

When to stop antiepileptic treatment

Franz Gerstenbrand, Holger Bauer

When to stop administering a drug is at least as important as a treatment decision to start. As a matter of fact, most patients and their relatives are asking this question at the beginning of an AED treatment. There is general agreement, that a withdrawal from AED should be tried after a distinct period of time being free of seizures with treatment. However, nagging questions unsolved by scientifically sound data make the decision a difficult one. Even the question why epilepsy should be cured by drugs treating the proneness to seizures and not its cause remains unsolved.

Slide 1: The decision for AED withdrawal

The decision for AED withdrawal represents an interaction of MDs advice with attitudes of the patient and his relatives. The decision is guided by toxic effects of AEDs on the one side and the risk of relapse on the other. Since both factors primarily affect the patient – he has to tolerate side effects or take the risk of seizure recurrence – it is his decision. As doctors we have the only assignment to give him advices as clearly and honestly as possible. We should not try to urge him for a certain option.

Slide 2: Risk of relapse after discontinuation of AEDs (Berg and Shinnar 1994)

Every trial for discontinuation has to have some inclusion criteria – i.e. who is suitable for withdrawal – numbers of relapses are based on these criteria. Inclusion criteria vary considerably with different centers, prospective studies are hampered by patient's decisions contrary to randomization, follow-up times vary considerably; thus extremely different figures between 12% and 67% are reported on patients with relapse.

Berg and Shinnar prepared a meta-analysis of corresponding reports in 1994 and figured out 25 studies with comparable variables. Average percentage of relapsing patients was 25% after one year and 29% after two years.

Slide 3: Risk of relapse after discontinuation of AEDs (American Academy of Neurology, 1996)

The American Academy of Neurology furnished comparable figures in 1996, slightly different for children with 31,2% and 39,4% for adults.

Slide 4: Actuarial percentage of seizure-free time in randomized groups

The Medical Research Council Antiepileptic Drug Withdrawal Study Group compiled a very helpful randomized study of antiepileptic drug withdrawal in patients in remission. Patients considered for withdrawal were randomly distributed to slow or no withdrawal. First of all, more than 20% relapsed even with continued therapy, most probable due to poor

compliance. Significantly fewer patients relapsed with continued AED treatment. After two years the curve becomes flat. There are some relapses later on, but these seizures might not be related to withdrawal but to the natural history of the epileptic disorder.

Slide 5: Gordon et al., 1996

This slide summarizes results of an interesting study of Gordon and coworkers investigating the attitude of families towards withdrawal. Whereas MDs yield consistent results that 40% relapse are acceptable for withdrawal trial, relatives are split into risk-takers and risk-averse families. 20% were willing to accept a 75% risk, whereas 42% were unwilling to accept a risk of 25%. Risk-takers virtually exhibited more persons participating in venturing. These attitudes seem to represent a personality trait rather than being connected with variables of the seizure disorder. These figures also demonstrate that there is much room for medical advice.

Slide 6: Clinical variables influencing outcome after AED withdrawal

Many variables might influence the outcome. For methodological problems – as already mentioned, you have to apply some criteria before withdrawal – the relative influence of these factors can hardly be determined.

Slide 7: Age at onset of seizures and relative risk of relapse (Berg and Shinnar, 1996)

Berg and Shinnar in their meta-analysis found 17 studies suited to find out the influence of age at onset of seizures on outcome. Adolescent-onset epilepsies have the highest risk. This might be influenced by some syndrome age peaks. Juvenile myoclonic epilepsy (JME) with a notoriously bad prognosis after withdrawal starts in adolescence and Rolando-epilepsy or benign childhood epilepsy with centrotemporal spikes (BCECTS) becomes seizure-free even without treatment.

Slide 8: Etiology and the risk of relapse (Berg and Shinnar 1994)

Berg and Shinnar analyzed the results of 14 studies according to the etiology of seizures. First of all, I want to explain the terminology of remote symptomatic versus idiopathic etiology. Hauser differentiates acute and minor symptomatic cases. Acute symptomatic corresponds to acute convulsions or situation-related respectively occasion seizures. Minor symptomatic means symptomatic epilepsies in the common understanding, for example post-traumatic epilepsy. Idiopathic as it is used here means without any etiological hints, different from the ILAE definition of proven or suspected genetic origin. Symptomatic cases have an increased risk for relapse, more so when the underlying disease leads to neurological symptoms like mental retardation or motor deficits. Together with Kristmann we conducted a retrospective study in our patients whose medication was withdrawn and found a post-infectious etiology significantly connected with a high risk of relapse.

Slide 9: EEG at the start of discontinuation and risk of relapse (Berg and Shinnar 1994)

There has been much controversy on the role of EEG. Any amount of studies gave conflicting results with positive results in studies exhibiting a high amount of EEG expertise and negative ones with a somewhat undifferentiated look on it. However, the EEG at the start of

discontinuation has a predictive value. Berg and Shinnar could not specify the relative value of diffuse slowing or epileptiform discharges. Furthermore, no comments are made about EEG monitoring during the withdrawal phase. Kristmann found the reappearance of spikes with reduced antiepileptic medication a highly sensitive predictor of relapses. We therefore strongly recommend EEG monitoring and stop the withdrawal process, in case spikes are observed.

Slide 10: Seizure-free period and risk of relapse (Medical Research Council MRC, Lancet 1991)

How long should a patient be free of seizures in case a withdrawal trial should be considered? Some convincing figures exist. The MRC found a distinct correlation between the period free of seizures at randomization and the relative risk. It has to be mentioned that these figures summarize results of the slow discontinuation group and the non-withdrawal group. The message reads that a further seizure is unlikely after a long seizure-free period regardless of AED treatment or no treatment.

Slide 11: American Academy of Neurology (1996)

The AAN states "The longer the duration of seizure control with AEDs, the better the prognosis after withdrawal". This is a sound statement and provides the basis for an advice to wait approximately for another year, provided that the patient shows no side effects. If a patient is reluctant to withdraw, let him continue to take his AEDs.

Slide 12: Strategies of AED withdrawal

There are many recommendations on how to perform the discontinuation of AEDs. Many studies deal with this problem, but no scientifically sound conclusions are possible on the basis of these reports. Even the question on significance of rapid versus slow reduction cannot be answered. Excess of single dose reduction, length of intervals and the role of EEG monitoring remain unclear.

Slide 13: Recommendations for AED withdrawal (AAN, 1996)

The Academy recommends a seizure-free period of 2 to 5 years, a single type of partial or generalized seizure (somewhat different to the results of the MRC study), normal results in neurological examination, normal IQ and normalized EEG with treatment. Many questions remain unsolved with these recommendations.

Finally, I would like to add some personal attitudes: better start late than too early, go slow, in small steps with long intervals and use EEG monitoring. Avoid withdrawal in patients suffering from epilepsy syndromes being notorious for their unpredictable course and their bad prognosis. Respect the wish of the patient.



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**Director-General of Department of Medical Science
Professor Dr Kyaw Myint**

Contact Address

No (249), Theinbyu Road, Mingalar Taung Nyunt Township, Yangon Region, Myanmar.
Ph : (+95 1) 378 863 Fax : (+95 1) 378 863
Email : info@mmacentral.com