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ORIGINAL RESEARCH ARTICLE

Cenobamate as an Early Adjunctive Treatment in Drug-Resistant Focal-Onset Seizures: An Observational Cohort Study

Yaroslav Winter[1,2] · Raya Abou Dargham[1] · Susana Patiño Tobón[1] · Sergiu Groppa[3] · Sven Fuest[4]

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Abstract

Background and Objectives Cenobamate (CNB) is a new antiseizure medication (ASM) to treat drug-resistant, focal-onset seizures. Data on its use in early therapy lines are not yet available, and clinicians frequently consider CNB to be a later ASM drug choice. We investigated the efficacy and safety of CNB as an early adjunctive treatment in drug-resistant, focal-onset seizures.

Methods The study population were patients with drug-resistant, focal-onset seizures who were initiated with CNB after they did not respond to two or three lifetime ASMs, including all prior and concomitant ASMs. These patients were matched (1:2) by sex, age, and seizure frequency to controls who were initiated with any ASM other than CNB. All participants participated in the Mainz Epilepsy Registry. We evaluated the retention rate after 12 months of CNB and after each new adjunctive ASM in the control group. In addition, seizure freedom and the response rate (reduction of seizure frequency by $\geq 50\%$ from baseline) after 12 months were estimated.

Results We included 231 patients aged 44.4 ± 15.8 years. Of these, 33.3% ($n = 77$) were on CNB, 19.0% ($n = 44$) on valproate (VPA), 17.3% ($n = 40$) on lacosamide (LCS), 16.4% ($n = 38$) on levetiracetam (LEV), and 13.9% ($n = 32$) on topiramate (TPM). The highest retention rate after 12 months since the beginning of the early adjunctive therapy was observed on CNB (92.0%), compared with LCS (80.0%), LEV (73.3%), VPA (68.2%), or TPM (62.5%) ($p < 0.05$). Seizure freedom and response rate were also the best on CNB (19.5% and 71.4%, respectively) compared with other ASMs (8.3% and 52.5%, respectively; $p < 0.05$). No significant differences in adverse events between CNB and other ASMs were observed.

Conclusions Our study provides evidence that CNB is an effective ASM with a good safety profile in the early therapy lines of drug-resistant, focal-onset seizures. This data should support medical decision making in the management of patients with refractory epilepsy.

Clinical Trial ID NCT05267405.

1 Introduction

Epilepsy is one of the most prevalent neurological disorders across all age groups. Despite the development of multiple antiseizure medications (ASMs) and non-pharmaceutical treatments over the last few decades [1], at least 30% of patients continue to suffer from refractory epilepsy [2]. Therefore, the development of novel ASMs with the focus on the treatment of refractory epilepsy would give the patients a new hope for a better quality of life and to help to decrease the social, health, and economical burdens from this severe type of epilepsy.

Cenobamate (CNB) is a novel tetrazole-derived carbamate, which was approved in 2019 by the US Food and Drug Administration (FDA) to treat uncontrolled partial-onset seizures in adult patients, and in March 2021 by the European Medicines Agency (EMA) for the adjunctive treatment of drug-resistant, focal-onset seizures in adults. Its dual mechanism of action includes an inhibition of the persistent voltage gated sodium current and an allosteric regulation of GABA-A receptors [3–5].

Owing to the rare cases of drug reaction with eosinophilia and systemic symptoms (DRESS), the global safety study (C021) on CNB was performed and proved its improved safety profile when administrated in a graduated titration scheme. Despite this solid and reliable data from one of the largest safety studies in the history of ASMs, many neurologists are still unsure of and reluctant to prescribe CNB, keeping it reserved for the advanced stages of refractory epilepsy. However, these therapeutic strategies are challenged by the high percentage of seizure freedom (21–28%) and reduction

Extended author information available on the last page of the article

Key Points

Cenobamate is approved to treat refractory focal onset seizures and is usually considered by clinicians in the later therapy lines.

We provide the first data on the use of cenobamate in early therapy lines to treat refractory focal onset seizures.

In early therapy lines, cenobamate had the highest retention rate compared with lacosamide, levetiracetam, valproate, and topiramate.

Seizure freedom and response rate were also the best on cenobamate.

No significant differences in adverse events between cenobamate and other antiseizure medications were observed.

of seizure frequency by approximately 55% shown in the approval trials (C013 and C017), making it meaningful to consider CNB as an early adjunctive therapy [6–8]. These data are supported by the results of post-approval real world study of Beltrán-Corbellini et al. showing high retentions rates of 80.4% after 6 months of treatment with CNB [9]. The median number of ASMs administered prior to initiation of CNB was 10, indicating that CNB is currently considered in later lines of ASM therapy. Villanueva et al. showed retention rate of 87% after 12 months while the median number of prior ASMs was 12 [10]. One of the reasons for the delay in early use of CNB is concerns about possible negative cognitive effects and high levels of interaction. These concerns are countered by data from recent studies showing improvement in cognitive function in patients receiving CNB owing to a reduction in pharmacological load [11].

Unfortunately, data on the administration of CNB as an early adjunctive treatment in refractory epilepsy in comparison to other ASMs are scarce. The objective of this observational study was to evaluate the safety and efficacy of CNB in routine clinical practice as measured by the 12-month retention rate in the early therapy lines of drug-resistant focal-onset seizures.

2 Methods

2.1 Study Design and Clinical Evaluation

All participants of the study were patients with drug-resistant epilepsy according to the definition of the International League Against Epilepsy (ILAE) [2]. They were all treated at the Mainz Comprehensive Epilepsy and Sleep Medicine Center, which is integrated into the Department of Neurology of the University Medical Center of the Johannes Gutenberg University Mainz. The clinical and demographic data was acquired from the Mainz Epilepsy Registry (MAINZ-EPIREG). The MAINZ-EPIREG is an ongoing observational cohort study focused on the evaluation of the disease course of patients with epilepsy.

The study population comprised patients with drug-resistant, focal-onset seizures who were initiated with adjunctive CNB after they did not respond to an adequate trial of two or three ASMs, including all prior and concomitant ASMs (defined for study purposes as “early adjunctive treatment”). Patients fulfilling this definition of early adjunctive treatment were selected from MAINZ-EPIREG. Benzodiazepines used short term as rescue medications were not considered as an adequate trial of ASM. Based on MAINZ-EPIREG, patients with early adjunctive treatment of CNB were matched (1:2) by sex, age, and types and frequency of seizures to patients (controls) who did not respond to two or three prior ASM and initiated with any other adjunctive ASM than CNB. Owing to the observational design of the study, the choice of medical treatment was made independently by the treating physician in the regular course of practice and was not influenced by participation in the study. The median ASM doses reported in the results were achieved after the dose titration phase according to the manufacturers' recommendations. A standard dosage regimen of CNB following the graduated titration scheme as recommended by the drug manufacturer was used: starting with the lowest daily dose of 12.5 mg and increasing the daily dose to 25 mg, 50 mg, and 100 mg at weeks 3, 5, and 7, respectively. Further increases by 50 mg every 2 weeks until a maximum approved dose of 400 mg were permitted after that. The exclusion criteria were: age less than 18 years, primary generalized seizures, participation in other clinical trials, and a refusal to provide informed consent for participation. Patients who were pregnant or breastfeeding and those with prior DRESS were excluded. No adjunctive bitherapies were employed in study participants. The following ASMs were chosen as comparators in the control group: lacosamide (LCS), levetiracetam (LEV), topiramate (TPM), and valproate (VPA). This choice was based on the statistics of the prescriptions at the Mainz Comprehensive Epilepsy and Sleep Medicine Center to build sufficiently large groups for comparisons (at least 30 patients in each ASM group). In addition, patients taking the following ASM were participating in other on-going trials during the period of the current study and were, therefore, not available: perampanel (PER), brivaracetam (BRV), eslicarbazepine acetate (ESL), and lamotrigine (LTG). To represent these ASM in our analysis despite the small number of available patients, we sorted them according to the mechanism of action in our plausibility analysis.

The primary outcome point was the 12-months retention rate. The study was powered (80%, one-sided test) to show the difference in retention rates of at least 10%. In addition, the efficacy was measured as reduction in the seizure frequency (number of seizures per month as a mean of the preceding 6-month period) at 12 months in comparison with baseline (≥ 50%, ≥ 75%, and 100% response rates). The baseline was defined as the visit on the day before the start of adjunctive treatment with CNB or a comparator ASM in the control group. The data on adverse effects were collected from patient diaries and standardized case report forms used during the observation period.

Seizures were stratified into different subtypes including focal to bilateral tonic-clonic seizures (FBTCS), focal aware motor seizures, focal aware nonmotor seizures, and focal impaired awareness seizures. Seizures were classified according to ILAE 2017 classification criteria [12].

To analyze whether ASMs are used in equivalent doses, the defined daily dose (DDD) was calculated according to the World Health Organization (WHO) methodology. For each ASM, the ratio of the individually administered daily dose to the DDD was calculated. The ratios for each ASM in a patient's therapy were summed to determine the measure of drug load for each individual patient [13].

All participants signed informed consent to participate. The ethic approval was received from the local ethics committee, and this register-based study was registered at ClinicalTrials.gov (NCT05267405).

2.2 Statistics

IBM SPSS Statistics Version 23.0 (IBM Corp., Armonk, NY, USA) was applied for statistical analysis. Collected data are represented as mean, standard deviation (SD), and range. Normally distributed variables were compared using *t*-tests. For not normally distributed data, the Kruskal–Wallis test (for more than two independent groups), the Mann–Whitney *U*-test (two independent groups), or the Wilcoxon rank test (two dependent groups) were performed. Statistical significance was considered at a p-value < 0.05. The 12-month retention rate and response rates were compared by means of analysis of variance (ANOVA).

3 Results

A total of 231 patients (77 on CNB and 154 controls) were included. The control population consisted of patients on adjunctive therapy with another ASM (LCS, LEV, TPM, or VPA) other than CNB. Demographics and clinical characteristics of the treatment groups were taken at baseline (Table 1). The median dose (range) of CNB was 200 mg/d (50–400 mg/d), LCS was 300 mg/d (100–600 mg/d), LEV was 2000 mg/d (1000–4000 mg/d), TPM was 300 mg/d (100–600 mg/d), and VPA was 2000 mg/d (900–4800 mg/d). CNB, LCS, and TPM were administered at a ratio of 1.0 to the DDD, while LEV and VPA were administered at a ratio of 1.3 to the DDD. The drug load at baseline did not show significant differences between the ASM groups (CNB: 1.7 ± 0.3; LCS: 1.6 ± 0.2, LEV: 1.8 ± 0.4, TPM: 1.7 ± 0.4, and VPA: 1.6 ± 0.3). After 12 months, adjunctive therapy with CNB or LCS resulted in a significant reduction in drug load of approximately 21–24% (CNB: −0.4 ± 0.2; LCS: −0.3 ± 0.3, $p < 0.05$), while other ASMs showed no significant effect in reducing drug load.

The highest 12-months retention rate was observed on CNB (92.0%, $p < 0.05$ compared with all other ASMs), followed by LCS (80.0%), LEV (73.3%), VPA (68.2%), and TPM (62.5%) (Fig. 1A). The plausibility analysis included the following groups of mechanisms of action: dual mechanism of action (CNB acting as a sodium channel blocker and GABA-ergic ASM, $n = 77$), slow inactivation of sodium channels (LCS, $n = 40$; ESL, $n = 21$); fast inactivation of sodium channels (LTG, $n = 16$; oxcarbazepine, $n = 2$); SV2A modulators (LEV, $n = 38$; BRV, $n = 17$); AMPA antagonist (PER, $n = 19$); multiple pharmacological targets (VPA, $n = 44$), and carbonic anhydrase inhibition (TPM, $n = 32$). Again, the highest 12-month retention rate was observed for the dual mechanism of action of CNB compared with other mechanisms of action (Fig. 1B).

CNB showed the highest responder rate (≥ 50% reduction of seizures) of 71% for all types of seizures compared with other groups of ASM ($p < 0.05$, Fig. 2). Seizure freedom was achieved by 20% of patients on CNB, which was significantly higher than in patients on LCS, LEV, and TPM ($p < 0.05$; Fig. 2), but not in comparison with VPA.

The responder rates and seizure freedom in different types of seizures (FBTCS, focal aware motor, focal aware nonmotor and focal impaired awareness) are displayed in Fig. 3. The best efficacy of CNB was observed in FBTCS with a responder rate (≥ 50% reduction of seizures) of 73% and seizure freedom of 20%, which were significantly higher compared with all other groups of ASMs ($p < 0.05$). A similar responder rate and seizure freedom were achieved in patients with focal impaired awareness seizures on CNB. However, seizure freedom for this type of seizures was not significantly different from VPA. In focal aware motor and nonmotor seizures, the responder rate (≥ 50% reduction of seizures) on CNB was significantly higher (67–81%) only in comparison with LCS (40–56%) ($p < 0.05$; Fig. 3). In addition, seizure freedom in patients with focal aware motor seizures was significantly higher on CNB than in other groups of ASM ($p < 0.05$).

The most commonly reported adverse effects under CNB therapy, as with the other evaluated ASMs, were somnolence (24.7–26.3%), dizziness (22.7-25.0%), and fatigue

Table 1 Baseline data on demographics and clinical characteristics

Clinical parameters	CNB ($n = 77$)	LCS ($n = 40$)	LEV ($n = 38$)	TPM ($n = 32$)	VPA ($n = 44$)
Age, years					
Mean ± SD (range)	44.2 ± 16.4 (19–42)	44.1 ± 17.0 (18–75)	44.4 ± 17.2 (19–75)	45.0 ± 14.9 (19–70)	45.1 ± 15.6 (21–69)
Sex, *n* (%)					
Male	42 (54.5%)	43 (55.8%)	41 (53.2%)	44 (57.1%)	40 (51.9%)
Female	35 (45.5%)	34 (44.2%)	36 (46.8%)	33 (42.9%)	37 (48.1%)
Duration of epilepsy, years					
Mean ± SD (range)	4.8± 1.4 (3.0–7.0)	5.2± 1.4 (3.0–7.0)	5.1 ± 1.5 (3.0–7.0)	4.9 ± 1.5 (3.0–7.0)	4.9± 1.5 (3.0–7.0)
Number of prior ASMs					
Mean ± SD (range)	2.5 ± 0.5 (2.0–3.0)	2.4 ± 0.5 (2.0–3.0)	2.5 ± 0.5 (2.0–3.0)	2.6 ± 0.5 (2.0–3.0)	2.4 ± 0.5 (2.0–3.0)
Number of concomitant ASMs					
Mean ± SD (range)	1.6± 0.6 (1.0–2.0)	1.6 ± 0.4 (1.0–2.0)	1.6 ± 0.7 (1.0–2.0)	1.7 ± 0.6 (1.0–2.0)	1.6 ± 0.5 (1.0–2.0)
Dose in mg					
Mean ± SD (mode/range)	216.9 ± 90.5 (200/ 50–400)	312.5 ± 126.4 (300/ 100–600)	2263.2 ± 852.1 (2000/ 1000–4000)	340.6 ± 129.2 (300/ 100–600)	2438.6 ± 1249.4 (2000/ 900–4800)
SSF by seizure type, mean ± SD (range)					
Focal bilateral to tonic-clonic seizures	3.0 ± 3.2 (0–18)	2.8 ± 3.3 (0–16)	2.9 ± 3.5 (0–17)	3.0 ± 3.6 (0–17)	2.8 ± 3.5 (0–18)
Focal impaired awareness	7.6 ± 6.9 (0–30)	7.4 ± 7.6 (0–34)	7.8 ± 7.5 (0–33)	7.5 ± 7.8 (0–34)	7.7 ± 8.2 (0–32)
Focal aware motor	3.1 ± 7.6 (0–32)	3.3 ± 8.1 (0–34)	3.2 ± 7.8 (0–28)	3.1 ± 7.3 (0–28)	3.0 ± 7.1 (0–29)
Focal aware nonmotor	3.8 ± 8.3 (0–33)	4.6 ± 9.8 (0–36)	3.3 ± 7.6 (0–30)	3.2 ± 8.0 (0–32)	3.7 ± 8.7 (0–34)

ASM, anti-seizure medication; CNB cenobamate; LCS lacosamide; LEV levetiracetam; TPM topiramate; VPA valproate; SD, standard deviation; SSF, standardized seizure frequency (per month)

(21.9–23.4%) (Table 2). Weight loss (28.1%) was one of the most reported side effects with TPM. Weight gain (27.3%) was only commonly reported under therapy with VPA. Irritability was reported in 13.2% of patients on LEV (Table 2). There were no serious side effects and none of the patients discontinued adjunctive therapy.

4 Discussion

Retention rates are an established compound measurement of tolerability, safety profile, and efficacy that could guide clinical therapy choices [6, 14–16]. Although randomized control trials are an essential steppingstone in establishing the safety and efficacy of drugs, shorter time frames and inflexible dosage regimens provide results that sometimes may not be extrapolated to the everyday clinical setting. This study showcases retention rate data from patients who received CNB early on in treatment within a real-life clinical context, where patients were given the therapy as early as permitted by authorization criteria (median number of prior administered ASMs was two). Furthermore, to our knowledge, there are no studies directly comparing the efficacy of CNB with other adjunctive therapies in a clinical setting. Privitera et al. put forth an indirect treatment comparison between adjunctive CNB therapy and seven other ASMs [17]. However, comparisons between retention rates or seizure freedom rates were not feasible owing to disparities in the analyzed study designs and endpoints of the studies included in the review [17]. The high retention rates demonstrated on CNB therapy (92.0%, $p < 0.05$) compared with control ASMs in this cohort, observational study indicate that CNB is a clinically effective and well tolerated early add on adjunctive therapy for the treatment of drug-resistant focal-onset seizures (Fig. 1). The obtained results are comparable to those published by Sander et al. in the analyses of

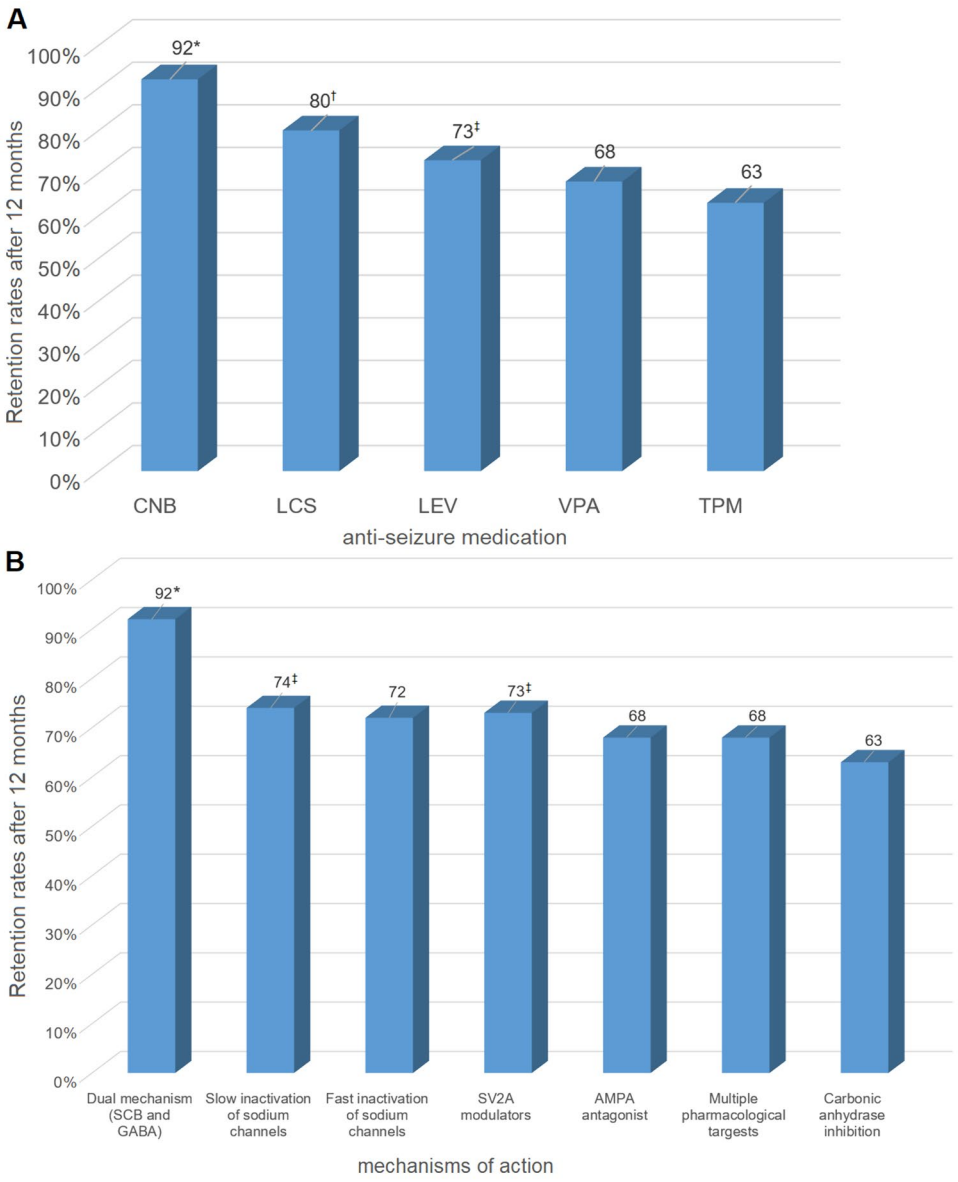

Fig. 1 12-month retention rates (%) across treatment groups. **A** *12-month retention rate of CNB was at $p < 0.05$ higher compared with LCS, LEV, TPM, or VPA. †12-month retention rate of LCS was at $p < 0.05$ higher compared with TPM, or VPA. ‡12-month retention rate of LEV was at $p < 0.05$ higher compared with TPM. **B** *12-month retention rate of dual mechanism of action (SCB and GABAergic) was at $p < 0.05$ higher compared with other mechanisms of action. ‡12-month retention rate of slow inactivators of sodium channels and SV2A modulators was at $p < 0.05$ higher compared with carbonic anhydrase inhibition. Abbreviations: CNB, cenobamate, LCS, lacosamide; LEV, levetiracetam; SCB, sodium channel blocker; TPM, topiramate; VPA, valproate

pooled data from two randomized controlled trials (RCTs) (C013 and C017 studies), as well as the open label safety study C021, where the cumulative retention rates were estimated at 71–92% on CNB doses ≥ 100 mg/day in the first 12 months [18]. The importance of this early adjunctive therapy study relies on confirming the retention rate data on CNB coming from trials with such rigid protocols in a more realistic clinical setting with a focus on patients who were initiated on the drug as an early add on (median of two lifetime drugs). Retention rates of the control adjunctive therapies were also in keeping with data from previous studies. Pooled data from the extension studies using adjunctive therapy with LCS showed 12-month retention rates between 74 and 76% [19]. Another open label extension (OLE) study reported a 1-year retention rate of 71% with TPM [20]. Analysis of results from the developmental program of LEV showed an estimated 1-year continuation rate of 60% [21].

The plausibility proof was carried out for the mechanisms of action and was able to replicate the comparison between the individual ASMs. In fact, the dual mechanism of action of CNB (sodium channel blocker and GABAergic activity) showed a better retention rate than other mechanisms of action. This is important information for the future development of ASMs.

Considering all seizure subtypes, the current data shows substantially higher ≥ 50% and ≥ 75% responder rates at 12-months for patients on CNB versus control ASMs (Fig. 2). Findings published by Klein et al. from the OLE trial for patients on CNB who completed the 18-week dose dependent RCT (C017 study) reported similar rates (76.4% and 51.8% for ≥ 50% and ≥ 75% reduction in seizure

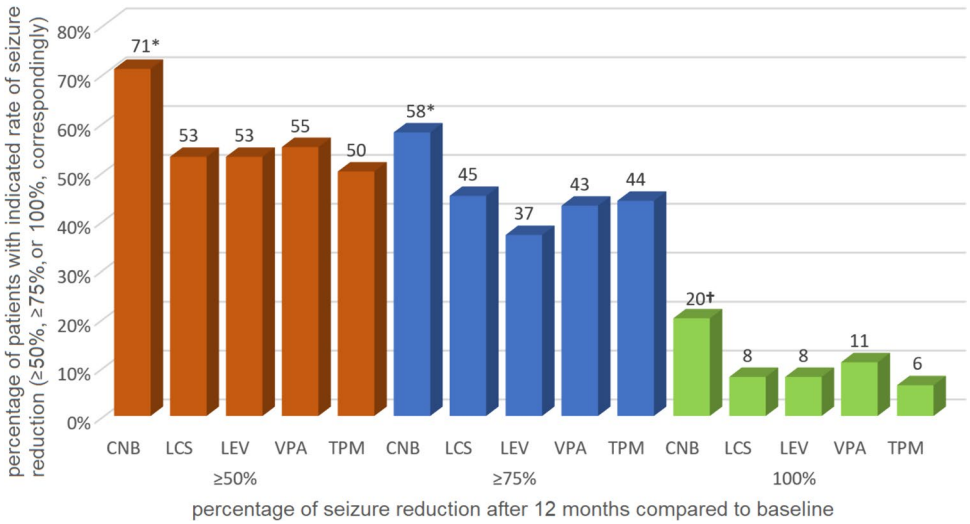

Fig. 2 Responder rates (%) after 12 months for all subtypes of seizures. Responder rates related to the percentage of patients reaching 50% or more, 75% or more, and 100% reduction in seizure frequency after 12 months in comparison with baseline. *Statistically significantly higher at $p < 0.05$ for the comparison of CNB with LCS, LEV, VPA, or TPM. †Statistically significantly higher at $p < 0.05$ for the comparison of CNB with LCS, LEV, or TPM. Abbreviations: CNB, cenobamate; LCS, lacosamide; LEV, levetiracetam; TPM, topiramate; VPA, valproate

frequency, respectively) for a duration of > 36–48 months [7], confirming our results and suggesting that these rates may be valid for much longer durations. Moreover, almost 20% ($p < 0.05$) of patients achieved seizure freedom with CNB, a rate significantly higher than that seen with LCS, LEV, and TPM for all types of seizure subtypes (Fig. 2). In the C017 study, albeit on the highest dose of CNB (400 mg), as well as in the C013 study, seizure freedom was similarly reported in 21% and 28% of patients, respectively [22, 23]. In our study, CNB was administered at a ratio of 1.0 to DDD. None of the other ASMs were used at a dose below a ratio of 1.0 to DDD.

Furthermore, we found a statistically significant reduction in seizure frequency across all measured response rates in patients on CNB therapy with FBTCS, the most life-threatening seizure subtype (Fig. 3A) [24, 25]. This is of great consequence considering the global burden of epilepsy resulting from repeating traumas/injuries, psychological and economic repercussions related to the disease, as well as the reduced life expectancy posed by symptomatic epilepsy [26–29]. The earlier administration of an efficacious ASM therapy in patients with this subtype of seizure would be advantageous considering the evidence from previous studies showing worse outcomes for achieving seizure freedom in patients with FBTCS compared with other seizure subtypes [30, 31].

It is important to note that seizure freedom was also reported in 20% ($p < 0.05$ in comparison to all ASMs except VPA) of patients with focal impaired awareness seizures, where the mean seizure frequency was 7.6 seizures per month, a rate significantly higher than in the other seizure subtype groups. In agreement with this finding, a recent report by Aboumatar et al. has also shown that CNB was efficacious irrespective of baseline seizure frequency [32]. Another report by Rosenfeld et al., wherein the effects of baseline clinical features on efficacy of add on CNB therapy were evaluated, showed that a significant reduction in seizure frequency was achievable with CNB therapy irrespective of the number of concomitant ASMs, duration of epilepsy, and frequency of seizures at baseline [33]. A longitudinal observational cohort study from the epilepsy unit of the Western Infirmary in Glasgow, Scotland also highlighted the decreased chances of seizure freedom with every subsequent failed ASM [34]. In the abovementioned study, only a 4.1% probability of seizure freedom was estimated with the third ASM [34]. All of this emphasizes the importance of utilizing CNB as an early add on therapy to ensure better therapeutic outcomes.

Events of idiosyncratic cutaneous adverse reactions have previously been reported with the use of alkyl-carbamates [35] and other ASMs [36]. In the C017 RCT, one case of DRESS was reported among the patients who were on the fast titration regimen with CNB [22]. Three other cases of DRESS have been identified in the early developmental phase of the medication [8, 37]. No cases of DRESS were reported in this study for patients on CNB over the period of 12 months. Likewise, information on long term safety from the C013 and C017 OLE trials, as well as from the C021 safety study, show no events of DRESS [6–8]. It is worth noting that lamotrigine, one of the ASMs associated with a higher risk of adverse cutaneous reactions [38], remains one of the widely prescribed medications for epilepsy, mood stabilization, and neuralgia. The most frequently reported adverse effects in this study included somnolence, dizziness, and fatigue. These are consistent with the side effects reported in previous

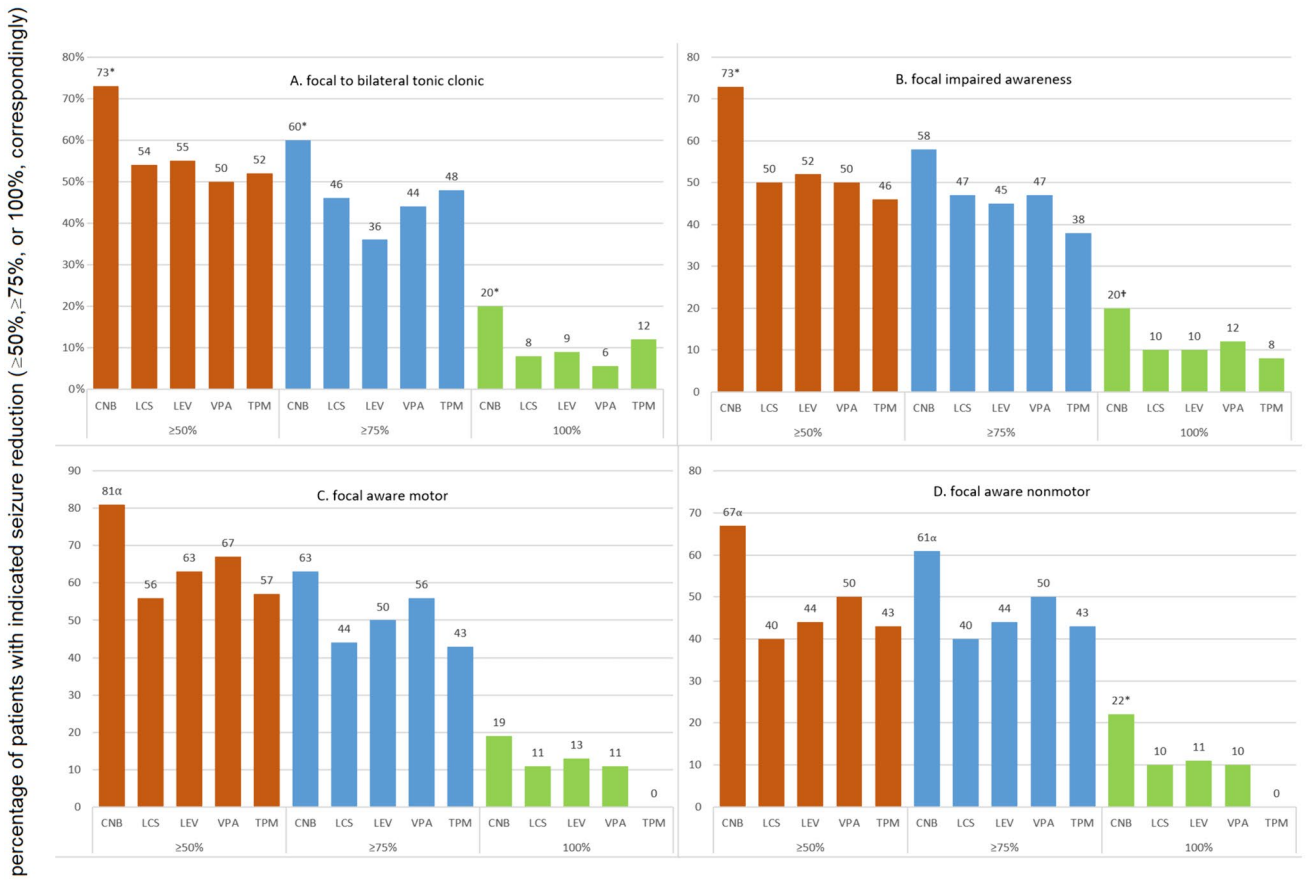

Fig. 3 Responder rates (%) after 12 months among different seizure subtypes. Responder rates related to the percentage of patients reaching 50% or more, 75% or more, and 100% reduction in seizure frequency after 12 months in comparison with baseline. *Significantly higher at $p < 0.05$ in comparison with LCS, LEV, VPA, and TPM. †Significantly higher at $p < 0.05$ in comparison with LCS, LEV, and TPM. ᵅSignificantly higher at $p < 0.05$ in comparison with LCS. Abbreviations: CNB, cenobamate; LCS, lacosamide; LEV, levetiracetam; TPM, topiramate; VPA, valproate

Table 2 Adverse side effects*

Adverse side effects	CNB	LCS	LEV	TPM	VPA
Somnolence	19 (24.7)	10 (25.0)	10 (26.3)	9 (28.1)	11 (25.0)
Dizziness	18 (23.4)	10 (25.0)	9 (23.7)	7 (21.9)	10 (22.7)
Headache	8 (10.4)	5 (12.5)	4 (10.5)	2 (6.3)	4 (9.1)
Nausea	9 (11.7)	5 (12.5)	4 (10.5)	4 (12.5)	5 (11.4)
Fatigue	18 (23.4)	9 (22.5)	9 (23.7)	7 (21.9)	10 (22.7)
Tremor	0 (0)	1 (2.5)	0 (0)	0 (0)	7 (15.9)†
Weight gain	0 (0)	0 (0)	0 (0)	0 (0)	12 (27.3)†
Weight loss	3 (3.9)	0 (0)	0 (0)	9 (28.1)†	0 (0)
Irritability	0 (0)	0 (0)	5 (13.2)†	0 (0)	0 (0)

ASM, anti-seizure medication; CNB cenobamate; LCS lacosamide; LEV levetiracetam; TPM topiramate; VPA valproate

*Data are presented as *n* (%)

†Significantly higher at $p < 0.05$ in comparison to other groups of ASM

studies using CNB [7, 8, 22, 23], and are comparable to adverse side effects described with other ASMs [3, 36, 39–42]. Provided the thus far non-alarming safety profile and robust seizure control with CNB, clinicians can be encouraged to consider administration of this ASM in the early adjunctive therapy of drug-resistant focal-onset seizures.

The reduction of drug load after the initiation of CNB therapy was similar to that calculated in the study by Aboumatar et al. [13]. In contrast to our study, Aboumatar et al. started CNB in later therapy lines with a higher drug load than in our study (3.57 versus 1.7). Interestingly, this effect in reducing drug burden was observed not only in advanced polytherapy but also in early lines of therapy, as our results show. The reduction of drug load is one of the factors that improve patients' cognitive performance, which was demonstrated in the study by Serrano-Castro et al. after the start of CNB therapy [11].

Among the limitations of this study are those inherent to observational study design. In contrast to the RCT, possible investigator bias cannot be excluded. Another limitation is that only LCS, LEV, TPM, and VPA could be included as comparators owing to the ongoing studies with other ASMs in our center. Although in Europe only CNB has specific approval for the treatment of drug-resistant seizures, the use of other ASMs that served as comparator drugs in our study is appropriate for this indication [43]. Women of childbearing potential were underrepresented among patients treated with valproate owing to its teratogenicity. Patients with topiramate were underrepresented because it is used less frequently owing to its cognitive side effects.

5 Conclusions

The results of this study based on real-life data showed that CNB is an effective ASM with a good safety profile in the early therapy lines of drug-resistant, focal-onset seizures. The 12-months retention rate was higher than on LCS, LEV, TPM, or VPA. This data should support medical decision making in the management of patients with refractory epilepsy.

Declarations

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Conflict of Interest Y.W. reports honoraria for educational presentations and consultations from Axsome Therapeutics, Bayer AG, BIAL, Eisai, LivaNova, Novartis, and UCB Pharma. S.F. received honoraria for educational presentations and consultations from Eisai. S.G. received compensation for professional services from Abbott, Abbvie, Bial, Medtronic, UCB, and Zambon; and research grants from Abbott, Boston Scientific, MagVenture, German Research Council, and German Ministry of Education and Health. R.A.D. and S.P.T. declare no conflicts of interest.

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Consent to Participate All patients signed informed consent for participation in this study.

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

Code Availability Not applicable.

Authors' Contributions Y.W. conceptualized the study and carried out the methodology, validation, formal analysis, investigation, resources, data curation, writing—review and editing, visualization, and supervision; R.A.D. conceptualized the study and performed project administration, validation, investigation, resources, writing—original draft, and writing—review and editing; S.P.T. performed project administration, data curation, and writing—review and editing; S.G. carried out visualization, and writing—review & editing; S.F. conceptualized the study and carried out writing—review and editing, supervision, and project administration. All authors have read and approve the final manuscript and agree to be accountable for the work.

References

1. Schulze-Bonhage A, Hirsch M, Knake S, Kaufmann E, Kegele J, Rademacher M, et al. Focal cortex stimulation with a novel implantable device and antiseizure outcomes in 2 prospective multicenter single-arm trials. JAMA Neurol. 2023;80(6):588–96.
2. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069–77.
3. Löscher W, Klein P. The pharmacology and clinical efficacy of antiseizure medications: from bromide salts to cenobamate and beyond. CNS Drugs. 2021;35(9):935–63.
4. Nakamura M, Cho JH, Shin H, Jang IS. Effects of cenobamate (YKP3089), a newly developed anti-epileptic drug, on

voltage-gated sodium channels in rat hippocampal CA3 neurons. Eur J Pharmacol. 2019;15(855):175–82.
5. Perucca E, Bialer M, White HS. New GABA-targeting therapies for the treatment of seizures and epilepsy: I. role of GABA as a modulator of seizure activity and recently approved medications acting on the GABA system. CNS Drugs. 2023;37(9):755–79.
6. French JA, Chung SS, Krauss GL, Lee SK, Maciejowski M, Rosenfeld WE, et al. Long-term safety of adjunctive cenobamate in patients with uncontrolled focal seizures: open-label extension of a randomized clinical study. Epilepsia. 2021;62(9):2142–50.
7. Klein P, Aboumatar S, Brandt C, Dong F, Krauss GL, Mizne S, et al. Long-term efficacy and safety from an open-label extension of adjunctive cenobamate in patients with uncontrolled focal seizures. Neurology. 2022;99(10):e989–98.
8. Sperling MR, Klein P, Aboumatar S, Gelfand M, Halford JJ, Krauss GL, et al. Cenobamate (YKP3089) as adjunctive treatment for uncontrolled focal seizures in a large, phase 3, multicenter, open-label safety study. Epilepsia. 2020;61(6):1099–108.
9. Beltrán-Corbellini Á, Romeral-Jiménez M, Mayo P, Sánchez-Miranda Román I, Iruzubieta P, Chico-García JL, et al. Cenobamate in patients with highly refractory focal epilepsy: a retrospective real-world study. Seizure. 2023;111:71–7.
10. Villanueva V, Santos-Carrasco D, Cabezudo-García P, Gómez-Ibáñez A, Garcés M, Serrano-Castro P, et al. Real-world safety and effectiveness of cenobamate in patients with focal onset seizures: outcomes from an Expanded Access Program. Epilepsia Open. 2023;8(3):918–29.
11. Serrano-Castro PJ, Ramírez-García T, Cabezudo-Garcia P, Garcia-Martin G, De La Parra J. Effect of cenobamate on cognition in patients with drug-resistant epilepsy with focal onset seizures: an exploratory study. CNS Drugs. 2024;38(2):141–51.
12. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE commission for classification and terminology. Epilepsia. 2017;58(4):522–30.
13. Aboumatar S, Ferrari L, Stern S, Wade CT, Weingarten M, Connor GS, et al. Reductions in concomitant antiseizure medication drug load during adjunctive cenobamate therapy: post-hoc analysis of a subset of patients from a phase 3, multicenter, open-label study. Epilepsy Res. 2024;200: 107306.
14. Chung S, Wang N, Hank N. Comparative retention rates and long-term tolerability of new antiepileptic drugs. Seizure. 2007;16(4):296–304.
15. Beghi E. Efficacy and tolerability of the new antiepileptic drugs: comparison of two recent guidelines. Lancet Neurol. 2004;3(10):618–21.
16. Weissinger F, Losch F, Winter Y, Brecht S, Lendemans D, Kockelmann E. Effectiveness of eslicarbazepine acetate in dependency of baseline anticonvulsant therapy: results from a German prospective multicenter clinical practice study. Epilepsy Behav. 2019;101(Pt A): 106574.
17. Privitera M, Richy FF, Schabert VF. Indirect treatment comparison of cenobamate to other ASMs for the treatment of uncontrolled focal seizures. Epilepsy Behav. 2022;126: 108429.
18. Sander JW, Rosenfeld WE, Halford JJ, Steinhoff BJ, Biton V, Toledo M. Long-term individual retention with cenobamate in adults with focal seizures: pooled data from the clinical development program. Epilepsia. 2022;63(1):139–49.
19. Kwok CS, Johnson EL, Krauss GL. Comparing safety and efficacy of "third-generation" antiepileptic drugs: long-term extension and post-marketing treatment. CNS Drugs. 2017;31(11):959–74.
20. Chung SS, Hogan RE, Blatt I, Lawson PB, Nguyen H, Clark AM, et al. Long-term safety and sustained efficacy of USL255 (topiramate extended-release capsules) in patients with refractory partial-onset seizures. Epilepsy Behav. 2016;59:13–20.
21. Krakow K, Walker M, Otoul C, Sander JW. Long-term continuation of levetiracetam in patients with refractory epilepsy. Neurology. 2001;56(12):1772–4.
22. Krauss GL, Klein P, Brandt C, Lee SK, Milanov I, Milovanovic M, et al. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. Lancet Neurol. 2020;19(1):38–48.
23. Chung SS, French JA, Kowalski J, Krauss GL, Lee SK, Maciejowski M, et al. Randomized phase 2 study of adjunctive cenobamate in patients with uncontrolled focal seizures. Neurology. 2020;94(22):e2311–22.
24. Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. Lancet Neurol. 2016;15(10):1075–88.
25. Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsy Curr. 2017;17(3):180–7.
26. de Boer HM, Mula M, Sander JW. The global burden and stigma of epilepsy. Epilepsy Behav. 2008;12(4):540–6.
27. Gaitatzis A, Johnson AL, Chadwick DW, Shorvon SD, Sander JW. Life expectancy in people with newly diagnosed epilepsy. Brain. 2004;127(Pt 11):2427–32.
28. Winter Y, Daneshkhah N, Galland N, Kotulla I, Krüger A, Groppa S. Health-related quality of life in patients with post-stroke epilepsy. Epilepsy Behav. 2018;80:303–6.
29. Winter Y, Uphaus T, Sandner K, Klimpe S, Stuckrad-Barre SV, Groppa S. Efficacy and safety of antiseizure medication in post-stroke epilepsy. Seizure. 2022;100:109–14.
30. Sinha N, Peternell N, Schroeder GM, de Tisi J, Vos SB, Winston GP, et al. Focal to bilateral tonic-clonic seizures are associated with widespread network abnormality in temporal lobe epilepsy. Epilepsia. 2021;62(3):729–41.
31. Bell GS, de Tisi J, Gonzalez-Fraile JC, Peacock JL, McEvoy AW, Harkness WFJ, et al. Factors affecting seizure outcome after epilepsy surgery: an observational series. J Neurol Neurosurg Psychiatry. 2017;88(11):933–40.
32. Aboumatar S, Biton V, Wechsler R, Ferrari L, Rosenfeld WE. Post hoc analysis of a phase 3 study for treatment of uncontrolled focal seizures: adjunctive cenobamate dose and seizure reduction by baseline seizure frequency. Epilepsy Res. 2022;186: 107014.
33. Rosenfeld WE, Nisman A, Ferrari L. Efficacy of adjunctive cenobamate based on number of concomitant antiseizure medications, seizure frequency, and epilepsy duration at baseline: a post-hoc analysis of a randomized clinical study. Epilepsy Res. 2021;172: 106592.
34. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA Neurol. 2018;75(3):279–86.
35. Löscher W, Sills GJ, White HS. The ups and downs of alkylcarbamates in epilepsy therapy: how does cenobamate differ? Epilepsia. 2021;62(3):596–614.
36. Zaccara G, Franciotta D, Perucca E. Idiosyncratic adverse reactions to antiepileptic drugs. Epilepsia. 2007;48(7):1223–44.

37. Roberti R, De Caro C, Iannone LF, Zaccara G, Lattanzi S, Russo E. Pharmacology of cenobamate: mechanism of action, pharmacokinetics, drug-drug interactions and tolerability. CNS Drugs. 2021;35(6):609–18.
38. Wang XQ, Lv B, Wang HF, Zhang X, Yu SY, Huang XS, et al. Lamotrigine induced DIHS/DRESS: manifestations, treatment, and outcome in 57 patients. Clin Neurol Neurosurg. 2015;138:1–7.
39. Winter Y, Sandner K, Glaser M, Ciolac D, Sauer V, Ziebart A, et al. Synergistic effects of vagus nerve stimulation and antiseizure medication. J Neurol. 2023;270(10):4978–84.
40. Winter Y, Sandner K, Vieth T, Groppa S. Eslicarbazepine acetate for the treatment of status epilepticus. Epileptic Disord. 2023;25(2):142–9.
41. Sáenz-Farret M, Tijssen MAJ, Eliashiv D, Fisher RS, Sethi K, Fasano A. Antiseizure drugs and movement disorders. CNS Drugs. 2022;36(8):859–76.
42. Winter Y, Sandner K, Vieth TL, Melzer N, Klimpe S, Meuth SG, et al. Eslicarbazepine acetate as adjunctive therapy for primary generalized tonic-clonic seizures in adults: a prospective observational study. CNS Drugs. 2022;36(10):1113–9.
43. Brodie MJ. Pharmacological treatment of drug-resistant epilepsy in adults: a practical guide. Curr Neurol Neurosci Rep. 2016;16(9):82.

Authors and Affiliations

Yaroslav Winter[1,2] · Raya Abou Dargham[1] · Susana Patiño Tobón[1] · Sergiu Groppa[3] · Sven Fuest[4]

✉ Yaroslav Winter
yaroslav.winter@unimedizin-mainz.de

Raya Abou Dargham
raya.aboudargham@gmail.com

Susana Patiño Tobón
spatioto@students.uni-mainz.de

Sergiu Groppa
segroppa@uni-mainz.de

Sven Fuest
Sven.Fuest@hephata.de

[1] Mainz Comprehensive Epilepsy and Sleep Medicine Center, Department of Neurology, University Medical Center of the Johannes Gutenberg University Mainz, Langenbeckstrasse 1, 55131 Mainz, Germany

[2] Department of Neurology, Philipps-University Marburg, Marburg, Germany

[3] Department of Neurology, Focus Program Translational Neuroscience (FTN), Rhine Main Neuroscience Network, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[4] Department of Neurology, Hephata Klinik, Schwalmstadt, Germany