Check for updates

Received: 16 November 2022 | Revised: 25 February 2023 | Accepted: 10 March 2023

DOI: 10.1111/epi.17583

Epilepsia®

COMMENTARY

The need for an individualized approach to what is considered a clinically significant reduction in seizure frequency: A patient's perspective

Mia L. van der Kop

Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden

Correspondence
Mia L. van der Kop, Department of Global Health, Karolinska Institutet, Widerströmska Huset, 3rd Floor, Tomtebodavägen 18A, SE-171 77 Stockholm, Sweden.
Email: miavanderkop@gmail.com

Keywords: drug resistant, epilepsy, minimal clinically important difference, patient outcome assessment

I am a researcher. I have investigated mortality in people with multiple sclerosis (MS),[1] carefully considered the nuances of different definitions of advanced human immunodeficiency virus (HIV),[2] and examined why people with HIV in slum settings drop out of care.[3] While I conducted my research, I did not try to put myself in the shoes of someone living with MS facing an early death from the disease, think about how it would feel to have advanced HIV whether it was defined one way versus another, or imagine being too afraid to go to a clinic for fear of seeing somebody I know who might discover my HIV status. Admittedly, I did not think about the lives of the human beings I was researching; however, there were people's stories that struck me. There was the time I was poring over patients' files in an MS clinic to extract data, and I came across a woman whose first realization that something was wrong was when her legs gave out from under her when she was dancing with friends. She was in her 20s. I read her case report more than 15 years ago, and I will not forget it. Another time, research notes revealed that a woman in Kenya was unable to adhere to her antiretroviral therapy because thieves broke into her home and stole her belongings, including her medication. These stories brought the people I was researching to life, but never more so than when I became a patient myself.

Six years ago, when I was nearing the end of my doctoral studies, I had a grand mal seizure and woke up in an ambulance en route to the hospital, where my brain cancer diagnosis awaited. A few months later, a craniotomy left me with not only a partially resected tumor, but drug-resistant epilepsy (DRE) as well. The words "drug-resistant epilepsy" do nothing to conjure up the horror of living with a disease in which you are constantly under threat of attack. With less than seconds of notice, I go from being a seemingly normal, healthy person to one who is drooling, whose face contorts and convulses, and who loudly moans and groans uncontrollably. When the surge of electricity finally releases me, I am left exhausted and literally speechless, as my seizures originate in Broca's area of my brain. Epilepsy affects my well-being far beyond my 1–2-min seizures. Prodromes last days, with symptoms including nervousness, nightmares, migraines, exhaustion, and a host of other signs that mimic serious mental health disorders, such as obsessive and intrusive thoughts. Then there is postseizure recovery, which entails at least 3 days of painful headaches and extreme fatigue.

When DRE landed me on permanent disability, I started to research ways to reduce my seizure frequency. I came across the ketogenic diet,[4] which helped somewhat. Then I started a high-intensity exercise program (CrossFit), and completely unexpectedly, it reduced the number of my seizures by 33% over a 6-month period. Having two or three seizures per month compared to four made a profound difference in my life. A reduction in seizures means fewer preseizure migraines and frightening prodromal symptoms, less time spent in bed recovering from a seizure, and

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2023 The Author. *Epilepsia* published by Wiley Periodicals LLC on behalf of International League Against Epilepsy.

a reduced risk of having a seizure in public. This allowed me to participate more fully in social activities and relationships. Fewer days in bed meant more time with my children, less chance of canceling plans to meet a friend, and reduced anxiety of being "hemmed in" at a restaurant or other public place where I might not be able to escape to endure my seizure in private. The problems I was having with suicide and death ideation started to disappear, and I became a much happier person. I wrote a case report on my experience,[5] during which I discovered that a 50% reduction in seizure frequency is commonly considered "clinically significant."[6]

The endpoint of a 50% reduction in seizure frequency originated from the US Food and Drug Administration and European Medicines Agency requirement of a standardized target for pharmaceutical companies when applying for drug approval. Although a 50% or greater reduction in the number of seizures came from antiepileptic drug trials, this endpoint is commonly used across a broad spectrum of interventions, including long-term outcomes of epilepsy surgery,[7,8] cannabidiol,[9] diet,[10,11] and exercise.[12] A single number, taken from regulatory approval purposes, does not necessarily correspond to a significant benefit for those with the disease. I am not suggesting that a threshold lower than 50% should become standard, but rather that using a 50% threshold needs to be thoughtfully considered. Even in clinical trials, a lower threshold may be supported if the adverse effects of an outcome are not serious, if there is a lack of availability of other interventions, or if a cost–benefit assessment supports using a lower threshold. In cases where patients have tried treatments that met the 50% threshold and those treatments were unsuccessful, clinicians need to be aware of other interventions that may be effective at lower degrees of magnitude that may help their patients.

As a researcher without epilepsy, I would have taken this conventional level of clinical significance at face value. I would not have questioned why 50% is commonly considered a clinically meaningful change. Had I been a researcher focusing on epilepsy, I imagine I would have included it as an outcome (if relevant) in any studies I were to design. As a person with epilepsy who has undergone countless drug switches, dosage increases, and other treatments to no effect, a 33% reduction in seizure frequency was life changing, whereas a 50% threshold of "meaningful" seems idealistic and out of touch with my reality. People with DRE deserve better than a 33% reduction in seizure frequency; however, when there is no choice between an intervention that meets the 50% threshold and those that can provide smaller reductions, many would consider any reduction better than no reduction at all. In my case, lower reductions have provided me with much-needed and gratefully received reprieves. For others with the disease, 50% might not represent enough improvement. Although seizure freedom is the goal of epilepsy treatment, seizure control cannot be obtained for approximately 35% of patients in clinic-based cohorts.[13] These individuals are at higher risk of suicide and psychiatric comorbidities, mortality, cognitive impairment, and decreased quality of life. Full-service epilepsy centres with multidisciplinary teams may help people with DRE meet the psychological and social challenges many of them face. Furthermore, little research has been done on recovery from seizures. New interventions in this area may help ameliorate recovery for those with DRE.

There are more than 20 types of epilepsy syndromes, which have different causes and electroencephalogram patterns, originate in different parts of the brain, and affect people of various ages. Seizures manifest themselves in many ways, from staring spells to jerking muscle movements to an abrupt loss of consciousness. People with epilepsy also have differences in the timing, severity, and frequency of their seizures. With such a varied disease, it is difficult to apply a common outcome to different treatments and patients expressing dissimilar symptoms of the disease. Although standardized outcomes are important for comparative purposes between studies, when recommending treatment to a person with epilepsy, what constitutes a clinically significant change for that particular individual must be considered. For many people, drug-resistant epilepsy is a truly terrible disease to live with, with its repeated cycles of pain, violence, and recovery. Every seizure from which I am spared enhances the quality of my life. To improve the lives of people with epilepsy, it is critical to bridge the gap between what is broadly considered a meaningful reduction in seizure frequency and the personal perspective of those living with this disease.

ACKNOWLEDGMENTS

I would like to thank my epileptologist, Dr. Moien-Afshari, for doing his best to help me navigate this terrible disease. I am also grateful to my children whose very existance helped me push through the hardest of times to be here now. Our discussions of this article have been invaluable to me in more ways than one.

CONFLICT OF INTEREST STATEMENT

I have no conflicts of interest to disclose. I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Mia L. van der Kop https://orcid.org/0000-0002-5590-6833

15281167, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.17583, Wiley Online Library on [10/04/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

REFERENCES

1. Kingwell E, van der Kop M, Zhao Y, Shirani A, Zhu F, Oger J, et al. Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. J Neurol Neurosurg Psychiatry. 2012;83(1):61–6.
2. van der Kop ML, Gichuki R, Kinagwi K, Muhula S, et al. Advanced HIV disease at first presentation to HIV care: cross-sectional analysis of baseline data from the WelTel retain study in Nairobi, Kenya. BMC Infect Dis. 2016;16:169.
3. van der Kop ML, Nagide PI, Thabane L, Gelmon L, Kyomuhangi LB, Abunah B, et al. Retention in clinic versus retention in care during the first year of HIV care in Nairobi, Kenya: a prospective cohort study. J Int AIDS Soc. 2018;21(11):e25196.
4. D'Andrea Meira I, Romão TT, Pires do Prado HJ, Krüger LT, Pires MEP, da Conceição PO. Ketogenic diet and epilepsy: what we know so far. Front Neurosci. 2019;13:5.
5. van der Kop ML, Ekström AM, Arida RM. Reduction in seizure frequency with a high-intensity fitness program (CrossFit): a case report. Epilepsy Behav Rep. 2018;13:100354.
6. Greb E. What constitutes a clinically meaningful reduction in seizure frequency? 2018: Conference Coverage. Accessed October 29, 2022 https://www.mdedge.com/neurology/epilepsyresourcecenter/article/190541/epilepsy-seizures/what-constitutes-clinically
7. Arya R, Tenney JR, Horn PS, Greiner HM, Holland KD, Leach JL, et al. Long-term outcomes of resective epilepsy surgery after invasive presurgical evaluation in children with tuberous sclerosis complex and bilateral multiple lesions. J Neurosurg Pediatr. 2015;15(1):26–33.
8. Mohan M, Keller S, Nicolson A, Biswas S, Smith D, Osman Farah J, et al. The long-term outcomes of epilepsy surgery. PLoS ONE. 2018;13(5):e0196274.
9. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of Cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med. 2017;376(21):2011–20.
10. Sharma S, Sankhyan N, Gulati S, Agarwala A. Use of the modified Atkins diet for treatment of refractory childhood epilepsy: a randomized controlled trial. Epilepsia. 2013;54:481–6.
11. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol. 2008;7(6):500–6.
12. Nakken KO. Physical exercise in outpatients with epilepsy. Epilepsia. 1999;40:643–51.
13. Sultana B, Panzini M-A, Veilleux Carpentier A, Comtois J, Rioux B, Gore G, Bauer PR, Kwon C-S, Jetté N, Josephson CB, Keezer MR. Incidence and Prevalence of Drug-Resistant Epilepsy. Neurology. 2021;96(17):805–817. https://doi.org/10.1212/wnl.0000000000011839.

How to cite this article: van der Kop ML. The need for an individualized approach to what is considered a clinically significant reduction in seizure frequency: A patient's perspective. Epilepsia. 2023;00:1–3. https://doi.org/10.1111/epi.17583

15281167, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.17583, Wiley Online Library on [10/04/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License