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 (ILAE) recently proposed a consensus definition to define drug-resistant epilepsy. This is the 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 of its use.

Keywords
Epilepsy, seizures, drug resistant, refractory, pharmacoresistance, antiepileptic drugs (AEDs), definition, International League Against Epilepsy (ILAE)

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Approximately 50 million people have epilepsy worldwide and up to one-third of these people continue to experience seizures despite drug treatment. 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 (ILAE) recently proposed a consensus definition of drug-resistant epilepsy. Given that most patients are initially managed by general physicians or 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. This article outlines the framework of the consensus definition, explains how to apply it in practice and discusses the future development of its use.

The Burden of Drug-resistant Epilepsy
Recurrent seizures are associated with a range of deleterious consequences. Seizure-related deaths may account for up to 40% of all deaths in patients with chronic epilepsy. The rate of sudden unexpected death, which accounts for 7–17% of deaths among epilepsy patients, is estimated to be up to 27-fold higher in those with ongoing seizures compared with those who are seizure free. Uncontrolled seizures restrict patients’ social activities, reducing their ability to hold a driving license or keep a job. Refractory epilepsy places substantial stress on the patient’s family members and care-givers. It is also a great economic burden for society through expenditures in healthcare and unemployment. In a study of the cost of epilepsy in the US, it was reported that the average monthly cost per individual in the patient-based analysis was US$1,490, whereas the average annual cost per individual in the population-based analysis was US$1,510 with average yearly costs between US$1,480 and US$1,740. In patients whose epilepsy failed to respond to several antiepileptic drugs (AEDs), the chance of significant benefit from a further AED change is estimated to be <5% per year. For these patients, resective surgery is a potential therapeutic option. Early diagnosis of drug resistance using a universally-accepted definition can facilitate the selection of patients for such non-drug therapies and potentially alleviate the medicosocial and economic burden of refractory epilepsy.

The International League Against Epilepsy Consensus Definition

The proposal defines drug-resistant epilepsy as failure of adequate trials of two or more tolerated, appropriately chosen and used 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 categorise the outcome to each therapeutic intervention (whether pharmacological or non-pharmacological). To categorise the outcome accurately, a minimum dataset of details of the AED history, including the dose and duration the drug was used for, must be available. This is the most important factor in determining whether the trial of an intervention is “informative” in an individual patient. The categories of outcome include “seizure-free”, “treatment failure”, and “undetermined”. These are further subdivided according to whether the patient experienced adverse effects (see Table 1). Level 1
Treatment failure is defined as recurrent seizure(s) after the intervention has been initiated for at least three times the longest pre-treatment 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.

Table 1: Scheme for Categorising Outcome of a Therapeutic Intervention for Epilepsy

<table>
<thead>
<tr>
<th>Outcome Category</th>
<th>Values of the Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Seizure-free*</td>
<td>A Simple and Objective System</td>
</tr>
<tr>
<td>A Adverse effects: no</td>
<td>** Early Pre-surgical Evaluation</td>
</tr>
<tr>
<td>B Adverse effects: yes</td>
<td>Selected patients with drug-resistant epilepsy may benefit from non-pharmacological interventions, such as epilepsy surgery and vagus nerve stimulation. Given that these interventions are invasive, costly, and not without risk, confirming the diagnosis of drug resistance is generally considered a prerequisite. There is no consensus definition of drug resistance for the purpose of selecting patients for epilepsy surgery. Diverse criteria used by different groups might have contributed to the disparity in post-surgery outcome reported. By providing the minimum core criteria, the proposed ILAE definition represents a common platform that can be adapted specifically for the purpose of selecting patients for non-drug therapies. This will avoid delay in evaluating patients for these therapeutic options and facilitate meaningful comparison of effectiveness reported in different studies.</td>
</tr>
<tr>
<td>C Adverse effects: undetermined</td>
<td>Promotion of a Global Outcome Database</td>
</tr>
<tr>
<td>2 Treatment Failure**</td>
<td>With a common language in categorising and defining treatment response, it becomes possible to establish a global database of epilepsy outcomes. Through adopting the same criteria to record information on drug response, research findings from different centres around the world may be compared more directly or even combined for analysis. We believe that such a worldwide database will greatly</td>
</tr>
<tr>
<td>A Adverse effects: no</td>
<td></td>
</tr>
</tbody>
</table>
improve our understanding of the long-term prognosis of epilepsy so that more rational treatment strategies may be formulated.

Future Work
The proposed definition should not be considered as a fait accompli but a work in progress that should be tested in rigorous prospective studies. Its limitations and areas that need to be refined as new evidence emerges will now be discussed.

Defining an 'Adequate' Drug Trial
There are multiple internal and external factors that influence the dose required for an ‘adequate’ trial of an AED, such as:

- the pharmacological properties of the drug;
- the age of the patient;
- any interaction with concomitant medications; and
- the patient’s hepatic and renal functions.

An individualised approach is needed in clinical practice. For the purpose of standardisation in the research setting, we suggest that referring to the WHO’s DDD may be a reasonable approach. The DDDs are for monotherapy uses, however, and might not be applicable for patients taking multiple AEDs that 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. If the DDDs are used, flexibility will be needed. More work is required to determine the most appropriate approach to defining an ‘adequate’ trial, perhaps by taking into account multiple factors simultaneously.

Classification of Breakthrough Seizures
It is increasingly recognised that epilepsy may display a fluctuating course in some patients. 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. However, 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, 25 of 25a seizure-free patients experienced seizure relapse due to ‘external reversible triggers’ (discontinuation of AED treatment, dose reduction, non-compliance, severe sleep deprivation, high fever). All of these patients were reported to regain seizure remission later.

In the ILAE definition, seizures that occur under external triggers are considered evidence of inadequate seizure control and hence treatment failure, but seizure relapse due to poor treatment compliance or planned dose reduction are not. The validity of this classification needs to be determined in future studies. In addition, there is uncertainty about 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 of drug-resistant epilepsy should be integrated into the routine medical record system. An electronic system that 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. As multiple parameters are required to categorise treatment outcome and drug responsiveness, software programs that automatically compute the classification may help minimise subjectivity in applying the definition. Training of GPs and neurologists is needed to improve their familiarity with the definition, which will help them refer patients to specialist centres in an appropriate and timely fashion.