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PRACTICAL APPROACH

Positioning Cenobamate in the Treatment Algorithm of Focal Epilepsy: Seizure Control and Benefits Beyond Seizures

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ABSTRACT

This work integrates the opinion on the current use of cenobamate (CNB) of an expert panel structured across seven thematic domains: efficacy, patient profiles, titration and dosing, pharmacokinetic interactions, safety, parallel effects, and therapeutic positioning. According to personal experience and scientific evidence, experts unanimously regarded CNB as likely more efficacious than other newer-generation antiseizure medications (ASMs), particularly based on the long-term sustained seizure-freedom rates, despite the absence of comparative head-to-head studies. Priority candidates are patients with focal epilepsy failing two or more ASMs, including older patients, with a clear inclination toward earlier introduction. Initial response is expected at 100–200 mg/day, although maintenance is typically 200 mg/day or higher, alongside reduction of concomitant ASMs particularly sodium channel blockers and benzodiazepines. The most relevant drug–drug interaction is with clobazam, which may have a synergistic efficacy effect and in parallel increases plasma concentrations of clobazam, thereby inducing adverse events. The most frequent adverse events (somnolence, dizziness, fatigue) are dose-dependent and are reduced by anticipatory reduction of concomitant medication. Beyond seizure reduction, an early intervention with CNB may modify the prognosis of epilepsy, reducing the long-term mortality risk, cognitive impairment, or psychiatric disorders. The panel converged on a priority to position CNB as a third-line treatment in the focal epilepsy treatment algorithm owing to its high efficacy, which will probably lead to modification of the long-term global outcomes of people with epilepsy.

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Key Summary Points

Why carry out this study?

Despite a growing number of antiseizure medications (ASMs), around 30% of the 50 million people living with epilepsy worldwide do not achieve seizure freedom, and persistent seizures carry a cumulative risk of impaired quality of life, cognitive decline, psychiatric comorbidity, and premature mortality. Cenobamate (CNB) has shown unprecedented seizure-freedom rates in this drug-resistant population, yet its use is often delayed to later treatment lines because of limited clinician experience with its titration and safety profile.

This study asked a panel of experienced Spanish epileptologists, informed by a national survey of the Spanish Epilepsy Society (SEEP), how CNB should be positioned within the focal epilepsy treatment algorithm and managed in routine clinical practice.

What was learned from the study?

The expert panel unanimously rated CNB as more efficacious than other latest-generation ASMs and recommended it as the adjunctive treatment of choice after failure of two prior ASMs, with a trend towards earlier introduction in patients at high risk of drug resistance.

Adverse events were dose-dependent and largely manageable through anticipatory reduction of concomitant ASMs (particularly sodium channel blockers and clobazam), and vulnerable populations required slower titration rather than being excluded from treatment.

These findings support a re-evaluation of current treatment algorithms towards earlier CNB use and suggest that sustained seizure freedom with CNB may modify the long-term prognosis of epilepsy beyond seizure control alone, an area that warrants further prospective research.

INTRODUCTION

Epilepsy affects approximately 50 million people worldwide, and 30% of them fail to achieve adequate seizure control with antiseizure medications (ASM) [1, 2]. Over the past 15 years, several ASMs have been approved in clinical practice [1]. Nevertheless, seizure-freedom rates in focal epilepsy do not exceed 8% with third-generation agents (i.e., eslicarbazepine, perampanel, brivaracetam, or lacosamide) [3, 4]. Those uncontrolled seizures are associated with a progressive impairment of quality of life and accumulative risks of cognitive decline, psychiatric comorbidities, or mortality [2].

Cenobamate (CNB) was approved in 2021 by the European Medicines Agency (EMA) as adjunctive therapy for focal-onset seizures in adults with uncontrolled focal epilepsy despite the use of at least two prior ASMs [5]. Data from pivotal clinical trials and the accumulated real-world clinical experience indicate that CNB may achieve seizure-freedom rates above 20% [3, 6–8]. The most compelling explanation for this efficacy profile lies in the unique dual mechanism of action, which combines preferential blockage of voltage-gated sodium channels with positive modulation of chloride current mediated by gamma-aminobutyric acid subtype A ($GABA_A$) receptors [9]. However, CNB prescription often remains among the last therapeutic options likely because of the relative short experience and other facts such as the slow titration, potential drug–drug interactions, or risk of adverse events [5, 10].

The present report comprises the qualitative perspectives of a panel of six expert epileptologists with more than 10 years of CNB use experience, captured through a structured questionnaire. These data are contextualized in light of available bibliographic evidence and quantitative results from a survey conducted by the Spanish Epilepsy Society (SEEP)-Spanish ILAE Chapter in the fourth quarter of 2025 on the positioning of newer ASMs [11].

The main objective of this manuscript is to obtain recommendations from experts in the use of CNB, which can be helpful in the clinical practice of less experienced neurologists.

METHODS

Study Design

A panel of expert adult epileptologists from the Spanish Epilepsy Society was selected according to their experience in the use of CNB and its associated publications. All of panel members had treated at least 100 patients in routine clinical practice and had been involved in the pivotal clinical trials and in the Spanish expanded access program. A two-round open-ended online structured questionnaire was developed by all participants. The questionnaire comprised seven thematic domains: (1) efficacy; (2) patient profiles; (3) titration and dose adjustment; (4) pharmacokinetic interactions; (5) safety; (6) effect on comorbidities (cognitive, psychiatric, sleep); and (7) positioning within the therapeutic algorithm (Fig. 1; Table 1). The second round was performed using feedback from the initial responses; a consensus statement was then developed after the discussion by following the Accurate Consensus Reporting Document (ACCORD) checklist.

Approval for this study was obtained from Spanish Epilepsy Society (Spanish Chapter of the International League Against Epilepsy [ILAE]; http://www.seepnet.es) according to the evaluation of the steering committee on September 17, 2025. The study did not involve any active research with the involvement of patients or data, so it was exempt from institutional review board (IRB) approval or consent.

The SEEP survey was a structured questionnaire, validated by expert consensus, and comprised multiple-choice questions grouped into seven thematic domains similar to the expert panel opinion. The questionnaire was distributed via e-mail to all members of the SEEP; 58 members completed the survey during October and November 2025 [11].

To contextualize the responses, a non-systematic review of the published literature on CNB up to April 2026 was conducted, encompassing randomized controlled clinical trials, open-label extension studies, real-world evidence studies, and consensus documents included in PubMed.

RESULTS

Table 2 summarizes the main conclusions from the questionnaire.

Efficacy

Comparative Efficacy of Cenobamate Versus Other ASMs

All experts unanimously rated the efficacy of CNB as superior to that of other currently available latest-generation ASMs, which is consistent with data from the pivotal clinical trials. In the phase II/III trials, CNB ≥ 200 mg/day showed responder rate > 55.6%, with 28.0% of patients achieving seizure freedom, findings unprecedented in adjunctive ASM trials [6].

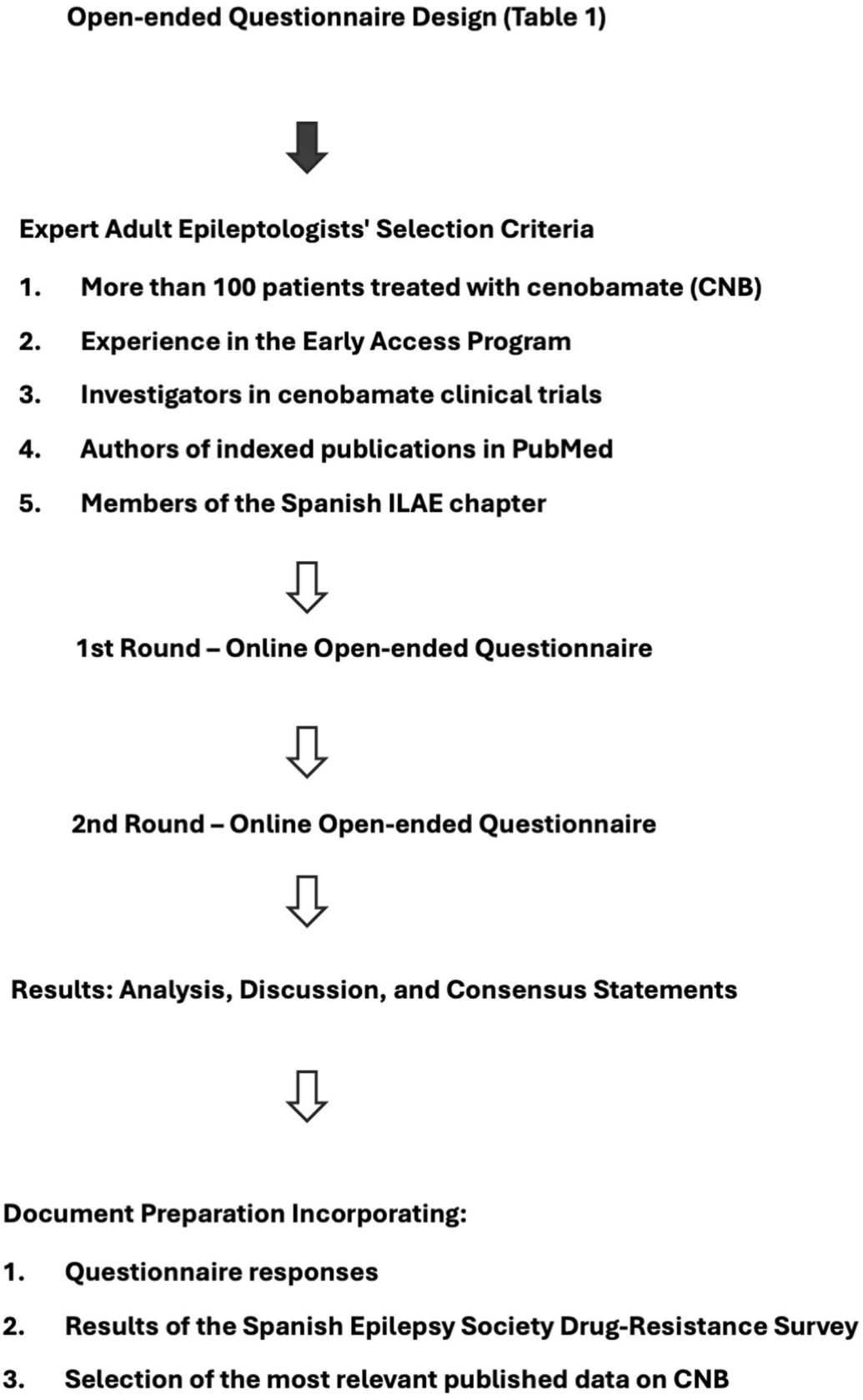
Real-world data from the Spanish expanded access program, evaluating patients that are highly refractory, reported that 56.7% were responders at 1-year follow-up and 25.1% were seizure-free. These results are substantially higher than those reported for third-generation ASM [4, 12].

In summary, all six experts affirmed that CNB demonstrates high efficacy relative to other third-generation ASMs [4], despite the absence of head-to-head trials, which characterizes CNB as a distinct efficacy outlier.

Complementary Efficacy Parameters Useful in Clinical Practice

The experts identified several efficacy parameters that collectively support the differential efficacy of CNB, which transcends the definition of treatment response:

- Achieving > 90% of seizure reduction is even possible in nearly one third of patients who had failed more than ten prior ASMs [13].
- Half of patients achieve ≥ 70% seizure reduction [13, 14].
- Sustained response, with 1-year retention rate in open-label studies exceeding 70–75% in European series [12, 15].
- Polytherapy reduction, as CNB efficacy permits the safe withdrawal of concomitant ASMs, at least one or two comedications [16].


Open-ended Questionnaire Design (Table 1)
Expert Adult Epileptologists' Selection Criteria
1. More than 100 patients treated with cenobamate (CNB)
2. Experience in the Early Access Program
3. Investigators in cenobamate clinical trials
4. Authors of indexed publications in PubMed
5. Members of the Spanish ILAE chapter
1st Round – Online Open-ended Questionnaire
2nd Round – Online Open-ended Questionnaire
Results: Analysis, Discussion, and Consensus Statements
Document Preparation Incorporating:
1. Questionnaire responses
2. Results of the Spanish Epilepsy Society Drug-Resistance Survey
3. Selection of the most relevant published data on CNB

◂**Fig. 1** Study workflow. Overview of the two-round structured questionnaire used to gather the expert panel's opinions on cenobamate

- Reduction in seizure severity and longer seizure-free intervals in those patients who are not completely seizure-free [13].

Sustained Response and Dose Adjustments Over Time

The majority of experts characterized the response to CNB as sustained once an optimal dose is established, with no significant tachyphylaxis in follow-up periods up to 4 years, a favorable aspect compared with some other ASMs acting through GABAergic mechanisms [9, 17]. Their opinion is consistent with the post hoc analysis of the phase III open-label trial that showed sustained seizure-freedom rates exceeding 20% in patients with highly refractory epilepsy [18]. Two of the experts acknowledged that patients that are highly sensitive to adverse events may require slight dose escalations likely induced by reduction in concomitant medication over time.

Patient Profiles

Candidates' Profiles for CNB Initiation

The experts identified as priority candidates for CNB initiation those patients with focal epilepsy who have failed two or more ASMs, independently of the treatment duration or the motivation to discontinue the first two lines, a recommendation aligned with the EMA-approved indication [5]. In general, all patients with focal seizures without exemptions are considered good candidates to receive CNB if they have uncontrolled seizures. Autoimmune epilepsies, particularly anti-GAD and Rasmussen's encephalitis, were highlighted by multiple respondents as interesting targets for CNB [19].

Treatment Lines

All respondents aligned on the current standard of failure of two previous ASMs, while expressing a clinical inclination toward earlier introduction. The failure of two previous ASMs independently of the time elapsed from the treatment onset, the dose achieved, or the presence of adverse events as the cause to discontinue the medication were also introduced. Two experts explicitly endorsed the early use in appropriately selected patients, particularly those with clinical predictors of refractoriness such as focal cortical dysplasia [20]. This reflects an evolving expert consensus that the formal indication may underrepresent the clinical potential of CNB in earlier-stage focal epilepsy.

Objective of Seizure Frequency Reduction and Seizure Freedom

The panel was asked whether the seizure reduction target with CNB should be more ambitious than with other ASMs. The general opinion was that rather than a qualitatively different treatment goal, seizure freedom is the universal goal of epilepsy treatment, and CNB increases the probability of achieving this target.

Vulnerable Populations (Older Age, Kidney and Liver Failure, or Systemic Disorders)

Respondents described their clinical experience with CNB in older patients, those with organ function impairment, and patients with systemic or autoimmune conditions.

Clinical experience in vulnerable populations suggests that CNB maintains the efficacy profile, with lower doses generally required in older patients and those with hepatic or renal failure [17]. Tolerability concerns, particularly somnolence and gait instability, are more frequent in older patients and patients that are polymedicated.

Regarding patients in hemodialysis, the drug prescribing information declares that CNB is not recommended and has not been studied in patients on hemodialysis [5]. Experts acknowledged limited experience and suggested that CNB is dialyzed as a result of its small molecular

Table 1 Structured open-ended questionnaire on cenobamate (CNB)

Efficacy	
1	How does the efficacy of CNB compare with that of other newer-generation ASMs?
2	Besides the high seizure-freedom rate, is there any other parameter of CNB efficacy you would highlight?
3	Do you consider the response to CNB to be sustained, or does it require long-term adjustments?
Patient profiles	
4	In which profiles of patients with focal epilepsy do you consider it most appropriate to start CNB?
5	At what treatment line do you think CNB should be initiated?
6	Should the seizure-reduction goal be more ambitious with CNB than with other ASMs?
7	What experience do you have with CNB in special populations, such as elderly patients, those with renal/hepatic impairment, or systemic diseases, including autoimmune conditions?
8	What would you advise regarding the use of CNB in women of childbearing potential?
Titration and dose adjustment	
9	What titration strategies do you use to optimize CNB, achieving the best balance between efficacy and tolerability?
10	At what dose of CNB do you typically expect to observe a clinical response?
11	What maintenance dose range do you generally recommend?
Pharmacokinetic interactions	
12	How do you manage the pharmacokinetic interactions of CNB, particularly with other ASMs that undergo hepatic metabolism?
Adverse effects	
13	How frequently are common adverse effects (somnolence, dizziness, fatigue) observed in clinical practice?
14	What are your recommendations regarding the tolerability of CNB in terms of transient adverse effects, dose dependence, or modification of concomitant medication?
15	In your experience, are there any concerning data on idiosyncratic or serious adverse effects suggesting that CNB carries a higher risk than other ASMs?

Table 1 continued

Potential parallel advantages of CNB	
16	What is your opinion regarding the effect of CNB on psychiatric, cognitive, and sleep-architecture aspects associated with epilepsy?
Positioning of CNB in treatment algorithms	
17	What role do you think CNB plays in future therapeutic algorithms for epilepsy?
18	Do you think CNB represents a new milestone in epilepsy treatment, or the start of a new generation of ASMs?
Free opinion on CNB	
19	Please highlight any aspects of CNB use that have not been covered in the questionnaire

ASM antiseizure medication, *CNB* cenobamate

weight and has a large volume of distribution, which means it is not abruptly cleared from tissues. Therefore, the dose in hemodialysis patients should be kept stable while monitoring for efficacy and potential adverse effects.

Recommendations in Women of Childbearing Potential

Given the absence of robust teratogenicity data for CNB, respondents were asked for their management recommendations in women of childbearing potential.

The panel demonstrated heterogeneity, ranging from absolute contraindication in two participants to conditional use contingent on epilepsy severity and pregnancy planning in the rest of them.

In general, endorsed transitioning to agents with established pregnancy safety profiles when pregnancy is actively planned was suggested. In cases of women with highly refractory epilepsy where switching treatments carries significant clinical risk, five experts would maintain CNB with close obstetric monitoring and comprehensive information.

While considering CNB use acceptable in non-pregnant women with refractory epilepsy who have not expressed imminent reproductive intent, there must be recommendations to use non-hormonal contraception or consider the potential interaction with hormonal contraceptives due to CNB enzyme-inducing effects.

Titration and Dosing

Titration Strategies to Optimize Efficacy

Titration strategies broadly adhered to the summary of product characteristics recommended schedule, optimizing the dose every 2 weeks until the target maintenance dose is reached.

The concurrent, stepwise reduction of sodium channel-blocking ASMs during CNB titration emerged as a recurrent clinical strategy to minimize overlapping CNS adverse effects [18, 21].

Initial Target Doses

The panel anticipated 100–200 mg/day as the dose range at which initial clinical response is typically observed. Three respondents cited 100 mg/day as the threshold for meaningful efficacy, while others indicated 150–200 mg as their experience-based threshold. A complete response is expected at a dose range between 150 and 400 mg/day. This variability likely reflects differences in patient populations, prior pharmacological burden, and individual pharmacokinetic/dynamic factors [16, 18].

Table 2 Summary of main conclusions from the questionnaire

Domain	Key conclusions
Efficacy	Superior efficacy compared with other ASMs Sustained response maintained over 4 years of follow-up Synergistic effect with CLB
Patient profiles	Candidates: ≥ 2 prior ASM failures (or ≥ 1 failure in clear cases of DRE) Suitable for vulnerable patients at lower CNB doses Pregnancy: individualized decision-making in patients with DRE
Titration and dose adjustment	Initial response observed at 100–200 mg/day Maintenance dose range 200–300 mg/day Once-daily dosing, preferably at bedtime
Pharmacokinetic interactions	Increases plasma levels of CLB, PHT, and PHB Decreases plasma levels of LTG and BRV Caution warranted with other medications, given CNB's activity as a CYP3A4 inducer and CYP2C19 inhibitor
Safety	Frequent: somnolence, dizziness, fatigue Common: weight loss, hyporexia Adverse effects are generally dose-dependent and transient, improving with dose or concomitant medication adjustment Very rare: hypersensitivity reactions and increased liver enzymes
Effect on comorbidities (cognitive, psychiatric, sleep)	Positive effect on sleep architecture No overall cognitive impairment or emotional decline Early positive impact on quality of life, with favorable long-term outcomes
Positioning within the therapeutic algorithm	First-choice option after two ASM failures May be considered after one ASM failure in patients at clear risk of DRE May reshape future treatment guidelines

ASM antiseizure medication, *BRV* brivaracetam, *CLB* clobazam, *CNB* cenobamate, *CYP* cytochrome P450, *DRE* drug-resistant epilepsy, *LTG* lamotrigine, *PHB* phenobarbital, *PHT* phenytoin

Maintenance Dose and Adjustments

The dose range interval most frequently cited as the therapeutic window was 200 to 300 mg/day. Patients that are drug-resistant often need maintenance doses over 300 mg/day.

Administration is preferable once-daily mainly at nighttime, though twice-daily dosing is occasionally employed to improve tolerability.

All experts recommended progressive reduction of concomitant ASMs, particularly sodium-channel-blocking ASMs (phenytoin, lacosamide, and carbamides), phenobarbital, and clobazam. Indeed, some experts suggested to proceed with comedication reduction simultaneously with CNB dose escalation, anticipating the presence of adverse events when CNB exceeds 100 mg daily. This strategy allows one to improve the efficacy/tolerability balance, reduce to once-a-day medication intake, and minimize pharmacological burden [18, 21].

Pharmacokinetic Interactions

Management of Drug–Drug Interactions

CNB is an inducer of cytochrome P450 (CYP)3A4 and an inhibitor of CYP2C19 enzymes, generating relevant interactions with numerous hepatically metabolized drugs. Additional data on interactions with chemotherapy and hormonal or anticoagulant agents are required. The most common clinically significant interactions with other ASMs are:

1. Increase of the active clobazam metabolite plasma concentrations up to 3–5-fold, potentially causing excessive sedation [9]. Highlighted as the most clinically relevant and commonly encountered interaction. Anticipatory reduction of clobazam is recommended when CNB exceeds 50 or 100 mg/day.
2. Increase of phenytoin and phenobarbital levels. Monitoring plasma levels and dose reduction are recommended. Several respondents noted that phenytoin and phenobarbital are infrequently encountered in their current practice [5].
3. Lamotrigine (LTG) plasma levels may decrease through CYP3A4 induction. Monitoring plasma levels and LTG dose may be required.
4. Mild decrease in brivaracetam levels is possible as a result of enzymatic induction; rarely requires significant dose adjustment according to panelists' experience.

The two principal strategies to manage interactions were:

1. Therapeutic drug monitoring of susceptible interacting ASMs according to the clinical response, particularly clobazam and lamotrigine.
2. Anticipatory simplification through stepwise dose reduction or discontinuation of pharmacodynamic interacting ASMs; particular emphasis was placed on the potential overdosing of clobazam.

Safety Profile

Incidence of CNB-Related Adverse Events

The most commonly reported dose-related adverse events were somnolence, dizziness, and fatigue in nearly half of the patients, followed by weight loss and dysarthria in one quarter, consistent with the profiles described in the pivotal trials and real-world studies [6–8]. The panel confirmed that most of these effects were sometimes transient and improved markedly with reduction of concomitant medications.

Recommendations to Improve Tolerability

To improve the tolerability and transient nature of some adverse events, the experts focused on reducing or discontinuing comedications rather than limiting CNB dose escalation, thereby preserving CNB's efficacy advantage while improving tolerability [18, 21].

The panel broadly endorsed patient communication as a key component of tolerability management, emphasizing the expectation of symptom resolution during titration as a strategy to improve adherence.

Risk of Idiosyncratic or Systemic Adverse Events

The panel unanimously reported no evidence of a higher idiosyncratic or serious adverse event risk with CNB compared to other last-generation ASMs.

Hypersensitivity reactions including skin rash were described as rare, even lower than with carbamides or lamotrigine, and avoided with slow titration protocols. No cases of hypereosinophilia or immune systemic reaction were noted in contrast to their own previous observations with previous drugs such as carbamazepine or lamotrigine.

Elevated liver enzymes were observed rarely by the experts, overall, when CNB was used in combination with other ASMs that may induce elevated liver enzymes, such as valproate or carbamides. No cases of liver failure or hepatitis were reported. However, regular liver enzyme monitoring was recommended.

According to the experts, hyporexia and weight loss are expected in the real-world setting in nearly one quarter of patients. The experts concluded that further evidence is needed to figure out the real frequency.

Parallel Effects of CNB on Sleep Architecture, Psychiatric Comorbidities, and Cognitive Function

Improvement in sleep architecture was perceived as clinically relevant. Overall, CNB dose was administered at bedtime.

The neuropsychiatric profile of CNB was characterized as neutral or exhibiting a favorable mood effect. Anxiety and depression outcomes were predominantly neutral, although significantly better in patients that remain seizure-free.

Cognitive effects were perceived as positive in cases who had a complete or almost complete response able to decrease comedication, in contrast to the mild impairment in those unresponsive with unmodified polypharmacy and high CNB doses.

The experts suggested that an early intervention with a more efficacious agent such as CNB may improve the course of the epilepsy beyond seizure-related risks [22]. Better seizure control has been associated with a decreased mortality risk [23] and, in addition, ongoing seizures may contribute to cognitive impairment or psychiatric disorders that lead to a progressive impairment of quality of life [24].

Clinical Position and Future Perspectives

Positioning of CNB in the Therapeutic Algorithm

All panelists advocate CNB use as the second or third ASM rather than reserving it for patients with many prior failures. They argued that the earlier seizure freedom is achieved, the greater the benefit in terms of quality of life, epilepsy-related comorbidity, and mortality [16, 25].

The early add-on therapy was justified under conditions of high risk of seizure recurrence such as focal cortical dysplasia. This trend towards earlier therapeutic positioning is supported by data from different studies [3, 8, 16] and the US Food and Drug Administration (FDA) approval.

Table 3 Selected expert commentary on the future role of CNB in epilepsy management

Expert commentary
"The potential use of CNB in postsurgical rescue scenarios, together with its efficacy in pediatric patients, may further define its role as a broader therapy for focal epilepsy"
"CNB may emerge as a modifier of the natural course of focal epilepsy and improve historically poor non-response rates"
"The role of CNB in generalized epilepsies or developmental and epileptic encephalopathies must be elucidated"
"The efficacy of CNB in focal epilepsy supports the rationale for further exploratory studies in refractory status epilepticus"

CNB cenobamate

CNB as a New Treatment Milestone or Potential New ASM Generation

The CNB trajectory suggested by the panel implies a potential paradigm shift from reactive introduction after confirmed drug resistance to proactive deployment as an early disease control strategy.

The majority of respondents were willing to characterize CNB as a significant therapeutic benchmark. They acknowledged that the current drug development pipeline lacks comparative results, suggesting that CNB has a milestone consolidated status [3].

Free Expert Commentary

Respondents were invited to highlight additional aspects of CNB use not covered by the structured questionnaire. Four respondents provided supplementary observations, which are described in Table 3.

DISCUSSION

The view of the current role of CNB in the treatment of focal epilepsy presented in this report is enriched by contrasting a panel of CNB experts' opinion with a survey conducted by the Spanish Epilepsy Society (SEEP) on the perception of drug-resistant focal epilepsy and the most relevant CNB recent publications [11].

Experts consulted in this report unanimously positioned CNB as the adjunctive ASM of choice after the failure of two ASMs. This specialized consensus receives notably broad endorsement from the wider epilepsy community, as half of the SEEP participants identified CNB as the most frequently used ASM [11]. Its position is consolidated by studies conducted in different clinical settings such as the CREW comparative real-world study with nearly 2000 subjects that confirmed the superior effectiveness of CNB over the other new ASMs [3, 4, 12].

According to experts, the frequency and profile of CNB-related adverse events are similar to those of other new ASMs and consistent with large series with long CNB exposure [6, 17]. Despite the good evidence of efficacy in vulnerable subgroups, in older patients and those with liver or kidney failure, CNB likely needs slower titration and lower dose adjustments according to clinical response [12, 17]. Given the lack of evidence during pregnancy, individualized decision-making is recommended for women of childbearing age with refractory epilepsy [26–28].

Quality of life in epilepsy is improved, among other factors, by seizure freedom and the absence of adverse effects, comorbidities, and polypharmacy. This hierarchy underlines that drug tolerability and regimen simplification occupy relevant positions [17, 18, 21]. These data support the experts' strategy of anticipatory polypharmacy simplification when initiating CNB as a method to avoid adverse events and increase the therapeutic effect, so that patients and caregivers significantly obtain better quality of life [25, 27, 29].

A significant proportion of epileptologists demand evidence of modification on the natural history of epilepsy beyond seizure freedom in patients treated with CNB [30]. Experience shows that sustained seizure freedom is the strongest positive factor for long-term favorable outcomes [22]. In contrast, increased mortality, cognitive decline, or psychiatric comorbidities are some of the cumulative risks associated with uncontrolled seizures [24, 31]. Evidence suggests that in a significant proportion of patients, an early intervention with CNB could lead to a better long-term global outcome, perceived as a favorable impact on quality of life [22–24, 31].

However, the experts still considered that the potential of CNB to reduce the proportion of patients that are truly drug-resistant deserves deeper exploratory approaches in a context where mainly CNB has substantially improved seizure frequency outcome in the later years [2, 20, 25]. This perception reinforces the need, already identified by ILAE working groups, to update the operational criteria for drug resistance in light of new therapeutic possibilities [6, 10].

The experts acknowledge that scientific evidence is needed, basically using long-term prospective cohorts in patients with newly diagnosed drug-resistant epilepsy. In addition, further data in pediatric populations, status epilepticus or generalized epilepsies, as well as studies in specific polytherapy combinations, cancer-related epilepsy, or women of childbearing potential are needed to complete the characterization.

CONCLUSION

CNB represents a therapeutic milestone in the treatment of focal epilepsy and should be considered the adjunctive ASM of first choice after failure of two ASMs, with a trend towards earlier positioning based on the following key points:

The efficacy of CNB seems qualitatively superior to that of other new ASMs in terms of seizure freedom, retention rate, and sustained response; Most common adverse events are described with a similar frequency to those of other newer ASMs, so use in vulnerable populations requires slower CNB titration and closer monitoring but

does not represent a contraindication; Expert epileptologists suggest that concomitant ASM burden must be commonly reduced to maximize CNB therapeutic effect, although the efficacy synergistic effect with clobazam must be considered in some cases; There is a caveat that early intervention with CNB provides an opportunity to shift the prognosis of epilepsy and not merely reduce seizures.

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Declarations

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Ethical Approval. Approval for this study was obtained from Spanish Epilepsy Society (Spanish Chapter of the International League Against Epilepsy [ILAE]; http://www.seepnet.es) according to the evaluation of the steering committee on September 17, 2025. The study did not involve any active research with the involvement of patients or data, so it was exempt from institutional review board (IRB) approval or consent.

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