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Response: ***Drug resistance in epilepsy: a reappraisal of the definition is needed*.**

We appreciate and welcome the comments of Dr Asadi-Pooya [1] that support the position of our report[2] prompting the re-evaluation of the concept of drug resistant epilepsy (DRE). As we also discuss in our manuscript, when defining DRE it is important to consider the complexity of clinical presentations of epilepsies, the impact of the associated comorbidities and sequelae, as well as the patients' perspectives on meaningful outcomes of treatments. We fully agree that the concept of DRE should consider a more holistic view of the clinical course and impact of the various types of epilepsies and seizures.

We wish however to acknowledge that the 2010 ILAE DRE definition was proposed after consideration of several papers,[3-5] and not a single study,[6] that described a "modest" probability of seizure freedom after failure to respond to two appropriate antiseizure medication (ASM) trials.[7] The authors also acknowledged existing retrospective studies that demonstrated some success in achieving seizure freedom with additional ASMs and also discussed the limitations in existing data.[8, 9] As discussed in both Dr Asadi-Pooya's letter and our report, more recent studies have further challenged the criterion of two failed ASM trials in defining DRE.

Working definitions of DRE need to consider data but also their intended purpose and clinically meaningful outcomes. Despite our critical review of the 2010 definition of DRE, this working

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definition enabled the earlier identification of people with epilepsy who are less likely to respond to ASMs and prompted for their earlier evaluation for presurgical evaluation or inclusion in clinical trials for new candidate treatments. Re-evaluation of the current evidence on the preferred cutoff number of failed ASM trials that not only identifies DRE but also helps improve management and outcomes would be important. However, as discussed in our report, defining DRE by the number of failed ASM may not be optimal for certain epilepsies, e.g. in developmental and epileptic encephalopathies where treatments that achieve seizure freedom may not be available and early effective treatments are needed. Furthermore, revisiting the DRE concept so as to capture the complex mechanisms of DRE could potentially enable research into novel and more precise and effective treatments. A multi-disciplinary, international community effort involving clinicians, preclinical scientists and patient representatives would be important to provide new DRE definitions and solutions to start tearing down the wall of 30% of epilepsy patients diagnosed with DRE.

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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.

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S. Auvin is Deputy Editor for *Epilepsia*. He has served as consultant or gave lectures for Angelini, Biocodex, Eisai, Encoded, Grintherapeutics, Jazz Pharmaceuticals, Neuraxpharm, Orion, Nutricia, Proveca, UCB Pharma, Vitaflo, Xenon, Zogenix. He has been investigator for clinical trials for Eisai, Jazz Pharmaceuticals, Marinus, Proveca, Takeda, UCB Pharma and Zogenix.

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References

1. Asadi-Pooya AA. Drug resistance in epilepsy: A reappraisal of the definition is needed. Epilepsia. 2023:in press.
2. Auvin S, Galanopoulou AS, Moshe SL et al. Revisiting the concept of drug-resistant epilepsy: A TASK1 report of the ILAE/AES Joint Translational Task Force. Epilepsia. 2023.
3. Mohanraj R, Brodie MJ. Diagnosing refractory epilepsy: response to sequential treatment schedules. Eur J Neurol. 2006;13:277-82.
4. Arts WF, Brouwer OF, Peters AC et al. Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. Brain. 2004;127:1774-84.

5. Berg AT, Levy SR, Testa FM et al. Remission of epilepsy after two drug failures in children: a prospective study. Ann Neurol. 2009;65:510-9.

6. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342:314-9.

7. Kwan P, Arzimanoglou A, Berg AT et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51:1069-77.

8. Callaghan BC, Anand K, Hesdorffer D et al. Likelihood of seizure remission in an adult population with refractory epilepsy. Ann Neurol. 2007;62:382-9.

9. Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. Ann Neurol. 2007;62:375-81.