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CONGRESS REPORT

ANGELINI PHARMA SATELLITE SYMPOSIUM AT ILAE 2023, September 4th, Dublin

The impact of time lost to achieving meaningful seizure control

Contributions from
Patrick Kwan, Manuel Toledo, Norman Delanty, Rhys Thomas

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The impact of time lost to achieving meaningful seizure control

INTRODUCTION

Patrick Kwan (Chairman)
Monash University and Alfred Health Hospital, Melbourne, Australia.

"...the anxiety, that I could have a seizure at any time. I think that's the biggest thing..."

"...it's going to be embarrassing when I have one at university. Imagine if I have one, if I'm at my girlfriend's house or I'm at a party or something like that."

"A lot of workplaces don't really know how to deal with it. There's a lot of discriminative thinking; they don't want to really take on the burden of someone that you can never be 100% sure that I'm not going to have a seizure".

"If I had found the right medication last year, I could have saved a lot of time and I could have been driving."

What you just read are actually quotes from the patients that we surveyed: patients who I see, and my colleagues see. We decided that we needed to really understand how their lives are impacted by epilepsy. And it's really moving. We performed a qualitative study highlighting patient experiences and perceptions of people with epilepsy "waiting to achieve seizure freedom" [1], using a semi-structured interview approach to collect experiences in working age adults who had been diagnosed with, and treated for epilepsy for <4 years. Some examples.

Thematic analysis was used to identify patterns in these interviews, which were analyzed using a framework approach, revealing that patients in this stressful situation often experience:

- vulnerability, uncertainty, and confusion;
- mental health and social impacts;
- health system-related challenges;
- optimism for improved seizure control.

The results underscore the need to provide support and reduce negative experiences and to restore a sense of control for patients with newly diagnosed epilepsy while they are waiting for effective treatment.

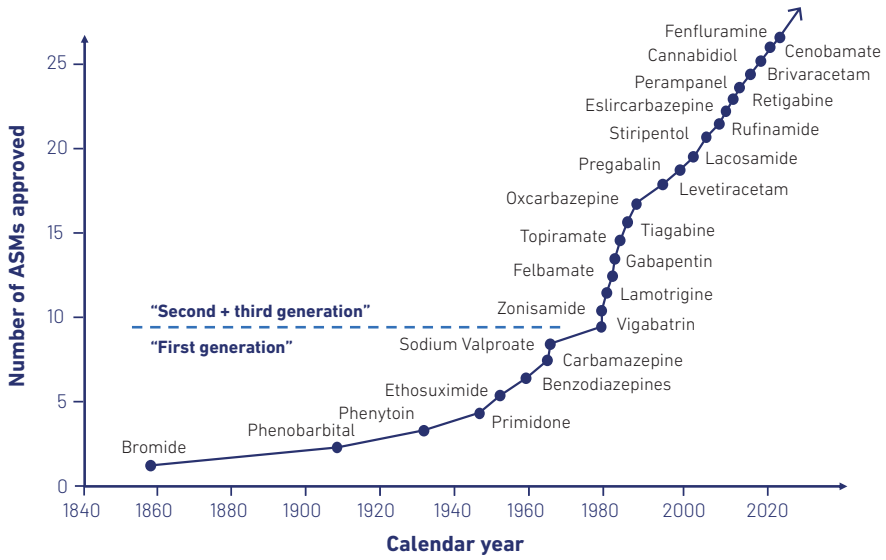
One theme in this symposium was to explore the impact of ongoing seizures in individuals with epilepsy and what can be done to help them regain their lives. Qualitative studies can complement quantitative research on drug-resistant seizures in people with epilepsy by capturing subjective experiences, perspectives, and emotions. This can inform healthcare decisions and improve patient-centered care.

EXPERIENCE OF PEOPLE WITH EPILEPSY WHILE WAITING FOR SEIZURE FREEDOM - Has the treatment outcomes landscape changed in 30 years?

Patrick Kwan (Chairman)
Monash University and Alfred Health Hospital, Melbourne, Australia.

The first reported use of an anti-seizure medication dates back to 1857, when Sir Charles Locock described having used potassium bromide to successfully stop epileptic seizures with a very high response rate; while this impressive response rate was not independently confirmed, a modest effect was confirmed with clinical evidence published by Samuel Wilks in 1861 [2].

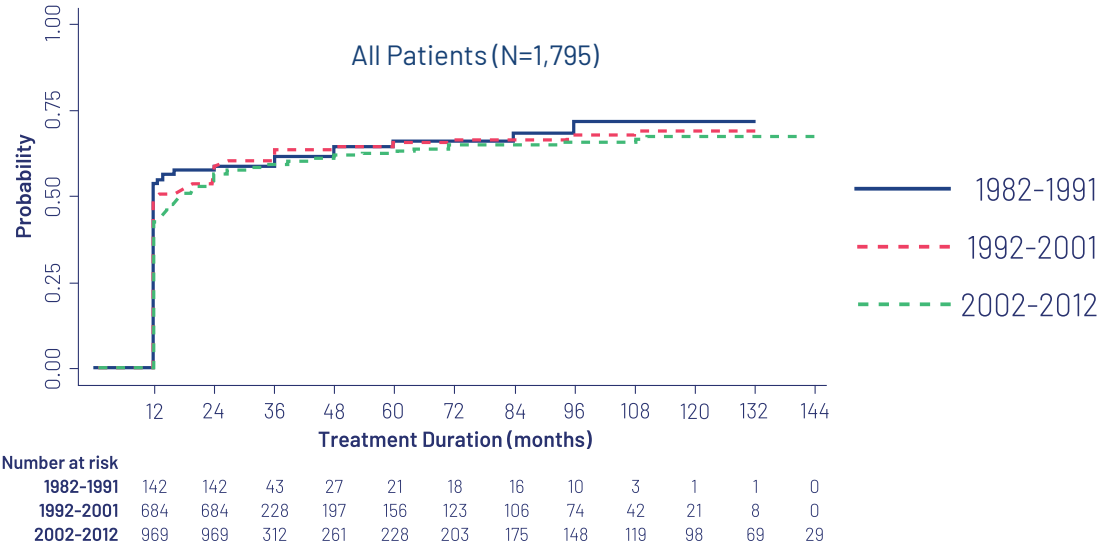
Despite the introduction and uptake of numerous first-, second-, and third-generation anti-seizure medications with various mechanisms of action over the past 30 years (**Figure 1**) [3], the proportion of people with epilepsy who have uncontrolled epilepsy (more than one-third) has remained unchanged (**Figure 2**) [4,5], as has the proportion of patients discontinuing treatment due to side effects [6].



Modified from Golyala A, et al. (2017). Seizure, 44, 147-156.

*The following drugs are not licensed for the treatment of epilepsy in Ireland or the UK: bromide, primidone (UK only), felbamate, tiagabine (UK only), retigabine

Figure 1 The history of antiseizure medication development. (Modified from [3])

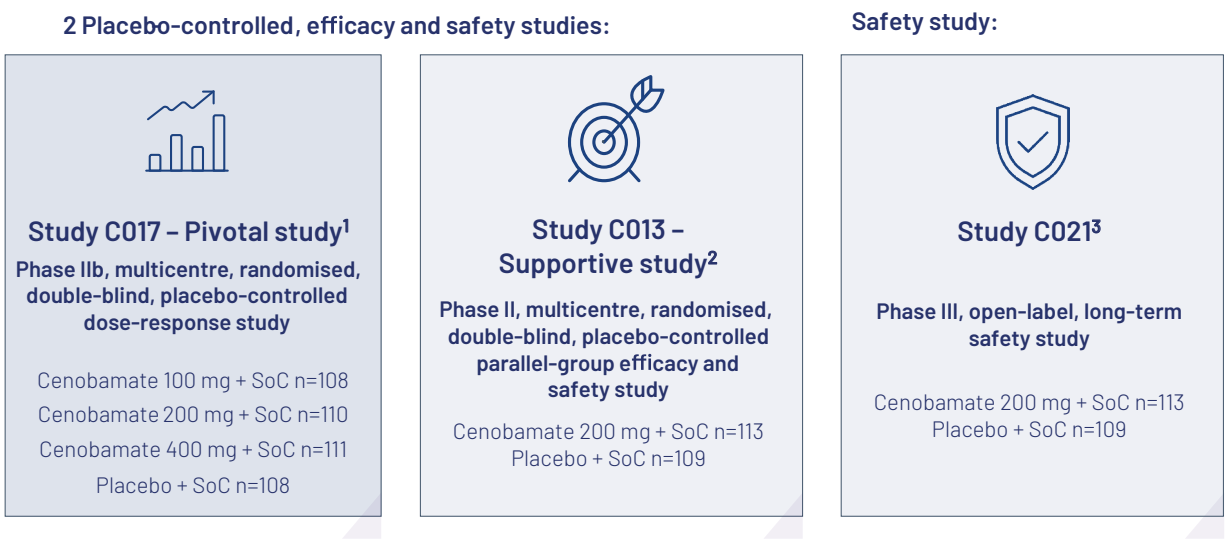


Number at risk

1982-1991	142	142	43	27	21	18	16	10	3	1	1	0
1992-2001	684	684	228	197	156	123	106	74	42	21	8	0
2002-2012	969	969	312	261	228	203	175	148	119	98	69	29

Modified from Chen Z, et al. (2018). JAMA Neurology, 75 (3), 279-286.

Figure 2 No change in probability of seizure freedom over time. (Modified from [5])



SoC = standard of care.
Modified from **1.** Krauss GL, et al.The Lancet Neurology, 19(1), 38-48. **2.** Chung SS, et al. Neurology, 94(22), e2311-e2322. **3.** Sperling MR , et al, Epilepsia, 61(6), 1099-1108.

Figure 3 Clinical development of cenobamate added to standard of care (SoC) [8–10]

We often remind ourselves that seizure freedom is not the only outcome: the effectiveness of a drug is measured by reducing seizures, but also by tolerability; these are two sides of the same coin. Looking at newly diagnosed patients, we see that among those who failed their first antiseizure medication did so because of adverse effects. When we looked at whether these intolerable adverse effect rates changed over time, we found again that the rate of withdrawal due to side effects didn't really change. As we hear in the real world where we practice, a feeling of life on hold is still true for the vast majority of patients when newly diagnosed with epilepsy or during their journey.

Fortunately, new tools to help patients restore normalcy to their lives have become available; among them there is cenobamate, which was recently introduced as adjunctive treatment for focal-onset seizures, with or without secondary generalization, in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 anti-epileptic medicinal products [7]. Some of its development milestones are shown in **Figure 3** [8–10].

KEY MESSAGES

- The proportion of people with uncontrolled epilepsy and discontinued treatments has remained unchanged in the past 30 years
- A feeling of life on hold is still true for the vast majority of patients when newly diagnosed with epilepsy or during their journey
- New tools to help patients restore normalcy to their lives include cenobamate, which was recently introduced as adjunctive treatment for focal-onset seizures

THE IMPACT OF TIME LOST TO ACHIEVING MEANINGFUL SEIZURE CONTROL IN ADULT PATIENTS WITH EPILEPSY

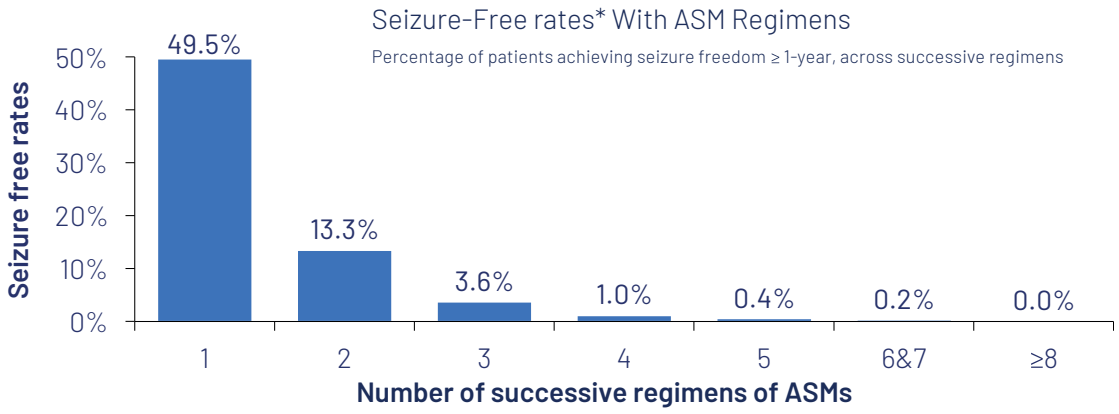
Manuel Toledo
Vall d´Hebron Hospital, Barcelona, Spain.

Delays in achieving effective seizure control impact the quality of life of patients with epilepsy [11]. While the first and second treatment regimens administered often provide substantial improvements in seizure-free rates, the same is not true of the successive regimens administered to patients with refractory seizures [12] (**Figure 4**). My question is should we wait until the third, fourth, fifth? Or should we save some time and try to do something more?

Analysis of data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2016 showed that epilepsy was ranked globally as the fifth cause of disease burden among neurological diseases, after stroke, migraine, dementias, and meningitis [13], and that it mainly affects adolescents and young adults. Geographically, the highest disease ranking was in Southern Sub-Saharan Africa, where it was ranked second, and in Central Asia (third), while it was eighth in Eastern Europe, and sixth in Western Europe and various high-income regions around the world.

Epidemiological data from US Veterans revealed that 1.7% had epilepsy, one third of whom had drug-resistant epilepsy [14]. Mortality rates were 50% higher among veterans with drug-resistant epilepsy, compared to the general population, while the use of diagnostic services, medications, and comprehensive epilepsy programs were each shown to reduce the rate of mortality, suggesting that close follow-up of patients may increase their lifespan. The magnitude of this burden is also supported by data on deaths from the Danish National Registry, which show mortality rates that are 2 to 3 times higher in people with epilepsy compared to the general population, and that life span was reduced by 10 to 12 years [15]. The presence of active seizures, intellectual disability or psychiatric disorders were all factors associated with reduced life expectancy in these patients.

A prospective, 5-year study of 112 patients with newly diagnosed epilepsy at Vall d´Hebron Hospital in Barcelona, Spain revealed that the probability of death was higher during the first 24 months, and that factors independently associated to mortality included uncontrolled seizures, polytherapy and both primary and secondary tonic-clonic seizures [16]. The standardized mortality rate for adults with epilepsy is 2.5 to 3.6 times higher than that of the general population; however, in drug-resistant epilepsy the risk of sudden death is 6 times higher than in patients with controlled epilepsy, and is associat-



Modified from Brodie MJ, et al. (2012). Neurology, 78(20), 1548–1554. *Seizure freedom is defined as not experiencing seizures for at least 1 year; Sources in notes section

Figure 4 The likelihood of seizure freedom decreases after three anti-seizure medication trials (drawn with data from [12])

ed with a higher risk of suicide, cardiovascular disorders, or psychiatric conditions that may include depression or anxiety [17–19]. The most important risk factors for Sudden Unexpected Death in Epilepsy (SUDEP) appear to be the presence of generalized tonic-clonic seizures or frequent seizures [20]. The burden of drug-resistant epilepsy goes beyond mortality, to include higher unemployment rates of up to 50% in Europe, compared to all people with epilepsy where it is 20%. Psychiatric comorbidities are a predictor of poor quality of life and increased risk of suicide, and these can be brought on by sleep disorders. Meanwhile, caregivers miss an average of 5.1 working days per year, impacting family incomes [21, 22].

The expression "Time is life in epilepsy" aims to raise awareness within the epilepsy community, including healthcare professionals and individuals in the patients' environment, regarding the crucial importance of managing and controlling epilepsy effectively.

KEY MESSAGES

- The presence of active seizures, intellectual disability or psychiatric disorders were all factors associated with reduced life expectancy
- Delays in achieving effective seizure control also have an impact on the quality of life of patients with epilepsy and increase the risk of SUDEP
- Controlling seizures, improving cognitive performance, and managing psychiatric comorbidities are fundamental to reducing disability and mortality in patients with epilepsy and active seizures

IS THERE CHANGE IN THE CLINICAL OUTCOME ON THE HORIZON FOR PEOPLE WITH DRUG-RESISTANT EPILEPSY?

Norman Delanty

Beaumont Hospital and FutureNeuro, the Science Foundation Ireland Research Centre for Chronic and Rare Neurological Diseases, Royal College of Surgeons in Ireland, Dublin, Ireland.

"The diagnosis that the patient has epilepsy is usually easy, but occasionally very difficult."
- Walter Bryan Matthews, in Practical Neurology, 1963 [23].

A similar situation exists regarding the treatment of people with epilepsy, which can be straightforward in many patients, but more than occasionally it can be very difficult, especially in patients with drug-resistant epilepsy. A first anti-seizure medication may fail for a variety of reasons, requiring dose escalations, add-on therapies, or switching to another anti-seizure medication. One third of patients will have refractory epilepsy, essentially defined as failing ≥ 2 adequate trials of anti-seizure medications [24]. More difficult patients will have ultra refractory epilepsy, which was defined as ongoing epilepsy after failing six or more treatments (i.e., six appropriate drugs, or five drugs and resective surgery or vagal nerve stimulation) [25].

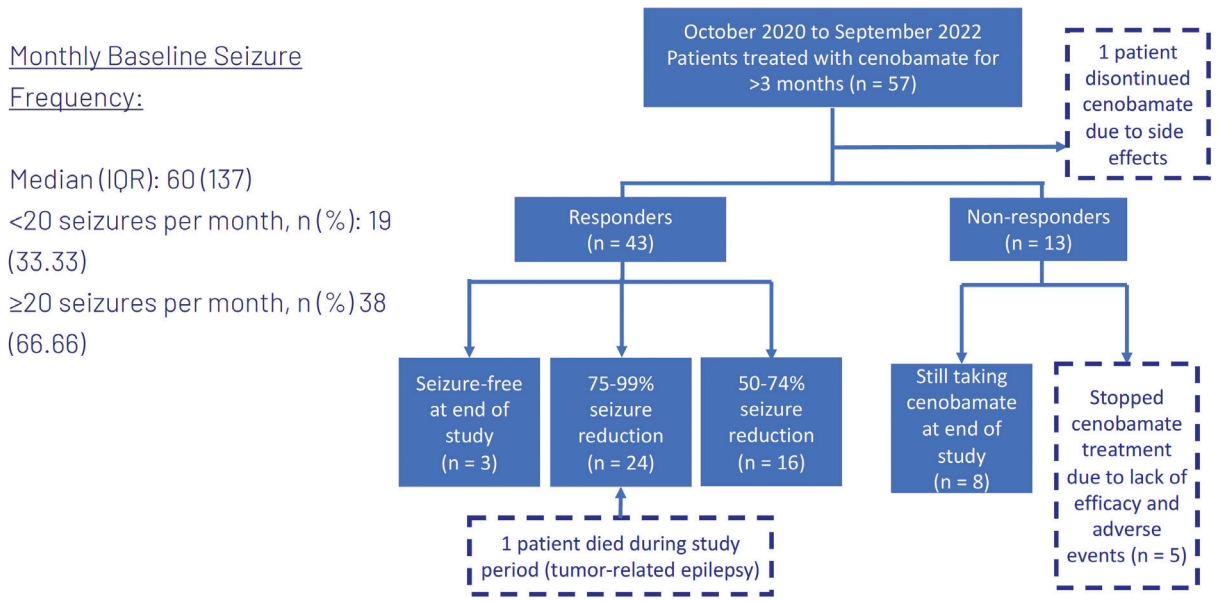
The consequences of refractory epilepsy include [26]:

- Seizures are unpleasant
- Seizures may cause injuries and burns
- Seizures are unpredictable
- Side effects of therapies
- Driving restrictions
- Employment restrictions
- Social anxiety
- Cognitive effects – acute and chronic
- Sudden unexpected death in epilepsy

However, several consequences tend to be undervalued, including the high risk of injuries and burns during seizures, and the high level of social anxiety that patients may experience.

We conducted a retrospective single-centre 2-year real-world study of cenobamate in a cohort of 57 patients with ultra-refractory epilepsy who failed a median of 9 anti-seizure medicines, 90% were receiving ≥ 3 concomitant anti-seizure medicines, and approximately 88% had undergone surgery and/or vagal nerve stimulation; despite this, the median baseline monthly seizure frequency was 60/month [25]. These patients were treated with cenobamate, accessed through compassionate use.

The results in this difficult cohort are presented in **Figure 5**.



Modified from Peña-Ceballos J, et al. Epilepsia 2023; 00: 1- 11.

Figure 5 Patient flow and dropouts, from [25]

The overall response rate, defined as a ≥ 50% reduction in seizures, was 60%, with 42.1% of patients achieving a ≥ 75% reduction, and 3 patients remaining seizure-free at study end. Five patients discontinued for lack of effectiveness or side effects.

Regarding tolerability, approximately 75% of patients reported adverse reactions, the most common being fatigue (n = 37), unsteadiness (n = 9), dizziness (n = 5) or nausea (n = 3). The titration scheme was strictly followed (see the SmPC for details on this, and on other possible adverse reactions [7]), and there were no cases of "drug reaction with eosinophilia and systemic symptoms" (DRESS) or seizure worsening. Adverse reactions tended to be dose-dependent and to be attributable to concomitant therapies. After adding cenobamate to ongoing treatment, it was possible to manage side effects by reducing the overall anti-seizure medication burden in 29/44 patients (66%). About one-third of patients (13/44, 30%) required either a reduction in dose, or discontinuation of cenobamate. One patient experienced phenytoin toxicity, highlighting the importance of considering pharmacokinetic interactions in this heavily treated population: concomitant administration of cenobamate 200 mg/day and phenytoin 300 mg/day increases the phenytoin Cmax by 67%, and the area under the time-concentration curve by 84% [7]. Phenytoin concentrations should be monitored during titration of cenobamate, and based on individual response, the dose of phenytoin may need to be reduced. Pharmacodynamic interactions with sodium channel blockers must also be avoided.

In our experience, cenobamate can improve quality of life and can have huge benefits to the family and potentially reopen educational and vocational opportunities. In our hospital we have had several patients and families who told us: "We wish we had this drug 20 years ago".

KEY MESSAGES

- The burden of drug-resistant epilepsy goes beyond mortality, to include high risk of injuries, unemployment rates and levels of social anxiety
- In a retrospective 2-year real-world study, the overall response rate with cenobamate was 60%, with 48% of patients achieving a ≥ 75% reduction, and 3 patients seizure-free
- After adding cenobamate to ongoing treatment, it was possible to manage side effects by reducing the overall anti-seizure medication burden

FROM AN EARLY ACCESS PROGRAM TO REAL-WORLD CENOBAMATE USE

Rhys Thomas

Newcastle University and Newcastle upon Tyne Hospitals, Newcastle upon Tyne, UK.

Cenobamate is a novel once daily anti-seizure medication with a long half-life. It is indicated for adjunctive use in adults with focal onset epilepsy meeting the ILAE definition of being drug refractory. Regulatory studies predict that a greater proportion of people will achieve seizure freedom, or near seizure freedom with cenobamate, compared with similarly designed trials of comparator drugs.

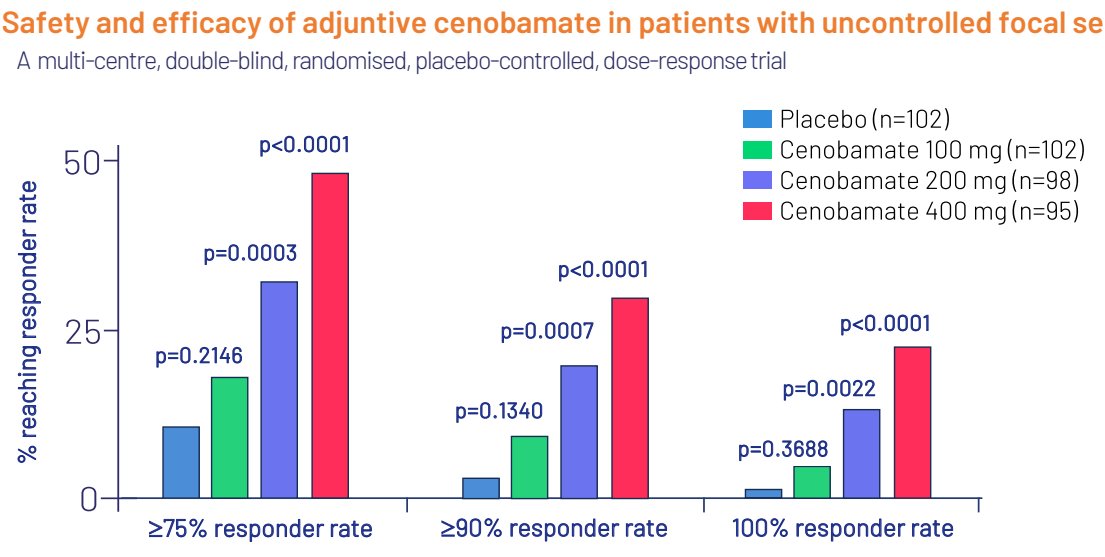
Regulatory studies are expensive to run and generally try to enroll patients who have lots of seizures; however, they must be patients who won't be harmed by being randomized to placebo. Titration is usually as rapid as can be conducted safely, and the standard FDA and EMA endpoint would be a 50% reduction in seizures after a short follow-up (e.g., 12 weeks).

Krauss et al. conducted a multicenter, double-blind, randomized, placebo-controlled, dose-response study in 437 patients with uncontrolled focal seizures despite receiving 1-3 anti-seizure medicines. Patients were randomly assigned to receive cenobamate at a dosage of 100, 200, or 400 mg, or placebo (standard of care, SOC). Primary efficacy endpoints were the change from baseline in focal seizure frequency at day 28, and the percentage of patients achieving at least a 50% seizure reduction in the maintenance phase [8].

In this scenario, achieving a 75% seizure reduction would be unusual and unexpected for such a drug refractory group. That is why the results of this study (**Figure 6**) are so surprising. If a 75% seizure reduction in 12 weeks is unusual, then a 90% seizure reduction, well, that's surprising.

However, this is a regulatory study in a selected population, and we were interested in assessing the effectiveness of cenobamate in a real-world setting. Instead, I would like to describe our real-world experience with cenobamate through the early access program.

In October 2020, our group was granted access to an early access scheme. One of our patients, a worker named Adam, from Newcastle, was among the first to be treated with cenobamate in the UK. He had been diagnosed with epilepsy at the age of ten, when regular seizures left him paralysed down the right side of his body up to ten times a day. By the



Modified from Krauss, G. L.,et al. (2020). The Lancet Neurology, 19(1), 38-48.

Figure 6 Efficacy of adjunctive cenobamate after 12 weeks in patients with uncontrolled focal seizures (data from [8])

time he was in his 20s, Adam was experiencing up to 50 seizures a day. When he started cenobamate, Adam went eight months without a single seizure, and although they do still sometimes occur, they are much less frequent; moreover, he has been able to discontinue almost all other treatments. He now maintains full-time employment and said, "because I'm on fewer medications, I have more energy to spend time with my wife, my son and my dog." This was truly heart-warming to hear.

Approval of cenobamate in England was based not only on efficacy data, but on a technology appraisal conducted by Laskier et al. [27], which assessed the potential impact of extrapolating the efficacy results from regulatory studies to effectiveness in the real world, and comparing cenobamate in this model with appropriate comparators (i.e., brivaracetam, eslicarbazepine, lacosamide, perampanel). The results predicted fewer medication trials, less hospitalization, possibility of avoiding vagal nerve stimulation and surgery, which predicted a substantial cost saving with cenobamate [27].

The Phase III CO21 study, designed after discussions with the FDA regarding the occurrence of DRESS in earlier studies, established an optimal, safe dosing schedule, the so-called "Start low, Go-Slow" approach, corresponding to 12.5 mg once daily starting dose, titrated up every fortnight (**Figure 7**) [7,10].

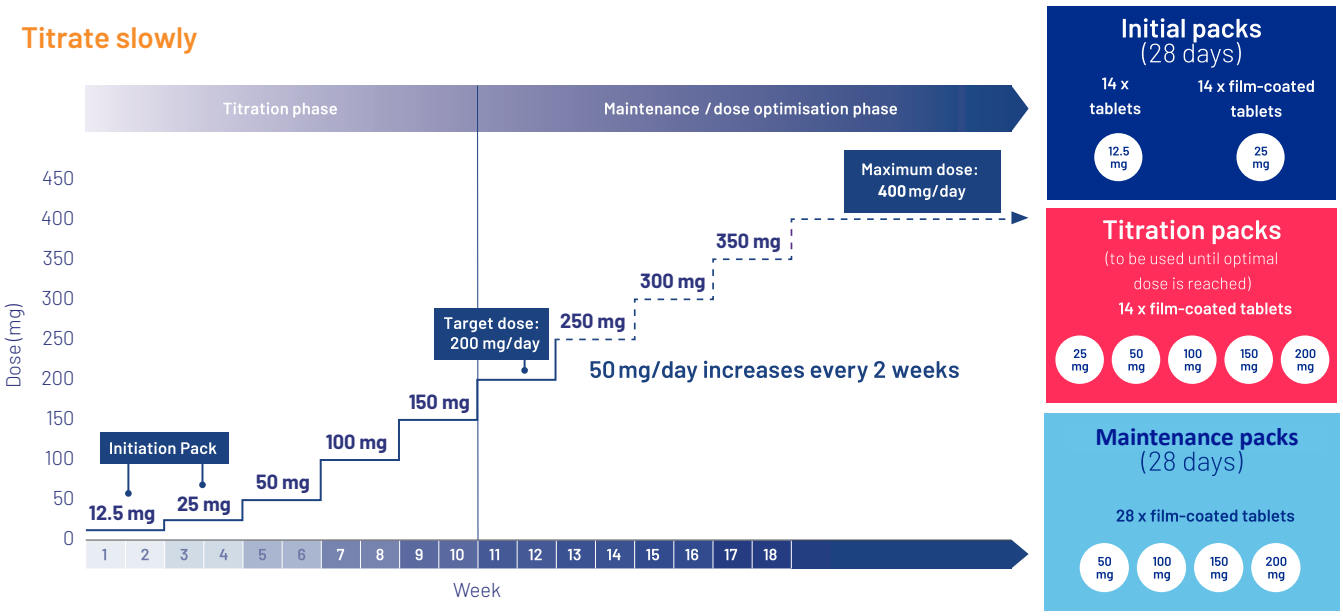
The safety of this titration schedule was confirmed in data from 1,339 patients treated with cenobamate, in which no cases of DRESS occurred.

Titration packs may facilitate titration and are appropriate for most patients (**Figure 7**). Two important titration milestone doses are 100 mg, at which point it is important to confirm that feedback is arriving regularly from the patient on tolerability and possible pharmacokinetic issues with concomitant treatment; and then at the target dose, when adjustments may be needed to establish the maintenance dose. Slower titration may be appropriate in patients with communication problems.

We think it is useful to look carefully at an ECG before starting, because of a very rare genetic disorder called "short PR interval", for which we recommend not prescribing. Before and after liver enzyme tests would be useful as a precaution, although hepatic enzyme elevation is not common.

In our experience, cenobamate can be used as a switch to replace one of the ongoing treatments, rather than as a mere add-on treatment. The choice of the drug to replace must be made carefully, based on tolerability and especially potential drug interactions.

In our experience, clinically meaningful drug interactions to watch out for include clobazam, phenytoin, phenobarbital, carbamazepine, lamotrigine, as well as tolerance issues with sodium channel blockers, particularly lamotigine and lacosamide, because they may reduce blood levels of cenobamate.



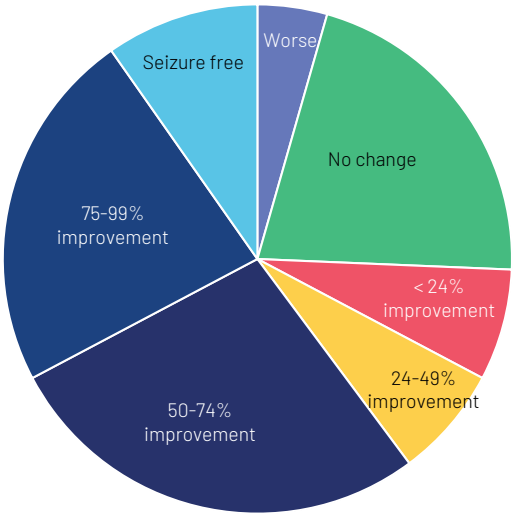
Modified from Steinhoff BJ et al. Epilepsy Behav. 2021;123:108270.

Figure 7 Practical guidance on titrating cenobamate: "Start low, Go-Slow" [28]

Newcastle experience 2023

In 113 patients, we could clearly ascertain seizure outcome

- 5 (4.4%) → seizures exacerbated
- 24 (21.2%) → no improvement
- 8 (7%) → less than 24% improvement
- 8 (7%) → 25-49% improvement
- 31 (27.4%) → 50-74% improvement
- 26 (23%) → 75-99% improvement
- 11 (9.7%) → seizure free



The data presented is based on the speaker's personal experience in the field. Participants are encouraged to consider the insights shared in light of the speaker's expertise

Figure 8 Efficacy findings in the Newcastle real-world experience with cenobamate, (Rhys Thomas, unpublished results)

As mentioned above, the 100 mg titration milestone is very important for assessing these effects.

Other side effects reported in clinical trials are listed in the Summary of Product Characteristics [7], and are those expected from cenobamate's mechanisms of action, which include positive modulation at GABAA receptors, and inhibition at voltage-gated sodium channels, with a preferential reduction in the persistent (INaP) Na+ current [29]. Common side effects are predictable and manageable since they are mainly those encountered and managed when using other anti-seizure medications or combinations that target one or more of these mechanisms.

The regulatory studies described above were necessarily conducted in selected patient populations; however, it is important to confirm that cenobamate efficacy is translated into effectiveness in a real-world setting. In addition to the retrospective 2-year real-world study of cenobamate in patients with ultra-refractory epilepsy published by Peña-Ceballos et al. [25], preliminary results from an ongoing prospective real-world study of cenobamate in patients with drug-refractory focal epilepsy at Newcastle upon Tyne Hospitals in the UK also appears to confirm this.

As of May 2023, 151 adults have been enrolled (60% male, mean age approximately 40 years). Focal epilepsy with structural MRI lesions was present in 68 patients, including 11 with focal cortical dysplasia, six with neuronal migration disorders, five with autoimmune encephalitis, two with Rasmussen's encephalitis, one with Alpers (POLG associated mitochondrial disorder). The mean cenobamate dose was 204 mg, although 37 were still in the titration phase. With a mean follow-up of 367 days, approximately 45% of patients had reported some dose related side effects and 24 patients (16.3%) discontinued due to tolerability. Their efficacy findings are presented in **Figure 8**.

Essentially, 1 in 10 was seizure free, and another quarter have experienced a reduction in seizure rates of between 75 and 99%. The < 5% of seizure aggravation is likely due to drug interactions, and for some patients this is simply not the right medicine. Most people have a seizure benefit from cenobamate, despite having drug-refractory epilepsy.

KEY MESSAGES

- The high number of drug-refractory patients responding to cenobamate within 12 weeks is surprising, and very encouraging
- Cenobamate can be used as a switch to replace one of the ongoing treatments, rather than as a mere add-on treatment
- Common side effects are predictable and manageable since they are mainly those encountered and managed when using other anti-seizure medications
- Cenobamate efficacy translates into effectiveness in a real-world setting
- Most people benefit from cenobamate, despite having drug-refractory epilepsy

QUESTIONS & ANSWERS

AMONG SPEAKERS

Prof. Kwan: Prof. Toledo, you have stressed the impact of mortality and morbidity on patients and their families. Can you expand on the economic burden of active seizures for the patient and for society?

Prof. Toledo: The impact for society is large, because it affects caregivers, families, and relatives, in addition to the patients. This reduces the possibility to be productive and socially active because patients depend on their relatives to take care of them. In addition to reducing family incomes, patients with epilepsy or drug-resistant epilepsy have limits on their social environment. Patients with drug-resistant epilepsy always need someone by their side, which is associated with stigma. The economic impact on society is large due to the social and economic support focused on these patients. If we can find a way to prevent seizures, we can improve the lives of these patients and provide savings for society.

Prof. Kwan: Prof. Thomas, what is your experience with cenobamate in older patients?

Prof. Thomas: For older adults, I'm using a similar sort of prescribing that I would for somebody with an intellectual disability. You know, 50% of people over 65 in the UK live alone. And so, I'm going a bit more slowly with them and using it as an opportunity to deprescribe drugs that people don't grow old well on, (e.g., perampanel).

Prof. Kwan: Would you be proactive in reducing concomitant medications?

Prof. Thomas: Yes, absolutely.

Q&A SESSION WITH THE AUDIENCE

Participant 1: Yes, I have a question for the panel, especially Prof. Delanty. In the cohort of highly drug-resistant patients in your article, you mentioned that it's difficult to go beyond a certain dose. For example, 250 mg because of the concomitant polytherapy. And this is also my experience, but lately I've been trying hard to increase the dose, and getting to 300, 350 and even 400 mg and with some good results. Can you all tell us about how you manage this, and how these high doses of cenobamate are tolerated? We know that in clinical trials there is a clear dose relationship in terms of response. So, should we attempt to go that high in our patients?

Prof. Delanty: Every patient is different, as you know, but in that cohort, we started getting into difficulty above 200, 250 mg, in terms of side effects. But of course, this is a work in progress. These patients are still coming to our clinic very regularly. We have managed to increase the dose in some of them. But you won't do this unless you remove some concomitant medications. For many patients, doing this allows you to increase the dose further. But we haven't looked at that systematically. If somebody is having significant side effects at 250 mg, that's not the end of the road for them, but it just needs a little bit more work.

Prof. Thomas: Sometimes I'll have a conversation with the patients, saying: "Nothing previously has worked. We've got some signal with cenobamate... something is working. Let's invest in it". And we're going to invest in this by increasing that dose to levels that you're suggesting and make capacity by removing some of the other medicines. Also, since we're only in year two of the current license, I think if I had the opportunity to speak to you next year, I'd know more about higher doses.

Prof. Delanty: Yeah, I think we're still learning about that in terms of experience necessarily.

Prof. Toledo: I believe that one of the aims of using cenobamate is to simplify treatments. It's so efficacious that sometimes you remove many other (medications).

Prof. Kwan: I noticed in your slide clobazam was the one with the highest rate.

Prof. Delanty: Yes, in terms of tolerability. But many of those are still on clobazam but at a lower dose. I have one patient on cenobamate < 300 mg and a very modest dose of lamotrigine: she's doing very well. Maybe we should ask the company about monitoring withdrawal (of other medications) in the real world, an interesting phenomenon and of course, patients like that.

Participant 2: What is unique about the structure of this molecule that leads to its blockbuster success? Is that the dual mechanism of action? Extrapolating further, could it be that 50 years from now we have one molecule that binds SV2 and $GABA_A$ and sodium channels, and does all those things at the same time?

Prof. Toledo: It has a combined mechanism of action; however, 100% of those patients had been previously treated with a combined mechanism of action, and yet this drug works better than those combinations. Something is going on that we don't understand yet.

Prof. Thomas: I completely agree with that. Although it works on a similar sodium channel as lacosamide, I wouldn't use non-response to lacosamide as a reason not to start cenobamate.

Prof. Kwan: It works on the persistent sodium current, rather than the rapid sodium current. So, perhaps that is a difference, although some of the drugs may also have that property, but usually only at supratherapeutic doses. There is an ongoing discussion about this very good question.

Participant 3: I have a question for Norman about the clobazam story. In the beginning, we were very aggressive at discontinuing clobazam, but we have changed our mind after analyzing the outcome of our series. We observed that the only combination that was associated to good outcomes, or to better outcomes, or the best outcome combination, was the one with clobazam. Another paper confirmed the value of this combination. So, now our strategy is to reduce the dosage because of somnolence and then to continue at 5 to 10 mg per day. What is your insight nowadays with clobazam?

Prof. Delanty: I think you're right, thanks for the question. It's about reducing the dose, not necessarily stopping it. And there may be a synergy between low dose clobazam and cenobamate. I absolutely agree. As I say, we're still learning. That was also our initial experience. It would be nice to conduct an observational study on low dose clobazam and see if it has a place.

Participant 4: It seems to be a very clean drug in terms of psychiatry. Is that really your impression? I've got about 160 patients currently and the side effects are of the nature that you've described, but not psychiatric. But is that your shared experience, that this is a drug that does not cause major psychiatric problems?

Prof. Thomas: I find it to be quite clean. The positive or negative for me come along when mood might drop because you've got neurotoxic side effects. I don't see it independently of that; mood might pick up because of the seizure benefits. So, I don't see it as a mood stabilizer, but I've not had a patient with a psychosis or a de novo psychotic (episode).

Participant 4: Depression?

Prof. Thomas: Not in excess of the sedation that I've seen. I think when people have had a (mood) worsening, there's an intrinsic factor of the individual, that could have been predicted.

Participant 4: You mentioned irritability.

Prof. Thomas: Yes, but in my experience, it doesn't "play" like levetiracetam or perampanel.

The whole panel: I agree.

Prof. Toledo: Cenobamate may be a good choice for patients with depression or behavioral disorders, because it is easy to use.

Prof. Kwan: Regarding cognition, in your cohort, we noticed about 30% or 35% of patients had intellectual disability. Do you notice any difference in patients with or without intellectual disability, or do you use the drug differently?

Prof. Delanty: I don't know about the others, but I don't think we have the numbers to analyze that. I don't think we've had differential experiences in that 35%. As I said, these were all patients with relatively mild intellectual disabilities, not LGS, because that's not the indication, but we haven't seen really a differential.

Prof. Thomas: I completely agree. I might be more likely to run two titration packs alongside each other, go up with monthly steps. And my feeling is that the seizure outcome benefits are similar, but I probably celebrate them more, because they carry more risk. And so, when you get seizure benefit in somebody in that situation, it's just a great thing.

Prof. Delanty: One thing I wanted to say for these kinds of patients that we've been treating. You know, epilepsy is a family disease, particularly when it's very difficult. And we've had experience, of course, again, with mothers and spouses coming in and they're smiling for the first time in a while. The group of patients who are not quite seizure free but, about 75%, they're doing so much better. We're told in some of these conferences that seizure freedom is the main objective, apart from side effects from treatment, is the main thing that determines quality of life in this kind of patient group. It isn't.

Prof. Thomas: I agree.

Prof. Toledo: The satisfaction is very good with patients.

Participant 5: It is mentioned that with a patient with familial long QT syndrome, you should be

careful when prescribing this medication. It will be necessary to meet always or regularly. What's your opinion?

Prof. Thomas: I'm not familiar with any data on long QT as an exclusion.

Prof. Delanty: I don't think there's any evidence of long QT from the trials - I'm getting agreements from Angelini Pharma colleagues.

Prof. Toledo: I perform ECGs on these patients, and I haven't seen any cardiac side effects.

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