Defining refractory epilepsy

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Nomenclature

- Drug resistant epilepsy
- Medically refractory epilepsy
- Medical intractable epilepsy
- Pharmacoresistant epilepsy

Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies: Patrick Kwan, Epilepsia 2010

Definition of drug resistant epilepsy

- Different definitions may be required for different purposes
- Drug responsiveness of a patient's epilepsy should be regarded as a dynamic process rather than a fixed state
- Objective
  - To improve patient care and facilitate clinical research
  - Fulfillment of the definition in a patient should prompt a comprehensive review of the diagnosis and management, preferably by an epilepsy center

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Evaluates at 2 levels

- Level 1
  - To categorize outcome to each therapeutic intervention
  - Include: ''seizure-free,'' ''treatment failure,'' and ''undetermined,''
- Level 2
  - To provide 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)

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Level 1:
Categorization of Outcome to a Therapeutic Intervention

- 2 outcome dimensions: seizure control & adverse effects

- Seizure control (3 categories)
  - Category 1: Seizure-free (the intervention must be ‘‘appropriate’’ and ‘‘adequate,’)
    - Freedom from all seizures, including auras
  - Category 2: Not seizure free (the intervention must be ‘‘appropriate’’ and ‘‘adequate,’)
  - Category 3: Undetermined
    - i.e. ethosuximide would usually not be considered an appropriate intervention for focal seizures
    - An ‘‘appropriate’’ intervention should have previously been shown to be effective, preferably in randomized controlled studies, which provide the highest level of evidence
- Adverse effects
  - A: No
  - B: Yes
  - C: Undetermined

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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.

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‘‘Adequate/informative’’ vs.‘‘uninformative’’ trial

- A valid assessment of the treatment outcome
- Intervention at adequate strength/dosage for a sufficient length of time
- Failure due to adverse event = undetermined
  - as ‘‘failure’’ was not because of lack of efficacy for seizure control
- Loss F/U patient = ‘‘undetermined.’’

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Interindividual variation to achieve seizure freedom

- it is difficult to rigidly define the ‘‘clinically effective dose range’’ for each AED
- Depending on
  - Monotherapy or polytherapy
  - Age of patients
  - Liver and renal function for drug clearance
  - Titration procedure

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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

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Breakthrough seizures

- Identify potentially seizure provoking external factors
  - Sleep deprivation, menstruation, intercurrent febrile illness, etc.
- In general, seizures that occur under these circumstances should still be considered as evidence of inadequate seizure control (treatment failure)
- Seizure relapse due to poor treatment compliance should not be treatment failure

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The duration of seizure free

- At least 2 seizures must have been documented to determine the preintervention interseizure interval
- The ‘‘rule of three’’ for calculating confidence intervals for zero events can be used in this setting (Hanley & Lippman-Hand, 1983).
- 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.
- Three times the longest interseizure interval be used as an indicator of positive treatment response

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A sustained response that is clinically meaningful

- Some studies found impact to quality of life if seizure free at least 12 months (Sillanp & Shinnar, 2005; Jacoby et al., 2007, Markand et al., 2000; Spencer et al., 2007)
- Driving restriction: seizure-free duration should be at least 12 months (Fisher et al., 1994; Berg & Engel, 1999)
- Therefore, there was consensus that seizure-free duration should be at least 12 months

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Category 1 outcome

- Seizure freedom 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.

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Category 2 outcome

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

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Catergory 3 outcome

- Undetermined
  - If a patient has been seizure-free for three times the preintervention interseizure interval but for <12 months

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Level 2: Definition of Drug Resistant Epilepsy

- The course of epilepsy and responsiveness of AEDS sometimes fluctuates (Berg et al., 2009)
  - Dynamic course depending of underlying processes
- 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.

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Scenarioes

Case 1

- A patient had 1 seizure in January 2006 and 2 seizures in October 2006
- After starting treatment in November 2006 he has been seizure free for 30 months with no adverse effect

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Case 1.

Patient history	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
Level 1—categorization of treatment outcome	One current drug with seizure-free outcome (Cat. 1A)
Level 2—classification of drug responsiveness of epilepsy	Drug responsive
Notes	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

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Case 2.

- A 16-year-old patient was started on valproate 2 years ago after experiencing 2 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

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Case 2.

Patient history	A 16-year-old patient was started on valproate 2 years ago after experiencing 2 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
Level 1—categorization of treatment outcome	One current drug with seizure-free outcome (Cat. 1B)
Level 2—classification of drug responsiveness of epilepsy	Drug responsive
Notes	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

Case 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

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Case 3.

Patient history	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
Level 1—categorization of treatment outcome	One previous drug with undetermined outcome (Cat. 3C). Two current drugs with treatment failure outcome (Cat. 2)
Level 2—classification of drug responsiveness of epilepsy	Drug resistant
Notes	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

Case 4.

- A patient was newly started oncarbamazepine after two partial seizures in 9 months. He has had no seizures for 12 months since

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Case 4.

Patient history	A patient was newly started oncarbamazepine after two partial seizures in 9 months. He has had no seizures for 12 months since
Level 1—categorization of treatment outcome	One current drug with undetermined outcome (Cat. 3)
Level 2—classification of drug responsiveness of epilepsy	Undefined
Notes	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

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Case 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

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Case 5.

Patient history	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
Level 1—categorization of treatment outcome	One previous inappropriate drug. One previous drug with undetermined outcome (Cat. 3B). One current drug with treatment failure outcome (Cat. 2)
Level 2—classification of drug responsiveness of epilepsy	Undefined
Notes	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

Case 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

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Case 6.

Patient history	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
Level 1—categorization of treatment outcome	Three previous drugs and one current drug with treatment failure outcome (Cat. 2)
Level 2—classification of drug responsiveness of epilepsy	Drug resistant
Notes	The patient has failed more than two appropriate AEDs

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Case 6.1

- After adding drug X, patient 6 has had no seizure for 8 months

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Case 6.1

Patient history	After adding drug X, patient 6 has had no seizure for 8 months
Level 1—categorization of treatment outcome	Four previous drugs with treatment failure outcome (Cat. 2). One current drug with undetermined outcome (Cat. 3)
Level 2—classification of drug responsiveness of epilepsy	Drug resistant
Notes	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

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Case 6.2

- With further follow-up patient 6 has had no seizure for 24 months

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Case 6.2.

Patient history	With further follow-up patient 6 has had no seizure for 24 months
Level 1—categorization of treatment outcome	Four previous drugs with treatment failure outcome (Cat. 2). One current drug with seizure-free outcome (Cat. 1)
Level 2—classification of drug responsiveness of epilepsy	Drug responsive
Notes	The patient has had no seizures for more than three times the pretreatment interseizure interval and for more than 12 months

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Case 6.3.

- Patient 6 has two seizures within 1 month

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Case 6.3.

Patient history	Patient 6 has two seizures within 1 month
Level 1—categorization of treatment outcome	Four previous drugs and one current drug with treatment failure outcome (Cat. 2)
Level 2—classification of drug responsiveness of epilepsy	Undefined
Notes	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)

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Case 6.4.

- Two more appropriate AEDs are added at adequate dosage but patient 6 continues to have seizures once per month

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Case 6.4.

Patient history	Two more appropriate AEDs are added at adequate dosage but patient 6 continues to have seizures once per month
Level 1—categorization of treatment outcome	Four previous drugs and three current drugs with treatment failure outcome (Cat. 2)
Level 2—classification of drug responsiveness of epilepsy	Drug resistant
Notes	After the relapse the patient has failed more than two adequate trials of appropriate AEDs

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Summary

- The definition aims to describe responsiveness to AED therapy but does not address the possible determining factors.
- 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.

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