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A Further Look at Rational Polytherapy in Patients With Uncontrolled Epilepsy: Insights From a Post hoc Analysis of Adjunctive Cenobamate

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THE GOAL OF EPILEPSY TREATMENT is to help patients achieve 100% seizure reduction (zero seizures) with minimal adverse events (AEs). Unfortunately, many patients with epilepsy continue to have uncontrolled seizures despite taking multiple antiseizure medications (ASMs).¹⁻³ Therefore, dose adjustments and medication changes are often necessary to find combinations that help reduce seizure frequency and minimize AEs, a practice referred to as rational polypharmacy. Specific guidance on how to combine ASMs is lacking, however, due in large part to the widely individualized nature of epilepsy treatment. In addition, the availability of several newer ASMs has provided an even greater number of possible ASM combinations.

The typical strategy for polytherapy treatment in patients with uncontrolled seizures includes combining ASMs with different mechanisms of action, essentially on a trial-and-error basis, while monitoring and adjusting for AEs and efficacy. Should intolerable AEs occur when a new ASM, particularly one that has been recently approved, is added to the treatment regimen, there is a tendency for the last drug added to be the first one down-titrated or removed before moving on to a different therapeutic combination or reverting to the previous regimen. This practice may not be the most beneficial since the rationale for adding on the new ASM was failure of the previous regimen. Instead, it may be sounder to examine the potential pharmacokinetic/pharmacodynamic interactions between the existing regimen and the newly added ASM and adjust the pre-existing regimen, since it was not successful in achieving zero seizures/seizure freedom. During titration of the new ASM, for example, the existing ASMs can be down-titrated, as needed, to minimize the AEs of the new combination until an acceptable therapeutic balance is achieved. The dose of the newly added ASM will of course vary from patient to patient and will also vary based on the existing combination of ASMs.

A case in point is the use of adjunctive cenobamate, which is approved by the FDA under the brand name XCOPRI (cenobamate tablets) CV, for the treatment of adult patients with focal seizures. When cenobamate was added to existing ASM regimens, approximately 20% more patients vs those on

a placebo regimen achieved seizure freedom,^{4,5} compared with 0.8% to 5.4% more patients than placebo for other adjunctive ASMs (pooled analyses).⁶⁻⁸ Yet many health care providers will discontinue a newly added ASM at the first sign of tolerability concerns and revert to the previous regimen, potentially limiting the patient's opportunity to reach seizure freedom. Recent post hoc analyses of study data published in *Epilepsia*⁹ provide support for a more rational approach to concomitant ASM dose adjustments when adding cenobamate.

CENOBAMATE POST HOC PHASE 3 STUDY RESULTS

A large (N=1340), long-term, phase 3, open-label study¹⁰ (C021) was conducted to focus on safety; however, given the importance of data on long-term seizure control in patients with uncontrolled seizures, a C021 protocol amendment allowed post hoc collection of seizure data from a subset of 10 US C021 study sites (n=240).⁹ One post hoc analysis from this subset of patients examined how dose adjustments to baseline concomitant ASMs affected tolerability, efficacy, and retention of patients receiving adjunctive cenobamate.⁹ While cenobamate monotherapy was not permitted during the study, most concomitant ASMs were adjusted to lower doses, and in some cases were removed completely, thereby lowering the total drug load, alleviating AEs, and most importantly, allowing many patients to achieve long-term seizure freedom.

Results from the post hoc analyses that looked at specific ASMs across regimens⁹ showed that greater percentages of patients remained on cenobamate than discontinued cenobamate for almost all concomitant ASMs taken at baseline, with approximately 70% of patients continuing treatment with cenobamate for most baseline ASMs.⁹ Dosages of concomitant ASMs were reduced most often because of AEs, such as somnolence, dizziness, ataxia, and fatigue, and the dose reductions were greater in patients who continued treatment with cenobamate vs those who discontinued cenobamate.⁹ These results suggest that patients who received dose adjustments of concomitant ASMs were more likely to stay on cenobamate and achieve better seizure control.

Further analysis found that doses of phenytoin, phenobarbital, clobazam, valproate, and lacosamide were decreased by investigators earliest in the study, during the 12-week titration phase for cenobamate.⁹ In spite of these concomitant ASM reductions, increased seizure control was observed early, during the first 4 weeks of titration, in many patients in the overall cohort, starting at cenobamate doses of 12.5 mg to 25 mg.¹¹ Most of the early dose reductions were likely in response to pharmacokinetic drug interactions that had led to alterations in drug exposure and subsequent issues with tolerability.

Some ASMs, as in the case of clobazam, can and should be reduced proactively because of known drug-drug interactions with cenobamate.¹² Other concomitant ASMs, such as carbamazepine, oxcarbazepine, and eslicarbazepine, were reduced later (or more reactively) in the study, during the early maintenance phase.⁹ These concomitant dose reductions likely were made later because there were few or no pharmacokinetic interactions with these drugs. Regardless of dose reductions or which concomitant ASM patients were taking, retention (ie, percentages of patients who remained throughout the study) was high, ranging between approximately 72% and 79% for the most common baseline ASMs, supporting the efficacy of cenobamate.⁹

Robust efficacy, including high rates of 100% seizure reduction, was also observed. Among all patients, 25.8% experienced 100% seizure reduction for at least 12 months and the mean duration of 100% seizure reduction for these patients was 23.5 months.¹¹ Reducing doses of the concomitant ASMs may have improved tolerability, allowing for cenobamate to be titrated to its optimal dose and thereby increasing the overall efficacy.⁹

TAKEAWAYS FOR RATIONAL POLYOTHERAPY

Results from this post hoc analysis provide guidance on how various concomitant ASMs may be adjusted while adding on cenobamate. They also provide further insight into the use of rational polytherapy for patients with epilepsy. The goal of optimal efficacy with acceptable tolerability can be attained through various avenues but requires attention on numerous moving targets, such as AEs that may occur with each drug and drug combination, potential drug-drug interactions, as well as varying levels of efficacy as the new ASM is titrated up. The high patient retention and continuous response observed from the post hoc cenobamate data, all while reducing baseline ASM doses, support the idea that the newest ASM added into a patient's treatment regimen should not always be the focus of initial reduction. Should new or worsening central nervous system-related AEs occur during the initiation of a new ASM, a better strategy to improve efficacy and reduce overall drug burden may involve reducing concomitant drugs in the original, unsuccessful regimen, while adding on the new treatment.¹³ In instances where there is a known drug-

drug interaction between the new ASM and an ASM in the existing regimen, proactive dose reduction of the baseline ASM may be appropriate.

ROLE OF THE PHARMACIST IN THE MANAGEMENT OF PATIENTS WITH EPILEPSY

Pharmacists provide a crucial role in patient counseling on medications and disease education, and they have the ability to perform pharmacotherapeutic monitoring for patients with chronic diseases, including epilepsy.¹⁴ Studies have shown that pharmacist interventions can improve the overall epilepsy-related health and quality of life of patients and improve medication adherence.¹⁴ For instance, pharmacist-led patient medication counseling and education can help identify and proactively alert the patient and the health care provider to potential therapeutic problems and prevent errors in dose and frequency of administration. Additionally, in the case of polytherapy in epilepsy, the pharmacist can educate the patient on their entire treatment regimen and explain how and why a new ASM is being added to their regimen. The pharmacist can help patients with epilepsy adhere to the sometimes complex instructions and prescription changes that can occur during titration of a new ASM.¹⁴ Advising patients that it may take several days or weeks to reach the full therapeutic benefit can help manage expectations. Counseling can also help mitigate the potential anxiety that patients can experience during periods of ASM changes.¹⁵

Finally, pharmacists have an important role in safety counseling and monitoring for potential drug-drug interactions during ASM polytherapy. Patients should be counseled on the potential risks, such as specific tolerability issues and AEs that may arise with a new adjunctive ASM treatment. These discussions may also help the patient manage their expectations should a new or worsening AE occur, and encourage them to work with their health care provider to discuss options, such as potentially lowering the doses of other concomitant ASMs, before deciding to down-titrate or discontinue the newly added medication.

Pharmacists have unique opportunities to impact the care of patients with epilepsy, particularly those receiving polytherapy. The individualized nature of epilepsy treatment requires close monitoring and frequent communication with patients and health care providers to help patients attain the best possible therapeutic outcomes and quality of life. ■

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References are available on PharmacyTimes.com.