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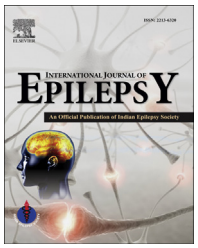

Review Article

Withdrawal of anti-epileptic drugs: A review

Dinkar Kulshreshtha[*], *Pradeep Kumar Maurya*, *Ajai Kumar Singh*, *Anup Kumar Thacker*

Department of Neurology, Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow, UP 226010, India

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ABSTRACT

Anti-epileptic drugs are the mainstay in treatment of epilepsy. It requires a strong clinical decision in patients who are well controlled on medications to withdraw anti-epileptic drugs. This decision has to be based on the clinical profile, epilepsy type, neuroimaging and electroencephalography (EEG) findings and has to be more individualized as per the patient needs. In the context of drug withdrawal, it is necessary to look into the details of why, how and when to withdraw anti-epileptics. In this article, we critically try to answer such queries and look into the established guidelines with respect to drug withdrawal. We shall look into the chances of recurrence on stopping these drugs. Also, in the end we shall discuss briefly some special clinical scenarios where decision to stop anti-epileptic drugs is a challenging task.

1. Introduction

Seizure freedom is achieved in about two thirds of the patients who are treated with anti-epileptic drugs (AEDs) in new onset epilepsy.[1] AED treatments suppress the seizures and some unknown phenomena "resolves" the tendency to throw a seizure.[2] Nevertheless, the most important consideration in such patients is whether to continue AEDs or stop them. Decision to withdraw anti-epileptic drugs in patients with epilepsy in remission requires a good clinical judgment and detailed discussion with the patient and family members. There are no established guidelines concerning this issue. The Medical Research Council (MRC) study was the first randomized trial that tried to answer this issue and since then there have been many studies and reviews about when and how to stops AEDs but the controversies still persist. In this review, we shall highlight on some important issues with regard to stopping AEDs:

1. Why to stop AEDs
2. Risk of recurrence on withdrawal of AEDs
3. When to stop AEDs
4. How to withdraw AEDs
5. Special situations

2. Why to stop AEDs

AEDs are associated with significant systemic and neurocognitive side effects. Teratogenic effects of AEDs are well known and decision to stop AEDs in females of child bearing

* *Corresponding author.*
E-mail address: dinkar.kulshreshtha@rediffmail.com (D. Kulshreshtha).
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age group with controlled seizures needs to be the primary concern of the treating physician. Most AEDs are partially or completely eliminated by hepatic metabolism. AEDs have enzyme inducing or inhibiting properties of their own and hence, can alter the clearance rates of other drugs e.g. carbamazepine induces the metabolism of oral contraceptives through hepatic enzyme induction and lowers the efficacy of oral contraceptives.[3] Thus, potentially harmful interactions should be considered in patients who are taking other drugs in addition to the AEDs.

Epilepsy treatment requires AEDs to be taken regularly, mostly in a twice daily dosage for prolonged periods. The cost related to epilepsy treatment comprises direct costs like hospital admissions, pharmacological therapies, consultation charges and indirect costs like absenteeism and unemployment. Das et al showed that 90% of the patients who discontinued AEDs after 1 year expressed their inability to continue treatment due to low annual income and comparatively large amount of their income being spent for the cost of treatment.[4] With the introduction of newer AEDs, the economic burden for epilepsy management has increased even further. Haroon et al compared the monthly costs of old and new AEDs prescribed and found that the cost of lamotrigine, levetiracetam and lacosamide was approximately more than 10 times as compared with the mean monthly cost of the traditional anti-epileptics.[5] Due to this financial burden, the first question asked to the attending physician with "control" of seizures is if the AEDs can be stopped.

Social stigma attached with epilepsy is a well-known phenomenon, especially in developing countries like India. In a study by Das et al, 130 out of 1450 patients with epilepsy had marital disharmony due to divorce or separation. Women with epilepsy discontinued treatment due to the misunderstanding with their husbands and family members that the disease may be transmitted to the offspring or baby may be physically and mentally abnormal. This eventually creates an enormous economic burden.[4]

Prolonged AED treatment impairs the quality of life of the epileptic patients. Nabukenya et al showed that the health related quality of life (HRQOL) mean score among patients on AEDs was low, thus suggesting their poor physical, psychological and mental functioning and poor emotional wellbeing.[6] Lossius et al in a double blinded, randomized study found an improvement in the neuropsychological functioning upon drug withdrawal in the form of an improved ability to perform activities demanding rapid cognitive performance and complex motor coordination.[7] Similarly, the MRC (UK) study reported an improved feeling of wellbeing after stopping AEDs, thus signifying an improvement in the cognitive function after stopping AEDs.[8]

Mood disorders are the most frequent psychiatric comorbidity in patients with epilepsy with a prevalence rate for depressive disorders in the order of 20%–22%.[9] Andersohn et al found that the use of newer AEDs with a high potential of causing depression increases the risk of self-harm/suicidal behavior by three times in patients of epilepsy.[10]

Thus, we can infer that withdrawing AEDs in patients, who have achieved seizure freedom, has obvious pharmacologic, financial and social implications. Majority of patients wish to discontinue AEDs at the first opportunity.

3. Risk of seizure recurrence on stopping AEDs

Recurrence of seizure is the most dreaded effect of stopping AEDs. About 50% recurrences are seen during the first 6 months of stopping therapy.[2] In a prospective, randomized study conducted by the MRC, 1013 patients participated, out of which, 59% patients who were randomized to the withdrawal group and 22% in the continuing therapy group had recurrence of seizures at the end of two years. Longer seizure free periods at randomization significantly reduced the risk while the number of AEDs at randomization and history of tonic-clonic seizures significantly increased the risk of recurrence.[8] Archana et al showed an overall risk of seizure recurrence of 31% over a period of 18 months after stopping AEDs.[11] As per a study done by Camfield et al in children, about 1% developed medically refractory epilepsy upon stopping medications.[12] The psychological impact of recurrence of seizures is detrimental to the quality of life of the patients and hence, in this scenario, patients usually prefer to continue AEDs.

What are the factors that may help to predict the chances of recurrence of seizures on AED withdrawal? The guidelines published by the American Academy of Neurology (AAN) in 1996 listed 4 primary characteristics that need to be considered before AED withdrawal: a seizure free period of 2–5 years, single type of partial or generalized seizure, normal neurological examination and intelligence quotient and electroencephalogram (EEG) normalized with treatment.[13] Olmez et al studied the risk of recurrence after drug withdrawal in childhood epilepsy and found that post withdrawal EEG abnormalities were significantly associated with seizure recurrence.[14] Su et al examined the role of EEG abnormalities at the time of, during and 1 year after AED withdrawal and found that patients with epileptiform EEG abnormalities within 1 year after AED withdrawal have an increased risk of seizure relapse.[15] Specchio et al recruited 330 patients, out of which, 225 discontinued treatment after a seizure free period of at least two years. They observed that the cumulative risk of a relapse in those who discontinued therapy was 2.9 times higher than that of patients continuing treatment. The factors affecting the risk of relapse were the duration of active disease and the number of years of seizure remission while on treatment. The 24-month risk of relapse was 0% in idiopathic partial epilepsies whereas it was higher for symptomatic partial epilepsies, cryptogenic partial epilepsies, idiopathic generalized epilepsies, and symptomatic or cryptogenic generalized epilepsies.[16]

Idiopathic generalized epilepsies (IGE) account for 20% of all epilepsies and refer to a diverse group of epileptic seizures and syndromes, which usually have a genetic basis. The common syndromic varieties of IGE are benign neonatal and infantile idiopathic generalized epilepsies, childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and epilepsy with primary generalized tonic-clonic seizures.[17] There are not many studies that have focused on the issues of risk of seizure recurrence after AED withdrawal in patients with different types of IGE. Pavlovic et al studied the risk of seizure recurrence after AED

withdrawal in 59 patients with IGE syndrome. They observed that the risk of relapse after AED withdrawal was maximum in JME (100%) and least in CAE (6%). EEG worsening and multiple seizure types were the significant factors associated with relapse after AED withdrawal.[18] Similarly, in a study by Murakami et al, AED withdrawal was studied in children with cryptogenic, symptomatic and idiopathic epilepsies. Of the 304 patients included in the study, 18% had IGE syndrome. The authors observed that after a seizure free period of three years, the relapse rate was 6% in childhood absence epilepsy (CAE), 25% in juvenile absence epilepsy (JAE) and 100% in juvenile myoclonic epilepsy (JME) after stopping AEDs.[19] Withdrawal of AEDs in IGE syndrome can thus result in definite recurrences in JME to occasional recurrences in CAE.

Benign epilepsy with centro-temporal spikes (BECTS) is considered to be the most common childhood epilepsy syndrome, accounting for 8–20% of pediatric patients with epilepsy.[20] It is characterized by brief, simple, orofacial partial seizures (paresthesias and tonic or clonic activity of the lower face, often spreading to the ipsilateral arm, associated with drooling and anarthria), often occurring during sleep or on awakening and associated with a slight male preponderance. This is a self-remitting syndrome with more than 99% patients achieving remission by the age of 18 years. The risk of recurrence in these patients on stopping AEDs is very low.[21]

A number of other predictors have been found to be associated with increased risk of relapse (Table 1).

Thus, we can infer that the risk of recurrence of seizures is high in the immediate post withdrawal period but it gradually reduces after the first 2 years. The factors that predict the chances of recurrence of seizures, especially EEG abnormalities, should be considered on an individual basis by the treating physician and the decision to withdraw antiepileptics should be well discussed with the patient and caregivers.

4. When to stop AEDs

There is no specified time period as to when AEDs need to be tapered in adults and children. Camfield et al, in their study on children found that out of 260 patients who were seizure free for 2.8 ± 1.4 years, AEDs were tapered over a period of 6 weeks and 66% (171) remained seizure free over a follow up period of 3.7 ± 2.3 years. Only 5 patients, who were seizure free for more than 2 years, developed intractable epilepsy on stopping AEDs (<1%). Hence, they proposed a seizure free period of 2 years prior to AED withdrawal.[12] Similarly, Lossius et al conducted a randomized trial in adult population where 79 patients were in the withdrawal arm and 81 in the continued treatment arm with a seizure free duration of 2 years. Within 12 months, 7% of the non-withdrawers and 15% of the withdrawers experienced seizure relapse ($p = 0.095$).[7]

Berg et al, in a meta-analysis reviewed more than 20 studies related to AED withdrawal in both children and adults and found that the rate of seizure recurrence to be 25% at the end of 1 year and 29% at the end of 2 years of seizure free period.[22] AAN guidelines published in 1996 advocated a seizure free period of 2–5 years prior to drug withdrawal.[13]

It can be summarized that there is no general consensus on an optimum seizure free period prior to AED withdrawal. However, in children, a seizure free period of two years appears justifiable though the same may not be true for adults, where the semiology of the seizure, neurological examination and imaging/EEG findings need to be considered prior to drug withdrawal.

Table 1 – Factors predicting increased risk of recurrence on AED withdrawal (Ref).

Onset of epilepsy in adolescent and adulthood[14,15,18]
Use of multiple AEDs[3,15]
Low IQ status[13,15]
Abnormal neurological examination[13,15,18]
Continuing 'epileptiform' discharges while on treatment[13–15,18]
Worsening 'epileptiform' discharges after AED discontinuation[14,15,18]
Epileptogenic lesion on neuroimaging[14]
Syndromic epilepsies like juvenile myoclonic epilepsy, Lennox-Gastaut syndrome, West syndrome, progressive myoclonic epilepsies, Tuberous sclerosis[42]

5. How to withdraw AEDs

One of the main goals of the treating epileptologist while withdrawing AEDs in a patient who has attained seizure freedom is to prevent the recurrence of seizures. Abrupt withdrawal of AEDs is not recommended due to the risk of recurrence. The time period over which these drugs should be tapered and stopped is again a matter of much debate with no definite consensus.[3]

Tennison et al studied the effect of relatively rapid tapering (over 6 weeks) to slow tapering over 9 month period in 149 children. They found that the length of the taper period did not significantly influence the seizure recurrence. Their results showed a higher recurrence of seizure in the first one or two years after rapid withdrawal of AED, compared to slow withdrawal. The factors that significantly affected the risk of recurrence during the tapering period were the presence of mental retardation and EEG abnormalities at the time of tapering.[23] In a similar study by Serra et al, AEDs were tapered over a period of either 1 or 6 months in 57 children. The results were similar to the previous study with no significant difference in seizure recurrence in the two groups.[24] In a Cochrane review of randomized trials comparing slow versus rapid tapering of AEDs, the authors were not able to draw any significant conclusions.[25]

In the MRC study, mean age at entry into the trial was 26–27 years while mean age at seizure onset was 13–14 years. Those randomized to slow withdrawal had AED withdrawn with dosage decrements every 4 weeks with the aim to extend the withdrawal to a minimum of 6 months. AEDs were withdrawn sequentially in the patients, who were on polytherapy.[8] Guidelines issued by the Italian League Against Epilepsy recommend slow discontinuation of the anti-epileptic drugs with tapering period tailored to the patient's needs and preferences.[26]

A special note has to be mentioned with regards to the use of benzodiazepines and barbiturates. These drugs have a

tendency to provoke withdrawal seizures and hence, require a longer tapering period compared to other AEDs.[27]

In summary, withdrawal and stoppage of AEDs depends on clinical profile of the patient, which can be safely achieved over the course of several weeks. If seizures recur on tapering dosage, pre seizure dosage can be resumed and continued.

6. Special situations

6.1. *Drug withdrawal after epilepsy surgery*

One of the main goals of epilepsy surgery in medically refractory cases is to reduce or stop the anti-epileptic drugs. Epilepsy is resolved in only about 20% of the patients following surgery, thereby indicating a protective role of AEDs in the post-operative period.[28,29] There are no established guidelines on AED withdrawal after surgery. Schiller et al evaluated the frequency of seizure recurrence associated with AED withdrawal in patients undergoing successful epilepsy surgery. Out of 210 patients who were seizure free for more than 1 year, 22 of the 84 patients who had stopped treatment had a seizure recurrence. Among these, reinstitution of AED treatment resulted in seizure control in 20 patients. The authors postulated that the surgical procedures in these patients resulted in subtotal excision of epileptogenic zone and hence, a combination of surgery and AEDs was useful. They found that seizure recurrence in the patients was unrelated to the duration of the seizure free postoperative AED treatment.[30] Park et al studied 283 patients who underwent AED withdrawal after neocortical epilepsy surgery including 100 patients with temporal lobe epilepsy. Seizures recurred in 78/147 patients where AED withdrawal was attempted. Multivariate analysis revealed that early drug tapering (<9 months post-surgery), normal MRI results, seizure before reduction, and longer epilepsy duration were associated with seizure recurrence.[29] The seizure outcome following extra temporal resections is generally less favorable as compared to temporal lobe resections. Menon et al studied 106 patients undergoing AED withdrawal after epilepsy surgery with a median time of starting AED tapering being 5 months (range – 3–124 months). Ninety four patients had a seizure recurrence but interestingly, there was statistically no significant difference in the timing of starting the AED tapering in patients who had seizure recurrence versus who did not have.[31]

Hence, as to when tapering of AEDs needs to be done following epilepsy surgery, is not well-defined and it has to be treating clinician's decision based on multiple factors. There is an increased chance of recurrence of seizures in patients who have undergone extra temporal epilepsy surgery, so AED withdrawal has to be done more cautiously in this group of patients.

6.2. *Drug withdrawal in solitary cysticercal granuloma*

Neurocysticercosis (NCC) contributes substantially to the burden of epilepsy. The geographic distribution of cysticercosis is wide, with high prevalence reported from India, Sub-Saharan Africa Mexico, Central and South America.[32] The clinical and radiologic manifestations of NCC vary depending upon the number, location and the stage of the cysticerci in the brain. A form of NCC most commonly seen in clinical practice as a cause of seizures is solitary cysticercal granuloma (SCG). It is a benign form of NCC where seizures are relatively well controlled with a single AED. An important issue to be addressed in this context is how long to continue AED in a patient with SCG. Three open labeled trials have compared the administration of AEDs for a short duration (6 months) vs a longer duration (12–24 months) in individuals with SCG and seizures.[33–35] An expert group meeting from India comparing these trials concluded that there was no additional benefit of the longer duration AED administration in individuals in whom the SCG had resolved. However, in those individuals where there is a calcific residue, the risk of seizure recurrence was significantly high. It was concluded that the AEDs have to be continued until the lesion (granuloma) is actively degenerating (i.e., appears as an enhancing lesion on imaging studies) and the decision to withdraw AED is to be taken once the complete resolution of the granuloma is demonstrated on follow-up imaging studies.[36] Verma et al randomized 206 subjects with SCG in two groups, one where patients were treated for 6 months and other where treatment was given for 2 years. They found that in patients where there was a complete disappearance of the lesion, there was statistically no significant difference in the recurrence of seizures. However, in patients having residual calcification, the short-term withdrawal group had a statistically significant recurrence of seizures (42% vs 21%, $p < 0.05$).[33]

We can infer that a longer duration of therapy is not warranted in patients having total resolution of lesion. But in patients with residual calcific lesions, chances of seizure recurrence are high and withdrawal should be attempted with great caution.

6.3. *Drug withdrawal in seizures associated with cortical venous thrombosis*

Cerebral venous thrombosis (CVT) is a rare type of cerebrovascular disease accounting for 0.5% of all stroke cases. The most common symptoms and signs are headache, seizures, focal neurological deficits and altered consciousness which can present in isolation or in association with other symptoms.[37]

Ferro et al analyzed the risk factors for seizures as a presenting symptom or early in the course (first two weeks) of CVT in 624 patients. 40% patients had presenting seizures and 6% had early seizures.[38] In an earlier study, Ferro et al found that out of 91 patients with CVT, 29 patients had seizures as a presenting feature (32%). Early symptomatic seizures were more frequent in patients with neurological deficits and imaging abnormalities on MRI/CT brain in the form of edema, ischemia or hemorrhage. The authors concluded that there is a moderate risk of seizure recurrence early in the course and during the first year after CVT.[39] In a retrospective analysis of 77 patients with CVT over a mean of 77 months, Preter et al observed that out of 28 patients who had seizures at the presentation, only 4 had recurrence (14%). In 3 out of these 4 patients, seizures occurred in the first year after CVT. The authors recommended that with a low risk of seizure

recurrence, it seems appropriate to maintain anticonvulsant therapy for a year and to taper off gradually thereafter.[40]

As per the guidelines issued by the European Federation of Neurological Societies (EFNS), treatment with AED in the patients of CVT for 1 year may be reasonable for patients with early seizures and hemorrhagic lesions on brain scan on admission, whereas AED therapy may be tapered off gradually after the acute stage in patients without these risk factors.[41]

7. Conclusions

Anti-epileptic drugs are the mainstay in the management of epilepsy. The exact duration of AED treatment in patients who are in remission is a matter of controversy and not yet established. The prognosis on AED withdrawal will vary according to the type of epilepsy syndromes and certain factors that are not firmly determined. In patients where seizures are adequately controlled, AED withdrawal should be encouraged because of substantial side effects, particularly in cognitive function. The duration of a two year seizure free period is well defined in children based on the available literature but in adults, this time period is not very definite though tapering should be attempted after due considerations. The duration of tapering is again a questionable issue but slow withdrawal should be attempted with sequential tapering in cases of polytherapy. The process of drug tapering should be discussed with the patient and caregivers in great detail and the risk of recurrence should be told to the patient well in advance. In the absence of well established guidelines, the process of AED tapering should be individualized.

Conflicts of interest

All authors have none to declare.

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