Epilepsy Currents
2023, Vol. 23(6) 348-350

DOI: 10.1177/15357597231197105
journals.sagepub.com/home/epi
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Cenobamate: Real-World Experience Matches Clinical Trials

Adjunctive Cenobamate in Highly Active and Ultra-Refractory Focal Epilepsy: A "Real-World" Retrospective Study

Pena-Ceballos J, Moloney PB, Munteanu T, Doyle M, Colleran N, Liggan B, Breen A, Murphy S, El-Naggar H, Widdess-Walsh P, Delanty N. *Epilepsia*. 2023;64(5):1225-1235. doi:10.1111/epi.17549

Objective: Recent clinical trials have shown that cenobamate substantially improves seizure control in focal-onset drug-resistant epilepsy (DRE). However, little is known about cenobamate's performance in highly active ($\geq$20 seizures/month) and ultra-refractory focal epilepsy ($\geq$6 failed epilepsy treatments, including antiseizure medications [ASMs], epilepsy surgery, and vagus nerve stimulation). Here, we studied cenobamate's efficacy and tolerability in a "real-world" severe DRE cohort. Methods: We conducted a single-center retrospective analysis of consecutive adults treated with cenobamate between October 2020 and September 2022. All patients received cenobamate through an Early Access Program. Cenobamate retention, seizure outcomes, treatment-emergent adverse events, and adjustments to concomitant ASMs were analyzed. Results: Fifty-seven patients received cenobamate for at least 3 months (median duration, 11 months). The median cenobamate dose was 250 mg/day (range 75–350 mg). Baseline demographics were consistent with highly active (median seizure frequency, 60/month) and ultra-refractory epilepsy (median previously failed ASMs, nine). Most (87.8%) had prior epilepsy surgery and/or vagus nerve stimulation. Six patients stopped cenobamate due to lack of efficacy and/or adverse events. One patient died from factors unrelated to cenobamate. Among patients who continued cenobamate, three achieved seizure freedom (5.3% of cohort), 24 had a 75%–99% reduction in seizures (42.1% of cohort), and 16 had a 50%–74% reduction (28.1% of cohort). Cenobamate led to abolition of focal to bilateral tonic–clonic seizures in 55.6% (20/36) of patients. Among treatment responders, 67.4% (29/43) were treated with cenobamate doses of $\geq$250 mg/day. Three-fourths of patients reported at least one side-effect, most commonly fatigue and somnolence. Adverse events most commonly emerged at cenobamate doses of $\geq$250 mg/day. Side-effects were partially manageable by reducing the overall ASM burden, most often clobazam, eslicarbazepine, and perampanel. Significance: Patients with highly active and ultra-refractory focal epilepsy experienced meaningful seizure outcomes on cenobamate. Emergence of adverse events at doses above 250 mg/day may limit the potential for further improvements in seizure control at higher cenobamate doses.

Commentary

Cenobamate, approved by the US Food and Drug Administration (FDA) in November 2019, is a recent addition to the inventory of anti-seizure medications (ASMs). This commentary examines the evidence of cenobamate efficacy and its current position in the array of treatment options for patients with focal-onset seizures. In this article, "responder rate" refers to the proportion of patients achieving a seizure reduction of at least 50% compared to their baseline, and "seizure-free" denotes a complete elimination of seizures in a specified time frame unless stated otherwise.

Cenobamate Efficacy in Clinical Trials

Phase 2 studies for cenobamate revealed an impressive short-term seizure-free rate, generating excitement around this medication. In one study involving 222 patients with uncontrolled focal-onset seizures, adjunctive treatment with a daily dose of 200 mg of cenobamate resulted in a 50% responder rate and a 28% seizure-free rate during 6-week dose maintenance.[1] Another phase 2 study with 437 patients exhibited similarly promising outcomes, with patients receiving 200 mg/day of cenobamate achieving a 56% responder rate and an 11% seizure-free rate during a 12-week maintenance phase.[2] Higher doses of 400 mg/day showed even better responder rates (64%) and seizure-free rates (21%) although with more adverse effects. Long-term results further solidified cenobamate efficacy, with 16% of 354 patients achieving seizure freedom for a median duration of 45 months.[3] Moreover, a post hoc analysis of a phase 3 open-label study reported a 72% responder rate and a 13% seizure-free rate.[4]

Cenobamate Efficacy in Real-World Experience

Several real-world studies have explored the utilization of cenobamate in diverse populations. Among them, the study conducted by Pena-Ceballos stands out, providing additional evidence focusing on patients burdened with significantly higher seizure frequencies compared to most participants in the clinical trials.[5]

This study enrolled 57 patients, with 95% categorized as having "ultra-refractory" focal epilepsy, defined by a minimum of 6 treatment failures, including ASMs and surgery. Almost 90% of the patients had previously undergone epilepsy surgery, including the implantation of a vagus nerve stimulator (VNS). The median baseline seizure frequency was 60 seizures per month, significantly exceeding the baseline observed in the phase 2 studies (7-11 seizures per month). The study reported a responder rate of 70%, in keeping with clinical trial results. "Seizure freedom" was defined as the absence of seizures for at least 3 times longer than the longest interseizure interval preceding the intervention (determined from seizures occurring within the past 12 months) or a minimum of 12 months, whichever duration was longer. Using this definition, only 5.3% of patients achieved seizure freedom. Cenobamate significantly reduced seizures at daily doses ranging from 200 to 300 mg, while side effects tended to manifest at doses exceeding 250 mg per day.

The authors effectively demonstrate the benefits of cenobamate in patients with a substantially high seizure burden, as evidenced by their baseline seizure frequency, concurrent and previous ASMs, and surgery that failed to control their seizures. It is important to consider that the number of ASMs used and the occurrence of epilepsy surgeries can be influenced by health care provider preferences, particularly in single-center studies.

Another real-world retrospective study evaluated 170 adults with uncontrolled focal-onset epilepsy with comparable baseline seizure frequency relative to those in phase 2 studies but with more concurrent ASMs.[6] The responder rate was similar (63%), but the seizure-free rates were less impressive. In the post hoc analysis, 18% of patients experienced 3 months of seizure freedom, 19% achieved 6 months of seizure freedom, and none achieved 1 year of seizure freedom. Limited studies, including small cohorts of children, showed short-term efficacy comparable to that observed in adults.[7,8]

Cenobamate Versus Other Anti-Seizure Medications

More ASM choices did not translate to more chance of seizure freedom in the past decades. A long-term cohort study spanning 3 decades, from 1982 to 2012, even before cenobamate entered the scene, demonstrated that although the prescription of newer ASMs evolved over time, the seizure freedom rate remained unchanged throughout the years.[9] However, there is a glimmer of hope. If an initial ASM fails to bring seizure freedom, further adjustments still offer a 3% to 12% chance of achieving it, although the probability decreases with each additional ASM used.[10]

Choosing the right ASM for our patients is not a simple task. Efficacy is a crucial factor, but comparing the efficacy of different ASMs presents challenges. Conducting direct head-to-head comparative studies on efficacy and safety is ideal but often costly and not mandatory for regulatory approval, resulting in limited availability. As a result, our options for comparing ASMs primarily rely on systematic reviews and meta-analyses of clinical trial data. While interpreting such comparisons requires caution, the information is valuable.

In comparing cenobamate to other new-generation ASMs, Dr Perucca set side-by-side randomized placebo-controlled adjunctive-therapy trials of recently introduced ASMs, including perampanel, brivaracetam, everolimus, cannabidiol, cenobamate, fenfluramine, and ganaxolone. Among patients who completed the maintenance phase and achieved seizure freedom, cenobamate stood out with a seizure-free rate of 9% to 14%, surpassing other ASMs, which generally exhibited rates below 5%.[11]

Moreover, another study demonstrated an indirect treatment comparison by analyzing randomized, double-blind, placebo-controlled trials in adults with uncontrolled focal seizures. They evaluated the responder rates of cenobamate compared to other ASMs at FDA-recommended daily maintenance doses.[12] The study showed that cenobamate displayed a 2-fold higher responder rate than other new-generation ASMs (brivaracetam, eslicarbazepine acetate, lacosamide, and perampanel), indicating more favorable benefits. However, there were no significant differences in responder rates between cenobamate and older ASMs (lamotrigine, levetiracetam, and topiramate). Furthermore, the study supported the comparable safety profiles of cenobamate compared to other ASMs based on withdrawal rates resulting from side effects.

Cenobamate and Epilepsy Surgery

For carefully chosen patients, epilepsy surgery can be a life-changing intervention, resulting in seizure freedom in 30% to 70% of individuals following the first procedure.[13] For neuromodulation, including VNS, anterior nucleus thalamic deep brain stimulation, and responsive neurostimulation, the responder rate at 1 year was 40% for all 3 methods. The 2-year seizure-free rate is 0%, 13%, and 9%, respectively.[14]

In cases where seizures persist after surgery, further ASM adjustments may hold additional value. The study by Pena-Ceballos found that adding cenobamate to the treatment regimen resulted in responder rates of 60% to 80% for patients who had undergone previous epilepsy surgery, along with seizure freedom rates ranging from 5% to 12%.[5] In contrast, a post hoc analysis of an open-label extension study analyzing the benefit of cenobamate in patients with previous epilepsy surgery showed a higher seizure-free rate at 30%.[15] By considering the baseline monthly seizure frequency (median 60 vs 4), the number of concurrent ASMs (median 2 vs 4), and the proportion of patients with past epilepsy surgery as indicators of the severity

of underlying seizures, it becomes apparent that the population in Pena-Ceballos' study likely had a significantly higher seizure burden at the outset.

Last Note

While I use the responder and seizure-free rates as key comparisons in this commentary, these are just fractions of the real-life factors we consider when choosing a treatment for our patients. Regardless, cenobamate has shown promising efficacy in clinical trials and real-world experience, solidifying its position as a valuable adjunctive treatment for patients with focal-onset seizures despite their baseline seizure burden. With ongoing exploration, cenobamate instills optimism and opens a new avenue for individuals seeking effective seizure control.

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Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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