

## LETTER

## Clinical predictors of response to adjunctive brivaracetam: Insights from real-world data

To the Editors:

We thank Prof. Adam Strzelczyk et al. for providing interesting and informative data on long-term efficacy, tolerability, and retention of brivaracetam (BRV) in epilepsy treatment up to 5 years of follow-up in a longitudinal multicenter study. Switching from levetiracetam (LEV) to BRV and fewer concomitant antiseizure medications correlated with better short-term response, but no investigated parameters correlated with 12-month outcome.<sup>1</sup>

In a cohort in which 90% of patients had previous LEV exposure, these findings suggest that history of LEV treatment may not preclude BRV introduction.<sup>1</sup> The lack of information about the reasons for LEV discontinuation and the baseline characteristics of patients according to LEV exposure may have hampered the likelihood of identifying additional predictors. In our recent analysis of real-world data about adjunctive BRV treatment in patients with focal seizures, history of LEV withdrawal for tolerability issues was an independent predictor of 12-month seizure freedom.<sup>2</sup> Furthermore, in a real-world time-based analysis, the median time-to-baseline seizure frequency was longer for patients who discontinued LEV due to adverse events in comparison to patients with prior LEV use and withdrawal due to insufficient efficacy, and the Kaplan–Meier estimated probability of not achieving baseline seizure count was higher in LEV-naïve patients.<sup>3</sup>

The lower burden of concomitant antiseizure medications was associated with better outcomes after 3 months, but favorable combinations of BRV with other drugs were not explored.<sup>1</sup> Recently, the combination of BRV with sodium channel blockers has been shown to result in better efficacy and tolerability being associated with a higher rate of seizure responders and lower rates of adverse events and treatment withdrawal due to poor tolerability.<sup>2</sup> Additive or synergic efficacy without increased toxicity is usually observed by combining antiseizure medications with different mechanisms of action<sup>4</sup>; additional studies are warranted to confirm the preliminary evidence regarding the advantageous association of BRV with drugs targeting sodium currents.

The identification of predictors of long-term treatment response has an important role in clinical practice, and real-world data may contribute to addressing this topic and providing guidance for clinicians.<sup>5</sup>

### KEYWORDS

antiseizure medications, brivaracetam, epilepsy, focal seizures

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## LETTER

## The EpiPick algorithm to select appropriate antiseizure medications in patients with epilepsy: Validation studies and updates

To the Editor,

Last year *Epilepsia* published our manuscript entitled “A pragmatic algorithm to select appropriate antiseizure medications in patients with epilepsy.”<sup>1</sup> The end result of this algorithm was a freely accessible web-based application (<https://epipick.org>) to help health care professionals select the most appropriate, patient-tailored antiseizure medication (ASM) in patients with epilepsy (seizure onset at 10 years of age or older). EpiPick considers seizure types and patient-specific variables to provide treatment recommendations, ranking ASMs in order of appropriateness based on the available scientific evidence and expert judgement. The app also provides a summary of prescribing information for each of the ASMs being suggested.<sup>1</sup> We regarded the app as a tool that would evolve as experience with its use progressed, new scientific evidence emerged, and new ASMs were developed.

Following the publication of the algorithm, we have further validated the app in three studies. In a large, multicenter, prospective study,<sup>2</sup> we validated the first part of the algorithm, which classifies seizure types to facilitate therapeutic decision-making. Agreement between the algorithm and the expert classification was 83.2% [95% confidence interval (CI) 78.6%–87.8%], with an agreement coefficient (AC1) of 0.82 (95% CI 0.77–0.87), indicating almost perfect agreement.<sup>2</sup> In another study<sup>3</sup> we investigated the agreement among experts in selecting an ASM as initial monotherapy and used their choices to validate the app. The percent agreement between the highest ranked selections of the app and the expert selections was 73% (95% CI 64%–82%). Agreement between the app and the majority decision of the experts was higher than the agreement among the experts.<sup>3</sup> Ninety-five percent of the experts considered that no incorrect or potentially harmful ASMs were ranked the highest by the application, and most experts strongly agreed with the app's selections.<sup>3</sup> Finally, in a more recent study, we conducted an external validation of the app using an independent real-life retrospective data set to assess whether

ASMs recommended by the algorithm were associated with better outcomes than ASMs considered less desirable by the algorithm.<sup>4</sup> Compared with ASMs considered less desirable by the algorithm, ASMs classified by the app as the best options were associated with a higher retention rate (79.4% vs 67.2%,  $p = 0.005$ ), a higher seizure-freedom rate (76.0% vs 61.6%,  $p = 0.002$ ), and a lower rate of discontinuation due to adverse effects (12.0% vs 29.2%,  $p < 0.001$ ).<sup>4</sup>

To optimize this application and improve it as new evidence and new drugs appear, the algorithm was updated on April 12, 2021. The updated algorithm takes into account that (a) cenobamate was approved by the U.S. Food and Drug Administration (FDA) for the treatment of focal seizures in adults<sup>5</sup>; (b) new evidence indicates that lacosamide is efficacious and safe as a treatment option for primary generalized tonic-clonic (GTC) seizures in patients with idiopathic generalized epilepsy (IGE)<sup>6</sup>; and (c) new data show that perampanel is efficacious and safe as a treatment option for primary GTC seizures in patients with IGE.<sup>7</sup>

The revisions include the following:

1. Cenobamate was added to “Focal group 3” and will be re-evaluated in 1 year. A comment clarifies that this drug has been recently introduced and additional safety data are required for a potential upgrade; its modifier is allergy to any drug, downgrade by one level due to phase II studies reporting Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome.<sup>5</sup>
2. Upgrade lacosamide and perampanel to group 2 (from group 3) for primary generalized tonic-clonic seizures (GTCS).

We will continue to update the algorithm to fulfill the goal of assisting health care professionals in epilepsy management. Our ultimate goal is to improve the quality of care for patients with epilepsy.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## CONFLICT OF INTERESTS

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## AUTHOR CONTRIBUTION

All authors contributed to the conception and design of the study. AAP drafted the manuscript. All authors contributed to editing the final manuscript.

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**ANNOUNCEMENT****Epilepsia – January 2022 – Announcements****ILAE CONGRESSES****20–25 March 2022****3rd International Training Course on Neuropsychology in Epilepsy**

Bordeaux, France

<https://www.ilae.org/congresses/3rd-international-training-course-on-neuropsychology-in-epilepsy>**10–13 April 2022****EEG in the First Year of Life – from newborn to toddler**

Cambridge, UK &amp; Virtual course

<https://www.ilae.org/congresses/eeg-in-the-first-year-of-life1>**May 2022 – Date TBD****2nd North American Epilepsy Congress**

Virtual congress

<https://www.ilae.org/congresses/2nd-north-american-epilepsy-congress>**9–13 July 2022****14th European Epilepsy Congress**

Geneva, Switzerland

<https://www.ilae.org/congresses/14th-european-epilepsy-congress>**16–23 July 2022****5th Dianalund Summer School on EEG and Epilepsy**

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<https://www.ilae.org/congresses/14th-asian-and-oceanian-epilepsy-congress>**35th International Epilepsy Congress****2–6 September 2023**

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<https://www.ilae.org/congresses/35th-international-epilepsy-congress>**OTHER CONGRESSES****24–28 January 2022****11th EPODES–Epilepsy Surgery – Basic**

Brno, Czech Republic

<http://www.ta-service.cz/epodes2021>**27 February–3 March 2022****American Society for Experimental Neurotherapeutics (ASENT) Annual Meeting 2022**

Virtual meeting

<https://asent.org/asent2022/>**24–27 March 2022****16th World Congress on Controversies in Neurology**

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<https://cony2022.comtecmed.com/>**3–8 April 2022****9th Eilat International Educational Course: Pharmacological Treatment of Epilepsy**

Jerusalem, Israel

<https://www.eilatedu.com/>

**8–10 April 2022**

**1er Curso Latinoamericano Teórico Práctico de Electroencefalografía Clínica**

Santiago, Chile

[https://www.clinicaepilepsia.cl/curso\\_electroencefalografia\\_clinica](https://www.clinicaepilepsia.cl/curso_electroencefalografia_clinica)

**26–28 April 2022**

**5th International Training Course on Neuroimaging of Epilepsy**

Virtual course

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**27–30 April 2022**

**60. Jahrestagung der Deutschen Gesellschaft für Epileptologie**

Leipzig, Germany

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**28 April–2 May 2022**

**14th European Paediatric Neurology Society (EPNS) Congress: Precision in Child Neurology**

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**14–15 May 2022**

**ILAE British Branch Virtual 18th Specialist Registrar Epilepsy Teaching Weekend**

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**Epilepsy Surgery Techniques Meeting (ESTM 2022)**

Geneva, Switzerland

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**18–29 July 2022**

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**23–25 September 2022**

**Canadian League Against Epilepsy 2022 Scientific Meeting**

Kelowna, BC, Canada

<https://www.ilae.org/congresses/canadian-league-against-epilepsy-2022-scientific-meeting>

**2023**

**20–24 June 2023**

**15th European Paediatric Neurology Society Congress (EPNS): From genome and connectome to cure**

Prague, Czech Republic

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