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Defining drug-resistant epilepsy

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Abstract

Drug resistant epilepsy remains a major clinical challenge. Diverse criteria have been used to define drug resistance by different researchers, making it difficult or even impossible to compare the results across different studies. To improve patient care and facilitate clinical research, the International League Against Epilepsy recently proposed a consensus definition to define drug resistant epilepsy as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. This article outlines the framework of the consensus definition, explains how to apply it in practice, and discusses the future development in its use.

INTRODUCTION

Drug-resistant epilepsy is associated with a range of deleterious consequences, including higher mortality and morbidity, restriction on social activities, and stress on the patient's family members and caregivers. It is also a great economic burden for the society through expenditures in healthcare and unemployment. For these patients, resective surgery may be a potential therapeutic option. Despite the importance of recognising drug resistance, diverse criteria have been used in its definition by different researchers, making it difficult or even impossible to compare the results across different studies. Early diagnosis of drug resistance using a universally accepted definition can facilitate selection of patients for non-drug therapies and potentially alleviate the medico-social and economic burden of refractory epilepsy.

To improve patients care and facilitate clinical research, the International League Against Epilepsy (ILAE) recently proposed a consensus definition of drug resistant epilepsy.[1] Given that most patients are initially managed by general physicians or general neurologists, it is hoped that the definition framework will provide clear and simple guidance in identifying patients with pharmacoresistance for early referral to specialist centres for evaluation.

THE ILAE CONSENSUS DEFINITIONS OF DRUG-RESISTANT EPILEPSY

Definition framework

The proposal defines drug-resistant epilepsy as failure of adequate trials of two (or more) tolerated, appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. The overall framework of the definition comprises two ''hierarchical'' levels. Level 1 provides a general template or scheme to categorize outcome to each therapeutic intervention (whether pharmacologic or non-pharmacologic). To categorise outcome accurately, a minimum dataset of the details of the AED history, including the dose and duration used, must be available. This is the most important factor to determine whether the trial of an intervention is "informative" in an individual patient. The categories of outcome include "seizure-free," "treatment failure," and "undetermined", and are further subdivided according to whether the patient experienced adverse effects (Table 1). Level 1 forms the basis for level 2, which provides a core definition of drug resistant epilepsy based on two or more "informative" trials of AEDs resulting in a "treatment failure" outcome.

Seizure freedom and treatment failure

Seizure freedom is defined as freedom from all seizures, including auras for at least three times the longest pretreatment interseizure

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Table 1: Scheme for categorizing outcome of a therapeutic intervention for epilepsy (level 1 of the ILAE's framework for the definition of drug-resistant epilepsy). Reproduced from ref. 2 with permission from Elsevier.

		Outcome category
1	**Seizure-free***	
A	Adverse effects: no	1A
B	Adverse effects: yes	1B
C	Adverse effects: undetermined	1C
2	**Treatment failure****	
A	Adverse effects: no	2A
B	Adverse effects: yes	2B
C	Adverse effects: undetermined	2C
3	**Undetermined*****	
A	Adverse effects: no	3A
B	Adverse effects: yes	3B
C	Adverse effects: undetermined	3C

* Seizure freedom is defined as freedom from seizures for a minimum of three times the longest pre-intervention inter-seizure interval or 12 months, whichever is longer.

** Treatment failure is defined as recurrent seizure(s) after the intervention has been adequately applied.

*** Undetermined is defined when the treatment has not been applied adequately for a valid assessment of the outcome, or information is lacking to make the assessment.

interval or 12 months if the longest pretreatment interseizure interval is less than 4 months. In the case of persistent seizures outcome should be defined as treatment failure. It should be noted that pretreatment interseizure interval should be defined for each intervention separately. It follows that if the seizures are very infrequent, the patient may need to be followed up for many years to determine outcome. In that case the longest preintervention interseizure interval should be determined from seizures occurring within the preceding 12 months.

Undetermined outcome and informative trial

Level 1 outcome should be categorized as undetermined if the minimum dataset is not available. The minimum dataset contains the details of the intervention history, such as the duration of treatment, the dosage of the AEDs, reason of withdrawal (if applicable). In the absence of such information, it cannot be confidently determined if the epilepsy was truly under control or unresponsive to treatment. In this situation, outcome to the intervention should be categorised as undetermined.

To determine treatment outcome, the AED should have been applied "adequately". This may not be the case in some circumstances, for example, when an AED is withdrawn due to an allergic rash or early due to poor tolerability at low dosage. In these situations outcome should be considered undetermined. The proposed definition does not specify the dose or duration of each drug that constitute an "adequate" trial because this is influenced by a range of intrinsic and extrinsic factors, but the definition requires a documented attempt to titrate the dose to a target clinically effective dose range.

FUTURE WORK

The proposed definition should not be considered as *fait accompli* but work in progress that should be tested in rigorous prospective studies.

Defining an "adequate" drug trial

There are multiple internal and external factors which influence the dose required for an "adequate" trial of an AED, such as the pharmacological properties of the drug, the age of patients, any interaction with concomitant medications, and the patient's hepatic and renal functions. An individualized approach is needed in clinical practice. For the purpose of standardization in the research setting, making reference to the WHO's defined daily dose scheme (DDD) may be a reasonable approach.[3] However, the DDDs are intended for monotherapy use, and might not be applicable in patients taking multiple AEDs which are prone to drug-drug interactions. In addition, the system is intended for use in adults because doses used in children are heavily influenced by body weight. Therefore, even if the DDDs are used, flexibility would be needed. More work is needed to determine the appropriate approach to define an "adequate" trial, perhaps by taking into account the multiple factors simultaneously.

Classification of breakthrough seizures

It is increasingly recognized that epilepsy may display a fluctuating course in some patients.[4] Seizures may relapse after a period of prolonged seizure freedom under a variety of circumstances, which may or may not have implications for predicting subsequent outcome. For instance, a patient who experiences a seizure relapse after omitting his usual medications may be expected to regain seizure freedom after improved drug compliance, but the causal relationship between seizure relapse and external factors such as sleep deprivation or intercurrent febrile illness is less clear-cut. In the study by Schiller and colleagues[4], 25 of 256 seizure-free patients experienced seizure relapse due to "external reversible triggers" (discontinuation of AED treatment, dose reduction, noncompliance, severe sleep deprivation, high fever), all of whom were reported to later regain seizure remission. In the ILAE definition, seizures that occur under external triggers are considered as evidence of inadequate seizure control and hence treatment failure, but seizure relapse due to poor treatment compliance or planned dose reduction is not. The validity of this classification needs to be determined in future studies. In addition, there is uncertainty in the most appropriate way to determine the pretreatment interseizure interval if a new AED is initiated after just one breakthrough seizure.

Practical application and training

For its effective and efficient use, the definition should be integrated into the routine medical record system. An electronic system which captures the essential information in defining drug response would greatly facilitate this process and should be promoted as part of an electronic health record system. Because multiple parameters are required to categorise treatment outcome and drug responsiveness, software programs that automatically compute the classification may help minimize subjectivity in applying the definition. Training of general physicians and neurologists would be needed to improve their familiarity with the definition which will help them refer patients to specialist centres in an appropriate and timely fashion.

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