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ORIGINAL RESEARCH

Early Introduction of Cenobamate in Uncontrolled Focal Epilepsy: Insights from a Structured Controversy

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ABSTRACT

***Introduction*:** Drug-resistant focal epilepsy, as defined by the International League Against Epilepsy (ILAE), is characterized by the failure to achieve seizure control despite the use of at least two appropriately chosen and adequately dosed antiseizure medications (ASMs). This condition affects approximately 30% of patients and represents a significant clinical challenge. Cenobamate, a novel ASM with a unique dual mechanism of action—enhancing inhibitory GABAergic currents and attenuating persistent sodium currents—has emerged as a promising therapeutic option for drug-resistant focal epilepsy.

***Methods*:** This expert consensus document was developed using a structured controversy methodology, integrating real-world experience and a narrative review of the literature focusing on the role of cenobamate in the management of

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drug-resistant focal epilepsy. This manuscript synthesizes current evidence on cenobamate and provides clinical recommendations for its integration into epileptological practice.

***Results*:** The expert panel findings support the early use of cenobamate following the failure of two ASMs, emphasizing its efficacy in achieving substantial seizure reduction and increasing the likelihood of seizure freedom. Early prescription of cenobamate may offer a valuable therapeutic opportunity for patients with refractory focal epilepsy, potentially reducing seizure-related complications and improving quality of life. Identified challenges include limited long-term safety data in specific populations and regional disparities in drug access.

***Conclusion*:** Cenobamate represents a significant advancement in the treatment of drug-resistant focal epilepsy. Its early adoption in clinical practice has the potential to enhance patient outcomes. The expert panel provides recommendations that underscore individualized treatment planning, close monitoring during titration, and advocacy for improved accessibility. Continued research and policy initiatives are essential to fully realize the therapeutic potential of cenobamate.

Keywords: Cenobamate; Drug-resistant focal epilepsy; Antiseizure medications (ASMs); Early add-on; Seizure control

Key Summary Points

Why carry out this study?

Drug-resistant focal epilepsy affects approximately 30% of patients and is associated with substantial clinical burden, including increased risk of sudden unexpected death in epilepsy (SUDEP) and impaired quality of life.

While clinical trials and real-world studies support cenobamate's efficacy, its optimal placement in the treatment algorithm remains unclear.

This expert opinion study used a structured controversy method to assess the rationale for early cenobamate introduction, based on a non-systematic review of the literature.

What was learned from the study?

Literature data, though non-systematically selected, consistently report high response and seizure freedom rates with cenobamate, particularly when used earlier in treatment.

Expert consensus supports introducing cenobamate after failure of two ASMs, citing its potential to reduce seizure burden, polytherapy load, and SUDEP risk.

This report offers a balanced expert perspective integrating available evidence and clinical reasoning, while acknowledging limitations such as the lack of systematic evidence appraisal and head-to-head comparisons.

INTRODUCTION

Drug-resistant focal epilepsy represents a critical clinical challenge, affecting approximately 30% of individuals who fail to achieve adequate seizure control despite treatment with two or more appropriately selected and administered antiseizure medications (ASMs), as defined by the International League Against Epilepsy (ILAE) [1–3]. This condition significantly impacts patients and caregivers, contributing to increased morbidity and mortality [4]. Among its most severe consequences is sudden unexpected death in epilepsy (SUDEP), a complication strongly associated with persistent focal to bilateral tonic–clonic (FBTC) seizures [5–7]. Additionally, uncontrolled epilepsy frequently coexists with cognitive impairments, psychological distress, and social stigma, further complicating management and reducing quality of life [1, 8–10].

Despite significant advances in ASM development, the therapeutic options for uncontrolled focal epilepsy remain limited [9, 11, 12]. Many treatments fail to balance effective seizure control with tolerability [13, 14]. Cenobamate, however, has recently emerged as a promising

addition to the ASM armamentarium, addressing critical unmet needs in this population [15–20]. With its dual mechanism of action—enhancing inhibitory GABAergic currents and attenuating persistent sodium currents—it stabilizes neuronal hyperexcitability [21, 22]. Clinical trials and real-world evidence have demonstrated its considerable efficacy in reducing seizure frequency, achieving seizure freedom more often than existing ASMs, and enabling reductions in polytherapy, all while maintaining good tolerability [23, 24]. These features position cenobamate as an appealing therapeutic option for uncontrolled focal epilepsy [25].

This manuscript aims to synthesize available clinical trial data, real-world studies, and expert opinions regarding the use of cenobamate, and to provide practical recommendations for its early introduction in patients with drug-resistant focal epilepsy, particularly following the failure of two adequately dosed ASMs. The recommendations stem from a structured controversy methodology applied during an in-person expert panel discussion, which critically assessed the drug's therapeutic potential, challenges, and optimal clinical positioning [26, 27]. By presenting a balanced evaluation of evidence and expert insights, this paper aims to deliver a practical framework for incorporating cenobamate into routine care, ultimately improving the management and outcomes of individuals living with drug-resistant focal epilepsy.

METHODS

Study Design

This manuscript represents a consensus-based expert opinion. The recommendations for the use of cenobamate were derived through a structured controversy methodology employed during a meeting of epilepsy specialists from leading Italian centers. This innovative approach was designed to foster dynamic and critical evaluation of key clinical questions related to the therapeutic use of cenobamate. The methodology centered on the systematic analysis of specific theses, each addressing clinically relevant aspects of cenobamate role in managing drug-resistant focal epilepsy [26].

Participants and Working Groups

The expert panel (represented by the authors of the present manuscript) consisted of clinical researchers with extensive expertise in epilepsy, with a focus on the management of drug-resistant focal epilepsy. Participants were randomly divided into two working groups in an equal fashion, each assigned predefined theses. The assertions were carefully crafted to reflect real-world clinical scenarios, such as the timing of cenobamate introduction, its potential as a monotherapy, and its ability to enhance long-term outcomes. Each working group was tasked with exploring the supporting and opposing evidence for their respective theses, incorporating data from clinical studies, guidelines, and clinical experiences.

Methodological Approach

Evidence was gathered through a narrative review approach. The authors did not conduct a formal systematic review, but rather aimed to synthesize the most relevant available data based on clinical experience and familiarity with the literature. No predefined PICO strategy was applied. Databases such as PubMed were consulted, focusing primarily on studies published between 2020 and early 2025. Key search terms included "cenobamate," "drug-resistant epilepsy," "focal seizures," "polytherapy," "SUDEP," and "early treatment."

No formal inclusion/exclusion criteria were predefined; instead, each working group was responsible for selecting pertinent studies to support or challenge their assigned thesis (summarized in Table 1). Limitations of this approach include the lack of reproducibility and potential omission of relevant studies.

Deliberation and Validation

During the joint deliberation phase, findings were presented in plenary sessions, where discussions were moderated to ensure equal

Table 1 Theses presented and discussed during the structured controversy

Number	Thesis
1	Cenobamate can be used after the failure of two antiseizure medications, rather than being reserved for later stages of treatment
2	Early use of cenobamate reduces the impact of uncontrolled seizures and improves long-term prognosis
3	Early use of cenobamate prevents long-term complications and improves clinical outcomes
4	Cenobamate represents the ideal treatment in the presence of predictors of drug resistance compared to standard therapies
5	Positioning cenobamate as an early add-on treatment after the failure of two antiseizure medications leads to better clinical outcomes
6	Early use of cenobamate not only controls seizures but also improves patients' quality of life and reduces the risk of SUDEP
7	Cenobamate should be considered a therapeutic option for patients with drug-resistant epilepsy before evaluating surgical intervention

participation. Divergent views were documented and debated in open dialogue. Consensus was not forced; instead, areas of disagreement were acknowledged and integrated into the manuscript discussion where relevant. No formal voting or Delphi rounds were conducted, as the goal was to capture clinical reasoning rather than achieve unanimity. Compared to the Delphi process, this method allows for dynamic interaction and exploration of evolving clinical views but lacks the anonymity and statistical consensus metrics of Delphi surveys. The absence of a Delphi design may limit reproducibility but was deemed appropriate given the exploratory and discursive nature of this expert panel.

Ethical Approval

Not applicable. This work is based on published studies and expert discussion; no human or animal research was conducted.

RESULTS

Thesis 1: Cenobamate Can Be Used After the Failure of Two Antiseizure Medications, Rather Than Being Reserved for Later Stages of Treatment

Cenobamate has demonstrated significant efficacy in managing focal seizures, supporting its early use after the failure of two ASMs. Rosenfeld et al. (2022), in a post hoc analysis of a multicenter, phase 3 study involving 240 patients, reported robust reductions in seizure frequency across all focal seizure subtypes, with 90.5% of patients with FBTC seizures achieving seizure freedom by months 25–27 [28].

Winter et al. (2024), in an observational cohort study using the Mainz Epilepsy Registry, compared patients initiated on cenobamate as an early adjunctive treatment (after failure of 2–3 ASMs) with those started on other ASMs. The retention rate at 12 months was significantly higher for cenobamate (92%) compared to lacosamide (80%), levetiracetam (73.3%), valproate (68.2%), and topiramate (62.5%). Additionally, cenobamate achieved the highest seizure freedom rate (19.5%) and response rate (71.4%), indicating greater effectiveness and tolerability in early therapy lines. Moreover,

cenobamate's safety profile was comparable to that of the other ASMs, although further studies are needed to evaluate potential drug–drug interactions, especially in polytherapy contexts [29].

Sander et al. (2022) pooled data from randomized and open-label trials, including 1844 participants, to assess long-term retention on cenobamate therapy. Kaplan–Meier analysis revealed retention rates of 80% at 1 year and 72% at 2 years, underscoring its long-term tolerability and efficacy. The most common reasons for discontinuation were adverse events, although serious adverse effects, such as drug rash with eosinophilia and systemic symptoms (DRESS), were notably absent [30].

Thesis 2: Early Use of Cenobamate Reduces the Impact of Uncontrolled Seizures and Improves Long-Term Prognosis

Studies such as those by Winter et al. (2024) and Serrano-Castro et al. (2024) demonstrated cenobamate effectiveness in patients with focal seizures after 12 months of treatment [29, 31].

In rapidly improving patients, data from Sperling et al. (2021) highlight significant reductions in seizure frequency as early as the titration phase, with responder rates of 48.1% during weeks 1–4 (12.5–25 mg/day cenobamate) and 61.7% during weeks 5–8 (50–100 mg/day cenobamate). Furthermore, during the maintenance phase, 40.2% of patients achieved ≥ 90% seizure reduction, with 13.1% reaching 100% seizure reduction for their entire treatment duration. Notably, 36.3% of patients achieved seizure freedom for any consecutive 12-month period [32]. Similarly, Aboumatar et al. (2022) provided additional evidence of rapid efficacy during the titration phase, with responder rates of approximately 81% (≥ 50% seizure reduction), 62% (≥ 75% seizure reduction), and 43% (≥ 90% seizure reduction) during the maintenance phase, regardless of baseline seizure frequency. Importantly, 33.9% of patients continuing cenobamate achieved seizure freedom for ≥ 12 months by data cutoff, including 44.4% of those with fewer than three seizures per 28 days at baseline and 23.0% of those with three or more seizures [33].

Moreover, Winter et al. reported seizure freedom in 19.5% of patients and a response rate (≥ 50% reduction in seizure frequency) of 71.4% after 12 months, outperforming other ASMs [29]. These findings were reinforced by interim results from the BLESS study, a large observational Italian cohort, in which 11.3% of 388 patients achieved sustained seizure freedom over 24 weeks, and nearly 60% experienced ≥ 50% seizure reduction. Notably, in patients with only 2–3 prior ASMs (early users), the median seizure reduction was 78.0%, with a 76.3% responder rate—supporting the utility of cenobamate even in earlier treatment stages [34, 35]. The BLESS data also documented a significant reduction in the number and burden of concomitant ASMs over time, consistent with previous findings from real-world registries. These reductions are relevant not only in terms of tolerability but also as a pathway to improved adherence and cognitive outcomes [34]

The ability of cenobamate to mitigate the burden of uncontrolled seizures while simplifying therapy through lower polytherapy requirements has further implications for quality of life and adherence. Serrano-Castro et al. highlighted cognitive benefits potentially linked to a reduction in polytherapy, as evidenced by improvements in verbal and visuospatial episodic memory scores over 6 months [31]. Catalan-Aguilar et al., in a prospective study of cenobamate on cognition, affectivity, and quality of life in focal epilepsy, similarly reported no adverse cognitive effects or negative impacts on quality of life, supporting cenobamate's long-term positive influence on prognosis [36]. These findings are echoed in the Italian Expanded Access Program, which reported that cenobamate reduced the defined daily dose (DDD) of concomitant ASMs by 22.2% at 12 months and allowed discontinuation of at least one ASM in over 40% of patients [37]. Exploratory analyses also suggested a favorable, albeit non-significant, trend toward improved response in patients co-treated with clobazam, highlighting the relevance of pharmacokinetic interactions in real-world optimization.

Studies by Chen et al. (2018) and Kwan et al. (2010) underscore the challenges of achieving sustained seizure control, particularly as

the probability of achieving seizure freedom decreases with each additional ASM prescription [3, 38]. Cenobamate high retention rate (92% at 12 months, per Winter et al.) is a promising indicator of its role in overcoming these challenges, but further evidence is needed to confirm these findings in different clinical contexts [29].

Thesis 3: Early Use of Cenobamate May Prevent Long-Term Complications of Uncontrolled Epilepsy and Improves Clinical Outcomes

Cenobamate's ability to achieve greater seizure control has been demonstrated in multiple studies, such as those by Rosenfeld et al. (2023) and Winter et al. (2024) [29, 39]. These studies highlight significant reductions in generalized tonic–clonic seizures, which are strongly associated with epilepsy-related mortality, including SUDEP. For example, Rosenfeld et al. reported a SUDEP rate of 0.88 per 1000 person-years, suggesting a potential protective role for cenobamate against epilepsy-related mortality when effectively controlling FBTS seizures [39].

Early use of cenobamate may offer indirect benefits by improving patients' autonomy and quality of life. Findings from Luoni et al. (2011) demonstrate that seizure control can reduce social and psychological burdens, allowing patients to engage in activities such as driving and working [40]. Similarly, Villanueva et al. (2023) reported significant reductions in seizure frequency (≥ 50% in 63% of patients) and improvements in quality of life, supported by a reduction in the number of concomitant ASMs in nearly half of the patients [23].

While real-world studies provide valuable insights into cenobamate safety and tolerability, the lack of robust long-term data on chronic metabolic effects, cognitive outcomes, and overall disease progression complicates the assessment of its broader impacts [23]. The relatively small number of patients in many studies and the underrepresentation of specific populations, including older patients and women of childbearing age, further limit generalizability. For example, Schmitz et al. (2023) noted that although approximately 50,000 patients have been treated with cenobamate, larger-scale data are required to fully establish its safety and efficacy profiles [20]. More recent updates indicate that this number has now surpassed 100,000 patients worldwide, with evidence suggesting a strong growth, further reinforcing the importance of large-scale studies to better evaluate its broader clinical impact [41].

Thesis 4: Cenobamate Represents the Ideal Treatment in the Presence of Predictors of Drug Resistance Compared to Standard Therapies

Cenobamate has emerged as a promising option for patients with predictors of drug resistance, demonstrating sustained seizure control in clinical trials and real-world studies. Vossler et al. (2023), in a post hoc analysis of a phase 3, open-label study, reported that 22% of patients achieved seizure freedom for at least 30 months, and 63% experienced minimal seizure recurrence during follow-up visits. Among those achieving ≥ 50% seizure reduction, the response was sustained for over 30 months in 53% of patients [42].

Rosenfeld et al. (2022) analyzed seizure reductions across subtypes in a phase 3 study and found that 90.5% of patients with FBTC seizures achieved seizure freedom during months 25–27 [28]. Winter et al. (2024) further supported these findings, demonstrating superior 12-month retention rates (92%) and seizure freedom rates (19.5%) compared to other ASMs like valproate, levetiracetam, and lacosamide [29].

While efficacy and tolerability of cenobamate are well documented, there is a lack of direct comparative studies with other newer-generation ASMs, which limits definitive conclusions about their potential profile as an "ideal treatment." Adverse effects, such as somnolence, vertigo and dizziness, and ataxia during the titration phase, have been documented [28].

Thesis 5: Positioning Cenobamate as an Early Add-On Treatment After the Failure of Two Antiseizure Medications Leads to Better Clinical Outcomes

Positioning cenobamate earlier in the treatment pathway, specifically after the failure of two

ASMs, may offer improved clinical outcomes by targeting a less refractory population. In an observational cohort study, Winter et al. (2024) demonstrated that cenobamate achieved higher rates of seizure freedom (19.5%) and response (71.4%) compared to other ASMs, including lacosamide, levetiracetam, and valproate, which showed lower seizure freedom (8.3%) and response rates (52.5%) at 12 months. The study population was less refractory, as patients were included after failing only two or three lifetime ASMs. Cenobamate also exhibited the highest retention rate (92%) among the ASMs studied. These outcomes indicate that cenobamate efficacy is not confined to highly refractory populations and may suggest potential advantages when applied earlier in treatment [29].

Villanueva et al. (2023), in a real-world expanded access program involving patients who were highly drug-resistant, found that cenobamate maintained high retention rates (87% at 12 months) while achieving substantial reductions in seizure frequency. The median seizure reduction was 66.7% at the last follow-up, regardless of the number of prior or concomitant ASMs. This consistent efficacy across different patient profiles supports its use in less refractory populations [23].

Chen et al. (2018) emphasized the diminishing likelihood of seizure freedom with each subsequent ASM regimen, reinforcing the need for effective treatments earlier in the epilepsy management timeline. By reducing the pharmacological burden and side effects associated with prolonged polytherapy, cenobamate offers an opportunity to enhance adherence and quality of life [38]. Roberti et al. (2021) highlighted cenobamate's dual mechanism of action which provides the benefits of a multi-target therapy without the complexity of combining multiple drugs [22].

These observations are further supported by a time-based analysis conducted within the Italian Expanded Access Program, showing that over 64% of patients reached their baseline seizure count within 12 months of cenobamate initiation. Exploratory subgroup analysis suggested a potentially more favorable time-to-response profile in patients co-treated with GABAergic agents and fewer sodium channel blockers, although statistical significance was not reached. These findings suggest that both timing and background regimen may influence therapeutic efficiency, providing a rationale for careful combination planning in clinical practice [43].

However, some limitations emerged. Villanueva et al. (2023) observed no significant differences in responder rates between patients who failed fewer ASMs and those with more extensive treatment histories, suggesting that cenobamate efficacy might be consistent across levels of refractoriness rather than uniquely enhanced in less refractory cases [23]. However, further investigations are needed to confirm this exploratory finding. Additionally, data on long-term cognitive, psychiatric, and teratogenic safety remain limited, particularly for special populations such as women of childbearing age.

Thesis 6: Early Use of Cenobamate Not Only Controls Seizures But Also Improves Patients' Quality of Life and Reduces the Risk of SUDEP

Cenobamate has shown efficacy in reducing FBTC seizures, which are strongly linked to an increased risk of SUDEP. Rosenfeld et al. (2023), in an analysis of cenobamate's clinical development program involving 2132 patients with focal epilepsy over 5693 person-years, reported a SUDEP rate of 0.88 per 1000 person-years. Importantly, all SUDEP cases occurred in patients with FBTC seizures, underlining cenobamate's potential role in indirectly reducing SUDEP by targeting FBTC [39]. Moreover, Catalan-Aguilar et al. (2024) conducted two prospective cohort studies and found no significant negative impact of cenobamate on cognition, negative affectivity, or quality of life over 6 months, further supporting its safety as an early add-on therapy [36].

Elizebath et al. (2021), in a long-term observational study of 49 patients treated with cenobamate for up to 8 years, demonstrated sustained improvements in seizure frequency and quality of life. Among these patients, 45% achieved ≥ 75% seizure reduction, and 29% achieved ≥ 90% reduction, correlating with high quality of life (QOLIE) scores. These findings

emphasize cenobamate 's potential to enhance daily functioning and reduce epilepsy-associated disability, thus improving overall quality of life [44].

Sveinsson et al. (2020), in a nationwide case–control study, identified polytherapy with three or more ASMs as associated with a significantly reduced SUDEP risk (OR 0.31, 95% CI 0.14–0.67). While cenobamate was not directly studied in this context, these findings underscore the importance of seizure control—particularly for FBTC seizures—in mitigating SUDEP risk, which cenobamate effectively addresses [45].

Furthermore, a multicenter real-world cohort emphasized meaningful improvements in general clinical status, including perceived well-being, sleep quality, and cognitive performance. These multidimensional effects—alongside seizure control—align with emerging expectations for epilepsy therapy to enhance daily functioning and autonomy [46].

Despite these promising results, limitations remain. Cenobamate's direct impact on SUDEP has been assessed in only one retrospective study, and there is a lack of long-term data specifically evaluating early add-on use. Additionally, data on its safety and efficacy in cognitively impaired populations are limited [47]. Nevertheless, the robust evidence for seizure reduction and improved quality of life supports cenobamate's early use in drug-resistant epilepsy management as a strategy to indirectly address SUDEP risk and enhance patient outcomes.

Thesis 7: Cenobamate Should Be Considered a Therapeutic Option for Patients with Drug-Resistant Epilepsy Before Evaluating Surgical Intervention

Cenobamate has shown potential as a valuable treatment for patients with drug-resistant focal epilepsy, particularly as a non-invasive alternative to surgical intervention. Laxer et al. (2024), in their expert panel recommendations, highlighted cenobamate's ability to achieve seizure freedom in a significant proportion of patients with treatment-resistant focal epilepsy, including those previously referred for surgery. The panel recommended a trial of cenobamate before surgical evaluation, especially for patients considered suboptimal candidates for surgery because of factors such as advanced age, comorbidities, or reluctance to undergo invasive procedures.

Furthermore, cenobamate was suggested as an alternative to neuromodulation therapies, such as vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS) [48]. Notably, a potential synergy between cenobamate and VNS was highlighted, as evidenced by reports of improved outcomes when the two are used together. For instance, in a recent case study, the combination of cenobamate and VNS led to significant seizure reduction, demonstrating the potential benefits of this integrated approach in managing drug-resistant focal epilepsy [49].

Wiebe et al. (2001), in a landmark randomized controlled trial comparing surgery to prolonged medical therapy for temporal-lobe epilepsy, demonstrated superior outcomes for surgical intervention, with 58% of patients in the surgical group achieving seizure freedom compared to 8% in the medical group. However, adverse effects of surgery were reported in 10% of cases, and surgery remains unsuitable for patients with multifocal or non-lesional epilepsy [50]. It is worth noting that this study predates the introduction of many newer ASMs, including cenobamate, raising questions about whether these outcomes would remain consistent if the study were conducted today. Additionally, advancements in surgical techniques since 2001 may have improved efficacy and reduced adverse event rates, further complicating direct comparisons to contemporary treatment options.

Before considering surgical intervention, a trial of cenobamate may be appropriate, particularly for patients who express apprehension about invasive procedures or have comorbidities that increase surgical risks. However, it is crucial to emphasize that for certain specific epilepsy syndromes, surgical intervention can be recommended even after the failure of a single ASM, as it may offer curative potential. In such cases, early evaluation for surgery must not be delayed unnecessarily. The use of cenobamate should be viewed as an option in selected cases,

particularly when patients themselves prefer to explore non-invasive alternatives before committing to surgery. Cenobamate may be considered as a non-invasive therapeutic option in selected cases, particularly for patients not eligible for or reluctant to undergo surgery. However, in syndromes where surgical treatment is curative, early surgical evaluation remains the recommended standard. Currently, no direct comparisons between cenobamate and surgery are available, and any positioning must be interpreted with caution. Supporting and participating in clinical studies that evaluate the long-term effectiveness and safety of cenobamate, especially in underrepresented populations, will further enhance our understanding of its role within a comprehensive epilepsy management strategy.

DISCUSSION

While the structured controversy method facilitates dynamic discussion and integration of diverse clinical perspectives, it does not substitute for formal evidence synthesis. The absence of a systematic review protocol and the reliance on narrative data selection limit reproducibility and introduce potential bias. As such, the recommendations presented should be interpreted as expert-informed, but not guideline-level evidence.

Cenobamate has emerged as a significant advancement in the management of drug-resistant focal epilepsy, offering a novel therapeutic option with a unique dual mechanism of action—enhancing inhibitory GABAergic currents and attenuating persistent sodium currents [22]. Evidence from clinical trials and real-world studies supports the early introduction of cenobamate after the failure of two ASMs, rather than reserving it for later stages of treatment.

Introducing cenobamate earlier in the treatment regimen may lead to better clinical outcomes by achieving substantial seizure reduction and increasing the likelihood of seizure freedom, similar to the outcomes observed with other effective ASMs. Studies by Rosenfeld et al. and Winter et al. [28, 29, 39] have demonstrated high retention rates and significant reductions in seizure frequency when cenobamate is used after the failure of two ASMs. Early intervention with cenobamate can reduce the cumulative burden of seizures, and potentially prevent long-term complications associated with uncontrolled seizures, such as physical injuries, hospitalizations, and neuropsychological decline.

While cenobamate requires a titration period to minimize adverse effects like somnolence and dizziness, post hoc analyses, such as those by Sperling et al. (2021) and Aboumatar et al. (2022), suggest that a certain degree in seizure reductions may occur during the titration phase [32, 33]. However, the full therapeutic efficacy is typically achieved at the recommended maintenance doses. This necessitates careful titration protocols, thorough patient education, and close monitoring to maximize therapeutic benefits while minimizing risks. Additionally, the lack of robust long-term safety data in specific populations—such as women of childbearing age, older patients, and individuals with comorbidities—raises concerns. Further research is needed to evaluate potential drug–drug interactions, especially in polytherapy contexts, and to understand its impacts across broader health domains [29].

Cenobamate's efficacy extends beyond seizure control to improvements in quality of life. Enhanced daily functioning, reduced seizure-related injuries, and the potential to decrease the risk of SUDEP in epilepsy collectively contribute to better long-term outcomes. By effectively controlling FBTC seizures, which are strongly associated with SUDEP, cenobamate may indirectly reduce SUDEP risk [39]. Studies have also reported cognitive benefit and improvement in verbal and visuospatial episodic memory scores, potentially linked to a reduction in polytherapy and associated side effects [31, 36]. The clinical and real-world outcomes observed with cenobamate appear consistent with broader trends in ASM development, particularly regarding the correlation between early effective treatment and improved seizure control, as highlighted in prior long-term cohort studies. However, the small sample size in these studies (e.g., 20 patients in Serrano-Castro et al. and 32 in Catalan-Aguilar et al.) and the lack of long-term

follow-up limit the generalizability of their findings and emphasize the need for larger, more representative cohorts [31, 36].

Defining "long-term prognosis" remains complex and multifaceted. While seizure freedom and cognitive stability are critical, outcomes such as autonomy, social integration, and survival must also be considered. Critics have pointed out the limited availability of long-term data on cenobamate's broader impacts, particularly in underrepresented populations. Gaps remain in understanding its effects on psychiatric outcomes, sleep quality, and functional independence. The relatively small number of patients in many studies and the underrepresentation of specific populations, including older patients and women of childbearing age, further limit generalizability. Moreover, while the pharmacologic effects of cenobamate are expected to be generalizable, healthcare system differences and population diversity may affect external validity. Further data from other regions are warranted. The importance of longitudinal studies is emphasized to clarify cenobamate's sustained impact on long-term outcomes, including SUDEP prevention, functional independence, and comorbidity management.

The potential of cenobamate to simplify treatment regimens is a critical consideration. Its robust efficacy and intrinsic dual mechanism of action allow for the possibility of reducing polytherapy, which is often associated with increased risks of drug–drug interactions and cumulative side effects. Simplifying treatment regimens can improve patient adherence, enhance quality of life, and reduce the healthcare burden associated with managing complex medication schedules. Cenobamate's once-daily dosing and its ability to lower the overall therapeutic burden of ASMs may also enhance patient adherence and simplify treatment regimens [29]. By effectively serving as a "rational monotherapy," cenobamate may indeed reduce the reliance on multiple medications, thereby minimizing the risks associated with polytherapy.

Despite these advantages, limitations exist in defining cenobamate as an "ideal treatment." Of note, the term "ideal" suggests a comparative claim that requires robust head-to-head data, which are currently lacking. Hence, available studies demonstrate cenobamate's efficacy, safety, and tolerability, although they do not provide definitive conclusions. Adverse effects remain concerns, as highlighted by Rosenfeld et al. [28, 39]. While direct head-to-head comparisons with other ASMs are lacking, indirect comparisons provide valuable insights. Lattanzi et al. (2022), through a network meta-analysis (NMA), ranked cenobamate highest for ≥ 50% responder rates compared to brivaracetam, eslicarbazepine, lacosamide, and perampanel. Although cenobamate showed trends favoring seizure freedom, they were not statistically significant [51]. Mullheron et al. (2024), in a separate Bayesian NMA, confirmed cenobamate's superior efficacy for both ≥ 50% responder rates and seizure freedom over all analyzed ASMs. Both studies noted that brivaracetam and lacosamide had more favorable tolerability profiles, with fewer treatment-emergent adverse events (TEAEs) [52].

Based on current evidence, practical recommendations for using cenobamate can be outlined. Clinicians should consider introducing cenobamate after the failure of two ASMs in patients with focal seizures, particularly when predictors of drug resistance are present, such as hippocampal sclerosis [53, 54]. Following recommended titration schedules, educating patients about potential side effects, and closely monitoring them during the initiation phase are crucial steps to minimize adverse effects. Additionally, evaluating opportunities to reduce the number of concomitant ASMs can help limit drug–drug interactions and enhance patient adherence.

Assessing the suitability of cenobamate on a case-by-case basis is essential, taking into account factors such as seizure type, treatment history, comorbidities, potential side effects, and patient preferences. Clinicians should remain vigilant for potential long-term adverse effects, particularly in special populations, and report any safety concerns to contribute to the growing body of evidence. Cenobamate should be considered before evaluating surgical interventions in patients with drug-resistant focal epilepsy [48]. However, for surgically remediable epilepsies, such as mesial temporal sclerosis or benign lesions, cenobamate should not delay timely

surgical intervention when the likelihood of a curative outcome is high.

With regards to the Italian context, ensuring equitable access to cenobamate is also critical, particularly in regions where availability is limited.

CONCLUSION

Cenobamate represents a promising addition to the therapeutic armamentarium for managing drug-resistant focal epilepsy. Its early introduction—following the failure of two adequately dosed ASMs—has the potential to significantly improve seizure control, enhance quality of life, and reduce the risks associated with uncontrolled seizures and complex polytherapy. Through careful titration, comprehensive patient education, and individualized treatment planning, clinicians can optimize its clinical benefits.

This manuscript contributes to the scientific understanding of treatment strategies in refractory epilepsy by applying a structured controversy methodology that integrates emerging clinical data, real-world evidence, and expert insights. By emphasizing early cenobamate use as a viable approach, it advances the ongoing conversation on how best to position newer antiseizure medications in clinical practice—particularly regarding timing, patient selection, and therapeutic optimization.

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Declarations

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