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Exit Strategy: Balancing the Risks and Rewards of Antiseizure Medication Withdrawal

Marian Galovic, PhD[1], Carolina Ferreira-Atuesta, MSc[2], Lara E. Jehi, MHCDS[3], Kees P. J. Braun, PhD[4], and Samuel W. Terman, MD, MS[5]

[1] Department of Neurology, Clinical Neuroscience Center, University Hospital and University of Zurich, Zurich, Switzerland
[2] Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[3] Cleveland Clinic Epilepsy Center, Cleveland, OH, USA
[4] Department of Child Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht and Utrecht University, Utrecht, the Netherlands
[5] Department of Neurology, University of Michigan, Ann Arbor, MI, USA
*Correspondence: Marian Galovic, Department of Neurology, University Hospital Zurich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland.
Email: marian.galovic@usz.ch

Abstract
The majority of people with epilepsy achieves long-term seizure-freedom and may consider withdrawal of their anti-seizure medications (ASMs). Withdrawal of ASMs can yield substantial benefits but may be associated with potential risks. This review critically examines the existing literature on ASM withdrawal, emphasizing evidence-based recommendations, where available. Our focus encompasses deprescribing strategies for individuals who have attained seizure freedom through medical treatment, those who have undergone successful epilepsy surgery, and individuals initiated on ASMs following acute symptomatic seizures. We explore state-of-the-art prognostic models in these scenarios that could guide the decision-making process. The review underscores the importance of a collaborative shared-decision approach between patients, caregivers, and physicians. We describe the subjective and objective factors influencing these decisions and illustrate how trade-offs may be effectively managed in practice.

Keywords
epilepsy, seizure, antiseizure medication, withdrawal, deprescribing, seizure-free, surgery, acute symptomatic seizure, prognostic model

Introduction

Withdrawing anti-seizure medications (ASMs) represents one of the great dilemmas of epilepsy treatment. Individuals who have attained seizure freedom often engage in discussions with their health care providers and caregivers regarding the appropriateness of discontinuing ASMs, as well as the optimal timing and strategy for initiating this process.

The withdrawal of ASMs can yield substantial benefits. Anti-seizure medication therapy may elicit adverse effects or interactions. Some ASMs may cause insidious effects that are difficult to spot during a consultation, including an increased risk of osteoporosis, dyslipidemia, cardiovascular disease, or even mortality.[1-4] Additionally, ASM treatment may carry teratogenic potential, affect cognitive functioning, cause costs, and intensify the stigma faced by individuals reliant on regular ASM intake.

Conversely, the decision to discontinue ASMs necessitates careful consideration of associated risks. The likelihood of

seizure relapse following ASM withdrawal varies among individuals, ranging from low to substantial.[5] Seizures pose risks of injury, sudden death in epilepsy,[6] and may lead to occupational or driving constraints.

The intricate process of balancing these risks and rewards, guided by patient preference, underscores a collaborative, shared decision-making approach involving patients, caregivers, and physicians. This review encapsulates the current state-of-the-art regarding ASM withdrawal in individuals with epilepsy.

Anti-Seizure Medication Withdrawal in Medically Treated Seizure-Free Patients

More than two-thirds of patients will reach remission with ASMs throughout the course of their disorder.[7] When seizure-freedom is reached with ASMs, the question may arise after a while whether drugs are still needed. Since ASMs suppress seizures rather than modify disease, withdrawal is expected to merely unveil the natural history of the patient's epilepsy.[8] There is no proof that ASM discontinuation itself causes epilepsy or aggravates epileptogenesis. Anti-seizure medication withdrawal may unmask the still active tendency of the brain to generate seizures in those who relapse.

Recommendations for ASM withdrawal policies are remarkably sparse. According to a recent American Academy of Neurology Practice Advisory Update Summary, "the long-term risk of seizure recurrence is *possibly higher* among adults who have been seizure-free for 2 years and taper ASMs versus those who continue. In children, there is *probably no significant difference* in relapse risk between those who taper after 2 versus 4 years, and *insufficient evidence of difference* between tapering after 18 or 24 months."[9] Two studies were instrumental; in the first double-blinded randomized controlled trial in 160 adults on 1 ASM who were seizure-free for at least 2 years, withdrawal led to a 1 year seizure recurrence relative risk (RR) of 2.46 (95% CI 0.85-7.08, $P = 0.095$) compared to continuing drugs.[10] The second randomized trial was non-blinded and showed in 1013 patients who were 2 or more years in remission that ASM withdrawal was associated with a 2 years relapse RR of 2.12 (95% CI 1.63-2.77, $P < 0.001$).[11]

A meta-analysis of 7082 medically treated patients in remission who withdrew ASMs revealed a cumulative seizure recurrence rate of 22% at 1, 28% at 2, and 34% at 3 or 4 years after withdrawal.[12] These group average risks, however, are of little use when counselling individual patients. Individualized risk assessment is key but requires knowledge of relevant predictors of relapse. Twenty-five variables were reported as significantly predictive in at least 1 of 27 studies reviewed. Results, however, were inconsistent and it remained unclear whether variables were independently predictive and to what extent each of them individually and combined contributed to the observed risk.[12] Two recent individual-patient-data meta-analyses tried to overcome this by producing online available individualized prediction tools. One is based on data of 1769 patients who withdrew medication,[13] the other specifically addresses the risk of withdrawal in juvenile myoclonic epilepsy (JME).[14] Despite the moderate discriminative ability of both models, these tools may help physicians to better inform patients and balance the pros and cons of withdrawal. See below for a detailed discussion. How predicted risks compare to the chance of relapse when continuing drugs, and to what extent prediction models influence decision-making remains to be investigated, as discussed below. At least, these models clearly demonstrated that there is no "magical threshold" of 2 years, an interval often considered safe before recommending withdrawal.[9,15] More likely there is a risk continuum, with longer proof of epilepsy control inherently predicting a lower risk of seizure recurrence following ASM discontinuation.

Anti-Seizure Medication Withdrawal in Surgical Treated Seizure-Free Patients

About 50% to 60% of patients who undergo resective epilepsy surgery are seizure-free a decade or more postoperatively.[16] Therefore, like the medically controlled group, the question of ASM withdrawal often comes up in clinic but additional considerations factor in the risk-benefit assessment. Adult surgical patients had drug-resistant epilepsy for an average of 20 years or more before surgery, facing the long-term side effects of ASM polytherapy and the lifestyle restrictions of chronic epilepsy. Eliminating ASM side effects is commonly cited as a motivation for surgery *before* the procedure. However, *after* attaining a hard-earned seizure-freedom, regaining driving privileges, achieving a more productive lifestyle with less side effects from reduced albeit not completely discontinued ASMs, adults may worry about the disruptions of a breakthrough seizure after ASM withdrawal (eg, losing driving privileges, or a job). For children, the promise of a lifetime free of cognitive and systemic ASM side effects may outweigh the fear of a seizure.

These pragmatic distinctions likely explain why ASM withdrawal after surgery remains a largely subjective and difficult decision. Data driving this decision are limited to the below:

1. One prospective study[17]: Between 1997 and 2003, 60 patients were offered ASM withdrawal 1 year after surgery, then stratified into 2 cohorts (34 in a withdrawal group and 26 in a control group) to find no differences in recurrence risk as 76.5% of those in the withdrawal group and 61.5% in the control group were seizure-free 5 years after surgery. This study is limited by its small sample size, selection bias (stratification was *based on patients' decision on withdrawal* rather than any consistent inclusion/exclusion criteria) and limited control for confounders. Still, it drove the most recent American Academy of Neurology Guideline Subcommittee's report,[9] stating that there is insufficient evidence that the rate of seizure recurrence with ASM withdrawal following epilepsy surgery after 1 year of seizure freedom versus after 4 years is not significantly different than maintaining patients on ASMs.

2. One observational retrospective study[18] with a control: Longitudinal rates of recurrence were compared among 229 patients who remained on baseline ASMs, 127 patients who stopped ASMs, and 253 cases who reduced them. Similar outcomes were seen when withdrawal occurred 1 or 2 years after surgery. Seizures breaking through after complete ASM discontinuation were typically controlled with resuming ASMs (83% seizure free at 10 years with ASMs stopped and 82% seizure free with ASMs continued), but control was more difficult when recurrence occurred after simply reducing ASMs (68% seizure free at 10 years). No clear a priori clinical characteristics enabled the identification of those at risk.
3. One observational study focused on children[19] also found that early ASM withdrawal does not affect long-term seizure outcome or cure, positing that it might instead unmask incomplete surgical success sooner.

Altogether, there is no Class I evidence to support decision-making. There may be no change in long-term outcomes with ASM withdrawal, no added risk with early versus late withdrawal, nor with rapid versus slow reduction. Nomograms to individualize risk predictions (described later) may help with informing the ASM withdrawal conversation following pediatric[20] and adult[21] epilepsy surgery.

Anti-Seizure Medication Withdrawal After Acute Symptomatic Seizures

Acute symptomatic seizures (ASyS) are defined as "events, occurring in close temporal relationship with an acute central nervous system insult, which may be metabolic, toxic, structural, infectious, or due to inflammation."[22] Acute symptomatic seizures are highly prevalent, constituting up to 55% of all recorded seizures.[23] Guidelines typically do not advocate routine treatment for patients experiencing ASyS,[24] a recommendation grounded in the comparatively low overall risk of spontaneous seizures following ASyS in comparison to a first unprovoked seizure.[25]

Despite this guidance, a significant proportion ($\sim$86%, according to one estimate)[26] of ASyS cases receive treatment in the acute setting. In instances where ASMs are initiated, a common recommendation is to gradually taper treatment immediately following the acute phase, that is, after 7 to 14 days. However, real-life data shows that 56% of adults with ASyS remain on ASMs at discharge, and 49% continue ASM use after 3 months, despite being free from unprovoked seizures.[26]

The rationale behind the prolonged ASM treatment for certain patients with ASyS lies in the variability of the risk of unprovoked seizures based on the type of brain insult. Individuals with nonstructural etiologies, such as metabolic or toxic abnormalities, or seizures arising from alcohol or benzodiazepine withdrawal, exhibit a markedly low risk of unprovoked seizures.[26,27] Similarly, patients with reversible etiologies, like eclampsia or posterior reversible encephalopathy syndrome, also demonstrate a low risk.[27] Conversely, those with structural etiologies, including cerebrovascular disorders or infections leading to a structural brain insult, face a risk ranging from 20% to 40% of developing unprovoked seizures.[26,28]

These risks are also influenced by the type of ASyS and individual characteristics. For instance, ASyS regardless of etiology presenting as status epilepticus carry a 41% risk of subsequent unprovoked seizures, with ASyS presenting as status epilepticus after ischemic stroke yielding a $>$80% risk.[28,29] Prognostic models, exemplified by the SeLECT score for ischemic and the CAVE score for hemorrhagic stroke (see next for details), aid in integrating other individualized factors such as the location and severity of the brain insult into the risk assessment.[30,31]

While the overall evidence regarding ASM withdrawal strategies following ASyS remains limited, certain recommendations can be extrapolated from existing observations:

1) Patients experiencing a singular and/or nondisabling ASyS may not necessitate the initiation of ASM treatment.
2) In cases where ASM treatment was commenced for nonstructural etiologies (such as metabolic or toxic insults) or reversible causes, rapid discontinuation of ASM treatment is advised after the acute phase.
3) In ASyS due to structural etiologies, there is insufficient evidence to compare the guideline-endorsed strategies (withdrawal of ASMs after 7 to 14 days) and prevalent real-world practices (withdrawal of ASMs after 3 to 12 months). Prognostic models, such as the SeLECT or CAVE scores estimating the risk of unprovoked seizures after ischemic or hemorrhagic stroke, may serve as valuable tools in guiding decision-making processes.
4) It is essential to recognize that ASM treatment functions solely to suppress seizures and, as per current knowledge, is neither anti-epileptogenic nor disease-modifying.
5) Some clinicians contemplate extended ASM treatment following ASyS presenting as status epilepticus and in stroke survivors exhibiting a $>$60% risk of unprovoked seizures as predicted by the SeLECT/CAVE scores. However, the efficacy of this strategy has not been evaluated.
6) In ASyS due to autoimmune encephalitis, persistent brain inflammation may necessitate prolonged ASM treatment. Determining the optimal moment to start withdrawing ASMs following autoimmune encephalitis may be challenging due to the difficulty in discerning when inflammation has subsided and it is safe to attempt discontinuation of ASMs.

Prognostic Models for ASM Withdrawal

The development of prognostic models to forecast patient outcomes and, thus, optimize clinical decision-making has

been an important step toward more personalized medicine. By incorporating individual patient characteristics and historical data, these models may help refine treatment plans tailored to individual needs rather than relying on population averages. The bedside use of these models is promoted by providing practical tools such as nomograms and online calculators.

Below, we present 4 well-validated and commonly used models for ASM withdrawal in 4 different settings: (1) seizure-free medically treated patients,[13] (2) seizure-free patients with JME,[14] (3) seizure-free surgically treated children and adolescents,[20] and (4) seizure-free surgically treated adults.[21]

First, a prognostic model for seizure-free medically treated patients was developed using meta-analysis of data from 1769 patients across 10 studies.[13] The model allows the prediction of seizure recurrence at 2 or 5 years after starting ASM withdrawal or the chances of being seizure-free in the last year of follow-up. The model demonstrated a discrimination, measured using an adjusted concordance (c) statistic, of 0.65 and 0.71, respectively, during in-sample cross-validation. Subsequent independent validation largely reproduced these findings, though demonstrating that the model slightly overpredicted risk in independent samples.[32] The model is available online: http://epilepsypredictiontools.info/aedwithdrawal.

Second, a model specific for ASM withdrawal in medically treated JME was developed because these patients were widely believed to require lifelong treatment.[14] The analysis focusing on ASM withdrawal included data of 368 patients with JME. The model predicting seizure recurrence demonstrated a c statistic of 0.70. The model is available online: http://epilepsypredictiontools.info/jme_one.

Third, a model for ASM withdrawal in seizure-free patients after pediatric epilepsy surgery was developed based on data of 766 children in whom it was decided to reduce medication.[20] The models allows the prediction of seizure recurrence 2 or 5 years after starting ASM withdrawal or the chance of being seizure-free in the last year of follow-up, with c statistics of 0.68 and 0.73, respectively. The model is available online: http://epilepsypredictiontools.info/ttswithdrawal.

Fourth, a model for ASM withdrawal in seizure-free patients after adult epilepsy surgery was developed based on data of 731 adults who started ASM reduction from 9 cohorts.[21] The model allows the prediction of recurrent disabling seizures (not counting auras, ie, focal nonmotor aware seizures) or recurrence of any seizures (including auras), with c statistics of 0.67 and 0.68, respectively. The model is available online: https://predictepilepsy.github.io.

No well-validated models are available to predict seizure recurrence after ASM withdrawal following ASyS. But models predicting the occurrence of remote symptomatic seizures after ischemic or hemorrhagic stroke may be helpful in this regard, even if they were not developed specifically in the setting of ASM withdrawal.

A model to predict remote symptomatic seizures after ischemic stroke, termed SeLECT, was developed[30] and later updated[28] to version 2.0 based on data from 4552 stroke survivors from 9 centers. The model had a c statistic of 0.77 and is available online: https://predictapps.github.io/select/. Another model has focused on hemorrhagic stroke and was termed CAVE, with a c statistic of 0.69 in the validation cohort.[31]

It should be noted that the discrimination, that is, the ability to separate between low- and high-risk cases measured using the c statistic, of most of the models mentioned above was moderate. Thus, their utility to determine whether ASM withdrawal should or should not be started in an individual is limited. But these models were well calibrated, that is, able to provide realistic probabilities for seizure relapses. In other words, they may be a helpful tool for counselling patients when attempting ASM withdrawal. Future models could utilize larger datasets, apply more precise variable selection, and integrate cutting-edge tools like artificial intelligence, neuroimaging, and genetic profiling to significantly improve model performance, thereby advancing the precision and accuracy of personalized treatment regimens.[33]

From Preference to Evidence: Subjective Risk Assessment Versus Prognostic Models

While most efforts to date have quantified seizure probabilities, scarce literature informs how patients or clinicians contextualize those probabilities. Examples:

Thirty-one patients who were seizure-free at least 1 year seen at an academic center evaluated how concerning different hypothetical seizure risks might be compared to hypothetical ASM side effects or inconveniences.[34] Inconvenience of having to take medication, occasional laboratory monitoring draws, and having a low to moderate copay were less concerning than typical post-withdrawal seizure probabilities. A 10% seizure chance in the next year was about equally concerning as weight gain or sedation side effects, whereas a 25% chance of seizure in the next year was rated as more concerning than any studied side effect, favoring continuation in many patients particularly if tolerating their ASMs well.

Seventy-six children who were at least 3 months seizure-free and their families provided what maximal seizure risk might be acceptable to discontinue ASMs.[35] Responses varied markedly, from 0% to >90% (median ~40%). Interestingly, while their physicians' median risk tolerance and physicians' estimates of their patient's risk tolerance were close, physician responses were almost completely uncorrelated with patient responses within dyads.

Finally, 287 neurologists reported their maximally tolerated seizure risk in the next 2 years when considering withdrawal.[15] Again there was wide variation ranging from near 0% to above 75%, but median responses were most conservatively 15% for adults with convulsions, up to about 30% with nonconvulsive seizures, with thresholds tending to be lower than typically used for starting ASMs in the first place.

These examples only begin to illustrate how patients and clinicians weigh the important tradeoffs and manipulate risk information. Ideally, as has been done in other conditions,[36] we

should focus more as a field on systematically studying patient preferences to align with physician practice for incorporation into care guidelines.

Conclusion and Outlook

Duration of ASM treatment represents a core determination. While much knowledge already exists, fundamental questions remain.

1) How can we improve seizure risk calculation? Complex machine learning models are unlikely to solve the problem, overdetecting noise without addressing data limitations.[33] Better data are needed to evaluate underexplored predictors (eg, specific epilepsy syndromes, genetics, sleep, substances [eg, illicit drugs or alcohol], and more advanced EEG and imaging analysis). Also, additional work should compute not only post-discontinuation risk but also individualized seizure risk *increases* due to withdrawal and evaluate the effect of withdrawal on different seizure types and frequency beyond dichotomizing as seizure-free versus not.
2) How should we optimally integrate seizure risk calculators into clinical practice and communicate that risk to patients, and what might be their impact on clinical care?[37] Many barriers exist to using seizure risk calculators such as lack of trust in its output, not being aware of its existence, and not being accessible when needed.[15]
3) Perhaps most importantly, what risk or risk difference is sufficiently low to justify a withdrawal attempt, and for what biopsychosocial profiles?

The 2021 American Academy of Neurology guidelines[9] describe considerable uncertainty. Much remains to be learned if we are to deliver optimally patient-centered and individualized care.

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ORCID iDs

Marian Galovic https://orcid.org/0000-0002-2307-071X
Lara E. Jehi https://orcid.org/0000-0002-8041-6377

References

1. Larsson D, Baftiu A, Landmark CJ, et al. Association between antiseizure drug monotherapy and mortality for patients with poststroke epilepsy. *JAMA Neurol*. 2022;79(2):169-175. doi:10.1001/jamaneurol.2021.4584
2. Josephson CB, Wiebe S, Delgado-Garcia G, et al. Association of enzyme-inducing antiseizure drug use with long-term cardiovascular disease. *JAMA Neurol*. 2021;78(11):1367-1374. doi:10.1001/jamaneurol.2021.3424
3. Josephson CB, Gonzalez-Izquierdo A, Denaxas S, Sajobi TT, Klein KM, Wiebe S. Independent associations of incident epilepsy and enzyme-inducing and non-enzyme-inducing antiseizure medications with the development of osteoporosis. *JAMA Neurol*. 2023;80(8):843-850. doi:10.1001/jamaneurol.2023.1580
4. Lossius MI, Nakken KO, Mowinckel P, Taubøll E, Gjerstad L. Favorable change of lipid profile after carbamazepine withdrawal. *Acta Neurol Scand*. 2016;134(3):219-223. doi:10.1111/ane.12534
5. Terman SW, Slinger G, Koek A, et al. Variation in seizure risk increases from antiseizure medication withdrawal among patients with well-controlled epilepsy: a pooled analysis. *Epilepsia Open*. 2024;9(1):333-344. doi:10.1002/epi4.12880
6. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. *Lancet Neurol*. 2011;10(11):961-968. doi:10.1016/s1474-4422(11)70193-4
7. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. *JAMA Neurol*. 2018;75(3):279-286. doi:10.1001/jamaneurol.2017.3949
8. Braun KPJ, Schmidt D. Stopping antiepileptic drugs in seizure-free patients. *Curr Opin Neurol*. 2014;27(2):219-226. doi:10.1097/wco.0000000000000075
9. Gloss D, Pargeon K, Pack A, et al, On behalf of the AAN Guideline Subcommittee . Antiseizure medication withdrawal in seizure-free patients: practice advisory update summary: report of the AAN Guideline Subcommittee. *Neurology*. 2021;97(23):1072-1081. doi:10.1212/wnl.0000000000012944
10. Lossius MI, Hessen E, Mowinckel P, et al. Consequences of antiepileptic drug withdrawal: a randomized, double-blind study (Akershus Study). *Epilepsia*. 2008;49(3):455-463. doi:10.1111/j.1528-1167.2007.01323.x
11. Randomised study of antiepileptic drug withdrawal in patients in remission. Medical Research Council Antiepileptic Drug Withdrawal Study Group. *Lancet (Lond, Engl)*. 1991;337(8751):1175-1180. http://pubmed.gov/1673736
12. Lamberink HJ, Otte WM, Geleijns K, Braun KPJ. Antiepileptic drug withdrawal in medically and surgically treated patients: a meta-analysis of seizure recurrence and systematic review of its predictors. *Epileptic Disord*. 2015;17(3):211-228. doi:10.1684/epd.2015.0764
13. Lamberink HJ, Otte WM, Geerts AT, et al. Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis. *Lancet Neurol*. 2017;16(7):523-531. doi:10.1016/s1474-4422(17)30114-x

14. Stevelink R, Al-Toma D, Jansen FE, et al. Individualised prediction of drug resistance and seizure recurrence after medication withdrawal in people with juvenile myoclonic epilepsy: a systematic review and individual participant data meta-analysis. *EClinicalMedicine*. 2022;53:101732. doi:10.1016/j.eclinm.2022.101732
15. Terman SW, Slinger G, Rheaume CE, et al. Antiseizure medication withdrawal practice patterns: a survey among members of the American Academy of Neurology and EpiCARE. *Neurol Clin Pr*. 2023;13(1): e200109. doi:10.1212/cpj.0000000000200109
16. Lamberink HJ, Otte WM, Blümcke I, Braun KPJ, EEBB Writing Group, Group Study, ERN EpiCARE. Seizure outcome and use of antiepileptic drugs after epilepsy surgery according to histopathological diagnosis: a retrospective multicentre cohort study. *Lancet Neurol*. 2020;19(9):748-757. doi:10.1016/s1474-4422(20)30220-9
17. Kerling F, Pauli E, Lorber B, Blümcke I, Buchfelder M, Stefan H. Drug withdrawal after successful epilepsy surgery: how safe is it? *Epilepsy Behav*. 2009;15(4):476-480. doi:10.1016/j.yebeh.2009.05.016
18. Yardi R, Irwin A, Kayyali H, et al. Reducing versus stopping antiepileptic medications after temporal lobe surgery. *Ann Clin Transl Neurol*. 2014;1(2):115-123. doi:10.1002/acn3.35
19. Boshuisen K, Arzimanoglou A, Cross JH, et al. Timing of antiepileptic drug withdrawal and long-term seizure outcome after paediatric epilepsy surgery (TimeToStop): a retrospective observational study. *Lancet Neurol*. 2012;11(9):784-791. doi:10.1016/s1474-4422(12)70165-5
20. Lamberink HJ, Boshuisen K, Otte WM, Geleijns K, Braun KPJ, TimeToStop Study Group. Individualized prediction of seizure relapse and outcomes following antiepileptic drug withdrawal after pediatric epilepsy surgery. *Epilepsia*. 2018;59(3):e28-e33. doi:10.1111/epi.14020
21. Ferreira-Atuesta C, de Tisi J, McEvoy AW, et al. Predictive models for starting antiseizure medication withdrawal following epilepsy surgery in adults. *Brain*. 2022;146(6):2389-2398. doi:10.1093/brain/awac437
22. Beghi E, Carpio A, Forsgren L, et al. Recommendation for a definition of acute symptomatic seizure. *Epilepsia*. 2010;51(4):671-675. doi:10.1111/j.1528-1167.2009.02285.x
23. Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. *Mayo Clin Proc*. 1996;71(6):576-586. doi:10.1016/s0025-6196(11)64115-3
24. Powers WJ, Rabinstein AA, Ackerson T, et al, On behalf of the AHAS Council. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12):e344-e418. doi:10.1161/str.0000000000000211
25. Hesdorffer DC, Benn EKT, Cascino GD, Hauser WA. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. *Epilepsia*. 2009;50(5):1102-1108. doi:10.1111/j.1528-1167.2008.01945.x
26. Herzig-Nichtweiß J, Salih F, Berning S, et al. Prognosis and management of acute symptomatic seizures: a prospective, multicenter, observational study. *Ann Intensive Care*. 2023;13(1):85. doi:10.1186/s13613-023-01183-0
27. Mauritz M, Hirsch LJ, Camfield P, et al. Acute symptomatic seizures: an educational, evidence-based review. *Epileptic Disord*. 2022;24(1):26-49. doi:10.1684/epd.2021.1376
28. Sinka L, Abraira L, Imbach LL, et al. Association of mortality and risk of epilepsy with type of acute symptomatic seizure after ischemic stroke and an updated prognostic model. *JAMA Neurol*. 2023;80(6):605-613. doi:10.1001/jamaneurol.2023.0611
29. Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Risk of unprovoked seizure after acute symptomatic seizure: effect of status epilepticus. *Ann Neurol*. 1998;44(6):908-912. doi:10.1002/ana.410440609
30. Galovic M, Döhler N, Erdélyi-Canavese B, et al. Prediction of late seizures after ischaemic stroke with a novel prognostic model (the SeLECT score): a multivariable prediction model development and validation study. *Lancet Neurol*. 2018;17(2):143-152. doi:10.1016/s1474-4422(17)30404-0
31. Haapaniemi E, Strbian D, Rossi C, et al. The CAVE score for predicting late seizures after intracerebral hemorrhage. *Stroke*. 2014;45(7):1971-1976. doi:10.1161/strokeaha.114.004686
32. Lin J, Ding S, Li X, et al. External validation and comparison of two prediction models for seizure recurrence after the withdrawal of antiepileptic drugs in adult patients. *Epilepsia*. 2020;61(1):115-124. doi:10.1111/epi.16402
33. Eriksson MH, Ripart M, Piper RJ, et al. Predicting seizure outcome after epilepsy surgery: do we need more complex models, larger samples, or better data? *Epilepsia*. 2023;64(8):2014-2026. doi:10.1111/epi.17637
34. Terman SW, Aschmann HE, Hutton D, Burke JF. Best-worst scaling preferences among patients with well-controlled epilepsy: novel questionnaire development. *ResearchSquare*. Published online 2022. doi:10.21203/rs.3.rs-1954083/v1
35. Gordon K, MacSween J, Dooley J, Camfield C, Camfield P, Smith B. Families are content to discontinue antiepileptic drugs at different risks than their physicians. *Epilepsia*. 1996;37(6):557-562. doi:10.1111/j.1528-1157.1996.tb00609.x
36. Blackwood J, Armstrong MJ, Schaefer C, et al. How do guideline developers identify, incorporate and report patient preferences? An international cross-sectional survey. *BMC Heal Serv Res*. 2020;20(1):458. doi:10.1186/s12913-020-05343-x
37. Terman SW, Griethuysen R, Rheaume CE, et al. Antiseizure medication withdrawal risk estimation and recommendations: a survey of American Academy of Neurology and EpiCARE Members. *Epilepsia Open*. 2023;8(2):386-398. doi:10.1002/epi4.12696