

How to stop antiepileptic drugs

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Abstract

The beginning of this new millennium is seeing a trend towards the earlier withdrawal of antiepileptic drugs (AEDs), particularly in children, because of the fear of undesirable side effects and cognitive decline. Certain childhood epilepsy syndromes often remit spontaneously, rather than because of the AEDs. Such children should not be on AEDs longer than six to 12 months. Likewise, most AEDs can probably be tailed down over a maximum period of only 6 weeks rather than months. It is imperative that AED withdrawal and its schedule are discussed in great detail with the patient, and often, his or her family.

WHY STOP ANTIEPILEPTIC DRUGS?

Although many patients choose to continue antiepileptic drug (AED) therapy for life, the possibility of long-term side effects and masking of spontaneous remission are important reasons for stopping AEDs. The duration of seizure freedom prior to stopping AEDs is arbitrary, and often not backed by good scientific evidence. Shorter durations are now being explored, particularly in children because of the potential effects on cognitive development. A sense of security and general well-being, employment and being able to drive without incident are some of the reasons for some patients wanting to prolong their AED therapy. On the other hand, the desire to bear children, possible teratogenic effects, potential cognitive effects on their children and the higher costs of the newer AEDs are some reasons why other patients choose to stop their treatment earlier.

WHEN TO STOP ANTIEPILEPTIC DRUGS?

The belief that all patients should be seizure free for at least two years before stopping AEDs was based on a study conducted more than ten years ago¹ and has not been challenged until recently. The ‘two-year’ cut-off point was deemed safe and reasonable but was highly arbitrary. If patients remained seizure free during the two-year period, both patients and physicians assumed that this was due to the AEDs, oblivious of the fact that some of these remissions might be spontaneous. More recently, there is good evidence that the outcome of AED cessation after shorter durations of seizure freedom was not significantly different

from longer durations. Hence, patients may come off their AEDs after a minimum of one year of seizure freedom^{2,3}, or in the case of children with ‘benign epilepsies’, six months of seizure freedom.⁴ Features that predict a good outcome after earlier AED withdrawal include age at seizure onset less than 6 years, a normal EEG, certain epilepsy syndromes (e.g. childhood absence epilepsy and benign epilepsy of childhood with centrotemporal spikes) and absence of problems immediately after an attack (e.g. hemiparesis, hemisensory loss).

WHAT IS THE RISK OF RECURRENCE/ INTRACTABILITY AFTER STOPPING AEDS?

The relapse rate after AED withdrawal is not insignificant, and is in the order of 30-40% at two years, overall.⁵⁻⁷ In a recent population-based study 71% of 367 children became seizure free after a mean follow up period of 2.8 years, and their AEDs were withdrawn.⁸ After a mean follow up period of 8.1 years, 75% of these children remained seizure free. Of the remaining children (25%) who had one or more recurrent seizures and who were recommenced their AEDs, 1.2 % developed medically intractable epilepsy. Factors associated with an increased risk of seizure relapse after AED withdrawal include age at seizure onset more than 16 years (relative risk [RR] 1.75), consumption of more than one AED (RR 1.83), history of seizures after commencing AED (RR 1.56), history of generalised tonic-clonic seizures (RR 1.56), history of myoclonic seizures (RR 1.84) and an abnormal EEG in the previous year (RR 1.32).⁷ Based on these predictive factors, the same group devised a formula to calculate a

score to predict the risk of seizure recurrence one and two years after seizure onset, and whether or not AEDs were withdrawn.⁹ However, this formula is rather cumbersome, and seldom used in everyday practice. In another study on children with epilepsy, the factors that were associated with an increased relapse rate were age at onset more than 12 years (RR 5.4), history of atypical febrile seizures (RR 2.8), a family history of seizures (RR 2.4), slowing of the EEG background (RR 2.4) and symptomatic epilepsies (RR 1.81).⁶ The presence of mental retardation and/or motor deficits, partial epilepsies, the female gender and spikes in the EEG at the onset of AED withdrawal have also been identified as risk factors for seizure relapse.^{1,2,10} Tinuper *et al*¹¹ showed that abnormalities picked up on serial EEGs during the course, rather than at the onset of AED withdrawal was predictive of seizure relapse. Relapse rates are somewhat higher in patients with non-epileptic seizures, and is in the order of 50% at 12 months after AED withdrawal.¹²

A recent study of partial epilepsy found lower seizure free rates in patients with a hyperintense T2 hippocampal signal (23%) and hippocampal atrophy (28%) compared with those without (62%).¹³ Hence, hippocampal abnormalities on MRI may be an additional risk factor for seizure recurrence following AED withdrawal.

HOW TO STOP AEDS?

The speed of AED withdrawal is variable and depends on the type of AED. Drugs like phenytoin and valproate may be tapered over a few days to zero, carbamazepine, lamotrigine and vigabatrin over 2-3 weeks and clonazepam, clobazam and primidone over weeks to months. It may take many years or even impossible to taper phenobarbitone to zero.¹⁴ Tennison *et al*.¹ showed that there was no difference in seizure relapse rates between withdrawing AEDs over 6 weeks and over 9 months in children with epilepsy. If AED withdrawal is necessary because of drug hypersensitivity or life-threatening idiosyncratic reactions, the drug must be withdrawn immediately and substituted with an AED with a rapid onset of action, e.g. clonazepam, as well as another AED appropriate for the particular epilepsy syndrome. The clonazepam may then be withdrawn once the new AED has achieved steady serum levels and/or the patient is free from withdrawal seizures, whichever is later. It is pertinent to note that AED withdrawal may increase cardiac sympathetic activity in sleep, which may contribute to sudden

unexpected death in epilepsy patients (SUDEP).¹⁵ Fifty percent of relapses occur during drug withdrawal and a further 20-30% occur during the subsequent year.

AEDs may be withdrawn after the patient has been free of seizures for a period of one to two years. In children with 'favourable factors' AEDs may be withdrawn if they have been free of seizures for a period between six and 12 months. The withdrawal of AEDs must be properly discussed with the patient, and often family as well. Patients may, firstly, choose not to withdraw their drugs at all because of fear of seizure recurrence. Such an attitude may be acceptable if the AEDs have not caused any serious harm to the patient, and the patient understands the consequences of his or her action. If patients agree to withdraw their drugs, the withdrawal schedule must be carefully explained. If patients are on multiple AEDs, they must be withdrawn sequentially, i.e. one at a time. If seizures recur during drug withdrawal, the dose of the AED being withdrawn should be stepped up to the dose prior to the current stepped down dose. If status epilepticus develops, the AED should be reintroduced at the original full dose.

CONCLUSION

There is a trend towards earlier withdrawal of AEDs, particularly in children because of the fear of their cognitive effects. Given the heterogeneity of epilepsy itself and the likelihood of spontaneous remission in certain epilepsy syndromes, earlier withdrawal of AEDs is conceivably harmless, and perhaps the correct thing to do. About 10-30% of patients will have at least one recurrent seizure after AED withdrawal, and of these, only 1% ever become intractable to AEDs. While several 'traditional' factors are known to increase the risk of seizure relapse after AED withdrawal, the presence of hippocampal abnormalities on brain MRI must now be added to this list. Above all, AED withdrawal must be individualised, and must take into account the views of the patient and his or her family.

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