

# Discontinuation of AEDs: When and how?

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## ABSTRACT

Once a patient has initiated an antiepileptic drug (AED) and achieved a sustained period of seizure freedom, the decision to discontinue AED should be balanced against continuation of AED therapy indefinitely. Studies show that the rate of seizure recurrence after AED withdrawal is about two to three times the rate in patients who continue AEDs. However, there are many benefits to AED withdrawal that should be evaluated on an individualized basis. AED discontinuation may be considered in patients whose seizures have been completely controlled for a prolonged period. There are several factors that would increase risk of recurrences which will be reviewed and discussed. As a consequence, the decision to withdraw or withhold treatment must be still individualized. In any patient, the decision to discontinue treatment should also take into effect the social aspects like driving license, job and leisure activities as well as emotional and personal factors and patients with adverse effects or drug interactions. Patients will ultimately have to decide themselves whether they wish to discontinue drug treatment.

**Keywords:** Epilepsy; Discontinuation of Antiepileptic Drugs (AEDs); Outcome of Recurrences

## 1. INTRODUCTION

Epilepsy is a common condition with a cumulative incidence of 3.0% through age 74 years [1]. However, epilepsy is not a lifelong condition in all patients. A total of 60% to 70% of patients will experience a 5-year remission on medication [2,3]. In a seizure-free patient, the issue may arise about whether medication is still needed. The decision to continue or to stop anticonvulsant treatment in patients with prolonged seizure remission is still a controversial issue. In fact, the decision to stop an-

antiepileptic drugs (AEDs) is probably more critical than starting treatment. Furthermore, there is no evidence that continued treatment with antiepileptic drugs (AEDs) guarantees permanent seizure freedom. In a prospective, long-term population-based study of 144 patients followed on average for 37.0 years, 67% were in terminal remission, with or without treatment [4]. On the other hand, despite experimental evidence of a preventive effect of AED treatment on provoking symptomatic seizures [5], AEDs fail to protect patients with epileptogenic clinical conditions from the occurrence of recurrent spontaneous seizures [6]. A long-term population-based study has shown that 5-year terminal remission (*i.e.*, off-drugs) of epilepsy is approximately 50% at 20 years after diagnosis [7]. Likewise, studies in untreated patients showed that almost half of individuals with chronic epilepsy are seizure-free for more than 5 years [8] and the number of individuals with continuing seizures tends to decrease over time [9] and, last but not least, there is a major concern that treatment may be unnecessary.

## 2. REASONS TO CONSIDER ANTIEPILEPTIC DRUG WITHDRAWAL

There are several reasons to consider discontinuation of AEDs in seizure free patients, mostly related to the negative impact of AEDs on health, cognition, and ultimately on quality of life (QOL). Furthermore, there is a growing evidence of the benefits of discontinuing AEDs on psychosocial wellbeing and, as importantly, on the economic burden on these patients. Finally, the patient plays a key role in this decision-making. Some patients are willing to stop AEDs even when the risk of relapse is substantial, whereas others fear the effects of seizure recurrence on quality of life and opt to continue AEDs.

### 2.1. Adverse Effects

Adverse effects are common in the treatment of patients with epilepsy. The idiosyncratic reactions to AEDs and their short-term and long-term adverse effects are well known and, undoubtedly, limiting these effects is

highly desirable. To varying degrees, all AEDs can cause symptoms affecting several domains of the quality of life of these patients; drowsiness, fatigue, and inattention are examples of these negative outcomes of treatment [10]. Additionally, older AEDs with effects on hepatic enzyme induction or inhibition can prove particularly problematic for patients taking multiple medications for other conditions. Indeed, one survey has reported 31% of patients taking AEDs complained of adverse effects, of which 53% were deemed clinically important. Likewise, certain medications are associated with undesirable long term side effects, such as, gumal hypertrophy, hirsutism, and weight gain. Additional disadvantages of continuing treatment indefinitely include the risk of teratogenicity [11], drug interaction with concurrent medications [12].

## 2.2. Cost

The cost of antiepileptic drugs continues to increase, especially with the advent of newer patented medications. The estimated cost of medication for all patients who developed epilepsy in 1995 alone was projected to exceed \$500 million over the lifetime of the patients [13]. A patient with epilepsy can easily spend more than \$200 to \$300 per month on medication. If medication allows a patient to drive or work, then this cost may be offset. However, if suitable patients for medication withdrawal could be identified reliably, substantial health care savings is expected.

## 2.3. Psychosocial Issues

For most patients, taking AEDs on a daily basis is a constant reminder, even to those with well-controlled epilepsy, simply because, they harbor an unpredictable disorder that may recur at any time. For these patients, seizure freedom off AEDs is the only convincing evidence that their condition is cured. In addition, the responsibility of remembering to take medication on time, calling the pharmacy for refills, packing medication for trips, is viewed by some as adding an unwanted level of complexity to their daily life. Neuropsychological improvement may be expected after successful antiepileptic drug withdrawal, although measuring these improvements is logistically difficult from a research standpoint [14-16]. Behavioral and cognitive side effects are among the commonest adverse events in patients on AEDs [17,18] and are shown to improve after drug withdrawal [19]. Several studies have documented improved outcomes on common neuropsychiatric batteries and mood assessment scales following AED discontinuation [14-20], further validating concerns about the impact of AED therapy on quality of life. Medications may lead patients to perform less efficiently at work and at home. Finally, there is also a certain stigma attached to needing daily

medications. If a medication may not be necessary, it is quite reasonable to offer the patient a trial of medication withdrawal

## 2.4. Overall Risks of Seizure Relapse after Treatment Discontinuation

The proportion of patients with relapses during or after treatment withdrawal ranges from 12% to 66% [21]. As a matter of fact, a review of the impact of planned discontinuation of AEDs in seizure-free patients on seizure recurrence yielded 14 observational studies of seizure recurrence rate after discontinuation and its treatment outcome. This differential risk of relapse was maximal between 1 and 2 years. Surprisingly, there is only one small class I evidence in the literature that is based on randomized double-blind trials for AED withdrawal of adults becoming seizure-free on AEDs [19]. Furthermore, the best evidence from the earlier literature comes from a large and frequently cited study, (MRC Antiepileptic Drug Withdrawal Group) [22], where patients randomized to continued treatment showed a 22% relapse at 2 years, while patients randomized to slow drug withdrawal had 41% relapse. In addition, several useful, but non-randomized observational studies [23-25] have provided us with a meaningful data. More importantly, in a meta-analysis of 25 studies by (Berg and Shinnar) , the pooled relapse risk was only 25% (95% CI, 21% - 30%) at 1 year and 29% (95% CI, 24% - 34%) at 2 years [26]. However, there are several methodological issues need to be recognized when interpreting these study results. Many of these studies enrolled a heterogeneous group of patients. For example, some studies contained a mixture of patients with favorable prognoses (such as those with benign childhood epilepsy with centrotemporal spikes [27] or a history of a single seizure [28]) and unfavorable prognoses (such as Lennox-Gastaut syndrome [29] and adult-onset partial epilepsy [22]). Other studies did not provide the types or the exact classification of epilepsy syndrome, in part because some of these studies were initiated before the development of the International League against Epilepsy (ILAE) Classification of Epilepsies and Epileptic Syndromes, or at least before its widespread acceptance. Therefore, in some studies several epilepsy syndromes are represented in each cohort, which makes applying these results to particular groups of patients difficult. Finally, the antiepileptic drug withdrawal literature is heavily weighted toward the pediatric population. Although the reasons for this are understandable, it makes counseling the adult patient with epilepsy difficult.

## 2.5. Factors Affecting the Risk of Relapse

Below, are some factors that affect the overall risk of recurrences following AEDs withdrawal.

### 2.5.1. Duration of Seizure Freedom

The duration of seizure freedom prior to drug withdrawal is a matter of a great debate. In the systematic review by Specchio and Beghi [21], prognosis following drug withdrawal was similar regardless of whether a 2-year or a 4-year seizure-free interval was considered. In contrast, in a long-term population-based study, treatment duration was shorter in patients who relapsed ( $6.1 \pm 6.2$  years, median = 4.0, range = 1 - 23) than in those who did not relapse ( $10.2 \pm 9.0$  years, median = 8.0, range = 1 - 36) [30]. However, the fairly high standard deviations and the wide ranges suggest that the risk of relapse varies significantly among patients and cannot be predicted by treatment duration. This observation is confirmed by a recent Cochrane systematic review of studies done in children and adults (Sirven *et al.* [31]), in which the pooled relative risk for seizure relapse in early (less than two seizure free years) versus late (more than two seizure free years) AED withdrawal was 1.32 (95% confidence interval 1.02 - 1.70), a statistically significant but clinically irrelevant difference.

### 2.5.2. Etiology

In general, patients with symptomatic or cryptogenic epilepsy fare less well than patients with idiopathic epilepsy as far as the prognosis for seizure control is concerned [32,33]. Therefore, withdrawal of antiepileptic drugs in patients with symptomatic or cryptogenic epilepsy is less likely to be successful [8,14,16,23,24]. In one study, the relapse rate in patients with symptomatic epilepsy was 45%, compared with 25% in those with idiopathic epilepsy [27].

### 2.5.3. Epilepsy Syndrome

Selected epilepsy syndromes (e.g. benign epilepsy with centrotemporal spikes and juvenile myoclonic epilepsy) may be associated with significantly different outcomes after treatment withdrawal. For example, benign childhood epilepsy with centrotemporal spikes, childhood absence epilepsy, and benign neonatal convulsions are associated with a favorable outcome for antiepileptic drug withdrawal [34,35]. Absence seizures were shown to be a good prognostic factor for withdrawal in some studies [22,27], although the prognosis is not as favorable as in benign childhood epilepsy with centrotemporal spikes. In one study, medication was successfully withdrawn from 57% of patients with childhood absence epilepsy, in contrast to more than 90% of patients with benign childhood epilepsy with centrotemporal spikes from whom medication was successfully withdrawn [36]. However, the underlying etiologic classification may be misleading in some cases. For example, in juvenile myoclonic epilepsy, a relatively common idiopathic epilepsy syndrome, the relapse rate associated with withdrawal is

prohibitively high, and antiepileptic drug discontinuation is generally discouraged [37]. However, a recent population based long term follow up study has questioned this long-held believe [38].

### 2.5.4. Previous Response to Antiepileptic Drug Treatment

Two unfavorable signs for eventual AED withdrawal are the continuation of seizure activity after treatment is initiated and multiple seizures that occurred before seizure control [22]. Similarly, taking more than one medication at the time of withdrawal is a poor prognostic risk factor [22,23]. Related to this is the observation that the rate for success is proportional to the duration of seizure freedom before withdrawal [22,28]. Patients with juvenile Myoclonic epilepsy, again, are an exception, since the initial response to medication is typically favorable in these patients, and a prolonged seizure-free duration may belie the high rate of relapse associated AED withdrawal.

### 2.5.5. Age at Onset

Age at onset was identified as an important risk factor in several studies. Seizure onset before age 10 to 12 years portends a favorable prognosis, whereas onset after this age range indicates a higher rate of relapse [27]. Age at onset is probably a surrogate marker for certain etiologies and epilepsy syndromes. For example, the peak age at onset of benign childhood epilepsy with centrotemporal spikes is younger than 10 years, whereas the mean age at onset of juvenile myoclonic epilepsy, a condition with a poor prognosis for withdrawal as, previously discussed, is 14.2 years [37].

### 2.5.6. Neurologic Deficits and Mental Retardation

The presence of mental retardation and other neurologic deficits was shown to be an unfavorable risk factor in some studies [29,39]. These factors tend to correlate with the presence of an underlying pathology in the brain and thus may serve as a surrogate marker for symptomatic epilepsy, which is, as previously discussed, associated with a relatively poor prognosis. The type of neurologic abnormality, however, may be more important than the mere presence of one. For example, in a study in which antiepileptic drug withdrawal was evaluated in patients with cerebral palsy, the relapse rate was higher in patients with hemiplegia (62%) compared with patients with spastic diplegia (14%) [40]. Of note, mental retardation is not a contraindication to antiepileptic drug withdrawal because some studies have shown success in patients with mental retardation [41]. In fact, such patients may particularly benefit from the elimination of unnecessary sedating medications if other risk factors for relapse are absent [42-44].

### 3. THE ROLE OF EEG IN SELECTING PATIENTS FOR ANTIEPILEPTIC DRUG WITHDRAWAL

The role of EEG in antiepileptic drug withdrawal is controversial. Although an abnormal EEG before drug withdrawal was a negative prognostic factor in many studies [24,25,28], the predictive value of EEG has not been confirmed universally [11,20,28]. In one study, patients with an abnormal EEG before drug withdrawal were twice as likely to relapse than were patients with a normal EEG [25].

However, these results have not been replicated in other studies.

For example, the relapse rate in patients with an abnormal EEG before drug withdrawal in another study was 47%, compared with a 33% relapse rate in patients with a normal EEG [45]. Although this difference was statistically significant, the clinical significance is questionable, given the inconclusive absolute difference in relapse rates in these 2 groups. Clearly, factors other than the EEG need to be considered when deciding whether to withdraw antiepileptic medication. Several factors account for the limited predictive value of the EEG before drug withdrawal. Epileptiform EEG activity may be suppressed by medication in some patients, which may lead to a false-negative result. The “normalizing” effect of the different antiepileptic medications varies. Phenytoin, carbamazepine, and phenobarbital may marginally affect the presence of abnormalities on the EEG, whereas valproic acid is believed to have a more substantial effect, at least in patients with idiopathic generalized epilepsy syndromes. In some patients, EEG abnormalities may not occur until medication is reduced, which may have prognostic value in patients during withdrawal. In one study, relapse occurred in 83% of patients in whom EEG worsened during dose reduction, compared with a relapse occurrence of 54% in patients in whom EEG remained unchanged [46]. Other studies have corroborated these observations [47]. Thus, the normalizing effect of medication seen in some patients may limit the usefulness of the EEG before drug withdrawal as an a priori tool in patient selection. Another factor affecting the predictive value of the EEG relates to the limited sensitivity of EEG in the epilepsy population in general. In one study involving a large population of US veterans with predominantly partial seizures, diagnostic EEG abnormalities were present in only 29% of patients on the initial recording. The yield increased to 59% after 3 or more EEGs [48]. The yield of EEG in the general epilepsy population has been reported to be higher in other studies. For example, in one study based at a tertiary center, the sensitivity of the EEG was found to be 82% [49]. This inherent limitation in the sensitivity of EEG affects its predictive value in selecting patients for antiepileptic drug withdrawal. A normal EEG

before drug withdrawal does not guarantee a seizure-free outcome, especially in the presence of other unfavorable prognostic factors. However, an abnormal EEG can serve as compelling evidence against drug withdrawal in a patient who remains unconvinced despite the presence of other negative risk factors. As indicated previously, serial EEG recordings may be useful for monitoring patients after drug withdrawal [47].

#### 3.1. Rate of Taper

In a Cochrane review [50] assessed the comparative effects of slow versus rapid AED withdrawal. Only one trial that was done in children satisfied the selection criteria. In that study, no differences were found in the risk of relapse comparing the rapid (6 weeks) to the slow (9 months) taper group. However, in view of the methodological deficiencies and small sample size in the solitary study identified, the authors could not derive any reliable conclusions regarding the optimal rate of tapering of AEDs [51].

#### 3.2. Seizure Control after Relapse

In a systematic review of 13 studies, seizure recurrence rate after AED discontinuation ranged between 12% and 66% (mean 34%, 95% CI 27 - 43) [52]. In these cases, reinstatement of AEDs brought to seizure remission in 64% - 91% (mean of 14 studies, 80%, 95% CI 75% - 85%) after a mean follow-up ranging from 1 to 9 years, with no differences between children and adolescents (84%, 95% CI 75 - 93) and adults (80%, 95% CI 74 - 86). Although seizure control was regained within approximately 1 year in half of the cases becoming seizure free, some patients regained seizure control in as many as 5 - 12 years. Factors associated with poor outcome after treating recurrences were symptomatic etiology, partial epilepsy, and cognitive deficits. Interestingly, a better seizure outcome was not predicted by resumption of AEDs [24]. In the MRC Antiepileptic Drug Withdrawal trial the risk of recurrence was also similar in patients who relapsed after withdrawal of AEDs and in those who relapsed while remaining on treatment.

#### 3.3. Recommended Groups to Offer Antiepileptic Drug Withdrawal

AED withdrawal should be considered for children after a reasonable seizure-free period if favorable prognostic factors are present [36]. In addition, drug withdrawals should be considered in children with a favorable epilepsy syndrome, such as benign childhood epilepsy with centrotemporal spikes, childhood absence epilepsy, and benign neonatal convulsions. Also, drug withdrawal should be considered in children whose condition does not fit into these defined epilepsy syndromes



if important risk factors for relapse are absent. On the other hand, in the adult population, the decision to withdraw treatment is more complicated. Unlike with children, adult syndromes with a high likelihood of remission have not been defined. Nonetheless, it is clear that medications can be successfully withdrawn from some adults. In the few clinical studies concentrating on the adult population, success rates from 34% to 77% have been reported [22,23,46]. In adult patients, risk is weighed on the basis of the number and type of risk factors present and the potential consequences of a seizure, given the patient's life circumstances. In all patients, a careful assessment of all risk factors, the likely benefit to be achieved from drug withdrawal, and the possible effects of seizure recurrence on employment and quality of life must be carefully weighed when making a final recommendation.

#### 4. CONCLUSION

AED discontinuation requires a careful risk-benefit assessment in view of the undeniable risks involved. These risks include difficulties to predict individual seizure outcome after discontinuation, frequent seizure recurrence, particularly in high-risk patients, and the often grave consequences of seizure recurrence. In addition, successful treatment of seizure recurrence is neither invariably immediate nor assured. Physician may prudently refrain from encouraging AED discontinuation in high-risk patients. However, before withdrawing AEDs, patients should be counseled about their individual risk for relapse and the potential implications of a recurrent seizure, particularly for safety and driving.

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