concomitant ASMs | |
| 2 | 46 (61.3) |
| 3 | 23 (30.7) |
| 4 | 6 (8) |
| Mean (range) | 2.5 (2–4) |
| Median (IQR) | 2 (2–3) |

Abbreviations: ASM, antiseizure medication; CNB, cenobamate; IQR, interquartile range; SD, standard deviation.

[a]Unless otherwise indicated.

the timing and reasons for ASM reduction are shown in Tables S4 and S5.

## 3.3 | Dosage

The mean dosage of CNB at the last visit was 285 ± 87 mg/day (range: 100–500 mg/day); the median CNB dosage was 300 mg/day (IQR 200–350). At the last visit, the dosage of CNB was significantly higher in those who achieved CNB monotherapy (mean CNB dosage 361 mg/day; median 350 mg/day) compared with those receiving a concomitant ASM (mean CNB dosage 277 mg/day; median 288 mg/day; $p=0.026$; Mann–Whitney test) (Table 3).

For CNB and ASM combinations used in at least five patients, there were statistically significant differences in the final dosage of CNB between groups ($p=0.036$; Kruskal–Wallis test), including higher dosages in those treated with levetiracetam (mean 310 mg/day; median

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**TABLE 2** Change in concomitant ASM usage between baseline and last visit (includes only ASMs taken by ≥2 patients at baseline).

| | Concomitant ASM at baseline *n* (%) | Discontinued during follow-up *n* | Added during follow-up *n* | Concomitant ASM at last visit *n* (%) | *p*-value |
|---|---|---|---|---|---|
| Clobazam | 32 (42.7) | 20 | 1 | 13 (17.3) | <0.001 |
| Carbamazepine | 20 (26.7) | 11 | 0 | 9 (12) | 0.001 |
| Lamotrigine | 19 (25.3) | 7 | 0 | 12 (16) | 0.016 |
| Lacosamide | 17 (22.7) | 12 | 0 | 5 (6.7) | <0.001 |
| Brivaracetam | 15 (20) | 6 | 2 | 11 (14.7) | NS |
| Perampanel | 13 (17.3) | 11 | 0 | 2 (2.7) | 0.001 |
| Eslicarbazepine | 13 (17.3) | 13 | 0 | 0 (0) | <0.001 |
| Zonisamide | 10 (13.3) | 9 | 0 | 1 (1.3) | 0.004 |
| Valproic acid | 9 (12) | 7 | 0 | 2 (2.7) | 0.016 |
| Levetiracetam | 8 (10.7) | 3 | 0 | 5 (6.7) | NS |
| Topiramate | 7 (9.3) | 6 | 1 | 2 (2.7) | NS |
| Pregabalin | 5 (6.7) | 4 | 0 | 1 (1.3) | NS |
| Phenobarbital | 5 (6.7) | 2 | 0 | 3 (4) | NS |
| Phenytoin | 3 (4) | 3 | 0 | 0 (0) | NS |
| Primidone | 2 (2.7) | 2 | 0 | 0 (0) | NS |
| Oxcarbazepine | 2 (2.7) | 1 | 0 | 1 (1.3) | NS |

Abbreviations: ASM, antiseizure medication; NS, not significant.

300 mg/day) and brivaracetam (mean 311 mg/day; median 300 mg/day), and lower dosages in those treated with lacosamide (mean 160 mg/day; median 200 mg/day).

## 3.4 | Effectiveness

Twenty-five of the 75 patients (33.3%) included in the study were seizure-free at their last visit, 51 (68%) had at least a 50% reduction in seizures (i.e., ≥50% responders), and one (1.3%) had a worsening of seizure frequency (this patient discontinued at 1 year). At the last visit, the seizure-freedom rate was numerically, but not significantly, higher in patients converted to CNB monotherapy (57.1%) versus those receiving a concomitant ASM (30.9%; $p = 0.16$; chi-square test). Similarly, 85.7% of patients in the monotherapy group were ≥50% responders versus 66.2% in those receiving combination therapy ($p = 0.29$; chi-square test) (Figure 2).

A post hoc analysis was conducted according to follow-up duration. Among patients whose last available follow-up was at 12 months, 6/30 (20.0%) were seizure-free and 17/30 (56.7%) had at least a 50% reduction in seizure frequency. Among patients with last available follow-up beyond 12 months, 18/43 (41.9%) were seizure-free and 33/43 (76.7%) had at least a 50% reduction in seizure frequency at the last visit.

Longitudinal follow-up data were available in 18/25 (72%) patients who were seizure-free at the last visit (Table S6). In this subset of patients, the median time since the previous visit was 3 months (IQR 3–6; range 3–12) and the median total duration of seizure freedom up to the last visit was 15 months (IQR 9–33; range 3–36).

For CNB and ASM combinations used in at least five patients, there were statistically significant differences between groups in rates of seizure freedom ($p < 0.001$; chi-square test) and ≥50% response ($p = 0.018$; chi-square test) when all combinations were compared; the highest rates of seizure freedom were in those receiving clobazam or lacosamide, and the highest ≥50% responder rates were in those receiving clobazam or carbamazepine.

## 3.5 | Safety

Fifty-five of the 75 patients (73.3%) included in the study reported AEs during follow up, the most common of which were somnolence (30.7%), dizziness/vertigo (28%), and fatigue (26.7%) (Table 4). No patients discontinued CNB due to AEs. There were no significant differences in AE rates between patients converting to CNB monotherapy and those receiving a concomitant ASM at the last visit, although AEs were numerically more frequent in those converting to CNB monotherapy versus combination therapy (7/7 [100%] vs. 48/68 [70.6%]; $p = 0.179$; Fisher's exact test).

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### 3.6 | Conversion to monotherapy

There were no statistically significant differences in baseline characteristics between those patients who converted to CNB monotherapy by the last visit and those receiving one concomitant ASM; there was a tendency for longer treatment duration with CNB in those converting to CNB monotherapy (Table S7).

## 4 | DISCUSSION

Among participants with highly drug-resistant focal epilepsy treated with CNB in EAPs around Europe, 10% either transitioned to CNB monotherapy or reduced their concomitant ASM to a single additional agent. Despite this reduction in concomitant ASM load, a pooled analysis of these patients found that 33.3% became seizure-free, 68% experienced at least a 50% reduction in their seizures, and 1.3% showed a worsening of seizures. The last available follow-up in this study was not homogeneous, and outcomes could have been impacted by differences in follow-up between studies. For patients with last available follow-up at 1 year, 20% were seizure-free and 56.7% had at least a 50% reduction in seizure frequency. These findings suggest that, in selected patients, concomitant ASM regimens may be simplified during CNB treatment while maintaining meaningful seizure control, and highlight the presence of super-responders even in a difficult setting such as an EAP. It is important to note, however, that the study population represents a highly selected subgroup of favorable responders, and these results should therefore not be extrapolated to overestimate the effectiveness of CNB in the broader patient population.

A reduction of concomitant ASMs during CNB treatment has been reported in other series. In a single-center study of 94 patients receiving CNB in clinical practice, the proportion of patients on ≥3 ASMs decreased from 62% at baseline to 14% at 12 months, while those on 1–2 ASMs increased from 38% to 81%. Overall, 5% converted to CNB monotherapy.[5] Similarly, a retrospective, real-world study of 298 patients with DRE included in the CNB EAPs in Germany, France, and the United Kingdom observed a slight decrease in the mean number of concomitant ASMs at 3–6 months. The possibility of optimizing and simplifying concomitant ASM during CNB treatment is clinically meaningful as treatment with multiple ASMs can increase AEs, impact patient quality of life, and increase treatment costs.[4,21]

Treatment with CNB has also been reported to allow postponement or cancellation of other non-medical treatments. In a study of 23 patients receiving CNB who were awaiting vagal nerve stimulation, 9 (39%) chose not to undergo insertion due to a reduction in their seizures.[22]

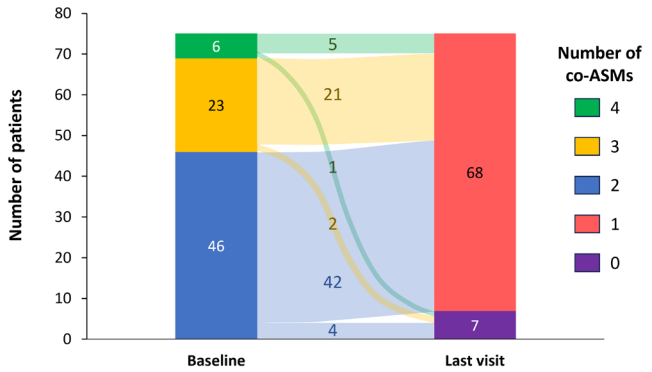



FIGURE 1 Change in concomitant ASM usage between baseline and last visit. ASM, antiseizure medication; co-ASMs, concomitant ASMs.

TABLE 3 CNB dosage at last visit.

| | | CNB dosage at last visit, mg/day | | |
|---|---|---|---|---|
| | *n* | Mean (SD) | Median (IQR) | Range |
| All patients | 75 | 285 (87) | 300 (200–350) | 100–500 |
| CNB monotherapy | 7 | 361 (91.1)* | 350 (325–400) | 200–500 |
| CNB + co-ASM | 68 | 277 (83.8) | 288 (200–350) | 100–400 |
| CNB + CLB | 13 | 292 (67.2) | 300 (250–300) | 200–400 |
| CNB + LTG | 12 | 271 (88.4) | 275 (200–325) | 100–400 |
| CNB + BRV | 11 | 311 (56.3) | 300 (250–350) | 250–400 |
| CNB + CBZ | 9 | 289 (89.4) | 250 (200–400) | 200–400 |
| CNB + LCM | 5 | 160 (54.8) | 200 (100–200) | 100–200 |
| CNB + LEV | 5 | 310 (65.2) | 300 (250–350) | 250–400 |

Abbreviations: BRV, brivaracetam; CBZ, carbamazepine; CLB, clobazam; CNB, cenobamate; co-ASM, concomitant antiseizure medication; IQR, interquartile range; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; SD, standard deviation.

*$p = 0.026$ versus CNB + co-ASM (Mann–Whitney test).

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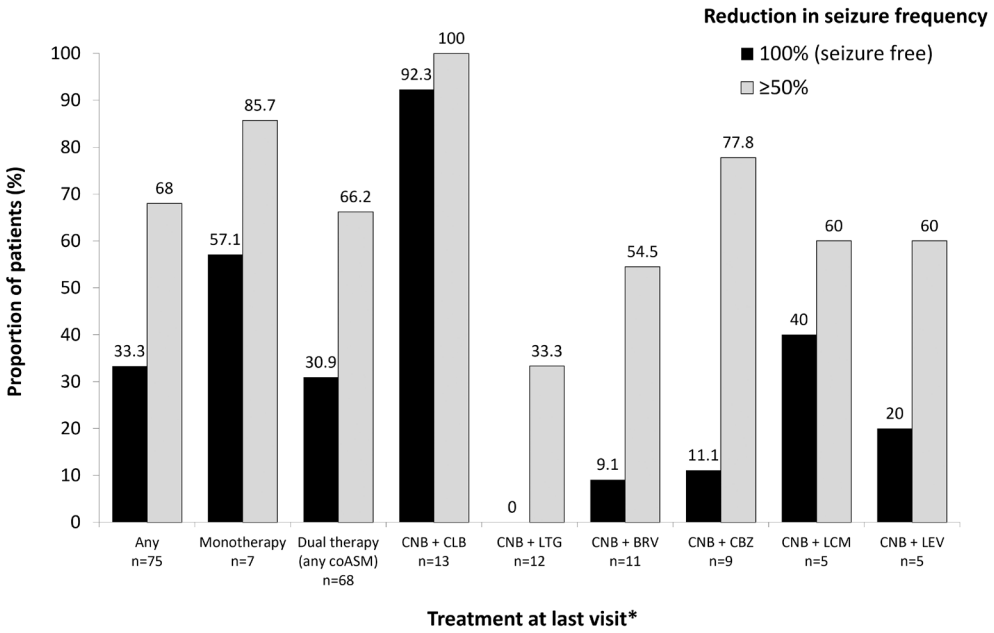



**FIGURE 2** Effectiveness outcomes between baseline and last visit. *Includes ASM groups with ≥5 patients. BRV, brivaracetam; CBZ, carbamazepine; CLB, clobazam; CNB, cenobamate; co-ASM, concomitant antiseizure medication; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine.

In patients with drug-resistant focal epilepsy undergoing evaluation for epilepsy surgery, those who received CNB during the presurgical evaluation were less likely to undergo surgery within 12 months than those not treated with CNB.[23]

Our analysis focused on the 10% of patients in the EAPs who were able to significantly reduce their concomitant ASM usage to either a single concomitant ASM or CNB monotherapy. The effectiveness and safety of CNB following conversion to monotherapy or as dual therapy have been reported previously in a multicenter, real-world study of 125 patients with DRE in clinical practice; 32% of patients achieved seizure freedom and 76% achieved a ≥50% reduction in seizure frequency by the last visit, aligning with our outcomes.[24] Considering other studies, the effectiveness of CNB in our pooled analysis is lower than reported in a post hoc analysis of 240 patients from a Phase 3 study; among patients with a high numerical decrease in concomitant ASM drug load (−3.3 to −0.59), 70% achieved sustained seizure freedom and 90.6% achieved a sustained ≥50% reduction in seizure frequency.[19] This difference could be explained by the substantially higher median seizure frequency at baseline in our study compared with the post hoc analysis (12 vs. 2.8 seizures/month), as well as by differences in study design. These positive outcomes also support significantly reducing concomitant ASM during follow up, even in a highly refractory population such as those included in the EAPs, in order to reduce the total drug load in patients. Our results support further investigation of CNB monotherapy or near-monotherapy strategies, and underline the guideline recommendation of the US Food and Drug Administration (FDA) for monotherapy approval.

With respect to combinations, exploratory analysis showed differences in effectiveness outcomes according to specific concomitant ASMs at last visit, with the highest rates of seizure freedom and ≥50% response in those receiving concomitant clobazam (a benzodiazepine) and the lowest in those receiving concomitant lamotrigine (a sodium channel blocker [SCB]). These results should be interpreted cautiously due to the low number of patients receiving clobazam. In line with these observations, a study of 231 patients with uncontrolled focal seizures in early lines of treatment found that CNB provided improved seizure control and health-related quality of life when combined with low-dose clobazam.[25] Similarly, in 85 patients with DRE and an incomplete response to CNB, addition of clobazam has been reported to lead to an improved response.[26]

Aside from clobazam, associations between specific combinations with CNB and treatment outcomes are not clear cut and may differ according to patient and disease characteristics, concomitant ASM dosages, and other factors. In a multicenter, retrospective cohort of 475 patients with DRE treated with CNB, concomitant valproate use at baseline was associated with a greater likelihood of seizure freedom and ≥50% seizure reduction whereas SCB use was linked to a reduced likelihood of achieving seizure freedom. At the final follow-up, however, concomitant SCB use showed a modest

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**TABLE 4** Adverse events.

| | $N=75$[a] |
|---|---|
| Patients with AEs, *n* (%) | 55 (73.3) |
| Patients with AEs leading to CNB discontinuation, *n* (%) | 0 |
| Patients with specific AEs[b], *n* (%) | |
| Somnolence | 23 (30.7) |
| Dizziness/vertigo | 21 (28) |
| Fatigue | 20 (26.7) |
| Diplopia/blurred vision | 18 (24) |
| Anomia | 9 (12) |
| Psychomotor slowness | 9 (12) |
| Dysarthria | 4 (5.3) |
| Headache | 2 (2.7) |
| Dysnomia | 2 (2.7) |
| Hyperactivity | 2 (2.7) |
| Lack of appetite | 2 (2.7) |
| Memory problems | 2 (2.7) |
| Tremor | 2 (2.7) |
| Gastrointestinal disturbances | 2 (2.7) |
| Patients with AEs according to treatment at last visit (≥5 patients), *n* (%) | |
| CNB monotherapy, $n=7$ | 7 (100) |
| CNB + any concomitant ASM, $n=68$ | 48 (70.6) |
| CNB + CLB, $n=13$ | 10 (76.9) |
| CNB + LTG, $n=12$ | 9 (75) |
| CNB + BRV, $n=11$ | 8 (72.7) |
| CNB + CBZ, $n=9$ | 6 (66.7) |
| CNB + LCM, $n=5$ | 2 (40) |
| CNB + LEV, $n=5$ | 4 (80) |

Abbreviations: AEs, adverse events; BRV, brivaracetam; CBZ, carbamazepine; CLB, clobazam; CNB, cenobamate; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine.

[a]Unless otherwise indicated.

[b]Adverse events reported by 1 patient (1.3%) included: alopecia, gait disturbance, increased appetite decreased appetite, disorientation, pain, excitability, constipation, suicidal ideation, weight gain, irritability myokymia, weight loss, dry skin, prolonged postictal psychosis, sedation, dry mouth, sleep disturbances.

association with achieving ≥50% seizure reduction.[27] In the FREEDON study, which included 486 patients with focal epilepsy receiving CNB in different lines of treatment, the most common concomitant ASMs at 1 year were the SV2A ligands levetiracetam and brivaracetam, lacosamide (an enhancer of slow inactivation of voltage-gated sodium channels), and the AMPA receptor antagonist perampanel, whereas the most frequently reduced concomitant ASMs were SCBs.[28] Consequently, further studies are needed to consolidate these outcomes and elucidate, other than clobazam, the most effective combinations with CNB.

Regarding CNB dosage, the mean at last visit was 285 mg/day (median 300 mg/day), reflecting the high dosage used in most refractory cases. This was similar to the dosage used in a German series (median 300 mg/day) in patients treated with >10 ASMs.[29] Moreover, the mean CNB dosage at the last visit was significantly higher in those who had converted to CNB monotherapy compared with those receiving one concomitant ASM. This may reflect higher CNB dosages leading to higher efficacy, thereby allowing for a reduction in concomitant ASM usage. Alternatively, improved tolerability following discontinuation of concomitant ASMs may have allowed for higher CNB dosages to be used to achieve appropriate efficacy. Indeed, higher CNB retention following concomitant ASM discontinuation has been linked to improved tolerability in a Phase 3 open-label study.[30]

The safety profile for CNB in our series was manageable, as despite 73.3% of patients reporting AEs, no discontinuations were attributed to these events. Other studies that evaluated a similar population reported AEs (generally mild-to-moderate) in 50% of patients, although only a small subset of these patients were part of an EAP.[24] Our safety outcomes are in line with data from other EAPs, which report AE rates of 56.4–74.1%.[7,9,10] In addition, the AE profile in our study was similar to that seen in other series. Somnolence, dizziness/vertigo, fatigue, and blurred vision are typically the most common AEs with CNB, with the majority of AEs mild-to-moderate in severity.[6,24]

In the current pooled analysis, the higher AE rate in patients who converted to CNB monotherapy versus those receiving one concomitant ASM (100% vs. 70.6%) could have been a reflection of discontinuation of concomitant ASMs in those patients with significant AEs. It may also reflect a higher CNB dosage among those patients converted to CNB monotherapy. The observation that no patient discontinued CNB because of AEs suggests that management of comedication may help to improve treatment retention. The significant reduction in concomitant ASM may account for the favorable long-term tolerability of CNB in this highly medicated patient group, and further supports the previously reported importance of reducing concomitant ASM burden.[31–33]

Considering AEs of special interest, our study reported no severe cognitive AEs leading to treatment discontinuation with CNB over the long term. In line with our data, an exploratory, real-world study in 14 patients with DRE reported no negative effects of CNB on cognition.[34] We also observed no relevant psychiatric AEs in our study. This is consistent with data from

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a single-center study of 60 patients with DRE which found no new psychiatric AEs after 6 months of CNB treatment, including in those with prior psychiatric conditions, although patients with intellectual disabilities and psychiatric comorbidities showed increased irritability with CNB.[35]

Our analysis has a number of limitations. First, the analysis used pooled data from studies with heterogeneous reporting, including single and multicenter, retrospective studies and patient registries. While a statistical approach was used to present data as comprehensively and consistently as possible, not all data were available for each patient at each timepoint and follow-up was not homogeneous. Moreover, information on the timing and reasons for ASM withdrawal or dose reduction was not standardized, limiting the interpretation of treatment simplification. As inclusion required successful treatment simplification and availability of follow-up data, retention rates may be inherently overestimated. Finally, subgroup analyses were exploratory and limited by small sample sizes and potential confounding by CNB dose, tolerability, and clinical decision-making. Moreover, the analyzed population may not fully reflect the true reduction in pharmacological burden, since dose reduction of concomitant ASM was neither an inclusion criterion nor consistently evaluated in all patients. Nevertheless, the analysis provides insights from a large, highly medicated, and drug-resistant population that significantly reduced concomitant ASM. While the findings should be interpreted with caution, they support outcomes observed in clinical practice.

## 5 | CONCLUSIONS

In this pooled analysis of patient data from CNB EAPs around Europe, CNB demonstrated sustained effectiveness and good tolerability, even in those patients with a significant reduction of ASM (to monotherapy or dual therapy). Although the reason for treatment simplification could not be elucidated in this analysis, these findings are particularly noteworthy given that the patient population was highly drug-resistant and polymedicated at baseline. It is important to note, however, that these outcomes were observed in a highly selected group of favorable responders and should not therefore be interpreted as representative of the effectiveness of CNB in the wider patient population. The study also indicates a manageable tolerability profile for CNB after reducing or discontinuing concomitant ASM.

## AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study and to the acquisition of data. Vicente Villanueva organized the database, analyzed the data, wrote the first draft, and created tables and figures. All authors discussed the results, revised the first draft, and approved the final manuscript.

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## CONFLICT OF INTEREST STATEMENT

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## DATA AVAILABILITY STATEMENT

Data published within this article are available on request from the authors.

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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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