Received: 29 May 2021 | Revised: 13 October 2021 | Accepted: 25 October 2021

DOI: 10.1111/epi.17120

Epilepsia®

SPECIAL REPORT

Proposal for an updated seizure classification framework in clinical trials

Claude Steriade[1,2] | **Michael R. Sperling**[2,3] | **Bree DiVentura**[2] | **Meryl Lozano**[2] | **Renée A. Shellhaas**[2,4] | **Sudha Kilaru Kessler**[2,5] | **Dennis Dlugos**[2,5] | **Jacqueline French**[1,2]

[1]New York University Comprehensive Epilepsy Center, New York, New York, USA

[2]Epilepsy Study Consortium, Reston, Virginia, USA

[3]Department of Neurology, Jefferson Comprehensive Epilepsy Center, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

[4]Department of Pediatrics, University of Michigan, Ann Arbor, Michigan, USA

[5]Departments of Neurology and Pediatrics, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence
Claude Steriade, NYU Comprehensive Epilepsy Center, 223 E34th St, New York, NY 10016, USA
Email: claude.steriade@nyulangone.org

Abstract

The International League Against Epilepsy (ILAE) seizure classification scheme has been periodically updated to improve its reliability and applicability to clinicians and researchers alike. Here, members of the Epilepsy Study Consortium propose a pragmatic seizure classification, based on the ILAE scheme, designed for use in clinical trials with a focus on outcome measures that have high reliability, broad interpretability across stakeholders, and clinical relevance in the context of the development of novel antiseizure medications. Controversies around the current ILAE classification scheme are discussed in the context of clinical trials, and pragmatic simplifications to the existing scheme are proposed, for intended use by investigators, industry sponsors, and regulatory agencies.

KEYWORDS

classification, clinical trials, epilepsy

1 | INTRODUCTION

The International League Against Epilepsy (ILAE) updated its seizure classification in the past decade, with the most recent iteration published 4 years ago.[1] Ideally, a seizure classification scheme is well suited for use by clinicians and researchers alike, but the needs of users may differ. Practicing neurologists classify seizures to speak a common language when communicating about patients to their colleagues. They may also wish to highlight clinically relevant information like the presence or absence of awareness, which impacts safety and ability to drive. Surgical epileptologists may use a seizure classification that includes semiologic information useful for localization purposes, which may explain why some have advocated for a modified seizure classification in that setting.[2] Another intended purpose, which has received less attention, is the use of a seizure classification scheme in clinical trials. Researchers rely on a classification scheme to ensure that diagnoses and

outcomes are measured uniformly, to enhance reproducibility of research methods, and to facilitate multisite collaboration. Seizure classification for clinical trials should (1) be readily interpretable by a range of stakeholders (trial participants, research staff, industry sponsors, regulatory agencies, and the clinicians who will eventually prescribe a new treatment), (2) have high interrater reliability across multiple study sites, and (3) provide relevant outcome variables.

In this paper, we discuss the ILAE seizure classification[1] and modifications of that system used in recent regulatory trials of antiseizure medications, and then make recommendations for standardized seizure categories that are optimized for clinical trials. This modification does not in any way represent a substantive change from the ILAE classification, but instead shows how to use that classification pragmatically for therapeutic trials. We hope trials conducted in the future will use this proposed system, which has clinical relevance and will permit better comparison of results between trials.

Key Points

- We recommend modifying terminology from focal aware with or without motor signs, to focal aware with or without observable signs.
- We recommend against distinguishing focal unaware with or without motor signs.
- We recommend against the use of the term "drop seizures" in clinical trials, and advocate for the use of recent classification terminology.
- We support integrating complementary surrogate markers (e.g., EEG) to count seizure types with poor self-report reliability.

2 | METHODS

We identified seizure classification terminology used in 19 recently completed or current epilepsy clinical trials (2017–ongoing), for which the Epilepsy Study Consortium has consulted for design, adjudication, and form review (seven adult focal; 12 pediatric, several indications). Only studies using the latest ILAE seizure classification were included, resulting in a lower number of adult studies. From there, the proposed classification was discussed and a series of iterations carried out until consensus was reached among the authors on the end result.

2.1 | Recommendations for focal epilepsy seizure classification in the context of clinical trials

The most recent 2017 ILAE seizure classification specifies three main categories of focal seizures: (1) focal aware (nonmotor or motor), (2) focal unaware (nonmotor or motor), and (3) focal to bilateral tonic–clonic seizures. For the purposes of a clinical trial for focal onset seizures, we propose quantifying only the following three seizure categories when defining the primary endpoint (i.e., change in seizure frequency): (1) focal aware *observable* (readily recognized by a caregiver, these may be motor, aphasic, or autonomic), (2) focal unaware (without the distinction between motor and nonmotor), and (3) focal to bilateral tonic–clonic seizures. This approach has been adopted in most recent trials.[3] Other types of focal aware seizures can continue to be included in a seizure diary, as participants and their physicians are likely already tracking these seizure types prior to enrollment in a trial, but should not be counted toward the primary outcome measure, for reasons explained below.

2.1.1 | Focal aware nonobservable seizures

Focal aware seizures without observable signs have traditionally not been included in seizure counts that contribute to the primary outcome in randomized controlled regulatory trials of antiseizure medications (ASMs). These seizures are typically excluded because they are difficult to distinguish from behavioral events or other nonseizure phenomena. Although diagnostic uncertainty can exist with any seizurelike events, the highest risk of misdiagnosis exists with focal aware nonmotor events. This uncertainty is increased by the low likelihood of electroencephalographic (EEG) confirmation, as most focal aware nonmotor seizures have no associated ictal EEG change.[4] The inclusion of events with low diagnostic certainty has been hypothesized to contribute to increased placebo response rates in epilepsy clinical trials.[5] For example, a patient may experience dizziness, which could represent a vertiginous seizure, but also ASM side effects or unrelated vertigo. Similarly, a patient may report paroxysmal episodes of anxiety with hyperventilation and palpitations, which could represent autonomic seizures or be nonepileptic and related to a primary psychiatric diagnosis.

In addition, focal aware nonmotor seizures are less likely to cause morbidities associated with epilepsy such as injury, and therefore have different clinical relevance than other more consistently disabling seizure types.

People who continue to experience focal aware nonmotor seizures are still considered to be free of disabling seizures after resective surgery (Engel IB).[6]

Therefore, although focal aware nonobservable seizures may be relevant in other contexts (e.g., epilepsy surgery, where focal aware nonmotor seizures may provide important localization information), they are too unreliable to be tracked as a primary outcome measure in clinical trials. Focal aware nonobservable seizures, if confirmed on central review as likely seizures, can be tracked as a secondary outcome measure if desired with the above cautions.

2.1.2 | Focal aware observable seizures

Focal aware motor seizures can be distressing and occasionally pose risk of injury, so they are a clinically relevant outcome measure. Similarly, focal aware seizures with aphasia or autonomic signs can be disabling. In addition, focal aware seizures with observable signs can be clinically confirmed as seizures, although the EEG is usually negative. Thus, these seizures can be reliably counted, and therefore produce less uncertainty and noise in analyses of trial data than focal aware nonobservable seizures. They merit inclusion as a primary outcome measure for clinical trials. We propose three categories of focal aware observable seizures: motor, aphasic, and autonomic.

2.1.3 | Focal aware observable seizures with aphasia

Aphasic seizures occur in patients with focal epilepsy with seizures initially or secondarily involving the temporal[7] or frontal lobe.[8] They manifest with arrest of speech production, jargon aphasia, or impairment of speech comprehension, and may not evolve to loss of awareness. People with documented evidence of expressive aphasia either through reliable history and home video documentation of seizures or video-EEG may be enrolled in clinical trials even if a focal aware seizure with aphasia is their only seizure type, provided the diagnosis of epilepsy is definitive and investigators determine that seizures are reliably counted. Given that aphasic seizures can only be observed if patients are engaged in a linguistic activity, we propose to separate aphasic seizures from other focal aware observable seizures that can be observed independently of a patient's activity (i.e., motor and autonomic seizures). We prefer not to include receptive aphasia lacking a concomitant expressive component in this seizure type, given potential issues with reliability.

2.1.4 | Focal aware observable seizures with motor signs

Focal aware seizures with motor signs, including elementary motor (e.g., myoclonic, clonic, tonic) or integrated motor (e.g., hyperkinetic) manifestations have high reliability and generally carry high diagnostic confidence. Negative motor seizures are also highly reliable, and similarly to aphasic seizures may require a patient to be engaged in a motor activity to be observable. These seizures are acceptable as primary outcome measures for clinical trials.

2.1.5 | Focal aware observable seizures with autonomic signs

Rarely, focal aware seizures may manifest with autonomic signs as the primary observable feature, including ictal tachy- or bradycardia, hyper- or hypoventilation, piloerection, retching or vomiting, hypersalivation, or pupillary mydriasis.[9] Although rare, we propose that these seizures be counted as observable seizures, provided there is adequate documentation of the observable autonomic signs (through home video or video-EEG) and reasonable confidence that the autonomic signs are not secondary to anxiety or another physiologic cause. We do not recommend including seizures in which the autonomic manifestations are subjective (e.g., vegetative auras such as nausea, sensation of flushing, or light-headedness without observable physical signs), given the diagnostic uncertainty associated with these events.

2.1.6 | Focal unaware seizures

The difficulty of reliably counting focal unaware seizures is well recognized. Multiple investigations of recall of seizures with impaired awareness in epilepsy monitoring units have revealed that patients and families underreport focal unaware seizures.[10–14] The negative impact of focal unaware seizures on patients' quality of life and daily functioning makes this seizure type a high priority as a primary outcome measure in clinical trials, given its clinical relevance despite the recognized limitations in quantifying their occurrence.

The distinction between motor and nonmotor focal unaware seizures serves little purpose in most clinical trials of adults and older children with focal onset seizures. Although presence of motor signs is associated with risk of injury, injury has not been used as an outcome measure in regulatory trials. Furthermore, the interrater reliability of this classification detail may be poor; one epileptologist may classify the presence of automatisms during a focal unaware seizure arising from the temporal lobe as representing "motor

signs," whereas another may deem the seizure as nonmotor if they view the predominant sign as behavioral arrest. In young children (<3 years of age), where verbal abilities may limit assessment of awareness, motor signs may have utility for improving reliability of seizure counting.

2.1.7 | Focal unknown awareness seizures

It may not be possible to assess awareness in some individuals, such as people with brief seizures, infants, some older children, and adults with intellectual disabilities. However, focal *observable* seizures (with either motor or autonomic signs), but with unknown awareness, could still qualify for inclusion in investigational trials.

2.1.8 | Focal to bilateral tonic–clonic seizures

Tonic–clonic seizures are strongly associated with excess morbidity and mortality,[15] and may be linked to progressive cognitive decline.[16,17] We therefore support counting focal to bilateral tonic–clonic seizures separately from other focal seizure types. This seizure type may also be assessed through seizure detection devices, which can complement seizure diaries by providing objective evidence of seizure frequency.[18] Lastly, noting a reduction in the frequency of focal to bilateral tonic–clonic seizures in a focal epilepsy trial may lead to testing that compound's efficacy for generalized tonic–clonic seizures, as in the case of perampanel,[19] lacosamide,[20] and cenobamate (NCT03678753).

2.1.9 | Complementary endpoints

Given difficulties in accurately quantifying focal seizures with impaired awareness, incorporating short-term and long-term EEG data may improve rigor and reproducibility for clinical trials. Intracranial EEG data recorded with responsive neurostimulation devices might be analyzed for evidence of the antiseizure effect of new agents. For example, a proof of concept study that demonstrates a reduction in "long episodes" after administration of a new agent could suggest antiseizure efficacy, thereby providing support for further development of that drug.[21]

2.2 | Recommendations for generalized epilepsy seizure classification in the context of clinical trials

The ILAE generalized seizure classification outlines motor seizure types according to observable semiologic features and their sequence (tonic–clonic, tonic, clonic, myoclonic, myoclonic–tonic–clonic, myoclonic–atonic, atonic, epileptic spasms), and nonmotor (i.e., absence) seizures according to their characteristics (typical vs. atypical) and associated motor features (myoclonic, eyelid myoclonia). For the purposes of clinical trials, many of these seizure types overlap in their impact on morbidity (e.g., drop attacks can be caused by many different seizure types, as described below), and others raise challenges regarding the reliability of seizure counting with traditional seizure diaries (e.g., absence seizures may be difficult to distinguish from behavioral staring episodes).

2.2.1 | Multiple seizure types can lead to drop seizures or drop attacks

There is an active drug development pipeline to address the unmet therapeutic needs of people with epileptic encephalopathies (e.g., Lennox–Gastaut syndrome), in which multiple generalized seizure types typically occur. Many ASMs are currently approved for Lennox–Gastaut syndrome (most recently cannabidiol[22] and clobazam[23]) or are being investigated with the potential for future approval (fenfluramine[24] and soticlestat[25]). In these trials, "drop" seizures were counted as a primary outcome seizure type to reflect the associated high morbidity produced by these seizures. Although commonly used to describe seizures, the term "drop seizures" does not exist in the ILAE seizure classification and is an "old term"[1] that usually refers to either tonic or atonic seizures. Multiple seizure types in the 2017 classification can lead to falls, including unilateral clonic, unilateral tonic, or tonic–clonic seizures. The inclusion of the latter seizure types as "drop seizures" may have led to an overcounting of these seizures.

We propose that the term "drop seizure" no longer be used in clinical trials, to improve the diagnostic clarity of outcome measures. Instead, any seizure type can be classified with the modifier of "likely (or unlikely) to result in a fall." If trial investigators wish to include multiple seizure types that produce falls, more precision is needed for purposes of replicating results and understanding drug effects. Thus, we advise avoiding use of a single term that encompasses a wide range of seizure types and ictal EEG patterns. The modifier "likely (or unlikely) to result in a fall" can be applied to other seizure types in trials if falling is a clinically relevant characteristic. This modifier is defined as follows: in ambulatory individuals, a seizure type has resulted in falls in the past, and in wheelchair- or bedbound individuals, a seizure type would be likely (>50% probability) to produce a fall if that person were standing independently. In addition, seizure diaries may

have an option to document whether a fall did occur with any seizure type.

2.2.2 | Seizure types with unreliable seizure counting

Some generalized seizure types are challenging to track reliably with traditional seizure diaries. Myoclonus may occur hundreds of times per day in people with Dravet or Lennox–Gastaut syndrome. Absence seizures can occur with very high frequency and extreme brevity in absence epilepsy syndromes, and may only be noted if a patient is actively engaged with another person. Infantile spasms may often exhibit subtle behaviors. Historically, when one of these seizure types has been used in a clinical trial, for example in the setting of childhood absence epilepsy or epileptic spasms, outcome has been determined through either self-report or objective measures (bedside hyperventilation, video-EEG).[26] Although generalized seizure types with known reliability issues can be used in clinical trials, we recommend that surrogate, objective markers be included in trials in addition to patient or caregiver report to improve rigor and reproducibility. For instance, monitoring of generalized spike wave complexes using limited electrode arrays may enable the feasibility of long-term ambulatory EEG monitoring for absence seizures for the entire duration of a trial period.[27] Innovative seizure detection devices may also be used as surrogate markers for absence seizure self-report; for example, an oculometric device tracking eye movements robustly detected absence seizures in a proof of concept study.[28] Seizure-free days may also be used as an outcome measure. Patient-reported seizure counts still carry clinical relevance, and should continue to be captured through seizure diaries.

2.3 | Recommendations for a clinical trial seizure classification scheme

We propose an amended seizure classification scheme in Table 1 that can be used in clinical trials of ASMs. The basic framework is similar to the ILAE 2017 seizure classification scheme, with the addition of "likely (or unlikely) to cause a fall" as a modifier that can be applied to a variety of seizure types. For people in whom it is difficult to distinguish between tonic and atonic seizures, we add a tonic/atonic subtype that expresses the ambiguity. The predominant motor feature (e.g., atonic in myoclonic–atonic seizures) serves as the primary header for motor seizures with multiple motor features.

For focal onset seizures, we removed the motor versus nonmotor focal unaware seizure types and added the

TABLE 1 Recommendations for updated seizure classification to be used in clinical trials

- Generalized onset 1.0[a]
  - Tonic–clonic 1.1
    - Tonic–clonic 1.1.1
    - Myoclonic–tonic–clonic 1.1.2
    - Clonic–tonic–clonic 1.1.3
  - Absence 1.2
    - Typical absence 1.2.1
    - Atypical absence 1.2.2
    - Myoclonic absence 1.2.3
    - Absence with eyelid myoclonia 1.2.4
  - Myoclonic 1.3
  - Clonic 1.4 (bilateral or generalized)
  - Tonic 1.5 (bilateral or generalized)
    - Tonic 1.5.1
    - Myoclonic–tonic 1.5.2
  - Atonic 1.6
    - Atonic 1.6.1
    - Myoclonic–atonic 1.6.2
  - Tonic/atonic (cannot differentiate) (bilateral) 1.7
  - Epileptic spasms 1.8
    - Infantile spasms (<3 years of age) 1.8.1
    - Epileptic spasms (3 years of age and older) 1.8.2
- Focal onset 2.0
  - Focal aware 2.1
    - Focal aware observable 2.1.1
      - Focal aware observable, not activity dependent 2.1.1.1
        - Focal aware motor 2.1.1.1.2
        - Focal aware autonomic 2.1.1.1.3
      - Focal aware observable, activity dependent 2.1.1.2
        - Focal aware aphasic 2.1.1.2.1
        - Focal aware negative motor 2.1.1.2.2
    - Focal aware nonobservable 2.1.2 (not to be included to calculate endpoint)
  - Focal impaired awareness 2.2
  - Focal unknown awareness observable 2.3
    - Focal unknown awareness motor 2.3.1
    - Focal unknown awareness autonomic 2.3.2
  - Focal to bilateral tonic–clonic 2.4
  - Hemiclonic 2.5
- Unknown (or undetermined) onset 3.0
  - Tonic–clonic of unknown onset 3.1
  - Tonic of unknown onset 3.2
  - Atonic of unknown onset 3.3
  - Epileptic spasms of unknown onset 3.4
- Status epilepticus 4.0
  - Convulsive status epilepticus 4.1
  - Nonconvulsive status epilepticus 4.2

[a]The modifier "with or without likely fall" may be applied to any seizure type with the following characteristics: (1) in ambulatory individuals, a seizure type has resulted in falls in the past; or (2) in wheelchair- or bedbound individuals, a seizure type would be likely (>50% probability) to produce a fall if that person were standing independently.

category of focal aware observable (which includes aphasic, motor, and autonomic) seizures, and specify that focal aware nonobservable seizures are not to be counted to calculate a primary clinical trial endpoint.

In addition, we include convulsive and nonconvulsive status epilepticus, as defined by the ILAE,[29] given the expanding pipeline for novel treatments of status epilepticus. Nonhabitual seizures exceeding the duration defined by the ILAE (5 min for convulsive status epilepticus and 10 min for nonconvulsive status epilepticus) can then be tracked accordingly.

Lastly, we include seizures with unknown mechanism of onset (generalized vs. focal) given their relevance in some unclassified epilepsies that are associated with tonic–clonic seizures.

3 | CONCLUSIONS AND FUTURE DIRECTIONS

We outline a pragmatic seizure classification scheme for use in clinical trials of focal epilepsy, with the goal of providing reliable and readily operationalized seizure types that have relevance to the morbidity and mortality of epilepsy. We also suggest integrating complementary surrogate markers (long-term scalp EEG and intracranial EEG, seizure detection devices) that provide objective and reproducible data to count seizure types with poor self-report reliability (e.g., generalized epilepsy trials), and for pilot proof of concept studies.

ACKNOWLEDGMENT

None.

CONFLICT OF INTEREST

C.S. receives New York University (NYU) salary support for consulting work on behalf of the Epilepsy Study Consortium for Baergicm, Biogen, BioXcel, Cerebral, Cerevel, Engage, Janssen, NeuCyte, Neurocrine, and SK Life Science. C.S. receives research support from Finding a Cure for Epilepsy and Seizures (FACES), the NYU Clinical Translational Science Institute Scholars Program, the National Organization for Rare Diseases, and the Dorris Duke Fund to Retain Clinician Scientists. She is an investigator on research grants awarded to NYU from Cerevel and Xenon. M.R.S. has received compensation for speaking at continuing medical education (CME) programs from Neurology Live, Medscape, Projects for Knowledge, International Medical Press, Eisai, and UCB Pharma. He is an advisor for scientific publications for Neurelis. He consults for Medtronic with payments to Thomas Jefferson University. He has received research support from Eisai, Medtronic, Neurelis, SK Life Science, Takeda, Xenon, Cerevel, UCB Pharma, and Engage Pharmaceuticals. He has received royalties from Oxford University Press. B.D. and M.L. are employees of the Epilepsy Study Consortium, which has received research and meeting support from and has provided consulting services to Acadia, Aeovian, Alterity Therapeutics, Anavex, Arkin Holdings, Arvelle Therapeutics, Athenen Therapeutics, Baergic Bio, Biogen, BioXcel Therapeutics, Cerebral Therapeutics, Cerevel, Corlieve Therapeutics, Crossject, Eisai, Eliem Therapeutics, Encoded Therapeutics, Engage Therapeutics, Engrail, Epalex, Epihunter, Epiminder, Equilibre BioPharmaceuticals, Fortress Biotech, Greenwich Biosciences, GW Pharma, Janssen Pharmaceutica, Knopp Biosciences, LivaNova, Longboard Pharmaceuticals, Lundbeck, Marinus, Medtronic, Mend Neuroscience, Merck, NeuCyte, Neurocrine, Neuropace, Otsuka Pharmaceutical Development, Ovid Therapeutics, Passage Bio, Praxis, PrevEp, PureTech LYT, Sage, SK Life Science, Sofinnova, Stoke, Sunovion, Supernus, Synergia Medical, Takeda, UCB, Xenon Pharmaceuticals, Xeris, Zogenix, and Zynerba. R.A.S. receives research support from the National Institutes of Health (NIH), the Patient-Centered Outcomes Research Institute, the Pediatric Epilepsy Research Foundation, and the University of Michigan. She receives honoraria from UpToDate for authorship on topics related to neonatal seizures, serves as a consultant for the Epilepsy Study Consortium, and is an associate editor for *Neurology*. S.K.K. is an investigator on research grants awarded to Children's Hospital of Philadelphia from Acadia, Eisai, SK Life Science, UCB, Zogenix, and Neuropace. D.D. receives salary support from the NIH, Commonwealth of Pennsylvania Department of Health, Pediatric Epilepsy Research Foundation, and Epilepsy Study Consortium. He is an investigator on research grants awarded to Children's Hospital of Philadelphia from Ovid/Takeda, Zogenix, Greenwich Biosciences, Neurelis, Bio-Pharm, SK Life Science, and Encoded Therapeutics. He has received travel expenses for protocol development conferences or investigator meetings from Marinus, Ovid/Takeda, Biogen, Zogenix, and Xenon. He has received honoraria and/or travel support for CME and other educational programs from Wake Forest University School of Medicine and the American Epilepsy Society. J.F. receives NYU salary support from the Epilepsy Foundation and for consulting work and/or attending scientific advisory boards on behalf of the Epilepsy Study Consortium for Adamas, Aeonian/Aeovian, Alterity Therapeutics, Anavex, Arkin Holdings, Arvelle Therapeutics, Athenen Therapeutics/Carnot Pharma, Baergic Bio, Biogen, BioXcel Therapeutics, Cavion,

Cerebral Therapeutics, Cerevel, Corlieve Therapeutics, Crossject, CuroNZ, Eisai, Eliem Therapeutics, Encoded Therapeutics, Engage Therapeutics, Engrail, Epalex, Epihunter, Epiminder, Equilibre BioPharmaceuticals, Fortress Biotech, Greenwich Biosciences, GW Pharma, Janssen Pharmaceutica, Knopp Biosciences, LivaNova, Longboard Pharmaceuticals, Lundbeck, Marinus, Mend Neuroscience, Merck, NeuCyte, Neurocrine, Neuropace, Otsuka Pharmaceutical Development, Ovid Therapeutics, Passage Bio, Praxis, PureTech LTY, Redpin, Sage, SK Life Science, Sofinnova, Stoke, Supernus, Synergia Medical, Takeda, UCB, West Therapeutic Development, Xenon, Xeris, Zogenix, and Zynerba. J.F. has also received research support from the Epilepsy Study Consortium (funded by the Andrews Foundation, Eisai, Engage, Lundbeck, Pfizer, SK Life Science, Sunovion, UCB, and Vogelstein Foundation), the Epilepsy Study Consortium/Epilepsy Foundation (funded by UCB), GW Pharmaceuticals/FACES, and the National Institute of Neurological Disorders and Stroke. She is on the editorial board of *Lancet Neurology* and *Neurology Today*. She is Chief Medical/Innovation Officer for the Epilepsy Foundation, for which NYU receives salary support. She has received travel reimbursement related to research, advisory meetings, or presentation of results at scientific meetings from the Epilepsy Study Consortium, the Epilepsy Foundation, Arvelle Therapeutics, Biogen, Cerevel, Engage, Lundbeck, NeuCyte, Otsuka, Sage, UCB, Xenon, and Zogenix. 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.

ORCID

Claude Steriade https://orcid.org/0000-0001-6799-9005
Michael R. Sperling https://orcid.org/0000-0003-0708-6006
Renée A. Shellhaas https://orcid.org/0000-0002-3175-3908
Jacqueline French https://orcid.org/0000-0003-2242-8027

REFERENCES

1. Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia. 2017;58:531–42.
2. Loddenkemper T, Kellinghaus C, Wyllie E, Najm IM, Gupta A, Rosenow F, et al. A proposal for a five-dimensional patient-oriented epilepsy classification. Epileptic Disord. 2005;7:308–16.
3. Krauss GL, Klein P, Brandt C, Lee SK, Milanov I, Milovanovic M, et al. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. Lancet Neurol. 2020;19(1):38–48.
4. Schulz R, Luders HO, Noachtar S, May T, Sakamoto A, Holthausen H, et al. Amnesia of the epileptic aura. Neurology. 1995;45:231–5.
5. Zaccara G, Giovannelli F, Schmidt D. Placebo and nocebo responses in drug trials of epilepsy. Epilepsy Behav. 2015;43:128–34.
6. Engel J Jr. Surgery for seizures. N Engl J Med. 1996;7(334):647–52.
7. Trebuchon A, Lambert I, Guisiano B, McGonigal A, Perot C, Bonini F, et al. The different patterns of seizure-induced aphasia in temporal lobe epilepsies. Epilepsy Behav. 2018;78:256–64.
8. Bonini F, McGonigal A, Trebuchon A, Gavaret M, Bartolomei F, Giusiano B, et al. Frontal lobe seizures: from clinical semiology to localization. Epilepsia. 2014;55:264–77.
9. Baumgartner C, Koren J, Britto-Arias M, Schmidt S, Pirker S. Epidemiology and pathophysiology of autonomic seizures: a systematic review. Clin Auton Res. 2019;29:137–50.
10. Blum DE, Eskola J, Bortz JJ, Fisher RS. Patient awareness of seizures. Neurology. 1996;47:260–4.
11. DuBois JM, Boylan LS, Shiyko M, Barr WB, Devinsky O. Seizure prediction and recall. Epilepsy Behav. 2010;18:106–9.
12. Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. Arch Neurol. 2007;64(11):1595–9.
13. Kerling F, Mueller S, Pauli E, Stefan H. When do patients forget their seizures? An electroclinical study. Epilepsy Behav. 2006;9:281–5.
14. Poochikian-Sarkissian S, Tai P, del Campo M, Andrade DM, Carlen PL, Valiante T, et al. Patient awareness of seizures as documented in the epilepsy monitoring unit. Can J Neurosci Nurs. 2009;31:22–3.
15. Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Combined analysis of risk factors for SUDEP. Epilepsia. 2011;52:1150–9.
16. Power KN, Gramstad A, Gilhus NE, Hufthammer KO, Engelsen BA. Cognitive function after status epilepticus versus after multiple generalized tonic-clonic seizures. Epilepsy Res. 2018;140:39–45.
17. Power KN, Gramstad A, Gilhus NE, Hufthammer KO, Engelsen BA. Cognitive dysfunction after generalized tonic-clonic status epilepticus in adults. Acta Neurol Scand. 2018;137:417–24.
18. Beniczky S, Wiebe S, Jeppesen J, Tatum WO, Brazdil M, Wang Y, et al. Automated seizure detection using wearable devices: a clinical practice guideline of the International League Against Epilepsy and the International Federation of Clinical Neurophysiology. Clin Neurophysiol. 2021;132(5):1173–84.
19. French JA, Krauss GL, Wechsler RT, Wang XF, DiVentura B, Brandt C, et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy: a randomized trial. Neurology. 2015;15(85):950–7.
20. Vossler DG, Knake S, O'Brien TJ, Watanabe M, Brock M, Steiniger-Brach B, et al. Efficacy and safety of adjunctive lacosamide in the treatment of primary generalised tonic-clonic seizures: a double-blind, randomised, placebo-controlled trial. J Neurol Neurosurg Psychiatry. 2020;91(10):1067–75.
21. Quraishi IH, Mercier MR, Skarpaas TL, Hirsch LJ. Early detection rate changes from a brain-responsive neurostimulation system predict efficacy of newly added antiseizure drugs. Epilepsia. 2020;61:138–48.

22. Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med. 2018;17(378):1888–97.
23. Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology. 2011;11(77):1473–81.
24. Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, et al. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 2020;21(394):2243–54.
25. Soticlestat meets primary end point in Dravet and Lennox-Gastaut syndromes. https://www.neurologylive.com/view/soticlestat-reports-positive-topline-data-in-dravet-and-lennoxgastaut-syndromes. Accessed 13 Apr 2021.
26. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med. 2010;362(9):790–9.
27. Kjaer TW, Sorensen HBD, Groenborg S, Pedersen CR, Duun-Henriksen J. Detection of paroxysms in long-term, single-channel EEG-monitoring of patients with typical absence seizures. IEEE J Transl Eng Health Med. 2017;5:1–8.
28. Eysz Lab. Available at: https://eyszlab.com/. Accessed 9 Mar 2021.
29. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus—report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia. 2015;56(10):1515–23.

How to cite this article: Steriade C, Sperling MR, DiVentura B, Lozano M, Shellhaas RA, Kessler SK, et al. Proposal for an updated seizure classification framework in clinical trials. Epilepsia. 2022;63:565–572. doi: 10.1111/epi.17120