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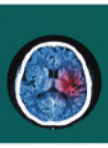

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ORIGINAL ARTICLE

Web-based decision support system for patient-tailored selection of antiseizure medication in adolescents and adults: An external validation study

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Abstract

Background and purpose: Antiseizure medications (ASMs) should be tailored to individual characteristics, including seizure type, age, sex, comorbidities, comedications, drug allergies, and childbearing potential. We previously developed a web-based algorithm for patient-tailored ASM selection to assist health care professionals in prescribing medication using a decision support application (https://epipick.org). In this validation study, we used an independent dataset to assess whether ASMs recommended by the algorithm are associated with better outcomes than ASMs considered less desirable by the algorithm.

Methods: Four hundred twenty-five consecutive patients with newly diagnosed epilepsy were followed for at least 1 year after starting an ASM chosen by their physician. Patient characteristics were fed into the algorithm, blinded to the physician's ASM choices and outcome. The algorithm recommended ASMs, ranked in hierarchical groups, with Group 1 ASMs labeled as the best option for that patient. We evaluated retention rates, seizure freedom rates, and adverse effects leading to treatment discontinuation. Survival analysis contrasted outcomes between patients who received favored drugs and those who received lower ranked drugs. Propensity score matching corrected for possible imbalances between the groups.

Results: Antiseizure medications classified by the algorithm as best options had a higher retention rate (79.4% vs. 67.2%, $p = 0.005$), higher seizure freedom rate (76.0% vs. 61.6%, $p = 0.002$), and lower rate of discontinuation due to adverse effects (12.0% vs. 29.2%, $p < 0.001$) than ASMs ranked as less desirable by the algorithm.

Conclusions: Use of the freely available decision support system is associated with improved outcomes. This drug selection application can provide valuable assistance to health care professionals prescribing medication for individuals with epilepsy.

KEYWORDS
adolescent, adult, adverse effects, antiepileptic drugs, epilepsy, neuropharmacology

INTRODUCTION

Choice of antiseizure medications (ASMs) in patients with epilepsy should be individually tailored to achieve optimal seizure control with the fewest possible adverse effects [1–5]. Choosing an ASM requires consideration of factors such as seizure type, age, sex, comorbidities, comedications, history of previous drug allergies, and relevance of specific adverse effects, including teratogenic risk [1–5]. Recommending the most appropriate ASM for an individual can be challenging, as more than 20 ASMs are now in common use, and weighing key clinical variables requires experience and expertise that is not available everywhere [1–6]. Moreover, it can be difficult for health care professionals to apply objective criteria consistently when making treatment decisions, leading to variability in clinical management.

To help address these challenges, we developed an algorithm-based decision support system that is freely available on the web (https://www.epipick.org) [7]. The application is designed to assist health care professionals to select an optimal ASM for individuals whose seizures begin at age 10 years or older [7]. The algorithm was tested and improved in an iterative process using 150 patient-cases [7].

The input into the algorithm consists of demographic information, seven simple questions aimed at identifying the seizure type(s), red-flag questions for nonepileptic seizures or syncope, and a checklist of 14 items related to comorbidities, comedications, and any history of previous allergic drug reactions [7]. Entry of the required information requires <2 min for any individual patient. Following data entry, the application recommends a list of ASM options tailored to that individual. Recommended ASMs are listed and ranked in three groups, with Group 1 medications considered the best options. A fourth group includes ASMs classified as the least desirable options, in case the recommended medications are not available. All other ASMs are considered not recommended and are not displayed on the output page of the application. For each of the ASMs listed, the web-based application provides a summary of dosing and prescribing information, in addition to an explanation on how the algorithm applied the information entered by the user to determine the final ranking [7].

In a previous study, we compared the recommendations of the algorithm with ASM choices made by 24 international experts on a dataset of 25 predesigned patient-cases covering a wide variation of seizure types and other factors influencing drug selection [8]. There was good agreement between the ASMs selected by the experts and those selected by the app [8]. However, variability in patient characteristics in a real-world setting is greater than represented in 25 sample cases, and whether the algorithm's recommendations lead to favorable clinical outcomes has yet to be established.

We now report a blinded validation study using a large clinical dataset of patients with newly diagnosed epilepsy, containing information on ASMs chosen for initial treatment, individual patient characteristics, and treatment outcomes over a follow-up period of 1 year after reaching the final maintenance dose. All patients were managed in a real-world clinical setting by health care professionals who were not epilepsy specialists. ASM selections were made prior to introduction of the web-based algorithm, and none of the experts who contributed to the development of the algorithm was involved in their clinical management. This validation dataset was independent from datasets used for developing the algorithm.

We hypothesized that (i) ASM choices matching the highest rank of the algorithm (best options) are associated with better clinical outcomes than all other choices combined, and that (ii) ASM choices matching all three ranks of recommended options are associated with better clinical outcomes compared with ASMs rated by the algorithm as least desirable or not recommended.

METHODS

The study was conducted at the Albert Szent-Györgyi Clinical Center of the University of Szeged, Hungary, which serves as the primary referral center for adult and pediatric neurology patients from a catchment area of 400,000 inhabitants. Data from consecutive patients with epilepsy treated at the center between 1 January 2005 and 1 March 2021 were extracted retrospectively from the electronic medical records. Criteria for inclusion in the study were (i) being newly diagnosed with epilepsy, and started on ASM treatment during the study period; (ii) seizure onset at age 10 years or

older; and (iii) availability of follow-up data for 1 year after reaching the final maintenance dose or until treatment failure (defined as discontinuation of the initially prescribed ASM, or addition of another ASM), whichever occurred earlier. Exclusion criteria were (i) brain surgery in the first year after starting treatment; and (ii) patients whose paroxysmal symptoms were determined not to be epileptic during the assessment period, although treatment had been started. The study was approved by the regional human biomedical research ethics committee of the University of Szeged (approval number 157/2020-SZTE).

For each patient, ASM selection and subsequent management were based on the clinical judgment of the treating physicians, including residents and specialists with no specific training in epileptology, and without assistance from the web-based application. The baseline (pretreatment) data extracted from electronic records included age, sex, seizure type and syndrome, comorbidities, ongoing treatments, and history of previous adverse drug reactions. Data recorded during follow-up consisted of details of ASM treatment, number of seizures between clinic visits, and adverse effects.

Pretreatment data for each patient were entered into the web-based application (epipick.org) by an external investigator blinded to ASM choice of the treating physician and outcome information. The output of the algorithm was registered for each patient. We then compared the ASM prescribed for each patient with the output of the algorithm for the same patient. Based on this comparison, the prescribed ASM was classified into any of the following categories: recommended by the algorithm as the best option (Group 1 ASM), recommended by the algorithm as the second-best option (Group 2 ASM), recommended by the algorithm as a still acceptable option (Group 3 ASM), listed by the algorithm as the least desirable option if none of the other listed ASM was available, and not listed by the algorithm and therefore not recommended. The last two categories were considered not favored by the algorithm.

For the primary outcome analysis, we compared time to treatment failure (retention on treatment, an estimate of effectiveness) [9] between patients who were prescribed ASMs classified by the algorithm as best options (ASM Group 1) and patients who received ASMs that were ranked lower by the algorithm. As a secondary analysis, we compared time to treatment failure between patients treated with any ASM recommended by the algorithm (ASM Groups 1 + 2 + 3) and patients who received ASMs not favored by the algorithm. Other secondary outcome measures compared across groups included proportion of patients who were seizure-free for 1 year after reaching the final maintenance dosage, and proportion of patients discontinuing the initially prescribed ASM because of adverse effects. In the whole cohort, time to treatment failure was evaluated by Kaplan–Meier analysis [10], using the Mantel–Cox test for survival analysis [11]. For between-group comparisons of proportions of patients achieving seizure freedom, and proportion of patients discontinuing treatment due to adverse effects, we used the chi-squared test. Statistical analysis was made by using R 4.1.1. software [12–15].

Due to the retrospective study design, the compared subcohorts were not balanced for demographic and clinical characteristics. As the algorithm accounts for these characteristics, we did not expect that this would bias the results. However, to control for these features and assess whether differences in patient characteristics may have influenced the results in the whole cohort, we added propensity score matching [16] to acquire comparable subcohorts, with similar distributions of patient characteristics. First, a logistic regression model was built using four factors (age, sex, type of seizures and epilepsy, and time from seizure onset to start of treatment), which yielded the propensity score for each patient. Due to the universal health care coverage and reimbursement system, socioeconomic status was not a factor influencing ASM selection. Matching was performed using the nearest neighbor method with 1:1 match ratio. Replacements were not allowed. Caliper width was set at 0.2 on the logit scale [17], and suitable balance was assumed, if standardized mean difference was <0.1 after matching. Two separate matching procedures were performed between patients who received Group 1 ASMs versus patients with all other ASMs, and between patients treated with Groups 1 + 2 + 3 ASMs versus those with ASMs not favored by the app. We used the Matching R package [18] for the propensity score matching. After the matching, chi-squared tests of independence and Kaplan–Meier analysis were used to compare the different ASM groups for all predefined outcome measures (retention rate, seizure freedom rate, and adverse effects leading to discontinuation). We considered $p < 0.05$ to be statistically significant.

RESULTS

Of 453 consecutive patients with seizure onset at age 10 years or older, newly diagnosed with epilepsy during the study period, a total of 425 patients (203 female and 222 male patients) met eligibility criteria. Of the 28 (6.2%) noneligible patients, 27 did not have sufficient follow-up data, and one was excluded because of change in diagnosis to nonepileptic seizures. Proportions of patients lacking sufficient follow-up data did not differ significantly among subcohorts (Table S1).

Median age at seizure onset of the patients included in the analysis was 44.5 years (range = 10–80 years, interquartile range = 22–62), and median age at start of ASM treatment was 45 years (range = 10–80 years, interquartile range = 23–62). The seizure type at diagnosis was focal seizures for 334 (78.6%) patients, generalized seizures for 52 (12.2%), and seizures of unknown onset for 39 (9.2%). Propensity score matching resulted in balanced subcohorts (Tables A and B in Table S2) for comparisons between patients who received best option ASMs ($n = 152$) and those who received ASMs ranked lower by the algorithm ($n = 152$), as well as for comparisons between patients treated with ASMs recommended by the algorithm ($n = 102$) and those treated with ASMs not favored by the algorithm ($n = 102$). There was no statistically significant difference in the patient characteristics between the compared subcohorts, after the matching (Table S2).

TABLE 1 Case examples of ASM selections and associated outcomes

Patient A

19-year-old female patient with primary generalized tonic–clonic seizures, taking oral contraceptive medication.

Recommendations of the algorithm:

- Group 1: lamotrigine and levetiracetam
- Group 2: No ASM met the algorithm criteria for classification as Group 2
- Group 3: Brivaracetam, clobazam, lacosamide, valproate, and zonisamide
- Least desirable: carbamazepine, oxcarbazepine, perampanel, topiramate, phenobarbital, and phenytoin
- ASM choice of the treating physician blinded to the algorithm: lamotrigine, corresponding to algorithm Group 1 (best option)

Outcome: complete seizure freedom, no adverse effects

Patient B

79-year-old female patient with focal seizures, Alzheimer disease, hypertension, and multiple ischemic strokes. The patient takes several comedications (metoprolol, perindopril, amlodipine, indapamide, pantoprazole, donepezil, atorvastatin, and alprazolam). She is allergic to penicillin.

Recommendations of the algorithm:

- Group 1: lacosamide and levetiracetam
- Group 2: lamotrigine
- Group 3: brivaracetam, gabapentin, and perampanel
- Least desirable: carbamazepine, clobazam, eslicarbazepine acetate, oxcarbazepine, pregabalin, topiramate, valproate, zonisamide, phenytoin, and phenobarbital

ASM choice of the treating physician blinded to the algorithm: levetiracetam, corresponding to algorithm Group 1 (best option)

Outcome: complete seizure freedom, no adverse effects

Patient C

13-year-old female patient with generalized myoclonic seizures and anxiety.

Recommendations of the algorithm:

- Group 1: clonazepam and levetiracetam
- Group 2: clobazam
- Group 3: nitrazepam, topiramate, valproate, zonisamide, and phenobarbital
- Least desirable: no ASM met the algorithm criteria for classification as least desirable

ASM choice of the treating physician blinded to the algorithm: carbamazepine, i.e., an ASM not recommended or listed by the algorithm

Outcome: seizures became more frequent on carbamazepine, leading to its discontinuation

Patient D

62-year-old female patient with focal seizures, hypertension, hypercholesterolemia, and osteoporosis. Drug allergy: Novocain and lidocaine. Comedications: antihypertensive drugs and simvastatin.

Recommendations of the algorithm:

- Group 1: lacosamide and levetiracetam
- Group 2: brivaracetam, lamotrigine, and perampanel
- Group 3: eslicarbazepine acetate, gabapentin, oxcarbazepine, topiramate, valproate, and zonisamide
- Least desirable: carbamazepine, clobazam, pregabalin, phenytoin, and phenobarbital

ASM choice of the treating physician blinded to the algorithm: carbamazepine, corresponding to the least desirable category of the algorithm

Outcome: although seizure freedom was achieved, the ASM was discontinued due to adverse effects

Abbreviation: ASM, antiseizure medication.

Examples of ASM choices recommended or not favored by the algorithm are shown in Table 1.

The relationship between ASM choices made by the treating physician and ASM recommendations provided for the same patients by the algorithm is shown in Table 2. Of the 425 patients, 175 (41.2%) were treated with an ASM ranked as the best option by the algorithm, whereas 102 (24.0%) received treatments not favored by the algorithm.

Figure 1a shows the Kaplan–Meier curves for the primary analysis. Patients who were prescribed an ASM ranked as the best option by the algorithm had higher retention on treatment than those treated with other ASMs ($p = 0.005$). Patients who received any ASM recommended by the algorithm also had higher retention on treatment than those treated with ASMs not favored by the algorithm (Figure 1b, $p = 0.04$). The same analysis applied to subcohorts after propensity score matching gave similar results ($p = 0.02$ and $p = 0.02$, respectively; Figure S1).

Seizure freedom rates at the end of follow-up in patients who received ASMs classified by the algorithm into different rankings are shown in Table 3. Seizure freedom rates decreased with decreasing algorithm ranking. Of note, patients treated with ASMs ranked as the best option (algorithm Group 1) had higher seizure freedom rates at the end of the follow-up (76.0%, 95% confidence interval [CI] = 69.2%–81.7%) than those treated with other ASMs (61.6%, 95% CI = 55.6%–67.65%, $p = 0.003$). Patients treated with any ASM recommended by the algorithm also had higher seizure freedom rates (70.6%, 95% CI = 65.4%–5.3%) than those treated with ASMs not favored by the algorithm (57.8%, 95% CI = 48.1%–67.0%, $p = 0.017$). Similar differences were found when subcohorts were compared after the propensity score matching (77.6%, 95% CI = 70.4%–83.5% vs. 62.5%, 95% CI = 54.6%–69.8%, $p = 0.004$ and 73.5%, 95% CI = 64.2%–81.1% vs. 57.8%, 95% CI = 48.1%–67.0%, $p = 0.02$, respectively; Table S3). Table S4 provides details for seizure freedom rates according to the ranking of the prescribed ASM in relation to seizure diagnosis. Results for the subgroup of patients with focal seizures were similar to those for the whole cohort (77.3%, 95% CI = 69.4%–83.6% vs. 64.7%, 95% CI = 57.9%–71.0%, $p = 0.01$ and 73.8%, 95% CI = 67.8%–78.9% vs. 59.1%, 95% CI = 49.0%–68.6%, $p = 0.009$, respectively). For the subgroup of patients with generalized seizures, results were similar when patients treated with the algorithm's best options were compared with the remaining patients (76.0%, 95% CI = 56.6%–88.6% vs. 33.3%, 95% CI = 18.6%–52.2%, $p = 0.002$), but no meaningful statistical comparison could be made between subcohorts treated with recommended and not favored ASMs, because only five patients with generalized seizures received ASMs not favored by the algorithm.

Proportions of patients with adverse effects leading to discontinuation of the initially chosen ASM are shown in Table 4. Patients treated with ASMs classified as the best option by the algorithm had a lower rate of discontinuation due to adverse effects (12.0%, 95% CI = 8.0%–17.6%) than patients treated with other ASMs (29.2%, 95% CI = 23.9%–35.1%, $p < 0.001$). The same was true for patients treated with any ASM recommended by the algorithm (Groups 1 +2 + 3) compared with patients treated with ASMs not favored by the algorithm (19.0%, 95% CI = 15%–23.5% vs. 32.4%, 95%

TABLE 2 Algorithm ranking of the antiseizure medications prescribed by the treating physicians for the 425 patients included in the study

Ranking		*n* (% [95% CI])	
Recommended	Group 1	175 (41.2% [36.6%–45.8%])	323 (76.0% [71.5%–79.6%])
	Group 2	44 (10.4% [7.8%–13.6%])	
	Group 3	104 (24.5% [20.6%–28.7%])	
Not favored	Least desirable	95 (22.4% [18.6%–26.5%])	102 (24.0% [20.2%–28.3%])
	Not recommended	7 (1.6% [0.8%–3.4%])	

Abbreviation: CI, confidence interval.

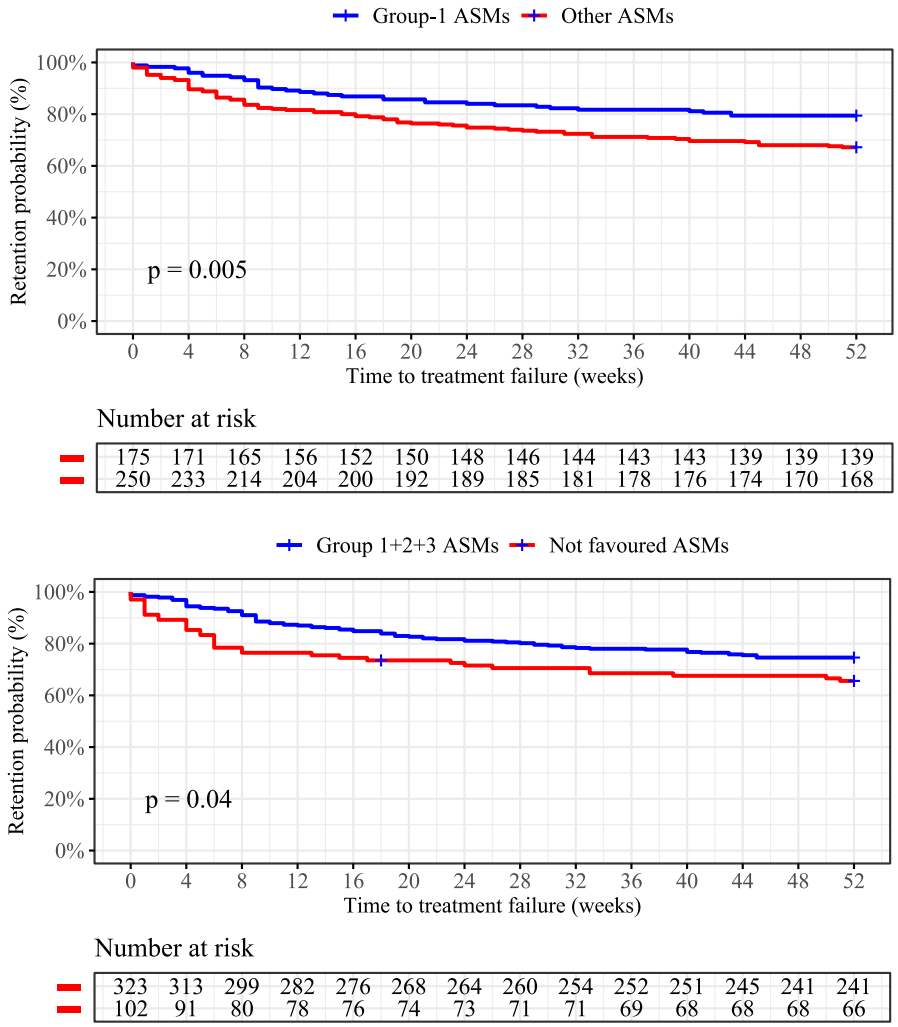

FIGURE 1 Kaplan–Meier analysis of the time to treatment failure. (a) Patients treated with best option antiseizure medications (ASMs) recommended by the algorithm (Group 1) versus patients treated with other drugs. (b) Patients treated with any ASM recommended by the algorithm (Groups 1 + 2 + 3) versus patients treated with not favored drugs. Vertical axis: retention rate. Horizontal axis: number of weeks from starting treatment [Colour figure can be viewed at wileyonlinelibrary.com]

CI = 24.1%–41.9%, $p = 0.004$). Similar differences were found when subcohorts were compared after propensity score matching (9.9%, 95% CI = 6.1%–15.6% vs. 25.7%, 95% CI = 19.4%–33.1%, $p < 0.001$ and 15.7%, 95% CI = 9.9%–24.0% vs. 32.4%, 95% CI = 24.1%–41.9%, $p = 0.005$, respectively; Table S5).

DISCUSSION

We analyzed outcome data from a large independent cohort of consecutive patients newly diagnosed and treated at a single center to validate the ASM selections recommended by the algorithm. When physicians prescribed ASMs designated as "best choice" by the algorithm, patient outcomes were clearly better. Superior results were noted for drug retention rate, seizure freedom rate, and ASM discontinuation rate due to adverse effects compared with outcomes in patients treated with other ASMs not considered the best option. Moreover, patients who received any ASM recommended by the algorithm showed better outcomes than patients receiving ASMs not favored by the app. Failure to achieve either seizure control or appearance of intolerable adverse effects tended to occur early in the course of treatment, as shown in Figure 1. Hence, this analysis demonstrates that the algorithm's preferred drugs would be expected to produce meaningful improvement in patient care.

TABLE 3 Seizure freedom rates according to the algorithm ranking of the prescribed ASMs

ASM ranking by the algorithm		Patients, *n*	Patients seizure-free, *n*	Patients seizure-free, % (95% CI)		
Recommended	Group 1	175	133	76.0% (69.2%–81.7%)*	70.6% (65.4%–75.3%)**	67.5% (62.9%–71.8%)
	Group 2	44	29	65.9% (51.1%–78.1%)		
	Group 3	104	66	63.5% (53.9%–72.1%)		
Not favored	Least desirable	95	56	58.9% (48.9%–68.3%)	57.8% (48.1%–67.0%)	
	Not recommended	7	3	42.9% (15.8%–75.0%)		

Abbreviations: ASM, antiseizure medication; CI, confidence interval.

*$p = 0.0026$ vs. lower ranked groups combined.

**$p = 0.017$ vs. not favored group.

TABLE 4 Rates of treatment discontinuation due to AEs according to the algorithm ranking of the prescribed ASMs

ASM ranking by the algorithm		Patients, *n*	Patients with AEs leading to ASM discontinuation, *n*	Patients with AEs leading to ASM discontinuation, % (95% CI)		
Recommended	Group 1	175	21	12.0% (8.0%–17.6%)*	19.0% (15.0%–23.5%)**	22.1% (18.4%–26.3%)
	Group 2	44	9	20.5% (11.2%–34.5%)		
	Group 3	104	31	29.8% (21.9%–39.2%)		
Not favored	Least desirable	95	30	31.6% (23.1%–41.5%)	32.4% (24.1%–41.9%)	
	Not recommended	7	3	42.9% (15.8%–69.5%)		

Abbreviations: AE, adverse effect; ASM, antiseizure medication; CI, confidence interval.

*$p < 0.001$ vs. lower-ranked groups combined.

**$p = 0.004$ vs. not favored group.

Seizure classification might have influenced the results. Most patients in this cohort ($n = 334$, 78.6%) had focal seizures, as would be anticipated for adolescents and adults with seizure onset at age 10 years or older [19,20]. Although the subcohort of patients with generalized seizures was smaller ($n = 52$, 12.2%), ASMs ranked as best options in this subcohort by the algorithm were also associated with better outcomes than ASMs ranked lower by the algorithm. Hence, the algorithm's therapeutic preference appears to have broad applicability, conveying benefit for both focal and generalized seizures.

Because the allocation of the patients to the different groups only depended on the ASM choice made by the treating physicians (blinded to the algorithm), groups in the whole cohort were not balanced for patient characteristics such as age, sex, type of seizures and epilepsy, and time from seizure onset to start of treatment. The algorithm takes these features into account when making ASM recommendations, and therefore we did not expect that an imbalance in distribution of patients based on these characteristics would substantially influence the results of the comparisons. In any case, when we corrected for unbalances using propensity score matching [16–18], all findings reported for the whole cohort remained substantially unchanged. Including patients from 2005 increased the probability of some patients receiving older drugs, thereby providing a partial assessment of the applicability of the algorithm to resource-restricted settings. Due to the universal health care coverage and reimbursement system, socioeconomic status did not play a role in ASM selection in this cohort.

The seizure freedom rate in the overall cohort was 67.5% ($n = 287$). In the subgroup of 175 patients treated with ASMs considered the best option by the algorithm, the proportion of seizure-free patients was even higher (76.0%), suggesting that the web-based application could improve patient outcomes by helping physicians optimize patient-tailored treatment. This is an important consideration, in view of the evidence that inappropriate or suboptimal ASM selection is relatively common in real-world practice and adversely effects clinical outcomes [21].

Since its release in July 2020, the web-based application has been used more than 6500 times by health care professionals from 55 countries. The instrument, however, has limitations. In its present form, it is only applicable to treatment selection in adolescents and adults (i.e., patients with seizure onset at age 10 years or older), and is designed to be used in patients on monotherapy. Potential interactions between ASMs are not accounted for in the current version. Lastly, the instrument does not take into consideration factors such as ASM availability, accessibility, and affordability in specific settings, nor does it control for regulatory status of medications (e.g., regulatory approval for specific indications) in different countries.

In conclusion, our results indicate that use of individually tailored ASMs recommended by the epipick.org algorithm is associated with higher retention rates, higher seizure freedom rates, and lower rates of drug discontinuation because of adverse effects compared with the use of ASMs that were not favored or ranked lower by the algorithm. This validated web-based algorithm provides a tool to improve

ASM selection that is not subject to the vagaries of human decision-making, thereby contributing to improved patient care.

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CONFLICT OF INTEREST

E.P. has received speaker's or consultancy fees from Arvelle, Biogen, Eisai, GW Pharma, Sanofi, Sun Pharma, UCB Pharma, Xenon Pharma, and Zogenix and publication royalties from Wiley and Elsevier. A.A.A.-P. has received honoraria from Cobel Daruo, Tekaje, Sanofi, and Raymand Rad; royalties from Oxford University Press (book publication); and a grant from the National Institute for Medical Research Development. G.R. has received speakers honoraria from UCB, Eisai, and Biocodex and has acted as scientific consultant for Ology Medical Education. M.R.S. has received personal compensation for speaking from Neurology Live, Eisai, Medscape, Projects for Knowledge, and International Medical Press and publication royalties from Oxford University Press. He is an advisor for scientific publications for Neurelis and consults for Medtronic with payments to Thomas Jefferson University. M.R.S. has received research support from Eisai, Medtronic, Neurelis, SK Life Science, Takeda, Sunovion, Xenon, Cerevel, UCB Pharma, Eisai, and Engage Pharmaceuticals. S.B. serves as scientific consultant for Epihunter and received speaker's fees from Natus, Philips, Eisai, UCB Pharma, GW Pharma, and BIAL. None of the other authors has any conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Levente Hadady: Data curation (equal), formal analysis (lead), investigation (lead), visualization (lead), writing–original draft (supporting). **Péter Klivényi:** Resources (equal), supervision (supporting), writing–review & editing (equal). **Emilio Perucca:** Conceptualization (equal), methodology (supporting), writing–review & editing (equal). **Stefan Rampp:** Conceptualization (equal), writing–review & editing (equal). **Dániel Fabó:** Supervision (supporting), writing–review & editing (equal). **Csaba Bereczki:** Resources (equal), writing–review & editing (equal). **Guido Rubboli:** Conceptualization (equal), writing–review & editing (equal). **Ali A. Asadi-Pooya:** Conceptualization (equal), writing–review & editing (equal). **Michael R. Sperling:** Conceptualization (equal), writing–review & editing (equal). **Sándor Beniczky:** Conceptualization (equal), data curation (equal), formal analysis (supporting), methodology (lead), supervision (lead), visualization (supporting), writing–original draft (lead).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Prior to use of the data, proposals need to be approved by an independent review panel at the ethics board of University of Szeged, and a signed data sharing agreement will then be approved.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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