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Review

Therapeutic strategies during cenobamate treatment initiation: Delphi panel recommendations

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***Abstract*:** The goal of epilepsy treatment is seizure freedom, typically with antiseizure medication (ASM). If patients fail to attain seizure control despite two trials of appropriately chosen ASMs at adequate doses, they are classified as having drug-resistant epilepsy (DRE). Adverse events (AEs) commonly occur in people with DRE because they are typically on ⩾2 ASMs, increasing the potential for drug–drug interactions. Early emerging AEs may impact adherence, decrease quality of life, and delay achieving optimal treatment dosages. Cenobamate is an oral ASM with a long half-life which has proven to be highly effective in clinical trials. An international Delphi panel of expert epileptologists experienced in the clinical use of cenobamate and other ASMs was convened to develop consensus best practices for managing patients during and after cenobamate titration, with consideration for its known pharmacokinetic and pharmacodynamic interactions, to allow patients to reach the most appropriate cenobamate dose while limiting tolerability issues. The modified Delphi process included one open-ended questionnaire and one virtual face-to-face meeting. Participants agreed that cenobamate can be prescribed for most patients experiencing focal-onset seizures. Patients initiating cenobamate therapy should have access to healthcare professionals as needed and their treatment response should be evaluated at the 100-mg dose. Patients with intellectual disabilities may need additional support to navigate the titration period. Proactive down-titration or withdrawal of sodium channel blockers (SCBs) is recommended when concomitant ASM regimens include ⩾2 SCBs. When applicable, maintaining a concomitant clobazam dose at ~5–10 mg may be beneficial. Patients taking oral contraceptives, newer oral anticoagulants, or HIV antiretroviral medications should be monitored for potential interactions. Because clinical evidence informing treatment decisions is limited, guidance regarding dose adjustments of non-ASM drugs was not developed beyond specific recommendations presented in the Summary of Product Characteristics.

Keywords: cenobamate, Delphi panel, drug–drug interactions, epileptologist, focal epilepsy, titration

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Introduction

The major goal of epilepsy treatment is seizure freedom, commonly achieved with antiseizure medications (ASMs). Approximately one-third of people with epilepsy will be classified as having drug-resistant epilepsy (DRE), failing to attain seizure control despite trials of two or more appropriately chosen ASMs at adequate doses.[1,2] Poor seizure control increases risk of mortality, including sudden unexpected death in epilepsy and other physical and psychological comorbid conditions.[1] Even while adhering to the principle of

rational polytherapy when ASMs with differing mechanisms of action (MoA) are used, adverse events (AEs) can be compounded. Pharmacokinetic (PK) interactions may be observed early in titration and are possible even when the patient is taking lower doses of ASMs, such as those involving metabolism through the cytochrome P450 (CYP450) pathway. These can alter drug exposures, leading to either higher or lower plasma concentrations of the concomitant ASM(s).[3] Medications that exhibit a long half-life or that have a similar MoA to cenobamate [e.g. sodium channel blockers (SCBs)], when taken concomitantly with cenobamate, may lead to pharmacodynamic (PD) interactions; however, these are typically observed at higher cenobamate doses and emerge later in the titration period.[3,4]

Cenobamate is an oral ASM with a long half-life and dual MoA that both blocks voltage-dependent sodium channels by preferentially inhibiting the persistent sodium current and functions as a positive allosteric modulator of γ-aminobutyric acid ($GABA_A$) receptors at non-benzodiazepine sites.[5–7] During the initial cenobamate clinical trial program, adjunctive cenobamate was shown to be effective in reducing focal-onset seizures and demonstrated a satisfactory tolerability profile, regardless of suspected, predicted, or known PK and PD interactions.[8–10] Sustained efficacy with cenobamate treatment was also observed over 41 months in the Polish Expanded Access Programme, which included ⩾50% seizure reduction (63.1% of patients) and an overall 100% retention rate; in addition, no new tolerability issues were reported.[11] The most commonly observed treatment-emergent adverse events (TEAEs) reported with adjunctive cenobamate therapy, which can be predicted based on the MoA, were related to the central nervous system and included dizziness, fatigue, and somnolence (these have also been reported following treatment with other ASMs such as SCBs or GABAergic drugs).[8–10,12–14] Product labeling for cenobamate in Europe stipulates that cenobamate should only be initiated as an adjunctive ASM for treatment of adults with focal-onset seizures who have failed two appropriate ASMs due to a lack of efficacy or tolerability. The United States Food and Drug Administration does not require the patient to have failed two prior ASMs and permits cenobamate use earlier. Practical guidance for managing adults receiving adjunctive cenobamate for treatment of focal epilepsy was published in 2021, offering treatment goals, suggested target doses, and strategies for mitigating potential AEs.[15] In 2022, an expert opinion paper was published that discussed dose adjustments of concomitant ASMs with adjunctive cenobamate treatment and provided specific recommendations for adjusting the doses of concomitant ASMs, including cannabidiol, carbamazepine, clobazam, lacosamide, lamotrigine, phenobarbital, phenytoin, and others.[4]

Additional expert opinion can further elucidate effective methods for successfully managing patients who initiate cenobamate treatment through the titration period and beyond. Recognizing that expert opinion evolves with greater experience and that wider use of cenobamate has created new questions to answer reflecting international clinical practice differences, a Delphi panel was assembled to develop consensus for patient management with the goals of identifying appropriate treatment candidates, addressing treatment challenges, optimizing efficacy with safety, and managing concomitant medications. The expert consensus presented in this manuscript augments prior recommendations and provides additional suggestions for guiding individuals through the cenobamate titration period to help achieve treatment goals.

Methods

A Delphi panel was convened to develop consensus on best practices/practical considerations for managing patients during the 10-week titration of cenobamate and beyond, with the goals of (1) identifying appropriate candidates for cenobamate therapy beyond those narrowly specified in the clinical trial protocols; (2) developing strategies to address challenges for patients and prescribers when initiating cenobamate treatment; (3) balancing efficacy and safety to achieve optimum patient outcomes, including seizure freedom; and (4) managing concomitant medications (ASMs and non-ASMs) during cenobamate titration.

The modified Delphi process utilized by the group is described in Figure 1 and included an open-ended questionnaire (round 1) and one virtual face-to-face meeting (round 2). Development of questions for the survey was based on clinical

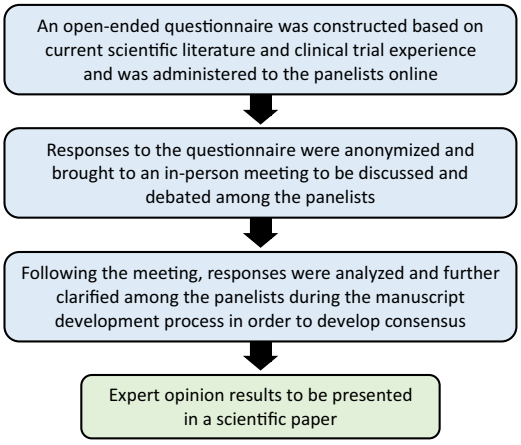

Figure 1. Modified Delphi process methodology.

trial experience and previously published consensus recommendations for dosing adjustments.[4,15] Expert opinions collected from the questionnaire were presented and debated in a group setting. Off-label use of cenobamate was considered out of scope.

Seven international epileptologists who are experienced in the clinical use of cenobamate were identified as experts for the Delphi panel based on their participation in the cenobamate clinical development program and/or treatment of at least 50 patients with adjunctive cenobamate. All panelists consented to participate in the meeting, understood the objectives of the project, and gave verbal agreement to participate in the development of the manuscript describing the output of the panel's discussion. Recommendations for management of patients who require dose adjustments of concomitant ASMs to maximize tolerability and safety during adjunctive cenobamate titration are presented herein.

Topics for discussion included the following: practical considerations for identifying appropriate candidates for cenobamate therapy, management of concomitant ASMs and other non-ASM co-medications, best practices for navigating the cenobamate titration period, continuation of titration to achieve seizure freedom (or, alternatively, until reaching maximum seizure reduction), and management of tolerability issues that may arise during titration. Key takeaways are shown in Figure 2, and full results of the Delphi process are presented in the supplemental material.

Results

Practical considerations for identification of potential candidates for cenobamate therapy

Panelists offered their recommendations for identifying suitable candidates for cenobamate therapy, which reflected the approved indication described in the Summary of Product Characteristics (SmPC). In Europe, appropriate candidates for treatment are those experiencing focal-onset seizures who have failed two appropriate ASMs due to a lack of efficacy or tolerability; however, in the United States, the FDA-approved use does not require the patient to have failed two prior ASMs and permits cenobamate use as initial monotherapy. The panelists recognized that patients with disabling or potentially hazardous seizures despite previous treatment with two ASMs may be prioritized as candidates for treatment.

Published data on surgical candidates demonstrated the efficacy of cenobamate treatment in patients whose seizures remained uncontrolled after epilepsy-related surgery; however, little information is available on cenobamate therapy as an alternative to surgery.[16] The panelists agreed that neurologists should consider treatment with cenobamate prior to recommending some specific types of surgery, but they did not reach agreement on whether a trial of cenobamate should always be initiated in patients prior to a surgery referral. Ultimately, each patient who fails 2 ASMs and for whom seizure control is a priority might benefit from cenobamate therapy and should be evaluated on an individual basis.

Best practices and practical considerations for navigating the cenobamate titration process

The panel discussed strategies to support patient adherence and limit titration-linked TEAEs, and members emphasized the importance of an open communication channel with patients at key milestones for the purpose of reevaluation. During the cenobamate titration period, patients should be followed closely and should have access to a healthcare provider, as needed, to manage patient expectations regarding efficacy and tolerability issues.

When initiating a protocol for cenobamate, as for any additional ASM, a 4-step process is helpful

➢ Cenobamate is a useful treatment for epilepsy patients who have failed 2 ASMs, especially where seizures are frequent or severe, and use should not be restricted to specific patient categories
➢ Titration should generally follow 2-week up-titration intervals but consider following up more closely and implementing individualized titration schedules for special patient groups to achieve the best balance between efficacy and tolerability
➢ A 4-step process was suggested for managing ASMs: Precontemplation, Contemplation, Preparation, and Action
➢ Open and regular communication between the patient and provider is critical to improve adherence, and it is recommended to check in with the patient before or when reaching the 100-mg dose
➢ Concomitant ASM discontinuation should use a slow withdrawal schedule unless the issue is tolerability, in which case a faster down-titration is suggested
➢ For patients with intellectual disabilities, additional support is needed to navigate the titration period; for those taking oral contraceptives, drug levels should be monitored
➢ Consult specialists when questions arise about concomitant medications for indications other than epilepsy
➢ The group generally agreed that non-ASM medications, especially those primarily metabolized by the liver (CYP3A4, 2B6, and 2C19), should be monitored more closely
➢ Short QT syndrome should only be a concern for patients with a significantly shortened QT on ECG or a family history of Short QT syndrome

Figure 2. Key takeaways from the Delphi panel.

and should also be used when amending ASM regimens. This process includes the following: (a) Background: acquiring clinical data, building rapport with the patient, and establishing expectations and goals; (b) Discussion of the new ASM: describing the drug MoA and discussing both the possibility of seizure freedom and the potential TEAEs patients may encounter; (c) Preparation: conducting laboratory testing including blood work and reviewing electrocardiogram (ECG) tracing if deemed necessary; and (d) Action: providing the patient with recommendations during the titration schedule and establishing a follow-up protocol.

To improve patient adherence, open communication between the patient and provider is critical. The panel recommended that a member of the healthcare team should evaluate patients taking cenobamate once they reach the 100 mg/day dose level to assess the response to treatment and the tolerability profile to inform subsequent clinical decision-making. Only one panelist disagreed with the group consensus on this point and emphasized the importance of closer patient monitoring prior to reaching the cenobamate dose of 100 mg/day. Finally, the panel agreed that patients should be informed that, although low, and minimized by the current titration schedule described in the SmPC, there is a risk of drug reaction with eosinophilia and systemic symptoms. If a new rash occurs, patients should be instructed to not take their next dose of cenobamate, to photograph the rash, and to contact their physician immediately.

Management of concomitant medications

Co-medication management is important during and after the cenobamate titration period to maximize seizure control and prevent or minimize tolerability issues. A concise guide is provided in

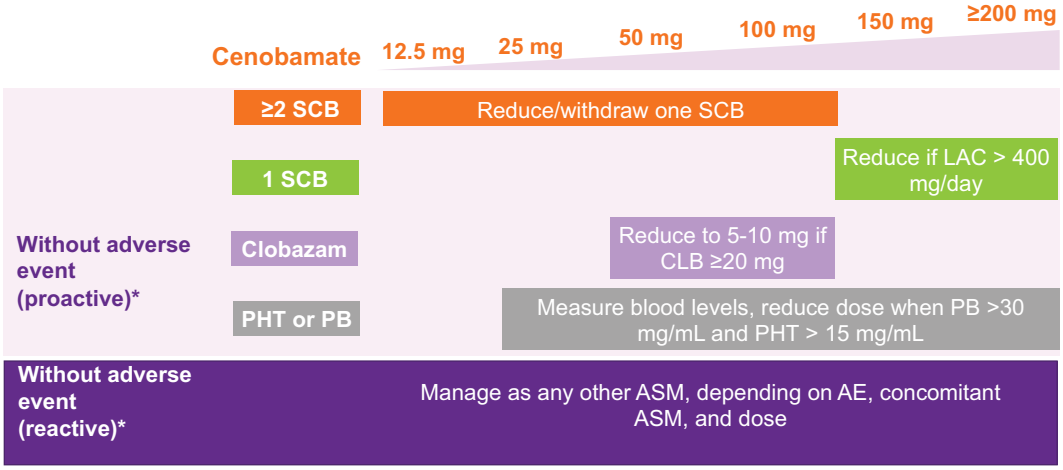

Figure 3. Summary of concomitant ASM management strategies.
*On a case-by-case basis, considering type of ASM, doses, blood levels, tolerability to ASMs, patients' comorbidities, and disease severity, type, and frequency of seizures.
ASM, antiseizure medication; CLB, clobazam; LAC, lacosamide; PB, phenobarbital; PHT, phenytoin; SCB, sodium channel blocker.

Supplemental Figure S1 that summarizes panel recommendations for proactive and reactive strategies to lower or monitor patient co-medications during and after the titration period. This guide also provides topics for communication between the patient and provider throughout treatment, with the goal of improving patient adherence and achieving treatment goals.

Proactive ASM management

Patients treated with multiple concomitant ASMs may require management of other medications during cenobamate titration (Figure 3). Proactive down-titration or withdrawal of SCBs is recommended when cenobamate is being added to an existing regimen that consists of two or more concomitant SCBs. Dose reductions of lacosamide should be considered for those taking ⩾400 mg/day. Lacosamide may have adverse PD drug–drug interactions (DDIs) with cenobamate. Proactive reduction of clobazam is recommended for patients who are prescribed a high dose of clobazam (e.g. ⩾40 mg/day). Complete withdrawal of clobazam may not be necessary as maintaining the dose at 5–10 mg can be beneficial.[17]

Reactive ASM management

During cenobamate titration, if a patient experiences TEAEs commonly associated with SCBs such as dizziness, headache, nausea, or vomiting, the concomitant SCB dosage should be reactively reduced (Figure 3). If a patient is experiencing somnolence or fatigue, the provider should consider reducing concomitant benzodiazepines. In addition, drug monitoring for patients who are prescribed concomitant phenobarbital or phenytoin is recommended to monitor for increased phenytoin and phenobarbital plasma concentration. A slower cenobamate down-titration schedule may be recommended when concomitant ASMs are being reduced due to lack of efficacy. A quicker cenobamate withdrawal schedule may be indicated when a serious TEAE develops. Processes for managing patient TEAEs during titration include proactively discussing potential side effects with individuals, checking in with the patient regularly while titrating to the optimal maintenance dose, contacting patients every month during titration either directly or with the help of a nurse when possible, and having the patient stay in touch *via* email or phone to report any emergent issues.

Management of non-ASM co-medications

When managing individuals with epilepsy who are also prescribed medications for indications other than epilepsy, specialist consultations should be sought when questions arise regarding polypharmacy. Clearance of drugs metabolized

by the liver may be altered by cenobamate. Specifically, levels of medications metabolized by CYP3A4 and 2B6 may decrease, while levels of drugs that are metabolized by CYP2C19 may increase.[4] Therefore, it is recommended to monitor drug levels of chronically used medications and those with narrow therapeutic indices.

Best practices for specific patient subpopulations

As general guidance, cenobamate should be up-titrated at 2-week intervals (per the SmPC). In clinically indicated cases, patients may need to follow a slower titration schedule than that recommended in the SmPC. Although a recent publication demonstrated that there were no differences in the incidence of TEAEs observed among patients undergoing titration according to the SmPC or at an even slower rate,[18] prescribers might consider utilizing a slower titration for special patient groups as follows: (1) patients who have manifested previous severe rashes on other therapies; (2) patients taking multiple concomitant medications who have previously experienced AEs associated with other ASMs; (3) patients who have a heavy burden of psychiatric medications; and (4) patients with a very high load of concomitant ASMs (three or more). Patients with intellectual disabilities may need additional support to navigate the titration process successfully.

Two particular groups of patients require additional attention when using cenobamate. Patients who are taking co-medications with potential PK interactions, such as newer oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) or HIV antiretroviral medications, may require regular monitoring to avoid clinically significant interactions. As with any ASM, care should be taken in treating women of childbearing potential as there are no data regarding cenobamate and pregnancy in humans. Women under consideration for cenobamate therapy should receive thorough counseling and consider alternative options to oral contraceptives, including the use of an effective long-term contraceptive such as an intrauterine device. In all cases, a follow-up visit in person or online is recommended when the patient reaches the 100-mg dose, and patients should be encouraged to communicate any issues that have emerged at that time.

Discussion

An international Delphi panel was convened to develop consensus recommendations for managing patients throughout cenobamate titration and beyond, with the primary goal of maximizing efficacy while preventing or managing tolerability issues, allowing patients to reach the most appropriate cenobamate dose. Polymedicated patients may require adjustment of one or more concomitant ASMs during cenobamate titration; therefore, recommendations for dose reduction of these drugs using both proactive and reactive strategies to mitigate TEAEs were discussed. Proactive down-titration or withdrawal of concomitant ASMs was recommended when existing treatment regimens include two or more or SCBs, as well as for regimens with lacosamide ($\geqslant$400 mg/day) or clobazam ($\geqslant$40 mg/day). In some instances, reduction of cenobamate should be considered if AEs occur without any improvement in efficacy despite the target dose having been achieved, and providers should plan for a more cautious up-titration when re-initiating cenobamate if seizures recur. Of note, early efficacy starting at cenobamate 25 mg/day has previously been observed.[19] Reactive down-titration of concomitant benzodiazepines is recommended when an individual experiences somnolence or fatigue. For individuals taking phenobarbital or phenytoin, drug monitoring is suggested. A *post hoc* analysis of the phase III open-label safety study evaluated concomitant ASM adjustment during cenobamate treatment initiation.[20] The analysis demonstrated that concomitant ASM dose reductions were associated with more patients remaining on cenobamate. The concomitant ASM reduction, commonly due to CNS side effects, occurred mainly during the cenobamate titration phase. No cases of seizure exacerbation with early concomitant ASM reduction were reported. Clinical experience by panel members who have each treated >100 patients with cenobamate corroborates these findings. Cenobamate plasma levels and the plasma level monitoring of concomitant drugs might be helpful in certain clinical situations; upcoming studies address these circumstances.[21] Plasma level monitoring was not prioritized for this panel deliberation given that cenobamate has low 'victim' potential and the interactions with cenobamate and most concomitant ASMs do not significantly affect the disposition of cenobamate.

Guidance regarding dose adjustments of non-ASM drugs in patients taking cenobamate is challenging due to limited clinical evidence informing treatment decisions. The selection of appropriate ASMs in women of childbearing age is a decision based on patient and disease characteristics as well as patient choice regarding potential future pregnancies. There is a predicted but as yet incompletely quantified interaction with oral contraceptives, so as with any new ASM, management of contraception in women of childbearing potential is necessary when initiating cenobamate therapy; this is especially important because no data are currently available on teratogenesis.[22] Women of childbearing age should be informed that there may be alternative medication options that have a relatively high safety profile in the case of pregnancy. When cenobamate is chosen as the appropriate drug, adjustment of contraceptive methods similar to that used with other hepatic enzyme-inducing ASMs should be considered. Pregnancy registries will potentially help to monitor the evolving pregnancy experience and reporting is encouraged (see https://eurapinternational.org/eurap-registry-organisation/ for more information on the central registry).

Measuring plasma levels of concomitant medications may not always be possible and care should be taken if there is clinical suspicion of the potential for a significant drug interaction. Although experience managing cenobamate and commonly prescribed concomitant ASMs is increasing, caution is still advised when using any ASM with infrequently prescribed or new-to-market medications. Some DDIs may be theoretical, while some may only affect certain individuals and, thus, are not commonly observed. Monitoring newer oral anticoagulants was suggested, along with proceeding cautiously during treatment with these drugs, due to the potential risk of serious AEs or loss of efficacy. For patients taking antidepressants or antipsychotics, hypnotics should be reduced if somnolence increases. Patients should be advised to consult appropriate specialists. For patients taking concomitant medications metabolized by the liver, the benefits of treatment should be balanced with the risks of any potential interactions. Input from pharmacist colleagues may be helpful in this regard. The effect on the electrical activity that occurs between the Q and T waves (QT interval) may be a concern for patients diagnosed with familial Short-QT Syndrome, a very rare condition; in this population, cenobamate is contraindicated. Future research is needed to assess the efficacy and tolerability of adjunctive cenobamate when a patient is concurrently undergoing chemotherapy or other oncology treatments. Oncology patients (in particular, older patients) are generally not included in registered clinical trials due to the risk of DDIs.

Cenobamate induces the CYP450 isoenzymes CA4 and 2B6 and moderately inhibits CYP2C19.[23] Previous research has indicated that PK interactions may occur between cenobamate and other drugs such as bupropion, midazolam, and omeprazole.[23] Coadministration of cenobamate with bupropion and midazolam was found to induce both CYP3A4/5 and CYP2B6 enzymes; the combination of cenobamate and omeprazole inhibited CYP2C19 activity; and no effect on CYP2C9 was observed following coadministration of cenobamate with warfarin.[23] While a clinically significant interaction between warfarin and cenobamate is unlikely, monitoring of the international normalized ratio should continue to ensure no variation in effect. These interactions may require dose adjustments of drugs that are metabolized by CYP450 pathways when administered in conjunction with cenobamate in order to maximize efficacy while minimizing tolerability issues.[23] The cenobamate mean plasma concentration/dose administered ratio may be reduced by strong concomitant inducers; however, these findings should not impact cenobamate's initial dosing because it is titrated slowly to clinical effectiveness.[24]

Almost all individuals referred for surgery are eligible for treatment with cenobamate, but it is unknown whether surgery or cenobamate treatment is more effective for patients. Prior evaluation of surgery in patients with focal seizures revealed that successful surgery could be neuroprotective and prevent ongoing neurodegeneration.[25] However, not all patients are willing to undergo surgery, and successful treatment with cenobamate could potentially reduce the waiting list time for those patients with a higher need for surgical intervention, based on previous clinical trial results in which cenobamate therapy following surgery in highly refractory patients was found to be effective.[18,26]

Limitations and strengths of the Delphi method

Advantages of the Delphi process include anonymity during the polling and questionnaire process

and the capability of reaching agreement among participants in a specific area that lacks sufficient evidence-based knowledge. It is also a relatively efficient, flexible, and adaptable method that can stimulate fresh ideas and provide motivation and further education for the panelists.[27] Limitations of the Delphi process include that it does not constitute empirical evidence and that results may be biased by the selection of panel members and the content of the questionnaire.[27] In addition, the panel was composed of seven participants, limiting the diversity of opinion, and the patient/caregiver perspective was not considered.[27]

Conclusion

To develop consensus on best practices for patient management during the 10-week titration of cenobamate and beyond, a Delphi panel was convened with the overarching goals of identifying appropriate treatment candidates, addressing challenges encountered during initiation of treatment, discussing strategies to balance efficacy and safety, and managing concomitant medications. The participants agreed that cenobamate is highly effective in reducing seizures for individuals with focal-onset epilepsy and provided additional suggestions for treating particular subgroups of patients. They also discussed considerations for dose adjustments of concomitant ASMs; however, panelists avoided providing specific recommendations on dose adjustments for non-ASMs due to the current limited clinical evidence informing treatment decisions. It is also suggested that health economics and outcome research should be conducted in the future to support evidence-based treatment guidelines. Recommendations provided by this Delphi panel expand upon previously published guidance and offer additional strategies for managing patients during cenobamate titration and throughout treatment.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

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Elinor Ben-Menachem: Conceptualization; Investigation; Writing – original draft; Writing – review & editing.

Pavel Klein: Conceptualization; Investigation; Writing – original draft; Writing – review & editing.

Jukka Peltola: Conceptualization; Investigation; Writing – original draft; Writing – review & editing.

Bettina Schmitz: Conceptualization; Investigation; Writing – original draft; Writing – review & editing.

Rhys H. Thomas: Conceptualization; Investigation; Writing – original draft; Writing – review & editing.

Vicente Villanueva: Conceptualization; Investigation; Writing – original draft; Writing – review & editing.

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Competing interests

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Availability of data and materials

Data related to this study are available from the corresponding author upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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