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SPECIAL REPORT

# Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies

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## Summary

**To improve patient care and facilitate clinical research, the International League Against Epilepsy (ILAE) appointed a Task Force to formulate a consensus definition of drug resistant epilepsy. The overall framework of the definition has two "hierarchical" levels: Level 1 provides a general scheme to categorize response to each therapeutic intervention, including a minimum dataset of knowledge about the intervention that would be needed; Level 2 provides a core definition of drug resistant epilepsy using a set of essential criteria based on the categorization of response (from Level 1) to trials of antiepileptic drugs. It is proposed as a testable hypothesis that drug resistant epilepsy is defined 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 definition can be further refined when new evidence emerges. The rationale behind the definition and the principles governing its proper use are discussed, and examples to illustrate its application in clinical practice are provided.**

**KEY WORDS: Epilepsy, Drug resistance, Refractory, Intractable, Definition, ILAE.**

Although the concept of drug resistant (often used interchangeably with "medically refractory/intractable" or "pharmacoresistant") epilepsy may appear self-explanatory and intuitive, a precise definition has remained elusive. This has resulted in diverse criteria used by different clinicians and researchers, or even a lack of explicit criteria in some cases, rendering it difficult to compare findings across studies and to make practice recommendations (Perucca, 1998; Tanganelli & Regesta, 1999; Berg et al., 2006; Kwan & Brodie, 2006; Arzimanoglou & Ryvlin, 2008). In response to this situation, the International League Against Epilepsy (ILAE) appointed a Task Force under the Commission on Therapeutic Strategies to formulate a proposal for a consensus definition of drug resistant epilepsy. The Task Force comprised members with diverse expertise, including epidemiology, adult and pediatric epileptology, neurosurgery, clinical pharmacology, and clinical trial design. Pertinent literature and discussion at relevant workshops (Kahane et al., 2008) were considered. This report sets out the proposed definition, the rationale behind it, the principles governing its proper use, and examples to illustrate its application in clinical practice. The report was circulated to all ILAE Commissions for

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comment and was approved by the Executive Committee of the ILAE during the 28th International Epilepsy Congress in Budapest, Hungary, June 28th to July 2nd, 2009. It should be emphasized that given the paucity of high quality data on the long-term prognosis of epilepsy, the proposed definition should not be regarded as a foregone conclusion, but is intended to represent a consensus opinion that needs to be tested in rigorous prospective studies and refined as new evidence emerges.

Any definition of drug resistant epilepsy should be understood and applied within the context of its intended use, because different definitions may be required for different purposes. The primary goal of this consensus definition is to improve patient care and facilitate clinical research. As such, by setting out the minimum criteria for defining drug-resistant epilepsy, it aims to serve as a working definition that is pragmatic and applicable for everyday clinical management. Fulfillment of the definition in a patient should prompt a comprehensive review of the diagnosis and management, preferably by an epilepsy center. In addition, by applying the definition, practitioners (and patients) can be alerted to the type of information that should be collected during clinical consultation.

The primary target users of the definition are medical practitioners at all health care levels (including primary care practitioners, general neurologists, and epileptologists) directly involved in the clinical care of people with epilepsy. With the appropriate information collected on treatment response, we believe the definition may aid nonspecialists in recognizing patients with drug resistant epilepsy for prompt referral to specialist centers for evaluation. Other target users are clinical researchers, because adoption of a consensus definition will facilitate comparison and meaningful synthesis of results across studies. The definition may also be valuable to patients and their caretakers, as well as other interest groups such as scientists in basic research, government regulators, legislators, health care administrators, insurers, educators, and employers.

## Framework of Definition

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 nonpharmacologic), including a minimum dataset about the intervention that would be needed for such purpose. Broadly, the categories of outcome include "seizure-free," "treatment failure," and "undetermined," which are elaborated below. Level 1 forms the basis for Level 2, which provides a core definition of drug resistant epilepsy based on how many "informative" trials of antiepileptic drugs (AEDs) resulted in a "treatment failure" outcome (as defined in Level 1). This core definition may then be adapted, where appropriate, for specific purposes or clinical scenarios.

## Level 1: Categorization of Outcome to a Therapeutic Intervention

There are many dimensions in a patient's outcome to a given therapeutic intervention. The categorization scheme should be simple and practical, rather than exhaustive, to facilitate its use across a broad range of clinical and research settings. Therefore, the proposed scheme contains the two most clinically relevant outcome dimensions, namely, seizure control and occurrence of adverse effects (Table 1). Outcomes to a given intervention are categorized based on whether it rendered the patient seizure-free (Category 1) or not (Category 2). For the outcome to fall into either category, the intervention must be "appropriate" and "adequate," each of which is defined in subsequent text of this article. Otherwise, the outcome is designated as undetermined (Category 3). Each category is then subdivided into A, B, and C, based on outcome with respect to adverse effects. This subdivision is included even though it does not contribute to the definition of drug resistance, because there is an important clinical difference between a seizure-free patient without any adverse effects, and one who is seizure free at the expense of substantial adverse effects. Capturing this information may aid clinicians in deciding interventions. The appropriate application of the scheme is based on the following assumptions and provisions.

### Appropriateness of intervention

To be regarded as an intervention in the scheme, it must be "appropriate" for the patient's epilepsy and seizure type. An "appropriate" intervention should have previously been shown to be effective, preferably in randomized controlled studies, which provide the highest level of evidence. Instead of listing all "appropriate" interventions, it is suggested that

**Table 1. Scheme for categorizing outcome of an intervention for epilepsy**

| Outcome dimension[a] | | |
|---|---|---|
| Seizure control | Occurrence of adverse effects | Outcome category |
| 1. Seizure-free | A. No | 1A |
| | B. Yes | 1B |
| | C. Undetermined | 1C |
| 2. Treatment failure | A. No | 2A |
| | B. Yes | 2B |
| | C. Undetermined | 2C |
| 3. Undetermined | A. No | 3A |
| | B. Yes | 3B |
| | C. Undetermined | 3C |

[a]See text for definitions of "seizure-free," "treatment failure," and "undetermined." The numeric and alphabetic nomenclature of categories does not imply gradation or hierarchy.

anyone using this scheme justify their choices in this regard. For instance, ethosuximide would usually not be considered an appropriate intervention for focal seizures. Under most circumstances, a trial of this drug in a patient with focal epilepsy would not "count" toward being defined as "drug resistance."

### "Adequate/informative" versus "uninformative" trial

In addition to being "appropriate," the intervention must have been applied "adequately" for a valid assessment of the treatment outcome. In general, this requires application of the intervention at adequate strength/dosage for a sufficient length of time. This may not be the case in some circumstances, for example, when a drug is withdrawn before it has been titrated to its clinically effective dose range because of an adverse effect. Although the drug has "failed" (i.e., it is not a suitable intervention for the patient), the "failure" was not because of lack of efficacy for seizure control. Such an outcome may have little bearing on the efficacy of other AEDs and generally is not considered as part of "drug resistance" per se. In these situations, outcome of the intervention in terms of seizure control should be categorized as "undetermined." If the patient is lost to follow-up before outcome to an intervention can be evaluated, then seizure control and occurrence of adverse effects will both be considered "undetermined."

Given the wide interindividual variation in the doses required to achieve seizure freedom (Kwan & Brodie, 2001), it is difficult to rigidly define the "clinically effective dose range" for each AED. This is further confounded by multiple internal and external factors, including the setting in which the AED is used (monotherapy or polytherapy), the age of the patient, and the presence of hepatic or renal impairment, which may affect drug clearance. As an example, for adults, reference may be made to the World Health Organization (WHO)'s defined daily dose (DDD), which is the assumed average maintenance dose per day for a drug used for its main indication (World Health Organization, 2008). It is important to note that there should be a documented attempt to titrate the dose to a target clinically effective dose range, particularly for AEDs, the tolerability of which is strongly dependent upon gradual titration (Perucca et al., 2001).

Table 2 lists the minimum dataset required to determine whether the trial of an intervention is informative in an individual patient. In the absence of this dataset, the response should be considered undetermined. In practice, the data may be adequate for assessing adverse effects but not seizure control, or vice versa. This is acknowledged in the scheme in Table 1.

**Table 2. Minimum dataset required to determine whether the trial of a therapeutic intervention is informative**

| |
|---|
| Nature of the intervention (e.g., type of drug, in the case of antiepileptic drug treatment) |
| Mode of application (e.g., formulation, dose, dosing interval, and patient's compliance in case of an antiepileptic drug) |
| Duration of exposure |
| Occurrence of seizures and adverse effects during the trial period |
| Whether there was any effort to optimize dose |
| Reason(s) for discontinuation (if applicable) |
| Unsatisfactory seizure control |
| Adverse effects |
| Long-term seizure freedom |
| Psychosocial reasons, for example, planning for pregnancy |
| Administrative reasons, for example, lost to follow up |
| Financial issues, for example, cannot afford treatment |
| Patient/caretaker preference |
| Other reasons |

### Seizure freedom and treatment failure

Lifelong seizure freedom without adverse effects can be considered the most clinically relevant outcome of any intervention for epilepsy (Sillanpää et al., 2004; Vickrey et al., 1995; Jacoby et al., 2007; Téllez-Zenteno et al., 2007). Therefore, under the scheme, seizure outcome is dichotomized into seizure-free (Category 1) or treatment failure (Category 2). The term "seizure-free" refers to freedom from all seizures, including auras. It is acknowledged that different seizure types in different individuals may be associated with variable degrees of impact, which is a matter of appreciation and would be taken into account by the treating clinician when deciding the most appropriate course of action for the patient. Therefore, for practicality, occurrence of any seizure is regarded to indicate failure of the treatment to lead to seizure freedom.

Breakthrough seizures that occur in temporal proximity to potentially seizure provoking external factors such as sleep deprivation, menstruation, intercurrent febrile illness, and so on, pose difficulties in categorization because the causal association between the external factor and the seizure is often uncertain. In general, seizures that occur under these circumstances should still be considered as evidence of inadequate seizure control and hence treatment failure, but seizure relapse due to poor treatment compliance should not.

In deliberating what constitutes an adequate period without seizures for a patient to be regarded as "seizure-free," two main factors were considered. First, the duration of follow-up required to determine whether a therapeutic intervention has had an appreciable impact on seizure occurrence is dependent on the preintervention seizure frequency. For instance, it would not be surprising for a patient with only one seizure in the previous year to remain seizure-free for the next 6 months after starting a new intervention, but it would be premature and unwarranted to claim that the therapeutic intervention is responsible for a patient's freedom from seizures until sufficient time has passed.

The "rule of three" for calculating confidence intervals for zero events can be used in this setting (Hanley & Lippman-Hand, 1983). To be 95% certain that a patient's seizure frequency has at very least decreased (i.e., there has been some therapeutic effect), a seizure-free duration that is at least three times the longest interseizure interval prior to starting a new intervention would need to be observed. For example, if prior to the intervention the patient had intervals without seizures of up to 6 months, a seizure-free period of 18 months would be required to reasonably conclude that his seizure frequency is lower than that prior to the intervention. It should be noted that, in theory, patients with even more infrequent seizures would have to be followed up for many years to determine whether their seizures had truly come under control. This is not practical, either in research or clinical settings. For this reason we recommend that three times the longest interseizure interval be used as an indicator of positive treatment response. Given that an initiation or change of intervention regimen is often not indicated for seizures occurring less than once per year, the longest preintervention interseizure interval should be determined from seizures occurring within the preceding 12 months. For practical purpose, interseizure interval should be derived according to days on which one or more seizure has occurred. Obviously, at least two seizures must have been documented to determine the preintervention interseizure interval; therefore, this approach cannot be applied to a patient treated after a single seizure.

The other main consideration is the need to document a sustained response that is clinically meaningful. Studies including patients treated medically (Sillanpää & Shinnar, 2005; Jacoby et al., 2007) or surgically (Markand et al., 2000; Spencer et al., 2007) show that absolute seizure freedom, usually taken as at least 12 months, is the only relevant outcome consistently associated with meaningful improvement in quality of life. In a community-based survey, patients with one or more seizures over the last 2 years had higher levels of anxiety and depression, greater perceived stigma and impact of epilepsy, and lower employment rates than did those who were seizure-free (Jacoby et al., 1996). In many countries, having even one seizure per year poses restrictions on driving (Fisher et al., 1994; Berg & Engel, 1999). Therefore, there was consensus that seizure-free duration should be at least 12 months.

Based on the preceding consideration, seizure freedom (Category 1 outcome) is defined as freedom from seizures for a minimum of three times the longest preintervention interseizure interval (determined from seizures occurring within the past 12 months) or 12 months, whichever is longer. On the other hand, treatment failure (Category 2 outcome) is defined as recurrent seizure(s) after the intervention has been adequately applied (as defined earlier). If a patient has been seizure-free for three times the preintervention interseizure interval but for <12 months, seizure control should be categorized as "undetermined." However, if the patient experiences another seizure before the end of the 12-month period, the treatment is considered "failed," even though the seizure frequency has reduced compared with baseline. We acknowledge that a therapeutic intervention may lead to a clinically meaningful reduction in seizure frequency (or severity) that stops short of seizure freedom. Categorization of such a response may be considered at a later date for incorporation into the scheme.

### Occurrence of adverse effects

By adapting the WHO's definition of adverse drug reaction (World Health Organization, 1972), an adverse effect to any therapeutic intervention for epilepsy may be defined as "any response to an intervention which is noxious and unintended, and which occurs when the intervention is applied with modalities normally used in humans for the treatment of epilepsy." The WHO definition has generally been interpreted as implying that there should be no error in the use of the intervention (Leape, 1995; Edwards & Aronson, 2000), an important consideration that is consistent with the concept of "appropriateness" of intervention, as already discussed.

Assessing adverse effects is fraught with difficulties, and some elements of subjectivity are unavoidable. Critical issues in the assessment are the methodology used to detect and quantify adverse effects, and the criteria applied to establish the causality link with the applied intervention. In particular, relying on unstructured interviews and a general medical examination may lead to underestimation of adverse effects, whereas the use of checklists and questionnaires can lead to overestimation (Baker et al., 1998; Carreño et al., 2008). Some important adverse effects, such as vigabatrin-induced visual field defects, may only be identifiable with specialized laboratory tests (Wild et al., 2007). Algorithms for causality assessment have been developed (Karch & Lasagna, 1977; Edwards & Aronson, 2000). Even when causality has been established, assessing the clinical impact of an adverse effect on the individual's well being or quality of life is a challenging task. In most clinical situations, however, treating physicians can make a reasonable subjective judgment based on results of medical examination and interviews with patient and family members, and we suggest that such judgment be applied when categorizing the presence or absence of adverse effects in response to an intervention.

### Other dimensions of outcome

For practical purposes, other dimensions of outcome are not included in the current scheme, but their importance is recognized and they may be incorporated into future schemes. These dimensions may include factors such as psychosocial outcomes and level of patient satisfaction. A variety of quality of life scales have been developed and are widely applied in research settings (Leone et al., 2005). From a patient-centered care perspective, patients'

satisfaction with an intervention should be the final arbiter in defining its success or failure. Patients' satisfaction extends beyond measurement of seizure control, adverse effects, or quality of life scores, and may be influenced by a broad range of internal and external variables, such as, in the case of epilepsy surgery, preoperative expectations, postoperative affect, ability to discard the sick role, subsequently obtaining employment, and perceived success (Wass et al., 1996; Wilson et al., 1999; Reid et al., 2004; Chin et al., 2006). Although the construct of patient satisfaction with an intervention is multifaceted and complex, it has been successfully evaluated using simple, single-item, or few-item rating scales, such as dichotomous yes/no questions, or graded point scales. Clinicians may be encouraged to include one of these measures in their assessment when assessing success or failure of an intervention and in clinical decision making.

## Level 2: Definition of Drug Resistant Epilepsy

Drug responsiveness of a patient's epilepsy should be regarded as a dynamic process rather than a fixed state. Instead of being constant, the course of epilepsy sometimes fluctuates (Berg et al., 2009), and apparent changes in responsiveness to AED treatment may merely represent shifts in the pathophysiology of the underlying disorder. The classification of a patient's epilepsy as drug resistant at a given point in time is valid only at the time of the assessment and does not necessarily imply that the patient will *never* become seizure-free on further manipulation of AED therapy (Huttenlocher & Hapke, 1990; Berg et al., 2001, 2006; Callaghan et al., 2007; Luciano & Shorvon, 2007; Schiller & Najjar, 2008).

The number of AEDs that needs to have failed for the epilepsy to be defined as drug resistant was extensively debated within the Task Force. An implicit assumption in any definition is that seizure freedom will not or is very unlikely to be attained with further manipulation of AED therapy. Therefore, any definition must be based on an assessment of the probability of subsequent remission after each drug failure. Ideally, the evidence should be derived from large-scale, prospective, long-term, population-based studies including both adults and children at the point of diagnosis or treatment initiation, and should be based on an assessment of outcome after failure of successive informative AED trials. Few, if any, studies in the literature meet such requirement. Observational cohort studies of newly diagnosed epilepsy in adults (Kwan & Brodie, 2000; Mohanraj & Brodie, 2006) and children (Arts et al., 2004) suggest that once a patient has failed trials of two appropriate AEDs, the probability of achieving seizure freedom with subsequent AED treatments is modest. Recent studies appear to suggest that a proportion of these patients may still become seizure-free with subsequent drug manipulation (Callaghan et al., 2007; Luciano & Shorvon, 2007), but these studies were retrospective and sampled prevalent cases, and did not take into account the reasons for failure which, as already discussed, may indicate that the AEDs have not been adequately tried. A recent report from a prospective study in children documented that although many patients who had failed two informative trials of AEDs had periods of seizure freedom with further drug trials, lasting remission remained elusive (Berg et al., 2009).

On the basis of a careful deliberation of the available evidence, building on Level 1 of the definition framework, for operational purposes, the following definition is proposed:

> **Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.**

It should be stressed that the consensus to adopt the failure of two (rather than greater numbers) AED schedules in the definition represents a testable hypothesis and aims to avoid unnecessary delay in evaluation, and may be revised as more high quality data become available.

In addition to number of AEDs failed, two other elements are most commonly included in definitions of drug resistant epilepsy in the literature, namely, the frequency of seizures and duration of follow-up. In the proposed definition, "failure" and "sustained seizure freedom" are as defined in Level 1 (categorization of intervention outcome) of the definition framework, which already incorporates seizure frequency and treatment duration, so that separate criteria for these elements are redundant. Applying the categorization of intervention outcome (Table 1), drug resistance is defined as having Category 2 outcome for trials of at least two AEDs (monotherapies or in combination) without a Category 1 outcome on the drug(s) currently taken. Drug resistance should be defined only by informative trials, that is, the two AEDs should have been appropriately chosen and adequately tried, and that none of the outcomes that will be counted toward the two drug failures should be "undetermined." In other words, some patients may "fail" many AEDs before they fail two that are "appropriate" and in a way that is "informative."

### Drug-responsive epilepsy and apparent fluctuation in drug responsiveness

It follows from Level 1 of the definition framework that a person's epilepsy can be classified as "drug responsive" if he/she is having a Category 1 outcome to the current AED regimen, that is, he/she has been seizure-free for a minimum of three times the longest pretreatment interseizure interval, or 12 months, whichever is longer.

During its long and sometimes fluctuating course a person's epilepsy may not fulfill the definition criteria for either drug resistant or drug-responsive epilepsy at certain time points. In such circumstances, drug responsiveness

**Table 3. Examples of how the definition framework can be applied in different clinical scenarios**

| Patient | Narrative drug history | Level 1—categorization of treatment outcome | Level 2—classification of drug responsiveness of epilepsy | Notes |
|---|---|---|---|---|
| 1 | A patient had one seizure in January 2006 and two seizures in October 2006. After starting treatment in November 2006 he has been seizure free for 30 months with no adverse effect | One current drug with seizure-free outcome (Cat. 1A) | Drug responsive | The longest pretreatment interseizure interval was 9 months (January–October 2006). The patient has had no seizure for more than three times the pretreatment interseizure interval and for more than 12 months |
| 2 | A 16-year-old patient was started on valproate 2 years ago after experiencing two seizures in 6 months, and has been seizure-free since with mild sedation. He reports a history of an apparently nonfebrile convulsive seizure when he was 6 years of age | One current drug with seizure-free outcome (Cat. 1B) | Drug responsive | The longest pretreatment interseizure interval was 6 months. The patient has had no seizure for more than three times the pretreatment interseizure interval and for more than 12 months. The seizure that occurred at 6 years of age (more than 12 months prior to starting treatment) is not relevant to determining the responsive ness of his current epilepsy |
| 3 | A 40-year old man was diagnosed to have partial epilepsy 20 years ago. He reported "I was on phenytoin initially for a short period, it didn't work and they took me off." He was then given an adequate trial of carbamazepine but continued to have monthly seizures. Levetiracetam was added 1 year ago and tried adequately. He now has seizures once every 3 months | One previous drug with undetermined outcome (Cat. 3C). Two current drugs with treatment failure outcome (Cat. 2) | Drug resistant | Outcome of phenytoin treatment was undetermined because of lack of sufficient data (see Table 2). Nonetheless, he has failed informative trials with two appropriate AEDs. Treatment with levetiracetam is considered failed because despite reduction in seizure frequency, seizure free duration is <12 months |
| 4 | A patient was newly started on carbamazepine after two partial seizures in 9 months. He has had no seizures for 12 months since | One current drug with undetermined outcome (Cat. 3) | Undefined | The pretreatment interseizure interval was 9 months. Although the patient has had no seizure for 12 months, the duration is less than three times the pretreatment interseizure interval, hence outcome to treatment is undetermined and drug responsiveness of epilepsy is undefined |
| 5 | A 16-year-old girl was started on carbamazepine a week after she had a tonic–clonic seizure in the morning, with a history (not recognized by her doctor at the time) of jerks over the past 3 months. The jerks got worse after 2 months on carbamazepine 800 mg/day. EEG later showed generalized polyspike and wave discharge. She was diagnosed to have juvenile myoclonic epilepsy and was switched to lamotrigine, which was stopped after 2 weeks (dosage at the time, 50 mg/day) because of a rash. She is now on valproate 2 g/day for 3 months, but occasional jerks continue | One previous inappropriate drug. One previous drug with undetermined outcome (Cat. 3B). One current drug with treatment failure outcome (Cat. 2) | Undefined | Carbamazepine is recognized to exacerbate myoclonic seizures and, in this case, is not considered an appropriate treatment for the patient's epilepsy syndrome. Lamotrigine and valproate are appropriate treatments, but outcome in terms of seizure control of lamotrigine is undetermined because it was stopped due to an adverse effect during titration, before a dose range usually regarded as optimal could be reached. Thus the patient has failed only one drug (valproate) so far, and the drug responsiveness of her epilepsy remains undefined |
| 6 | A patient is having more than one seizure per day for 3 months despite adequate trials of four appropriate AEDs. Patient is taking one drug currently | Three previous drugs and one current drug with treatment failure outcome (Cat. 2) | Drug resistant | The patient has failed more than two appropriate AEDs |

Continued

**Table 3. Continued.**

| Patient | Narrative drug history | Level 1—categorization of treatment outcome | Level 2 classification of drug responsiveness of epilepsy | Notes |
|---|---|---|---|---|
| 6 | After adding drug X, patient 6 has had no seizure for 8 months | Four previous drugs with treatment failure outcome (Cat. 2). One current drug with undetermined outcome (Cat. 3) | Drug resistant | Outcome of treatment with drug X is undetermined and the epilepsy remains drug resistant because the patient has not been seizure-free for 12 months |
| 6 | With further follow-up patient 6 has had no seizure for 24 months | Four previous drugs with treatment failure outcome (Cat. 2). One current drug with seizure-free outcome (Cat. 1) | Drug responsive | The patient has had no seizures for more than three times the pretreatment interseizure interval and for more than 12 months |
| 6 | Patient 6 has two seizures within 1 month | Four previous drugs and one current drug with treatment failure outcome (Cat. 2) | Undefined | The patient is no longer seizure free, treatment of drug X is failed, but the "clock" is "reset" for considering the epilepsy to be drug resistant again in future after it has been drug responsive. Thus at present the epilepsy does not fulfill the criteria of drug resistant (unless the patient fails at least one further drug after the relapse) |
| 6 | Two more appropriate AEDs are added at adequate dosage but patient 6 continues to have seizures once per month | Four previous drugs and three current drugs with treatment failure outcome (Cat. 2) | Drug resistant | After the relapse the patient has failed more than two adequate trials of appropriate AEDs |

AED, antiepileptic drug; EEG, electroencephalography.

should be temporarily classified as "undefined." This occurs, for instance, in a newly diagnosed patient who has not experienced the duration required for defining seizure freedom, or in a patient who has failed informative trials of less than two AEDs.

Other scenarios that pose difficulty in classification occur when there appears to be a change in drug responsiveness of the epilepsy during its dynamic course. In these scenarios the classification should be reviewed and revised accordingly. For instance, a patient with drug-resistant epilepsy stops having seizures upon receiving a new AED regimen but the duration does not yet meet the criteria for defining seizure freedom. For clarity, it is proposed that outcome of the individual drug (Level 1) should be categorized as "undetermined" and the overall drug responsiveness (Level 2) should remain as drug resistant unless and until sufficient time has passed to reclassify the epilepsy as drug responsive (i.e., seizure-free for three times pretreatment interseizure interval, or 12 months, whichever is longer).

In the opposite scenario, seizure relapses in a seizure-free patient. In this situation clearly the epilepsy is no longer drug responsive, but it can only be considered drug resistant if it subsequently meets the criteria for resistance. It is proposed that, if only one seizure has recurred, the outcome of the individual drug (Level 1) should be categorized as "undetermined" and the overall drug responsiveness (Level 2) should be classified as "undefined." If two seizures have recurred, outcome to the individual drug(s) should be categorized as treatment failure, and the overall drug responsiveness remains "undefined." If an additional AED is adequately tried and failed, then the epilepsy is redefined as drug resistant. If the patient has had no further seizure for three times the interseizure interval (of the relapsed seizures) or 1 year, whichever is longer, the epilepsy is redefined as drug responsive. It is proposed that this classification approach also applies to the scenarios where the epilepsy had been drug resistant before the patient became seizure free. Because there is a paucity of data on the seizure pattern in such scenarios it is acknowledged that such a classification approach is largely empirical and needs to be tested for its validity in prospective studies.

## Application of the Definition in Specific Scenarios

We recommend application of the consensus definition to diverse clinical and research scenarios. For instance, the core definition may be applied, after adaptation, to the selection of candidates for epilepsy surgery or for referral to an epilepsy center for a comprehensive evaluation. Obviously, because presurgical evaluation and surgery

itself may entail risks, the decision to offer surgical treatment requires individual risk–benefit analysis that includes an assessment of possible success with additional trials of AEDs. The proposed definition also has implications for the design of randomized drug trials and should prove useful in the selection of patients for such trials, in which the criteria for considering a patient drug resistant are often poorly described. In this setting, a standard definition of drug resistance is important to ensure that results are comparable across trials. It would be particularly important to have clear documentation of previous AEDs that failed to control seizures, excluding those "uninformative" trials, and including the reasons for failure.

## Conclusion

The development of the proposed consensus definition was driven by the growing need among medical practitioners and clinical researchers to adopt a common language in recognizing drug resistant epilepsy in the face of rapidly expanding therapeutic options. The definition aims to describe responsiveness to AED therapy but does not address the possible determining factors. Indeed, it is hoped that adoption of a common definition of drug resistance by researchers will facilitate the identification of such factors. During the process of formulating the definition, we were aware of deficiencies in the knowledge base, and inevitably assumptions were made that require testing and validation in future studies. In particular, there is a need for better documentation of the often fluctuating pattern of seizure occurrences and of the time course of treatment response in newly diagnosed patients. These data are required to provide a better understanding of the dynamic relationships among the various dimensions of treatment outcome. The proposed definition, therefore, is not intended to be prescriptive but represents a working framework. Clinicians and researchers should exercise their judgment in interpreting the principles described in this report when applying the definition to diverse settings. Some examples of how to apply the definition in various clinical scenarios are illustrated in Table 3. Because, as stated by Voltaire, the 18th century French Enlightenment writer and philosopher, "the perfect is the enemy of the good," we hope that this consensus definition will serve its pragmatic purpose. Its adoption by the epilepsy community will allow future testing and refinement as and when new evidence emerges.

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## Glossary

| | |
|---|---|
| Adverse effect | Any response to an intervention that is noxious and unintended, and which occurs when the intervention is applied with modalities normally used in humans for the therapy of a disease |
| Appropriate intervention | An intervention that has been shown to be safe and effective with appropriately documented evidence |
| Drug responsiveness | Whether the epilepsy is drug resistant, drug responsive, or neither (undefined) |
| Drug resistant epilepsy | Epilepsy in which seizures persist and seizure freedom is very unlikely to be attained with further manipulation of AED therapy. In the current proposal, it is defined as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" |
| Drug-responsive epilepsy | Epilepsy in which the patient receiving the current AED regimen has been seizure-free for a minimum of three times the longest preintervention interseizure interval or 12 months, whichever is longer |
| Intervention | A substance, device, or action applied to an epilepsy patient with the primary aim of reducing or preventing the occurrence of seizures |
| Seizure freedom | Freedom from all types of seizures for 12 months or three times the preintervention interseizure interval, whichever is longer |
| Treatment failure | The outcome whereby the patient did not attain seizure freedom after an informative trial of an intervention |
| Treatment outcome | Effect of an intervention as categorized by seizure control and occurrence of adverse effects |
| Undefined drug responsiveness | Drug responsiveness that cannot be classified as either drug responsive or drug resistant |
| Undetermined outcome | The situation whereby there is insufficient information to determine the outcome of an intervention in terms of seizure control or occurrence of adverse effects, or both |
| Uninformative trial | An intervention for which there is insufficient information to determine its outcome in an individual patient |

## References

Arts WF, Brouwer OF, Peters AC, Stroink H, Peeters EA, Schmitz PI, van Donselaar CA, Geerts AT. (2004) Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. *Brain* 127:1774–1784.

Arzimanoglou A, Ryvlin P. (2008) Towards a clinically meaningful definition of drug-resistance. In Kahane P, Berg A, Löscher W, Nordli D, Perucca E (Eds) *Progress in Epileptic Disorder (Volume 7): Drug-resistant epilepsies*. John Libbey Eurotext, Montrouge, France, pp. 1–6.

Baker GA, Camfield C, Camfield P, Cramer JA, Elger CE, Johnson AL, Martins da Silva A, Meinardi H, Munari C, Perucca E, Thorbeke R.

(1998) Commission on Outcome Measurement in Epilepsy. 1994–1997: Final report. *Epilepsia* 39:213–231.

Berg AT, Engel J Jr. (1999) Restricted driving for people with epilepsy. *Neurology* 52:1306–1307.

Berg AT, Shinnar S, Levy SR, Testa F, Smith-Rapaport S, Beckerman B. (2001) Early development of intractable epilepsy in children: a prospective study. *Neurology* 56:1445–1452.

Berg AT, Vickrey BG, Testa FM, Levy SR, Shinnar S, DiMario F, Smith S. (2006) How long does it take epilepsy to become intractable? A prospective investigation. *Ann Neurol* 60:73–79.

Berg AT, Levy SR, Testa FM, D'Souza R. (2009) Remission of epilepsy after 2 drug failures in children: a prospective study. *Ann Neurol* 65:510–519.

Callaghan BC, Anand K, Hesdorffer D, Hauser WA, French JA. (2007) Likelihood of seizure remission in an adult population with refractory epilepsy. *Ann Neurol* 62:382–389.

Carreño M, Gil-Nagel A, Sánchez JC, Elices E, Serratosa JM, Salas-Puig J, Villanueva V, Porcel J. (2008) Strategies to detect adverse effects of antiepileptic drugs in clinical practice. *Epilepsy Behav* 13:178–183.

Chin PS, Berg AT, Spencer SS, Lee ML, Shinnar S, Sperling MR, Langfitt JT, Walczak TS, Pacia SV, Bazil CW, Vassar S, Vickrey BG. (2006) Patient-perceived impact of resective epilepsy surgery. *Neurology* 66:1882–1887.

Edwards RI, Aronson JK. (2000) Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 356:1255–1259.

Fisher RS, Parsonage M, Beaussart M, Bladin P, Masland R, Sonnen AE, Rémillard G. (1994) Epilepsy and driving: an international perspective. Joint Commission on Drivers' Licensing of the International Bureau for Epilepsy and the International League Against Epilepsy. *Epilepsia* 35:675–684.

Hanley JA, Lippman-Hand A. (1983) If nothing goes wrong, is everything alright? *JAMA* 259:1743–1745.

Huttenlocher PR, Hapke RJ. (1990) A follow-up study of intractable seizures in childhood. *Ann Neurol* 28:699–705.

Jacoby A, Baker GA, Steen N, Potts P, Chadwick DW. (1996) The clinical course of epilepsy and its psychosocial correlates: findings from a U.K. Community study. *Epilepsia* 37:148–161.

Jacoby A, Gamble C, Doughty J, Marson A, Chadwick D; Medical Research Council MESS Study Group. (2007) Quality of life outcomes of immediate or delayed treatment of early epilepsy and single seizures. *Neurology* 68:1188–1196.

Kahane P, Berg A, Löscher W, Nordli D, Perucca E. (2008) *Drug-resistant Epilepsies. Progress in Epileptic Disorders*, Vol. 7. John Libbey Eurotext, Montrouge, France.

Karch FE, Lasagna L. (1977) Toward the operational identification of adverse drug reactions. *Clin Pharmacol Ther* 21:247–254.

Kwan P, Brodie MJ. (2000) Early identification of refractory epilepsy. *N Engl J Med* 342:314–319.

Kwan P, Brodie MJ. (2001) Effectiveness of first antiepileptic drug. *Epilepsia* 42:1255–1260.

Kwan P, Brodie MJ. (2006) Issues of medical intractability for surgical candidacy. In Wyllie E (Ed.) *The Treatment of Epilepsy: Principles and Practice*. 4th ed. Lippincott Williams & Wilkins, Philadelphia, pp. 983–991.

Leape LL. (1995) Preventing adverse drug events. *Am J Health Syst Pharm* 52:379–382.

Leone MA, Beghi E, Righini C, Apolone G, Mosconi P. (2005) Epilepsy and quality of life in adults: a review of instruments. *Epilepsy Res* 66:23–44.

Luciano AL, Shorvon SD. (2007) Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. *Ann Neurol* 62:375–381.

Markand ON, Salanova V, Whelihan E, Emsley CL. (2000) Health-related quality of life outcome in medically refractory epilepsy treated with anterior temporal lobectomy. *Epilepsia* 41:749–759.

Mohanraj R, Brodie MJ. (2006) Diagnosing refractory epilepsy: response to sequential treatment schedules. *Eur J Neurol* 13:277–282.

Perucca E. (1998) Pharmacoresistance in epilepsy. How should it be defined? *CNS Drugs* 10:171–179.

Perucca E, Dulac O, Shorvon S, Tomson T. (2001) Harnessing the clinical potential of antiepileptic drug therapy: dosage optimisation. *CNS Drugs* 15:609–621.

Reid K, Herbert A, Baker GA. (2004) Epilepsy surgery: patient perceived long-term costs and benefits. *Epilepsy Behav* 5:81–878.

Schiller Y, Najjar Y. (2008) Quantifying the response to antiepileptic drugs: effect of past treatment history. *Neurology* 70:54–65.

Sillanpää M, Haataja L, Shinnar S. (2004) Perceived impact of childhood-onset epilepsy on quality of life as an adult. *Epilepsia* 45:971–977.

Sillanpää M, Shinnar S. (2005) Obtaining a driver's license and seizure relapse in patients with childhood-onset epilepsy. *Neurology* 64:680–686.

Spencer SS, Berg AT, Vickrey BG, Sperling MR, Bazil CW, Haut S, Langfitt JT, Walczak TS, Devinsky O; Multicenter Study of Epilepsy Surgery. (2007) Health-related quality of life over time since resective epilepsy surgery. *Ann Neurol* 62:327–334.

Tanganelli P, Regesta G. (1999) Clinical aspects and bioloogical bases of drug-resistant epilepsy. *Epilepsy Res* 34:109–122.

Téllez-Zenteno JF, Dhar R, Hernandez-Ronquillo L, Wiebe S. (2007) Long-term outcomes in epilepsy surgery: antiepileptic drugs, mortality, cognitive and psychosocial aspects. *Brain* 130(Pt 2):334–345.

Vickrey BG, Hays RD, Rausch R, Engel J Jr, Visscher BR, Ary CM, Rogers WH, Brook RH. (1995) Outcomes in 248 patients who had diagnostic evaluations for epilepsy surgery. *Lancet* 346:1445–1449.

Wass CT, Rajala MM, Hughes JM, Sharbrough FW, Offord KP, Rademacher DM, Lanier WL. (1996) Long term follow up of patients treated surgically for medically intractable epilepsy: results in 191 patients treated at Mayo Clinic Rochester between July 1972 and March 1985. *Mayo Clin Proc* 71:1105–1113.

Wild JM, Ahn HS, Baulac M, Bursztyn J, Chiron C, Gandolfo E, Safran AB, Schiefer U, Perucca E. (2007) Vigabatrin and epilepsy: lessons learned. *Epilepsia* 48:1318–1327.

Wilson SJ, Saling MM, Lawrence J, Bladin PF. (1999) Outcome of temporal lobectomy: expectations and the prediction of perceived success. *Epilepsy Res* 36:1–14.

World Health Organization. (1972) *International Drug Monitoring: the Role of National Centres*. Techn Rep Series WHO, Geneva, p. 498.

World Health Organization Collaborating Centre for Drug Statistics Methodology. (2008) *About the ATC/DDD system*. Accessed December 1, 2008 at http://www.whocc.no/atcddd/.