

The National Center for Epilepsy



The definition of pharmacoresistance

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A Bill Clinton quotation

- "It depends on the definition of the definition"

*Various terms – often used
synonymously*

- Pharmacologic- or drug resistant epilepsy
- Therapy resistant epilepsy
- Intractable epilepsy
- Refractory epilepsy
- Severe and disabling epilepsy
- Difficult-to-treat epilepsy

The importance of defining pharmacoresistance

- To assess the incidence of pharmacoresistance it is necessary to estimate the resources that should be allocated to this patient population
- We should know when further drug trials are redundant - and non-pharmacological treatment options should be considered

Pharmacoresistance

– a major problem

- Despite the availability of ten new AEDs over the past 10-15 years, the drug-resistant group is not dramatically decreased
- The figures of pharmacoresistant patients varies - depending on
 - The population studied
 - The definition of pharmacoresistance employed
- Pharmacoresistance affects a substantial minority
- 20-40 % of the epilepsy population (?)
- According to Hauser (1993), only 5-10 % is "truly intractable"

Pharmacoresistance

– what is it?

- The term remains controversial
- The underlying pathophysiological mechanisms are mainly unknown
- A multifaceted phenomenon; drug resistant individuals do not share a common reason (except for some with a common genetic predisposition?)
- All causes of pseudoresistance should be ruled out

Pseudoresistance *- possible causes*

- Non-epileptic seizures, including psychogenic non-epileptic seizures (PNES)
- Misclassification of seizures/epilepsy and thus using inappropriate drugs; e.g. using sodium channel blockers or GABAergic drugs to patients with generalized seizures
- Too few drugs tried
- Using the drugs suboptimally
- Too short observation period
- Non-compliance, or other unrevealed seizure precipitating factors

Pharmacoresistance

– what is it?

- Several aspects should be considered:
 - Expected prognosis?
 - Time aspect?
 - Seizure frequency and severity?
 - Appropriate drugs?
 - No. of drugs tried?
 - Dosing?
 - Serum concentrations?

Factors influencing the drug response

- Epilepsy syndrome
- Epilepsy etiology
- Seizure frequency
- Genetic factors that predetermine
 - the rate of absorption
 - metabolism
 - uptake of drug in target tissue

The time aspect

- In the course of the epilepsy – when can intractability be ascertained?
- In some patients, a poorly controlled epilepsy is evident from the outset
- In others, pharmacoresistance may be delayed – especially in those with focal epilepsies

The time aspect

- For how long time should drugs be tried – and failed – before the term pharmacoresistance is justified?
 - Six months?
 - One year?
 - Two years?
 - > Two years?
- One treatment schedule should be tried in at least three months

Number of drugs

- How many AEDs should be tried – without achieving seizure control – before the patient is called pharmacoresistant?
 - Two appropriate monotherapies?
 - Three appropriate monotherapies?
 - AED combinations?
 - Old vs. new AEDs?

Which drugs appear ”appropriate”?

- In focal epilepsies the following drugs should have been tried:
 - CBZ/OCBZ
 - LEV
 - TPM
- In generalized epilepsies the following drugs should be tried:
 - VPA
 - LTG
 - LEV

Response rate to AEDs

- Response rates to the first, second and third treatment schedules were:
 - 50.4 %
 - 10.7 %
 - 2.7 %
- Only 0.8 % responded optimally to further drug trials
- Those who not attain long-term seizure freedom with the first three treatment schedules are likely to have refractory epilepsy

AED doses

- Increase the dose until toxicity?
- Dosing aiming at a serum concentration in the upper part of the therapeutic range?

Seizure frequency and severity

- To term the condition pharmacoresistant, is a certain number of seizures/month an absolute demand?
- Or, should we leave it to the patients to evaluate how the seizure disorder affects their everyday life?

Pharmacoresistance – according to Anne T. Berg

- > One seizure/month the last 18 months
 - Not > three months of seizure freedom the last 18 months
 - Failure of two appropriate AEDs
- referring to surgery

*How can we assess the
degree of
pharmacoresistance?*

- What are the best markers of pharmacoresistance?
 - The number of drugs tried – and failed?
 - The scores on seizure severity scales?
 - The scores on QOLIE tests?

Consensus guidelines?

- Different definitions of pharmacoresistance create difficulties for comparison of results across studies
- Do we need different definitions for different purposes?
- Operational concept for research and clinical purposes?