

Clinical guide: discontinuing chronic antiepileptic drug treatment

María del C. Loy-Gerala¹, Octavio M. Ibarra-Bravo², María del R. Márquez-Estudillo³, Francisco Mena-Barranco⁴, Francisco J. Rogel-Ortiz⁵, Sandra E. Silva-Sánchez⁶, Hilda Villegas-Peña⁷ and Avril Molina-García⁸

¹Hospital General de Puebla "Dr. Eduardo Vázquez Navarro" SSA, Puebla; ²Hospital General "Dr. Miguel Silva", Morelia, Michoacán; ³Hospital Regional de Alta Especialidad, ISSSTE, Puebla; ⁴Hospital General ISSSTE, La Paz, Baja California Sur; ⁵PPE, Veracruz, Veracruz; ⁶Hospital Central Universitario, Chihuahua, Chihuahua; ⁷PPE Guadalajara, Jalisco; ⁸Hospital Infantil de Especialidades, Chihuahua, Mexico City, Mexico

Abstract

The decision to continue or withdraw the antiepileptic drugs (AEDs) should be taken jointly by the patient, family and/or caregivers, and the specialist physician, after extensive information and discussion about the risks and benefits of withdrawing the AED. The patient and family members must understand that there is a risk of the recurrence of seizures with and without AED. The type of epilepsy, the prognosis, and the patient's lifestyle should be taken into account. Withdrawal should be carried out under the supervision of a specialist (clinical neurologist) and will be considered when the patient has been seizure free for at least 2 years. The treatment must be withdrawn gradually for a period of at least 2-3 months and the antiepileptics must be removed one by one. Withdrawal of benzodiazepines and barbiturates should be slower, in 6 months or more. An agreement must be made that in the event of a seizure relapse, the patient must return to taking the last dose before the dose in which the relapse was presented and request assessment by clinical neurologist.

Key words: Withdraw. Antiepileptic drugs. Stop antiepileptic drugs.

Question 1. How long must the patient be seizure free before considering antiepileptic drug (AED) withdrawal?

In 1996, the American Academy of Neurology proposed a guide for discontinuing antiepileptics in patients that are seizure free, with the following criteria: seizure free after 2-5 years of treatment, only one type of epilepsy, normal neurological examination, and a normal electroencephalogram (EEG)¹. There have been very few changes with respect to the previous proposal.

There are a number of prospective studies and meta-analyses in this respect, but there has not been a uniform consensus about how long the patient must be in remission before treatment can be discontinued; these studies propose from 1 to 5 years of remission²⁻⁸. The risk of recurrence is greater when the epileptic seizure-free period before discontinuing the medication is <2 years than when it's longer⁹. For patients that have been seizure free for 2 or more years, the risk of recurrence after discontinuing medications is lower; the longer the patient has been seizure free. Furthermore, the

Correspondence:

María del Consuelo Loy-Gerala
Hospital General de Puebla "Dr. Eduardo Vázquez Navarro", SSA
Puebla, Mexico City, Mexico
E-mail: marialoy1@gmail.com

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risk of recurrence is lower for patients that did not have a seizure after beginning their treatment with AEDs².

Various studies have demonstrated that one of three patients relapse within a period of 2 years after suspending antiepileptics. The risk of seizure recurrence in the same period of time is 2 or 3 times that observed for patients that remain on AEDs. The 2015 Cochrane review¹⁰ of randomized controlled trials about epileptic drug withdrawal defines withdrawal of antiepileptics after < 2 years of treatment as “early withdrawal” and “late withdrawal” when they are discontinued after 2 years of treatment. The seizure-free period for children necessary to consider antiepileptic withdrawal is considerably shorter compared to that of adults and depends on the epileptic syndrome. This is true for those cases with favorable evolution, such as benign childhood epilepsy and Rolandic epilepsy¹¹. In these cases, treatment can be suspended after a maximum of 1 year¹².

Recommendation	Level of recommendation and level of evidence
Consider withdrawing medication in patients with at least 2 years in complete seizure remission.	Evidence level 1 Recommendation level A

Question 2. What are the risk factors for recurrence of epileptic seizures after AED withdrawal in pediatric patients?

- Generalized non-motor absence seizures: 20-30% relapse.
- Focal seizures: 44% relapse. Focal seizures with diminished awareness have greater risk of relapse.
- Juvenile myoclonic epilepsy: recurs in 33-78%, only 25-26% can undergo treatment withdrawal.
- West, Lennox-Gastaut, and Dravet syndromes have a high risk of recurrence.
- Other factors:
 - Symptomatic epilepsies: 41-42% risk
 - Neurological anomalies present at birth.
 - Average of five seizures per year: 68% relapse
 - Prolonged seizures
 - History of febrile seizures has 2 times the risk of relapse.
 - Prolonged epilepsy before remission.
 - Age of onset of epilepsy younger than 2 or older than 12 years old.
 - ≥ 10 seizures before remission
 - Impaired neurodevelopment, intellectual quotient < 70
 - EEG with epileptiform activity before withdrawal.
 - < 2 years without seizures¹⁰

There are a few studies that show that female gender and family history of epilepsy are risk factors that increase the probability of relapse¹³⁻¹⁹.

Recommendations when faced with risk factors for recurrence of epileptic seizures in children	Level recommendation
Antiepileptic drugs can be suspended in cases of focal epilepsy and most generalized genetic epilepsies. Assess whether or not to withdraw treatment in generalized symptomatic or unknown cause epilepsies, juvenile myoclonic epilepsy, and partial symptomatic epilepsy, due to a high risk of relapse.	B
In children, the main risk factor is etiology. Continued treatment does not guarantee the absence of recurrence.	A
An abnormal electroencephalogram, age of onset of seizures, intellectual disability, abnormal neurological examination at birth, altered neuroimaging studies, family history of epilepsy, and febrile seizures, alone, should not be taken as justification to avoid suspending treatment if there are no other associated negative predictors.	B
Gender should not be an isolated factor to decide not to withdraw antiepileptic drug treatment.	C
Inform the patient that two or more epileptic drugs at the onset of withdrawal may be associated with increased risk of relapse. However, this does not contraindicate withdrawal.	C
The decision to stop or continue treatment does not depend on the type of drug that will be withdrawn.	C

Question 3. What are the risk factors for recurrence of epileptic seizures in adult patients after suspending antiepileptic?

There are multiple studies that assess the risk factors for recurrence of epileptic seizures in adults. In 2017, a predictive model for recurrence was published which described the most important factors⁹. This was based on multiple studies, considering that the methodology, the types of patients and types of epileptic seizures are very varied.

- Age. One study reported a greater possibility of remission when withdrawing AED at an older age ($p = 0.02$), finding remission in 45% of the patients. Various other studies demonstrated that the earlier the age of onset of epilepsy before the period of control of seizures, the greater the risk of recurrence, as well as a greater risk of recurrence when the age of onset is late infancy or adolescence^{1,9,16,20}.

- b. Mental retardation. An intelligence quotient < 70 and motor deficits are independent predictors of recurrence^{16,20}.
- c. Abnormal neurological examination. A 15% seizure recurrence is reported during the 1st month in patients with abnormal neurological examinations^{21,22}.
- d. Abnormal interictal encephalogram (EEG). The presence of an abnormal EEG before AED withdrawal or during the 1st year after AED withdrawal indicates greater risk of recurrence^{1,22,23}.
- e. Focal and generalized symptomatic tonic-clonic epilepsies have a greater risk of recurrence^{9,20}.
- f. Age of onset of epilepsy^{9,20}.
- g. Family history of epilepsy. Increased risk of recurrence^{9,20}.
- h. Number of AEDs. The greater the number of AED, the greater the risk of recurrence after withdrawal^{9,20}.

Recommendation	Level of recommendation and level of evidence
For patients with epilepsy that has been seizure free for >2 years, without risk factors, the gradual withdrawal of antiepileptic drugs is recommended. The decision should be made in conjunction with the patient and/or the caretakers.	Evidence level 1 Recommendation level B
For patients with epilepsy that has been seizure free for >2 years, with risk factors, the risk/benefit of AED withdrawal should be assessed.	Evidence level 1 Recommendation level A

Question 4. What are the risk factors for recurrence of epileptic seizures after withdrawing AEDs in patients following epilepsy surgery?

In 2011, a prospective study was published with 311 patients after mesial temporal epilepsy surgery, who underwent AED withdrawal after being seizure free between 3 months and 1 year. The results showed that the absence of hippocampal sclerosis and the presence of interictal discharges in the EEG were independent predictors of seizure recurrence²⁴. The majority of studies report the same requirement of 1-2 years seizure free, without increase in recurrence in up to 10 years of follow-up^{25,26}. A Class II, prospective, randomized study published in 2009, which included post-surgical patients that were seizure free for 1 year demonstrated a greater rate of recurrence for patients with hippocampal sclerosis compared with those with lesional epilepsy²⁷. The only work that included extratemporal surgery is a retrospective study with 106 patients diagnosed with

epilepsy that presented evident lesions by magnetic resonance imaging, which evidenced greater risk for older patients, longer course of epilepsy, abnormal post-operative EEG, early post-operative seizures, gliosis or cortical focal dysplasia, and interictal discharges in the EEG and during the 1st year after surgery²⁸.

The largest study in pediatric population is a European multicentric, retrospective, uncontrolled study that included 766 patients under 18 years of age that was seizure free after surgery (temporal and extratemporal) who were subjected to AED withdrawal. Results showed a seizure recurrence of 12%, and of these patients, 30% did not achieve seizure control after reintroducing medication²⁹.

Good prognosis	Bad prognosis
Surgery at an early age	Surgery after 30 years of age
Hippocampal sclerosis	Long-term epilepsy
Anterior temporal lobectomy	Normal anatomopathological examination
Seizure free for 1-2 years after surgery	Neocortical resection

Question 5. What is the usefulness of an EEG to decide on AED withdrawal?

Although there are no examinations that are completely reliable to predict the recurrence of seizures, many studies have demonstrated that abnormalities in the EEG, before or after AED withdrawal, increase the risk of recurrence^{15,16}. A recent meta-analysis reported that the presence of EEG paroxysms before AED withdrawal predicts a high percentage of recurrences (Table 1)²³.

Recommendation	Level of recommendation and level of evidence
In patients that are seizure free but show paroxysmal EEG patterns and other risk factors, AED withdrawal is not recommended due to a high risk of recurrence.	IA

Question 6. What are the probabilities of the recurrence of epileptic seizures for patients undergoing AED withdrawal?

The probability for seizure recurrence after stopping treatment varies among different studies and oscillates from 20% to 46%⁹. Different studies have found risk factors that significantly impact the probability of recurrence. These risk factors are as follows: duration of epilepsy before achieving control, total number of seizures (fewer or more than 10), time in remission, age at seizure onset

(with a discreetly greater risk when epilepsy begins in adolescence or adulthood), intellectual quotient < 70, abnormal EEG at the time of AED withdrawal, remote symptomatic epilepsy (defined as epilepsy caused by an old brain lesion), absence of an epileptic syndrome related to age, and history of febrile seizures^{13-19,30-32}.

These risk factors have different prognostic weight. The most important are as follows: duration of epilepsy, total number of seizures, intellectual disability, remote symptomatic epilepsy, and absence of an autolimited epileptic syndrome. Tables that assign a numeric value for each of these risk factors have been developed⁹. The information found in these tables is simple: the greater the high significance risk factors, the greater the risk of seizure recurrence (Level I).

Regarding epilepsy of genetic origin, it must be pointed out that juvenile myoclonic epilepsy has a very high risk of recurrence after treatment withdrawal (Relative Risk RR: of 70 up to 95%), even after very long periods of remission^{33,34}. It's very important that the patient receives clear information during the decision-making process (R-PPE) (Level I).

Question 7. How should AED be withdrawn?

There is no clear consensus among different studies that analyze this aspect since the period of time proposed for AED withdrawal varies from 4 weeks to 12 months. In a controlled randomized study with 149 children, no differences were found with regard to recurrence of seizures when AEDs were withdrawn in a period between 6 weeks and 9 months. In another study involving 56 children, no differences in RR were found after assessing periods of AED withdrawal lasting 1-6 months. Finally, another study with 216 children that assessed AED withdrawal periods of 4-6 weeks versus 4-6 months also did not find significant differences in RR. Thus, we recommend gradual withdrawal of AED in an interval of 4-6 months^{35,36}.

Recommendation	Level of recommendation and level of evidence
Gradual withdrawal of AED in an interval of 4-6 months is recommended	Level of evidence 2 Level of recommendation: PPE consensus

Question 8. What other risks, besides recurrence, are there when withdrawing AEDs?

In addition to the risk of recurrence, other factors must be considered: adverse effects of the drugs, risk

of physical lesions or death, quality of life, and social and psychological problems. Always consider the risk of losing a driver's license or a job, since this is a determinant factor for some adults^{1,37}.

A prospective study found that after AED withdrawal and relapse of epileptic seizures, there is little risk of epileptic seizures resistant to treatment. This risk corresponds to 1%, compared to 97% of recurring after treatment is reinitiated. A review from 2005 reported treatment refractory epilepsy in 19% of the patients that had previously undergone treatment withdrawal, which was associated with a symptomatic etiology, location of the epilepsy, and abnormal neurological examinations. In some patients with controlled epilepsy and associated comorbidity, this can be increased under AED withdrawal since valproic acid and lamotrigine are indicated for stabilizing emotional states, as in bipolar disorder, and topiramate is also used as prophylactic treatment for migraines^{17,37}.

Relapse of epileptic seizures after AED withdrawal may have psychosocial repercussions and important financial effects. Depending on the legislation regulating the area where the patient resides, this situation indicates that he will be restricted from driving for a period of 3-12 months, as well as a greater risk of having epileptic seizures during work, and repercussions on quality of life and social stigma since everyday activities may have to be modified²².

Question 9. What are the benefits of withdrawing epileptic drugs?

AEDs are associated with long-term adverse effects that may include cognitive and behavioral alterations. Suspending antiepileptics can benefit persons in long-term remission if the benefit of withdrawing treatment is greater than the alterations caused by taking the antiepileptics.

Some of these effects are attention reduction, alterations in memory and mood, and depression. In addition, they can cause problems in daily activities resulting in an affected quality of life, although these may be slight. Their daily, chronic use offers other risk factors such as teratogenesis, possibility of infertility in males, interactions with other drugs and long-term toxicity, and pseudodementia as can be caused by phenytoin, even at therapeutic doses. Conversely, seizure recurrence can also be devastating from the emotional point of view, and in social life, there is risk of losing work and autonomy, and especially for obtaining a driver's license¹.

Table 1. Prognostic factors for recurrence after epileptic surgery

Recommendation	Level of recommendation and level of evidence
Considering withdrawal of AED is recommended for patients having had epilepsy surgery, after 1-2 years seizure free with good prognostic factors.	Level of evidence II Level of recommendation B
In patients with bad prognostic factors, seizure free for 1-2 years, withdrawal of AED is not recommended after epilepsy surgery.	Level of evidence II Level of recommendation C

Taking AEDs imply a continuous economic expense for the individual and their families, as well for the public health system, when they are administered unnecessarily (World Health Organization, 2012). Therefore, when epilepsy is in remission, withdrawing antiepileptics can favor quality of life¹⁷.

In general, cognitive function is improved. In a prospective, placebo-controlled, double-blind study, 139 patients that were seizure free for at least 2 years, underwent neuropsychological tests before and after AED withdrawal finding better performance after stopping treatment. In addition, there were lower levels of depression and irritability after withdrawing the medication²².

In a retrospective study that included 766 patients under 18 years of age, with pre- and post-surgical neuropsychological assessment and at least 1 year after AED withdrawal, results showed that withdrawal of phenobarbital and primidone was associated with an increase in intellectual quotient of 10 or more points. The fact of reducing the doses of antiepileptics and complete withdrawal of the drugs predicted better results in psychometric tests compared to children that continued their antiepileptic treatment before surgery. Verbal memory developed better in children that underwent drug withdrawal. These cognitive and behavioral effects were also observed with the new AEDs^{38,39}.

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