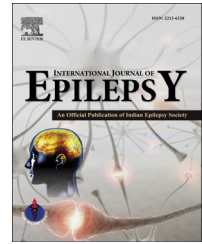


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Review Article

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.

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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 stop 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 blind, 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

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