Is earlier better?

One-year cenobamate outcome in a large real-world population

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BACKGROUND AND PURPOSE

Cenobamate (CNB) is a recently approved antiseizure medication (ASM) for adjunctive treatment of focal drug-resistant epilepsy (DRE). To date, several studies have described the efficacy of CNB in highly drug-resistant epilepsies; however, observations regarding the use of CNB at an earlier stage are limited and confined to a small number of patients. This study aimed to investigate potential differences related to earlier versus later initiation of CNB treatment.

METHODS

We conducted a retrospective real-world study evaluating the use of CNB over 12 months in a large cohort of DRE patients. All patients from the 16 participating centers in the Veneto region who had received at least one dose of CNB between June 2022 and December 31, 2023, were enrolled. Patients were stratified into early adopters (EA, ≤5 ASMs before CNB) and late adopters (LA, >5 ASMs) to explore differences in treatment outcomes.

Table. Study population characteristics

Characteristic	Overall	Early Adoption (n = 88)	Late Adoption (n = 193)	p-value
Age (years), median (range)	38 (18–92)	40 (18–71)	37 (18–92)	0.4601
Male, n (%)	140 (50%)	46 (52%)	94 (49%)	0.667
Age at epilepsy onset (years), median (range)	8.5 (0–84)	15 (0–56)	6 (0–84)	**<0.0001**
Epilepsy duration (years), median (range)	24 (0–71)	19 (0–58)	26 (0–71)	**<0.0001**
Lifetime ASMs, n, median (range)	8 (2–21)	4 (2–5)	9 (6–21)	**<0.0001**
Sodium channel blockers, mean (range)	3 (0–7)	1 (0–3)	3 (1–7)	1
Previous carbamazepine use, n (%)	111 (40%)	16 (14%)	95 (86%)	**<0.0001**
Seizure frequency at baseline (3 months), median (range)	24 (1–1800)	9.5 (0–930)	35 (2–1800)	**<0.0001**
Concomitant ASMs, n, median (range)	3 (1–7)	2 (1–4)	3 (1–4)	**<0.001**
Concomitant carbamazepine use, n (%)	71 (25%)	20 (7.2%)	51 (18.4%)	0.600
Concomitant clobazam or clonazepam use, n (%)	108 (38%)	15 (18%)	94 (51%)	**<0.0001**
Surgical treatment for epilepsy, n (%)	34 (12%)	6 (7%)	28 (15%)	0.170
Coexisting intellectual disability, n (%)	144 (47%)	29 (35%)	115 (60%)	**<0.0001**
Coexisting psychiatric disability, n (%)	92 (34%)	18 (20.5%)	74 (39%)	**0.005**

RESULTS

A total of 281 eligible patients were included (88 EA, 193 LA). EA and LA groups significantly differed in median epilepsy onset age (15 vs. 6 years, p < 0.0001), median disease duration (19 vs. 26 years, p < 0.001), prevalence of intellectual and psychiatric disabilities (35% vs. 61%, p < 0.0001; 22% vs. 40%, p = 0.005), prior carbamazepine use (14% vs. 86%, p < 0.0001), median number of concomitant ASMs (2 vs. 3, p < 0.001), and baseline seizure frequency (9.5 vs. 35 seizures/month, p < 0.0001). (See table)
Effectiveness and safety data were available for 60 EA and 150 LA patients at 3 months, 46–118 at 6 months, 25–77 at 9 months, and 23–57 at 12 months.

Retention rate.

The estimated cumulative probability of CNB discontinuation at 12 months was 10.0% (95% CI: 6.5–15.4%).
See Kaplan-Meier in figure 1.

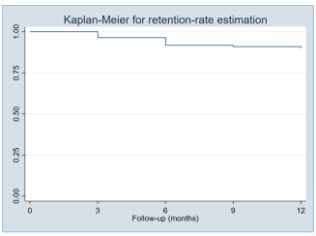

Figure 1. Kaplan-Meier curve estimated retention rate was 96.4% at 3 months, 91.7% at 6 months, 90.0% at 9 months, and 89.9% at 12 months

Effectiveness.

- The responder rate (RR ≥75% seizure reduction) was consistently higher in EA patients at all time points (42% vs. 21%, p = 0.0028; 45% vs. 36%, p = freedom over 12 months was observed in 15% of patients. 0.25; 46% vs. 39%, p = 0.36; 75% vs. 36%, p = 0.0039). Seizure freedom was achieved at two- to threefold higher rates in EA compared to LA patients at 3, 6, 9, and 12 months (32% vs. 12%, p = 0.0005; 24% vs. 10%, p = 0.014; 36% vs. 12%, p = 0.0062; 36% vs. 9%, p = 0.0039). See figure 2.
- Sustained seizure

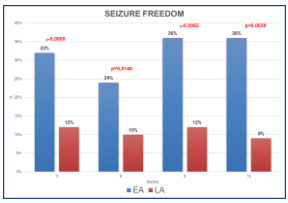

Figure 2. Seizure freedom percentages in EA and LA patients at 3, 6, 9, 12 months follow-up.

- Multivariate and stepwise logistic regression identified early cenobamate adoption (OR ≈ 2.2) and younger epilepsy onset age (OR ≈ 1.03) as independent predictors of ≥50% seizure reduction. Other factors (epilepsy duration, sex, prior CBZ use, cognitive comorbidity) showed no significant association. See figure 3

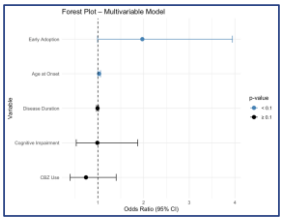

Figure 3. Multivariate logistic regression model assessing predictors of seizure response (≥50% reduction at last follow-up). Adjusted odds ratios and 95% confidence intervals (CI) are shown on a logarithmic scale. Variables with p < 0.1 are highlighted in blue

Safety and drug burden.

- Most adverse events (AEs) occurred within the first three months (34%), mainly somnolence (23%) and fatigue (13%), with no differences between EA and LA.
- The proportion of patients on a single ASM increased from 14 to 75% in EA and 3 to 30% in LA. Clobazam and lacosamide were the most discontinued or reduced ASMs.

CONCLUSIONS

- CNB demonstrated sustained high effectiveness over 12 months, with a significantly better overall response and notably higher seizure freedom rates in patients treated earlier.
- An earlier introduction of CNB and younger age were identified as predictors of greater treatment success.
- The safety profile was favorable, with a progressive reduction in total drug burden.

Bibliography

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