The Need for a Pragmatic Seizure Classifications in Clinical Trials

Nathan A. Shlobin BA[a], Josemir W. Sander MD PhD FRCP[b,c,]

[a]Department of Neurological Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
[b]UCL Queen Square Institute of Neurology, NIHR University College London Hospitals Biomedical Research Centre, London WC1N 3BG, & Chalfont Centre for Epilepsy, Chalfont St Peter, UK
[c]Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, the Netherlands
[d] Department of Neurology, West China Hospital, Sichuan University, Chengdu, China

Corresponding author:
Prof Ley Sander, MD PhD FRCP
Box 29, UCL Queen Square Institute of Neurology
London WC1N 3BG, United Kingdom
E-mail: l.sander@ucl.ac.uk

Acknowledgements

JWS is based at the NIHR University College London Hospitals Biomedical Research Centre, which receives a proportion of funding from the UK Department of Health's Biomedical Research Centres' funding scheme. He receives support from the UK Epilepsy Society, the Dr. Marvin Weil Epilepsy Research Fund and the Christelijke Vereniging voor de Verpleging van Lijders aan Epilepsie, Netherlands.

Dear Editor,

We read with interest the report by Steriade et al. of a pragmatic seizure classification based on the International League Against Epilepsy scheme for use in clinical trials.[1] The authors sought to shift the focus to outcome measures that are reliable, interpretable by various stakeholders, and clinically relevant to the development of new antiseizure medications.[1] This is a welcome practical proposal and expand on the importance of pragmatic seizure classification.

The utility of seizure classification categories is critical. Previously, we have noted the limitations of existing seizure classifications based on semantics, syntax, and semiotics of seizures.[2] For example, "dialeptic seizures" are unnecessarily broad. Steriade et al. recommended utilizing "focal aware with or without observable signs" instead of "focal aware with or without motor signs" and not distinguishing focal unaware with or without motor signs. This modified epilepsy classification will place clinically relevant outcomes at the forefront of randomized controlled trials.

The precision of seizure classification categories must be addressed. Utilizing precise language when describing seizure types is essential for localizing and managing epilepsy medically or surgically and facilitating communication to specific groups.[2, 3] Steriade et al. recommended avoiding the term "drop attacks", noting that multiple seizure types produce falls.[1] In contrast, the term "tonic-clonic" has a specific definition and does not refer to all seizures with motor activity.[3] When classifying seizures, utilizing additional terms appended to standard categories in an extended classification, such as cognitive effects or automatisms, may render diagnosis more specific.[3] Incorporating factors such as comorbidities, the changing demographics of epilepsy, brain age, genetic etiologies and environmental triggers will provide further granularity.[2, 4]

Additionally, existing and emerging technologies should be used to increase the granularity and utility of epilepsy classification. The first ILAE seizure classification was published in 1981 following video electroencephalography (EEG) development.[5] It was recommended to integrate complementary surrogate markers such as short and long-term EEG data into seizure types with poor self-report reliability.[1] EEG findings may be useful for all seizure types, rather than simply those with poor self-report reliability. Technologies likely to impact future classifications include 7 Tesla magnetic resonance imaging, genome sequencing, and artificial intelligence.[2]

Additional factors are essential to consider. Epilepsy classification schema must be sufficiently flexible to allow clinically useful classification in a variety of social, political, economic, and cultural contexts in addition to the clinical trial settings proposed by Steriades et al.[2, 4] The classification must be helpful for a variety of stakeholders.[1]. Incorporating the epilepsy classification into a comprehensive team-based approach to clinical trials with the input of clinical and non-clinical stakeholders may enhance the clinical relevance of the outcomes under study.[2, 4] In aggregate, these modifications will increase the patient-centeredness of research and empower people with epilepsy.

References

1. Steriade C, Sperling MR, DiVentura B, et al. Proposal for an updated seizure classification framework in clinical trials. *Epilepsia*. 2022;
2. Shlobin NA, Singh G, Newton CR, Sander JW. Classifying epilepsy pragmatically: Past, present, and future. *Journal of the Neurological Sciences*. 2021;427:117515.
3. Falco-Walter JJ, Scheffer IE, Fisher RS. The new definition and classification of seizures and epilepsy. *Epilepsy research*. 2018;139:73-79.
4. Shlobin NA, Sander JW. Towards a pragmatic epilepsy classification: Future considerations. *Seizure*. 2020;79:95-96.
5. Angeles D. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*. 1981;22(4):489-501.