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# WHAT TO DO IF SURGERY FAILS?

A lot of patients show variable and dynamic course of their epilepsy with spontaneous remissions and relapses that are hard to explain (*Neligan A, et al. How refractory is refractory epilepsy? Patterns of relapse and remission in people with refractory epilepsy. Epilepsy Res. 2011; 96: 225–230.*). Although we may explain variability by a couple of causes such as regression towards the mean; deviation from best-possible therapy or true pharmacoresistance. We usually regard pharmacoresistance as failure to obtain complete cessation of seizures with two AEDs used in informative trials (use of appropriate drug/dose for syndrome and seizure type during adequate period of time) for 1 year or 3 times the longest inter seizure interval during recent active phase of epilepsy, whichever is greater (*Kwan P, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010; 51: 1069–1077.*).

Refractory epilepsy may be present from the beginning rather than evolve over time, since the clinical characteristics of this type may be apparent early in the course of disease. Such patients are more likely to have underlying structural cerebral abnormalities, to have had more than 20 seizures before treatment is initiated, and to have an inadequate response to the first AED prescribed (*Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000; 342: 314–349.*). Minority of cases with refractory epilepsy are characterized by shifting of remissions and relapses that finally fail to achieve remission (*Brodie MJ, et al. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012; 78: 1548–1554.*).

The definition of pharmacoresistence bears practical implications because if the diagnosis of pharmacoresistence is fulfilled one could refer patient for comprehensive presurgical evaluation early in the course of epilepsy. The problem rises if patient is not good surgical candidates or surgery fails. Such a situation occurs in at least two thirds of pharmacoresistant cases and pharmacotherapy re-

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mains the mainstream of their treatment options. General view of the pharmacotherapy of pharmacoresistant epilepsy is gloomy regarding the success of the seizure control. The goal of the pharmacotherapy of pharmacoresistant epilepsy is to lessen the seizure burden, to prevent status epilepticus and to treat comorbidities. However, there is a rationale to treat pharmacoresistant epilepsies with new, unused antiepileptic drugs, by adding previously unused/new drug, by the increase the drug dosage if previously insufficient, or by the revise of drug combinations („rational polypharmacy"). It is quite reasonable to think that new, chemically distinct AEDs, with new mechanism of action and simpler pharmacokinetics could have new antiepileptic potency, different or superior to previous drugs. So, the nihilism in the pharmacotherapy of pharmacoresistant epilepsies may not be justified (*French JA, Faught E. Rational Polytherapy. Epilepsia 2009 Sep; 50 Suppl 8: 63–68.*).

The basic principal in the treatment of patient with pharmacoresistant epilepsy is to never give up from patient and his/her treatment (*Treiman DM. Management of refractory complex partial seizures: current state of the art. Neuropsihiat Dis Treat 2010; 6: 297–308.*). Logical approach towards patients with pharmacoresistant epilepsy is to rotate a patient through only a single trial of all potentially suitable, previously unused drugs. In other words, one should start previously unused antiepileptic drug with relatively rapid escalation of dose (but sufficiently slow not to produce significant side effects) to achieve high therapeutic plasma levels. The duration of therapy should not be too long (less than a couple of weeks or months) during which, in the case of new seizure occurrence, immediate drug failure could be confirmed. If drug failure is diagnosed next unused drug trial should ensue. Although theoretically simple, prolonged periods are required to titrate up and to withdraw therapies. This is resource intensive, but it should be a major function of a dedicated doctor (*Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. Ann Neurol 2007; 62: 375–381.*).

In the systematic review and meta analysis of 55 articles with 11.106 pharmacoresistant patients treated with new antiepileptic drugs as add-on therapy (efficacy of placebo is subtracted from antiepileptic drug efficacy), probability of >1 year remission is 6% (95%IP 4–8; p<0,001), and the probability of the decrease in number of seizures for >50% is 21% (95%IP 19–24; P<0,001). No matter how many AEDs have been tried, there is always hope that a patient with pharmacoresistant epilepsy will have a significant seizure remission with new antiepileptic drug. Probability for ≥1 year remission in pharmacoresistant epilepsy with new drug regimen is up to 4–6% per year, but probability of subsequent seizure relapse is 40% after 1 year of follow-up and as much as 70% after 7 years of follow-up (*Callaghan B, et al. Remission and relapse in a drug-resistant epilepsy population followed prospectively. Epilepsia. 2011 Mar; 52: 619–626.*).

Strictly speaking, in contrast to aforementioned definition, drug resistance (pharmacoresistance) is a graded process that evolve during time and follows a „mono-exponential course with a half-decay constant of 1.5 – 2 antiepileptic drugs"

(*Schiller Y, Najjar Y. Quantifying the response to antiepileptic drugs: effect of past treatment history. Neurology 2008; 70: 54–65.*). That means that relative pharmacoresistency could be diagnosed after failure of 2 drugs that could lead to the presurgical work-up, while absolute pharmacoresistency could be diagnosed after failure of >6 drugs. Even after failure of 6 or more antiepileptic drugs, there is probability of obtaining small but significant seizure improvement with the application of brand new antiepileptic drug.