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Commentary on “Do neurologists agree in diagnosing drug resistance in adults with focal epilepsy?”.

Defining drug resistance in epilepsy: are we agreed?

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Recognising drug resistance for a patient with epilepsy may have important practical implications, for instance in consideration of non-drug therapies, participation in experimental clinical trials, and social and educational support. For some time a variety of definitions had been employed, leading to confusion for patients, carers, clinicians as well as researchers. To enable a common language, the ILAE appointed a special task force to propose, for the first time, a global consensus definition of drug-resistant epilepsy.

Since its publication in 2010¹ the definition has been widely adopted in clinical trials, although its application in everyday clinical care has been evaluated in few studies. Two previous studies assessed the interrater reliability retrospectively in relatively small number

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of patients, demonstrating a high level of agreement^{2,3}. In this issue of *Epilepsia*, Zaccara and colleagues⁴ report a multicentre prospective observational study in Italy to evaluate the agreement among clinicians of different levels of expertise when applying the definition.

The study clearly has many strengths. The design was rigorous and the study was carefully conducted. The study focused on adults with focal epilepsy, reducing the variability from other clinical factors. Each treatment response was independently assessed by a pair of expert epileptologists blinded to the identity of the patient, treating hospital, as well as their counterpart, ensuring unbiased assessment. An impressive number of over 1,000 patients and 6,000 antiepileptic drug (AED) trials were evaluated over the study period. In each patient the evaluation included both previous AEDs retrospectively and newly prescribed AEDs prospectively, reducing the impact of inadequate information because of failure to access medical records.

Given that the definition was largely conceptual the overall results are reassuring. It is particularly encouraging to see that there was agreement in many important aspects which are subject to operator's interpretation, such as duration of treatment. There was almost perfect agreement between pairs of expert epileptologists in classifying response to individual AED and overall drug responsiveness, although the agreement was more moderate between the epileptologists and investigators who were neurologists working in epilepsy centres.

The largest source of discrepancy was the dose of AED deemed sufficient to qualify the trial as adequate. The authors did not provide details of the AED doses used. As the ILAE report acknowledges it would not be possible to dogmatically stipulate the adequate dosage for each marketed AED, although 50% of the WHO defined daily dose has been proposed as a practical benchmark.⁵ A prospective study showed that raising the dosage to this level was able to render 17% of patients with previously uncontrolled epilepsy seizure-free.⁶

The authors found that 19% of patients thought to be drug-resistant by the investigators did not fulfil the ILAE definition. It would be interesting to see how many did turn out to be drug resistant upon further drug manipulation, which might be used to assess the sensitivity of the definition.

Arguably defining drug resistance is as important as defining epilepsy and the seizure/syndromic classification. This study is an important step in validating the ILAE definition of drug resistance in everyday clinical use.

I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure

I have no conflicts of interest to disclose.

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