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Quality of life and synergistic combinations of antiseizure medication in patients treated with cenobamate in early therapy lines for focal-onset seizures

Yaroslav Winter [a,b,1,*], Raya Abou Dargham [i,1], Erik Ellwardt [c], Thilo Hammen [d,j], Christoph Massing [e], Sarah Gößling [f], Marina Flotats-Bastardas [g], Sergiu Groppa [a], Michael Zemlin [g], Christopher Meudt [h]

[a] Department of Neurology, Saarland University Medical Center, University of Saarland, Homburg, Germany
[b] Department of Neurology, Philipps-University Marburg, Marburg, Germany
[c] Department of Neurology, Helios-HSK Wiesbaden, Wiesbaden, Germany
[d] Clinic for Neurology, Westpfalz-Klinikum Kaiserslautern, Kaiserslautern, Germany
[e] Department of Neurology, Caritas-Klinikum Saarbrücken St. Theresia, Saarbrücken, Germany
[f] Department of Neurology, DRK Krankenhaus Saarlouis, Saarlouis, Germany
[g] Department of General Pediatrics and Neonatology, Division of Neuropediatrics, Saarland University, Homburg, Germany
[h] Department of Pediatrics, Frankfurt Hoechst Hospital, Frankfurt, Germany
[i] Department of Neurology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany
[j] Neurologial Clinic, University Hospital Erlangen, Erlangen, Germany

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ABSTRACT

Background: Quality of life is an important outcome measure for patients with epilepsy (PWE). However, data on health-related quality of life (HRQoL) in PWE treated with cenobamate (CNB), a new antiseizure medication (ASM) that achieves a high level of seizure freedom, is scarce. These data are especially important for evaluating the use of CNB in early therapy lines for focal-onset seizures.

Methods: The study population consisted of patients with focal-onset seizures that could not be controlled by fewer than three lifetime ASMs. They began treatment with CNB („CNB group“) or another ASM (controls). Both groups were matched at a ratio of 1:2 based on sex, age, and seizure frequency. HRQoL was evaluated using the Quality of Life in Epilepsy-10 (QOLIE-10), the EuroQol Visual Analogue Scale (EQVAS), and the EuroQol-5-Dimensions (EQ5D) questionnaire. The drug combinations were analyzed.

Results: Of the 231 study participants, 33.3 % were treated with CNB, 19.0 % with valproate, 17.3 % with lacosamide, 16.4 % with levetiracetam, and 13.9 % with topiramate. The percentage improvement in the EQ5D index score from baseline to the 12-month follow-up was higher for CNB (32.2 %) than for other ASMs (3.2 %–17.5 %, $p < 0.05$). Similar results were obtained for EQVAS (31 % vs. 3.2 %–17.5 %) and QOLIE-10 (46.9 % vs. 13.4 %–28.2 %), $p < 0.05$. CNB demonstrated superior seizure control and HrQoL when combined with low-dose clobazam and a trend for combination with SV2A modulators.

Conclusion: Our study provides evidence that CNB in early therapy lines for focal-onset seizures is associated with an increased HrQoL. Low-dose clobazam can wok synergistically with CNB. The combination with SV2A modulators showed a positive trend.

Abbreviations: ANOVA, analysis of variance; ASM, antiseizure medication; BRV, brivaracetam; CLB, clobazam; CNB, cenobamate; DDD, daily defined dose; ESL, eslicarbazepine acetate; EQVAS, EuroQol Visual analogue scale; EQ5D, EuroQol-5-Dimensions Questionnaire; HrQoL, Health-related Quality of Life; LCS, lacosamide; LEV, levetiracetam; LTG, lamotrigine; QOLIE10, Quality of Life in Epilepsy-10; PWE, person with epilepsy; SD, standard deviation; SV2A, synaptic vesicle glycoprotein 2A; TPM, topiramate; VPA, valproic acid.

* Corresponding author at: Department of Neurology, Saarland University Medical Center, University of Saarland, D-66421 Homburg, Germany.
E-mail address: yaroslav.winter@uks.eu (Y. Winter).

[1] These authors contributed equally to this work as co-first authors.

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1. Introduction

Epilepsy is a chronic neurological disease with significant social impact on patients and their families [1]. A European survey including data from five European countries emphasized the broad physical and psychological effects of epilepsy on health-related quality of life (HrQoL) [2]. The evaluation and measurement of HrQoL has garnered significant attention as an outcome measure in clinical research and daily practice [3]. In addition to the common primary clinical endpoints, such as seizure severity, frequency, type and side effects, HrQoL significantly contributes to the evaluation of distress experienced by persons with epilepsy (PWE), even with good seizure control [4,5]. Seizure control does not necessarily imply a better perception of health in PWE. Other factors, including medication side effects and disease-related factors, may negatively affect the health of PWE. Multiple studies have shown that evaluating HrQoL based on a reduction in seizure frequency yields inconsistent results across different antiseizure medications (ASMs) [3,4]. A survey of PWE in Australia also demonstrated that subjective memory problems and psychiatric issues were linked to the most significant negative effect on HrQoL, despite controlled seizures [6]. A recent multicenter cross-sectional study in Germany found that high Liverpool Adverse Events Profile scores was the strongest predictor of lower HrQoL, underscoring the significance of therapy-related adverse effects on HrQoL [7].

Cenobamate (CNB) is a new, third-generation ASM approved in Europe for treating focal-onset seizures not controlled by at least two ASMs and in the USA as monotherapy [8,9]. Prior work has primarily focused on efficacy and safety parameters, which do not reflect patient-oriented outcomes. Consequently, knowledge of patient-oriented outcomes in early ASM therapy is limited. To date, only two small studies from Spain with three- or six-month follow-ups have examined HrQoL in patients treated with CNB [10]. Patients were included in the usual treatment setting, with no focus on CNB use in early lines of therapy. Previously, we published data on the safety and efficacy of CNB, demonstrating its benefits in early lines of therapy for focal-onset seizures [11]. Since HrQoL is a more comprehensive indicator of patient-related outcomes than efficacy, we focus on HrQoL it in the current analysis of early lines of CNB therapy. We choose a larger observational period (12 months) than in previous studies. Additionally, we evaluated possible synergistic combinations of CNB with other ASM.

2. Methods

2.1. Study design and clinical evaluation

Patient recruitment and follow-ups were carried out in the outpatient neurological departments of the South-West German Epilepsy Network, which is a collaborative initiative involving neurological departments in south-western Germany. The South-West German Epilepsy Network traces its origins to the Mainz Comprehensive Epilepsy and Sleep Medicine Centre. The network has undergone a period of restructuring. This has seen the University Epilepsy and Sleep Medicine Centre of Saarland become the leading centre of this network. Upon presentation at outpatient neurological departments within the South-West German Epilepsy Network, all study participants underwent examination by epileptologists, with their clinical data documented in the network's epilepsy register. Patients were included in the study if they had focal-onset seizures that could not be controlled by at least two, but no more than three, lifetime anti-seizure medications (ASMs), including all prior and concomitant ASMs (excluding benzodiazepines used short-term as rescue medications). Patients were informed about possible treatment options, and the decision was made in consultation with the attending epileptologist in accordance with standard practice. Patients who initiated CNB treatment (the 'CNB group') were matched at a ratio of 1:2 with patients who received ASMs other than CNB (the 'control group') based on sex, age, and seizure frequency. For matching purposes, patients were categorised according to seizure frequency as follows: one seizure per month or less; two to three seizures per month; or at least four seizures per month (i.e. weekly seizures). The controls were recruited prospectively within the South-West German Epilepsy Network and their clinical data were recorded in the network's epilepsy register. The following alternative ASMs were administered to the control group: lacosamide (LCS), levetiracetam (LEV), topiramate (TPM) and valproate (VPA). These ASMs were chosen because they were the most frequently prescribed as third- or fourth-choice ASMs in our epilepsy register. Newer ASMs, such as perampanel or brivarecetam, were usually proscribed in later therapy lines in our study population, and the amount of these patients in early therapy lines was not sufficient for matching. The 1:2 matching ratio was used because the control group consisted of more than one alternative ASM and therefore had to be larger than the CNB group. All eligible patients (n = 436) were recorded in an epilepsy register. Of these, 265 were enrolled in the study. A total of 171 potential controls (i.e. patients taking LCS, LEV, TPM or VPA) were not included because they did not meet the matching criteria. A total of 231 patients completed the 12-month follow-up.

The sample size was based on a power calculation that considered the minimal clinically important difference (MCID) of five points on the QOLIE [12]. We considered the mean baseline QOLIE score to be approximately 40 points in each ASM group and hypothesised that, if the QOLIE score increased by 5 points in the control group, the CNB group would have to show an increase of at least 5 points higher than the control group. With a study power of 80 % and a significance level of 95 % ($p < 0.05$), the required sample size was approximately 77 patients in the CNB group and 154 in the control group.

Clinical parameters evaluated in the study included type of seizures (focal to bilateral tonic-clonic seizures, focal impaired awareness seizures, focal aware motor and focal aware non-motor seizures), monthly seizure frequency, prior and concomitant medication, and adverse effects. The parameters reported by patients were the type and frequency of their seizures, adverse effects, as well as quality-of-life measures. Information on combinations with other ASMs was documented and included in the analysis. Data were collected using standardized case report forms (CRFs) and stored electronically in an epilepsy register.

Participants signed an informed consent form to take part in the study and approval for the study was received from the local ethics committees (Nr: 837.560.17 and 118/25).

2.2. Evaluation of HrQoL

We used standardized questionnaires including the Quality of Life in Epilepsy-10 (QOLIE-10), the EuroQol Visual Analogue Scale (EQVAS) and the EuroQol-5-Dimensions Questionnaire (EQ5D), which are commonly used to evaluate HrQoL in PWE. Questionnaires were collected from patients during their outpatient department visits at baseline and at the 12-month follow-up, following the initiation of the new treatment. We analyzed the results of the individual questionnaires for each ASMs.

The questionnaire EQ5D is a validated tool for assessing subjective HrQoL in PWE[13]. It evaluates health status via five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with three levels (1 = no problems, 2 = moderate problems, 3 = severe problems), as well as via a visual analog scale (EQVAS) ranging from 0 ("worst conceivable health status") to 100 ("best conceivable health status").

The QOLIE-10 (Quality of Life in Epilepsy-10) is a validated disease-specific questionnaire to assess HrQoL in PWE [14]. The QOLIE-10 is a tool designed to assess quality of life in epilepsy patients across three specific domains: The impact of epilepsy on psychological well-being, cognitive function, and occupational performance. The Epilepsy Effects section encompasses items pertaining to memory and medication effects, while the Mental Health section addresses domains such as energy, depression, and overall quality of life. The Role Functioning

domain encompasses seizure worry, social limitations, and restrictions related to driving and professional activities. A lower total score of the QOLIE-10 indicates a better HrQol.

EQ5D index score, EQ visual analogue scale/EQVAS and Quality of life in epilepsy (QOLIE 10) health index were assessed at baseline and 12 months post treatment with adjunctive ASM in all treatment groups. The minimal clinically important difference (MCID) for the EQ5D index score and EQVAS was set at 0.5 of the standard deviation of their respective baseline values. For the QOLIE, the MCID was set at 5 points, taking into account data from previous literature [12].

2.3. Statistics

IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA), was used for the statistical analysis. The collected data are represented as the mean, standard deviation (SD) and range. Demographic and other baseline characteristics will be summarized using descriptive statistics. The 12-month CNB retention rate, response rate and seizure freedom rate were compared to the rates of other ASMs using analysis of variance (ANOVA). Normally distributed variables were compared using t-tests. For non-normally distributed data, the Kruskal–Wallis test was performed for more than two independent groups, the Mann–Whitney *U* test for two independent groups, and the Wilcoxon rank test for two dependent groups. Statistical significance was considered at a P-value of less than 0.05. Missing data was addressed using multiple imputation. The daily defined dose (DDD) of the evaluated ASMs was considered according to the World Health Organisation recommendations. We evaluated independent factors influencing the HrQoL by applying multivariate regression analysis in terms of sensitivity analysis. The dependent variables were the EQ-5D index score, the EQ-VAS score and the QOLIE-10 score. The independent variables were age, gender, employment status, ASM dose, duration of epilepsy, number of previous and concomitant ASMs, number of different seizure types, and comorbid depression or anxiety. The stepwise regression algorithm with backward elimination was applied. We used the R^2 method to estimate the variability accounted for by the HrQoL independent factors.

3. Results

Of the 265 patients initially chosen for the study, 34 either declined to participate, withdrew their informed consent, or moved location and were therefore unavailable for follow-ups. There were no statistically significant differences between the study participants and the dropouts in terms of age, gender or seizure frequency. A total of 231 participants were included in the study, 45.5 % of whom were female. With regard to the administration of early adjunctive therapy, 77 patients were prescribed CNB, 44 of whom were administered valproate, 40 lacosamide, 38 levetiracetam and 32 topiramate. The demographic and clinical parameters of the study population are presented in Table 1. No significant differences in baseline characteristics between the treatment groups were observed. The mean final doses of the initiated ASMs were as follows: CNB, 216.9 ± 90.5 mg; LCS, 312.5 ± 126.4 mg; LEV, 2,263.2 ± 852.1 mg; TPM, 340.6 ± 29.2 mg; and VPA, 2,438.6 ± 1,249.4 mg. Major adverse effects are presented in Table 1.

A statistically significant improvement of HrQoL was observed for early adjunctive therapy with CNB compared to baseline values (Table 1). The percentage improvement in EQ5D index score, EQVAS and QOLIE-10 between baseline and the 12-month follow-up was higher with cenobamate than with other ASMs (Table 1). The improvement in QOLIE values in the CNB group after 12 months was greater than the MCID (5 points) compared to the baseline and 12-month values in the other ASM groups. The MCIDs for the EQ-5D index score and EQ-VAS were 0.14 and 13.8, respectively. Taking these MCIDs into account, the improvement in EQ5D index score and EQVAS in the CNB group after 12 months was greater than the baseline values and greater than the 12-month values of VPA and TPM, but not greater than the 12-month

Table 1
Demographics, clinical data and health-related quality of life.

Clinical parameters	CNB (n = 77)	LCS (n = 40)	LEV (n = 38)	TPM (n = 32)	VPA (n = 44)
Age (years), mean ± SD	44.2 ± 16.4	44.1 ± 17.0	44.4 ± 17.2	45.0 ± 14.9	45.1 ± 15.6
Gender female/ male, %	45.5/ 54.5	44.2/ 55.8	46.8/ 53.2	42.9/ 57.1	48.1/51.9
Duration of epilepsy, years, mean ± SD	4.8 ± 1.4	5.2 ± 1.4	5.1 ± 1.5	4.9 ± 1.5	4.9 ± 1.5
Monthly SF*, mean ± SD	3.0 ± 3.2	2.8 ± 3.3	2.9 ± 3.5	3.0 ± 3.6	2.8 ± 3.5
Concomitant ASM, % / DDD at 12 months					
LEV	28.6 / 102	30.0 / 103	NA	31.3 / 108	29.5 / 101
BRV	23.4 / 121	25.0 / 120	21.0 / 102 18.4 / 101	25.0 / 123	22.7 / 124 20.5 / 105
CLB	19.5 / 50	20.0 / 101	15.7 / 102 10.5 / 104	21.8 / 104	NA 15.9 / 104 11.4 / 102
VPA	18.2 / 100 15.6 / 96 11.7 / 94 7.8 / 125	17.5 / 102 15.0 / 95 NA 7.5 / 122	7.9 / 123	18.8 / 104 15.6 / 101 12.5 / 100 9.4 / 124	9.1 / 125
LTG					
LCS					
ESL					
Number of ASMs, mean ± SD	2.6 ± 0.9	2.6 ± 0.8	2.6 ± 1.0	2.7 ± 0.9	2.6 ± 0.7
EQ5D, mean ± SD					
at baseline	0.62 ± 0.29	0.63 ± 0.26	0.62 ± 0.27	0.62 ± 0.30	0.63 ± 0.28
at 12 months	0.82 ± 0.23**	0.74 ± 0.25	0.69 ± 0.28	0.64 ± 0.24	0.67 ± 0.27
% of change	32.3 %***	17.5 %	11.3 %	3.2 %	6.3 %
EQVAS, mean ± SD					
at baseline	60.6 ± 27.6	61.8 ± 26.6	61.1 ± 26.4	59.8 ± 27.3	61.3 ± 26.7
at 12 months	79.4 ± 21.2**	71.8 ± 23.8	67.0 ± 24.5	61.7 ± 22.3	64.9 ± 26.2
% of change	31.0 %***	17.5 %	9.7 %	3.2 %	5.9 %
QOLIE 10, mean ± SD					
at baseline	40.1 ± 19.1	39.0 ± 16.0	40.2 ± 17.0	39.5 ± 16.9	38.9 ± 15.6
at 12 months	21.3 ± 14.5**	28.0 ± 13.6	31.1 ± 15.3	34.2 ± 14.8	32.0 ± 15.2
% of change	46.9 %***	28.2 %	22.6 %	13.4 %	17.7 %
Adverse effects, n (%)					
Headache	8 (10.4)	5 (12.5)	4 (10.5)	2 (6.3)	4 (9.1)
Somnolence or fatigue	21 (27.3)	11 (27.5)	11 (28.9)	10 (31.3)	12 (27.3)
Dizziness or nausea	20 (26.0)	11 (27.5)	10 (26.3)	8 (25.0)	11 (25.0)
Behavioral side effects	0 (0)	0 (0)	5 (13.2)****	1 (3.1)	0 (0)
Weight gain	0 (0)	0 (0)	0 (0)	0 (0)	12 (27.3)****

Abbreviations: BRV, brivaracetam CNB, cenobamate; DDD, daily defined dose; CLB, clobazam; ESL, eslicarbazepine acetate; LTG, lamotrigine LCS, lacosamide; LEV, levetiracetam; SD, standard deviation; SF, seizure frequency; TPM, topiramate; VPA, valproic acid.
* monthly seizure frequency of focal bilateral to tonic-clonic seizures.
**p value < 0.05 for the comparison of the baseline values with the 12-month follow-up values.
*** p-value < 0.05 for the comparison between CNB and other antiseizure medications.
**** p-value < 0.05 for comparison with other ASMs.

values of LCS and LEV.

The domains of the QOLIE-10 that had the best values were "psychological effects of ASM" and "seizure worry".

We assessed the proportion of patients with no problems in the corresponding dimensions of the EQ5D (Fig. 1.). For all ASMs, the most pronounced improvements over a 12-month treatment period were observed in the dimensions "mobility" and "self-care". The least measurable changes were achieved in the dimension "pain/discomfort". The values in the dimension "usual activities" showed a statistically significant improvement with CNB, LCS and LEV but not with other ASM. A deterioration in the dimension "anxiety/depression" was observed with LEV, though this did not reach statistically significant level. In all dimensions of EQ5D, the percentage improvement between baseline and 12-month follow-up was greater with cenobamate than with other ASM.

With regard to concomitant medication, early adjunctive treatment with CNB helped to reduce the drug load by up to 53 % depending on the ASM (Table 2). The most marked dose reduction was observed in CLB followed by sodium channel blockers. The analysis revealed that CLB administered at a low dose (5–10 mg) lead to higher rate of seizure freedom and response rate than with other ASMs ($p > 0.05$). Furthermore, HrQol after 12 months of treatment was higher for the combination of CNB with CLB than for combinations with other ASMs (Table 2). The combination of CNB with SV2A modulators (LEV, BRV) was associated with a higher rate of seizure freedom and response rate than the combination with sodium channel blockers or VPA. However, these findings did not reach a statistically significant level (Table 2).

Multiple regression analysis revealed that the type of ASM initiated after two or three previous ASM had failed, the duration of epilepsy (in years), the number of previous medications, comorbid depression or anxiety and the frequency of focal-to-bilateral tonic-clonic seizures were independent predictors of quality of life, as measured by the EQ-5D index score, EQ-VAS and QOLIE (Table 3). Quality of life deteriorated with a longer duration of epilepsy, an increased number of previous ASMs, the presence of comorbid depression or anxiety, and a higher frequency of focal-to-bilateral tonic-clonic seizures. Other seizure types (focal impaired awareness, focal aware motor and focal aware non-motor) did not independently influence quality of life.

4. Discussion

The use of health-related quality of life as a common measure of patient-reported outcome is of particular significance because it provides the patient's perspective on the assessment of treatment results. It is important to note that the efficacy of ASM, or the achievement of adequate seizure control, does not necessarily translate into an improvement in quality of life [3,4,6]. In the preceding analysis, the efficacy and tolerability of early adjunctive therapy with CNB in difficult-to-treat focal epilepsy were demonstrated [11]. In the present work, it was shown that the administration of CNB in the early therapy lines was associated with better seizure control and a higher HrQoL in comparison with other early adjunctive ASMs. To the best of our knowledge, this is the first study concentrating on HrQoL in the early therapy lines of CNB. Previous studies evaluated HrQoL in patients treated with CNB in more advanced stages of epilepsy. Results from an open-label extension study of placebo-controlled approval studies (YKP3089C013 and YKP3089C017) and an open-label safety study (YKP3089C021), with an observation period of up to eight years, showed that CNB significantly improved the HRQoL of patients, as measured by the QOLIE-31 questionnaire [15]. The HrQoL domains with the best scores in that study were emotional well-being and worry about seizures. These results are similar to those of our study, and are consistent with CNB's high antiseizure potency and the absence of behavioural side effects. Another important finding of the study by Elizebath et al. was that patients with an intellectual disability also experienced an improvement in their HrQoL, demonstrating the positive effects of CNB treatment event in socially vulnerable populations [15]. In contrast, two studies by Catalán-Aguilar et al. from Spain summarized in one publication found no statistically significant effect of CNB on HrQoL [10]. However, there was a trend towards improvement in QOLIE-31 scores, which did not reach the level of significance, probably due to smaller number of patients in both studies (32 and 22 patients). The observation period of three to six months was also shorter than in our study (12 months).

Post-hoc analysis of pooled randomized trials involving a total of 442 participants also documented the low incidence of cognitive or psychiatric treatment-emergent side effects of CNB [16]. In our analysis, we observed an improvement in the "depression and anxiety" domain of the EQ-5D. 12 months post therapy, 83.1 % of patients reported not suffering from depression or anxiety, compared to 46.8 % at baseline.

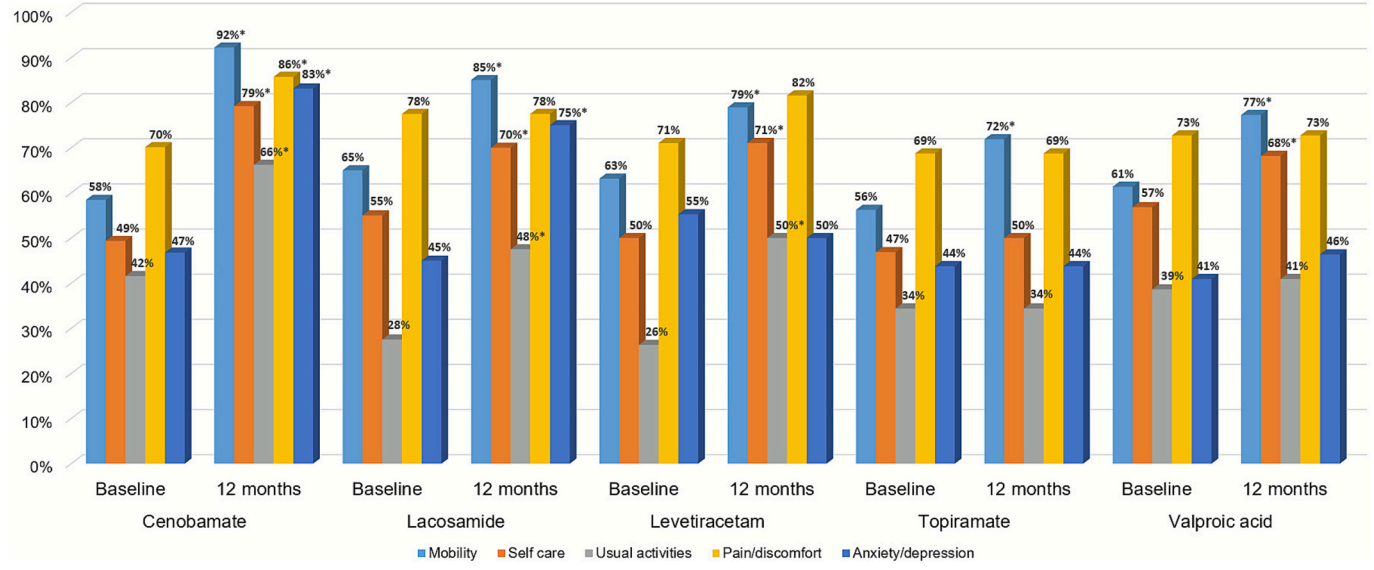

Fig. 1. Proportion of patients with no problems in the corresponding dimensions of the EuroQol-5 Dimension (EQ5D) * p-value < 0.05 for comparison of different dimensions of the ED5D at baseline vs. 12-month follow up.

Table 2
Comparison of drug load, seizure control and HrQoL by concomitant ASM in patients treated with cenobamate.

	Concomitant antiseizure medication in patients treated with cenobamate						
	LEV	**BRV**	**CLB**	**VPA**	**LTG**	**LCS**	**ESL**
N	22	18	15	14	12	9	6
(%)	(28.6)	(23.4)	(19.5)	(18.2)	(15.6)	(11.7)	(7.8)
Dose reduction, mg mean ± SD (median)	56.8 ± 149.5 (0)	9.7 ± 14.8 (0)	11.3 ± 6.9 (15)	200.0 ± 309.4 (0)	70.8 ± 43.1 (50)	83.3 ± 57.7 (100)	266.7 ± 188.6 (400)
DDD reduction, %	2.9	7.6	53.3*	12.3	19.3	23.0	23.4
Seizure freedom, %	22.7	22.2	46.7*	14.3	8.3	12.2	16.7
Response rate, %	77.3	77.8	86.7*	57.1	58.3	66.7	66.7
EQ5D Index, mean ± SD	0.81 ± 0.2	0.82 ± 0.2	0.88 ± 0.2*	0.72 ± 0.2	0.71 ± 0.3	0.76 ± 0.2	0.77 ± 0.2
EQVAS, mean ± SD	80.7 ± 9.1	81.9 ± 8.6	87.0 ± 14.3*	73.7 ± 20.3	74.2 ± 20.0	74.4 ± 16.9	74.2 ± 22.5
QOLIE-10, mean ± SD	18.1 ± 9.0	17.7 ± 8.8	15.7 ± 14.2*	24.0 ± 15.6	26.3 ± 17.0	26.2 ± 13.7	24.2 ± 16.1

Abbreviations: ASM, antiseizure medication; DDD, daily defined dose; HrQoL, health-related quality of life; BRV, brivaracetam; CLB, clobazam; ESL, eslicarbazepine acetate; LCS, lacosamide; LEV, levetiracetam; LTG, lamotrigine; VPA, valproic acid; EQVAS, EuroQol Visual analogue scale; EQ5D, EuroQol-5-Dimensions Questionnaire; HrQoL, Health-related Quality of Life; QOLIE10, Quality of Life in Epilepsy-10; SD, standard deviation
* $p < 0.05$ for comparisons: CNB vs. VPA, LTG, LCS or ESL.

Table 3
Independent determinants of quality of life measures in multiple regression analysis.

	EQ5D Index			**EQVAS**			**QOLIE**		
	B	95 % CI	p-value	B	95 % CI	p-value	B	95 % CI	p-value
Age	0.01	−0.01; 0.02	0.49	0.02	−0.08; 0.12	0.48	−0.02	−0.13; 0.08	0.47
Female gender	0.04	−0.01; 0.09	0.06	2.83	−0.63; 6.30	0.12	−2.49	−5.48; 0.52	0.10
Employment status***	−0.02	−0.04; 0.02	0.42	−0.26	−0.71; 0.34	0.45	0.91	−0.21; 3.02	0.23
ASM**	**−0.04**	**−0.05; −0.02**	**<0.01**	**−2.92**	**−4.24; −1.59**	**<0.01**	**2.11**	**0.96; 3.24**	**<0.01**
ASM dose	**−0.01**	**−0.02; 0.01**	**0.27**	**−0.01**	**−0.01; 0.02**	**0.10**	**0.01**	**−0.01; 0.02**	**0.15**
Epilepsy duration (years)	**−0.02**	**−0.04; −0.01**	**0.04**	**−0.80**	**−1.40; −0.24**	**0.04**	**0.78**	**0.14; 1.32**	**0.04**
Number of previous ASM	**−0.04**	**−0.06; −0.02**	**0.02**	**−3.54**	**−6.87; −1.84**	**0.03**	**1.64**	**1.03; 4.21**	**0.03**
Number of focal to bilateral tonic clonic seizures	**−0.07**	**−0.08; −0.06**	**<0.01**	**−7.81**	**−8.63; −6.94**	**<0.01**	**5.54**	**4.79; 6.31**	**<0.01**
Number of focal impaired awareness	−0.02	−0.04; 0.01	0.07	−0.19	−0.05; 0.44	0.14	0.81	−0.39; 0.23	0.48
Number of focal aware motor	−0.01	−0.02; 0.01	0.46	−0.01	−0.24; 0.44	0.43	0.98	−0.44; 0.26	0.46
Comorbid depression or anxiety	**−0.08**	**−0.12; −0.05**	**<0.01**	**−8.01**	**−9.91; −7.02**	**<0.01**	**6.01**	**4.94; 7.77**	**<0.01**
Adjusted Rb *		0.57			0.67		0.59		

* Total adjusted R^2 for each model.
**CNB = 1, LCS = 2, LEV = 3, VPA = 4, TPM = 5.
*** employed was coded as 1 and unemployed as 0 in this analysis.
Abbreviations: B, regression coefficient; CI, confidence interval; ASM, antiseizure medication

Similar to the results of previous studies [17–19], CNB treatment in our study was associated with reduction of drug load. The interim analysis of an ongoing multicenter study of 50 centers in Italy (The BLESS Study) showed that the proportion of patients treated with > 2 concomitant ASMs decreased from 52.5 % to 40.0 % after initiating the CNB treatment [18]. Another study from Spain showed that reduction of drug load following the initiation of CNB treatment can lead to improvement of cognitive function [20].

The synergistic combination of CNB with other anti-seizure medication (ASMs) is an important aspect of managing difficult-to-treat epilepsy. Interestingly, independent studies from different countries have reported higher percentages of responders to the combination of CNB and CLB[19,21]. Our study also confirms this observation. Despite reducing the CLB dose by more than 50 %, the combination of CNB and low-dose CLB resulted in a significantly higher percentage of seizure-free patients and a higher response rate than combinations with VPA, LTG, LCS, or ESL. Low-dose CLB is well tolerated by patients taking CNB and exhibits a synergistic effect. Seizure control can even deteriorate if CLB is withdrawn from the combination with CNB [21]. Interestingly, combination of CNB and CLB might be particularly effective in autoimmune-associated epilepsy with antiglutamic acid decarboxylase 65 (GAD65) antibodies [22]. The combination of CNB and SV2A modulators showed a trend to be more effective than the combination of CNB and VPA, LTG, LCS, or ESL, though these results were not statistically significant.

In our study population, sodium channel blockers and GABAergic medications were reduced, while SV2A modulators remained largely unchanged. This finding is consistent with those of other studies [23,24], which demonstrate good tolerance of CNB with SV2A modulators. The dose adjustments of sodium channel blockers and GABAergic medications were consistent with the international recommendations for managing concomitant medications in patients with CNB [25–27]. There is also a recent report on the possible synergistic combination of CNB and perampanel [28]. However, none of our patients were taking perampanel. A recent study from Belgium demonstrated that add-on therapy with CNB in patients with vagus nerve stimulation can improve response rate by 20 % and results in seizure freedom in 11 % of patients. Synergistic combinations of ASM with neuromodulation are important to improve outcomes and HrQoL not only in vagus nerve stimulation but also in new neuromodulative approaches [29–32].

The participants of our study represent adult subjects diagnosed with focal onset seizures who have received treatment in a real-world setting. Consequently, the results of this study can be generalized to this population, and CNB can be considered in early therapy lines in this setting. CNB is not approved for epilepsies with generalized onset seizures or for children with epilepsy, and the results of this study cannot be generalized to these populations.

This study has the limitations inherent to observational designs and lack of randomization. Possible investigator bias cannot be ruled out. Due to cenobamate's approval status in Europe, we could not examine add-on therapy following the failure of one ASM and had to concentrate on the failure of two or three therapeutic attempts. Furthermore, the

decision was taken not to include more recent comparator agents, such as brivaracetam or perampanel, in the present study. This was due to the comparatively lower number of patients who initiated these ASMs as early lines of therapy in our database. The subsequent 12-month period does not yield any additional insights beyond the current time point. The patient's self-reported outcomes, such as health-related quality of life (HrQoL) measures, are susceptible to potential bias. Our study did not address the role of cultural differences between countries on quality of life; however, we focused on health-related quality of life, which is less influenced by regional and cultural differences.

In conclusion, our study provides evidence that, for patients with difficult-to-treat epilepsy and focal-onset seizures, CNB in early therapy lines is associated with increased HrQoL. Synergistic combinations of CNB with other ASMs should be considered when searching for the most effective treatment strategies. According to our findings, low-dose CLB have the potential to be combined synergistically with CNB. The combination with SV2A modulators showed a positive trend and should be evaluated in future studies.

CRediT authorship contribution statement

Yaroslav Winter: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Raya Abou Dargham:** Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Erik Ellwardt:** Writing – review & editing, Validation, Supervision. **Thilo Hammen:** Writing – review & editing, Validation, Supervision. **Christoph Massing:** Writing – review & editing, Validation, Supervision. **Sarah Gößling:** Writing – review & editing, Validation, Supervision. **Marina Flotats-Bastardas:** Writing – review & editing, Validation, Supervision. **Sergiu Groppa:** Writing – review & editing, Validation, Supervision, Conceptualization. **Michael Zemlin:** Writing – review & editing, Validation, Supervision. **Christopher Meudt:** Writing – review & editing, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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