

Antiepileptic drugs withdrawal in children: An update.

Operto FF^{1*}, Mazza R², Pastorino GMG¹, Amadori E¹, Aiello S³, Campanozzi S², Verrotti A⁴, Matricardi S⁵.

¹Child and Adolescent Neuropsychiatry Unit, Medical School, University of Salerno, Italy.

²Child Neuropsychiatry Unit, Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari "Aldo Moro", Italy.

³Department of Translation Medical Sciences, University of Naples Federico II, Italy.

⁴Department of Pediatrics, University of L'Aquila, Italy

⁵Department of Neuropsychiatry, Children's Hospital "G.Salesi", Ospedali Riuniti Ancona, Italy.

Abstract

Background: Stopping antiepileptic drugs is routinely done in patients who have epilepsy in remission. However, in literature there are no unique data that can lead to the constant application of a universally accepted suspension protocol.

Methods: In this manuscript, our purpose was to revise literature scientific articles of the last 10 years concerning antiepileptic drugs withdrawal in pediatric age.

Results: At the time of suspending antiepileptic treatment, it is necessary to consider three main questions: 1) why suspend therapy; 2) when and to which patients suspend it; 3) how to discontinue treatment. Therapy is suspended when it is no longer necessary, for concerns related to toxicity/side effects of antiepileptic drugs (behavioral, cognitive and chronic side effects) and since the remission of ongoing therapy seizures is possible in the 65-85 % of patients.

Conclusion: In order to decide when and to which patients withdraw antiepileptic drugs, it is necessary to consider factors related to patients themselves, to characteristics of epilepsy and to the specific pharmacological treatments.

Keywords: Childhood epilepsy, Remission, Therapy, Withdrawal.

Accepted on April 25th, 2019

Introduction

Epilepsy is a condition in which the brain becomes capable of generating spontaneous seizures. In around two-thirds of epileptic patients, these seizures can be suppressed with the use of antiepileptic drugs (AEDs) [1]. Stopping AEDs is routinely done in patients who have epilepsy in remission. However, in literature there are no unique data that can lead to the constant application of a universally accepted suspension protocol. At the time of suspending antiepileptic treatment, it is necessary to consider three main questions: 1) why suspend therapy; 2) when and to which patients suspend it; 3) how to discontinue treatment.

Regarding to question 1: it is obvious that the therapy is suspended when it is no longer necessary; for concerns related to toxicity/side effects of antiepileptic drugs (behavioural, cognitive and chronic side effects); since the remission of ongoing therapy seizures is possible in the 65-85 % of patients [2], with percentage of recurrences, after complete suspension of treatment, which is around 23.7 % in children [3].

In order to decide when and to which patients withdraw

antiepileptic drugs, it is necessary to consider factors related to patients themselves, to characteristics of epilepsy and to the specific pharmacological treatments. The minimum period of seizure freedom before stopping AEDs has been indicated in 2 years by most studies [4]. In clinical practice and in literature tapering periods varies between 1 month and >4 years [4]. Surely there is a shared opinion on the slow discontinuation. Hence there is a need for reliable criteria to correctly identify patients to which withdraw therapy in the right way, by running the least possible risks. In this manuscript, our purpose was to revise literature scientific articles of the last 10 years concerning AEDs withdrawal in pediatric age.

Methods

In this manuscript, we have revised literature scientific articles in PubMed, selecting the articles of the last 10 years concerning antiepileptic drugs withdrawal in pediatric age. We have also expanded the topic using the guidelines provided by ILAE (International League Against Epilepsy) and LICE (italian league against epilepsy) and by enriching it with our knowledge derived from daily clinical practice in epileptic pediatric population.

Observations and Discussion

Outcome in children after stopping AEDs

The risk of seizure recurrence after stopping AEDs in children with epilepsy in clinical remission has been well reviewed in literature.

Children with seizure relapse during or after treatment withdrawal range from 12 to 66%. The probability of remaining seizure-free in children is estimated to be 66-96% at one year and 61-91% at two years, with a highest relapse rate in the first year (especially in the first 6 months) after discontinuation starts [5]. Thereafter the probability of seizure recurrence tends to decrease with increasing time without seizures.

Factors influencing prognosis after AEDs withdrawal

Factors influencing the overall risk of seizure relapse after treatment discontinuation has been well reviewed in the literature. However, there is no general agreement. Predictors for seizure recurrence after stopping AEDs can be divided into factors related to patients (Table 1), factors related to epilepsy (Table 2) and factors related to therapy (Table 3).

Factors related to patients: Neuropsychiatric conditions:

Other neuropsychiatric conditions have to be all considered as possible factors influencing the overall risk of seizure recurrence.

Olmez et al. in 2009 found that abnormal neurological examination, intellectual disability of varying degree and history of febrile seizures are not related to the risk of seizure recurrence [6,7].

According to Ramos-Lizana [6], patients with global developmental delay or intellectual disability have a higher risk of seizure recurrence after AEDs withdrawal, as well as patients with a history of prior neonatal or febrile seizures. These findings are consistent with another study of the same year [8], in which the presence of intellectual disability in patients discontinuing AEDs was associated with a higher risk of relapse, compared with patients who had normal mental status.

Factors related to epilepsy: Absence of a known etiology:

Olmez et al. in 2009, stated that epilepsy etiology, either symptomatic-cryptogenic or idiopathic, was not a possible risk factor for seizure relapse after AEDs withdrawal [7]. On the contrary, in 2010, Ramos-Lizana found that recurrence risk was low for benign childhood epilepsy with centrotemporal spikes, benign infantile seizures,

childhood absence epilepsy, West syndrome and epilepsy without unequivocal partial or generalized seizures; instead it was high for remote symptomatic generalized and partial epilepsies and intermediate for cryptogenic partial epilepsies and Panayiotopoulos type. In the opinion of the Authors etiology is the main predictive factor for recurrence, so that the absence of a known etiology is an important element of doubt about the risk of recurrence [6].

Other studies in literature found a higher risk of recurrence in patients with symptomatic partial epilepsies, compared to patients with symptomatic/cryptogenic generalized ones [9]. In the same year Vurucu et al. found that relapse rate was higher in symptomatic epileptic patients, compared with idiopathic epileptic ones, even if the difference was not statistically significant, whereas the same Authors did not find any difference between patients with generalized and partial epilepsy [8].

According to ILAE (Italian League Against Epilepsy) Guidelines [4], a patient with a documented epilepsy etiology, should be informed of an increased risk of relapse, but he/her should not continue treatment if it is the only negative prognostic factor. In a more recent study [10], symptomatic partial epilepsy was found to be a significant risk factor related to seizure recurrence.

Age of seizures onset: In literature, results from studies about the age of onset of seizures are controversial. Most old studies in literature have found that epilepsy with onset in childhood has a more favorable prognosis than epilepsy with onset in adolescence. In 2010, Ramos-Lizana showed only a non-significant trend toward a higher recurrence risk in children older than 10 [6]. This finding is consistent with another study by Vucuru et al. [8], in which authors found that an age of epilepsy onset >5 years is an important risk factor for seizure recurrence, whereas children who had the first seizure before 6 year-old had lower seizure relapse rates after AEDs withdrawal. More recently, Lee et al. found that recurrence was more frequent in children aged <2 years, compared to children older than 2 years of age at seizures onset [10]. According to Italian League Guidelines, these data suggest that patients with epilepsy onset in late childhood and adolescence are at higher risk of relapse [4].

Type of seizures/Presence of more types of seizures:

Evidences about the predictive value of seizure types are conflicting, probably because of the use of different classification criteria. Among old studies in literature, some of them consider an higher risk of recurrence for partial seizures, others for generalized ones.

Table 1. Factors related to patients.

Variables		Increased risk of recurrence		Decreased risk of recurrence
		Yes	No	
Factors related to patients (neuropsychiatric conditions)	Global developmental delay	Ramos-Lizana et al. [6]	--	--
	Intellectual disability	Ramos-Lizana et al. [6]	Olmez et al. [7]	--
	Abnormal neurological examination	Vurucu et al. [8]	Olmez et al. [7]	--
	History of febrile seizures	Ramos-Lizana et al. [6]	--	--
	History of neonatal seizures	Ramos-Lizana et al. [6]	--	--

Table 2. Factors related to epilepsy.

Variables		Increased risk of recurrence		Decreased risk of recurrence
		Yes	No	
Factors related to epilepsy	Absence of a known etiology	Ramos-Lizana et al.[6]	Olmez et al. [7]	
	Symptomatic epilepsy	Ramos-Lizana et al. [6]		
		Geerts et al. [9]		
		Vurucu et al. [8]		
		Lee et al. [10]		
	Age at seizures onset	>10 years: Ramos-Lizana et al. [6]	--	<6 years: Vurucu et al. [8]
		>5 years: Vurucu et al. [8]		
		<2 years: Lee et al. [10]		
		Late childhood/adolescence: Italian League Guidelines [4]		
	Presence of different types of seizures	Ramos-Lizana et al. [6]	Olmez et al. [7]	
	Types of seizures	Generalized seizures: Pavlovic et al. [11]	Partial seizures: Ramos-Lizana et al. [6]	
	Number of seizures before remission	>5 seizures: Vurucu et al. [8]	Italian League Guidelines [4]	
	Presence of status epilepticus	Lee et al. [10]		
	Duration of seizure-free period before remission		Ramos-Lizana et al. [6]	>3 years: Olmez et al. [7]
Relationship between seizures and the sleep-wake rhythm	No data			
Duration of epilepsy	No data			
Abnormal EEG	Ramos-Lizana et al 2010 [6]			
	Generalized abnormalities: Vurucu et al 2010 [8]			
	Su et al. [12]			
	Focal slow abnormalities: Lee et al.[10] Paroxysmal abnormalities: Tang et al. [13]			

Table 3. Factors related to therapy.

Variables		Increased risk of recurrence		Decreased risk of recurrence
		Yes	No	
Factors related to therapy	Type of drug used at the time of suspension	No data		
	Number of medications used before remission	Polytherapy: Vurucu et al. [8] 2 or more drugs: Italian League Guidelines [4]	--	--
	Blood level of drugs at the time of suspension	No data		

Olmez et al. in 2009 did not find any significant difference according to different seizure types, as regard to risk of recurrence [7]; whereas Ramos-Lizana found that various seizure types significantly increase recurrence risk, except for partial seizures [6]. Generalized tonic-clonic seizures, with or without myoclonic or absence seizures, predicted an

increased risk of seizure relapse in children and adolescents [11].

According to Italian League Guidelines [4], seizures type should be assessed along with all other patient's variables when the decision to stop treatment is taken.

Number of seizures before remission: To our knowledge, only one recent report in literature has assessed the role of the number of seizures before remission as predictor for seizure recurrence. According to Vucuru et al. [8], the total number of seizures (more than 5 seizures) can be considered a relevant factor. Nevertheless, according to Italian League Guidelines, high seizure frequency before entering remission should not be a contra-indication to treatment discontinuation [4].

Relationship between seizures and the sleep-wake rhythm: In literature there are no recent studies assessing the possible relationship between seizures and the sleep-wake rhythm as predictor of seizure recurrence after AEDs discontinuation.

Presence of status-epilepticus: A history of status epilepticus as a predictive factor of seizure recurrence after discontinuing AEDs is little investigated. In a recent follow-up study, Lee et al. indicate that a history of status epilepticus might lead to seizure recurrence, more than patients without it [10].

Duration of epilepsy: To our knowledge, no recent studies in literature investigated the possible role of the duration of epilepsy as predictor of seizure relapse after AEDs withdrawal.

Duration of seizure-free period before remission: Olmez et al. in 2009 found that a seizure-free period of more than 3 years is an important factor associated with a lower risk of relapse [7]. According to Ramos-Lizana [6], time to seizure control was not a significant predictor of recurrence.

EEG: The role of EEG abnormalities has been investigated by a number of groups, with contrasting evidence. In 2008, Lossius et al. did not support any prognostic role of epileptiform EEG abnormalities [14]. In 2010, also Ramos-Lizana found only a non-significant trend toward a greater recurrence risk in patients with an abnormal EEG [6].

On the contrary, according to Olmez et al. abnormal EEG obtained after withdrawal was an important factor for predicting risk of recurrence [7]. In 2010 Vurucu et al. found that generalized abnormalities at last EEG before withdrawal were associated with a higher risk of relapse [8]. In 2013, Su et al. examined the role of epileptiform EEG abnormalities at the time of during, and 1 year after AEDs withdrawal. He found that epileptiform EEG abnormalities, both during and after AEDs withdrawal, were related to increased seizure recurrence risk [12].

In more recent studies, Lee et al. showed that an abnormal EEG, when discontinuing AEDs, was associated with an increased risk of seizure recurrence [10]; in particular, focal slow EEGs were greater in patients with seizure recurrence, but not significantly. Tang, in his meta-analysis, revealed that abnormal EEG and especially paroxysmal abnormalities, prior to drug suspension, predicted a high risk of seizure relapse [13].

Factors related to therapy: Type of drug used at the time of suspension: In literature there are no recent studies assessing the contribution of individual drugs on the relapse rate after treatment discontinuation; few old studies report mostly inconsistent results of Italian League in 2013 [4]. According to Italian League Guidelines, the decision to stop or withhold

AEDs in seizure-free patients should not be affected by the type of drug. In daily clinical practice, the commonest AEDs used in pediatric epilepsy are Valproate, Levetiracetam, Carbamazepine and Ethosuximide, depending on the clinical indications and the characteristics of each patient.

Number of medications used before remission: To our knowledge, in literature few recent reports assessed the correlation between relapse and the number of drugs at the time of withdrawal. In 2010, Vurucu et al. in their study involving 266 children discontinuing AEDs, found that the number of antiepileptic drugs taken, was the only significant risk factor for seizure recurrence, as the need for polytherapy was an important risk factor for seizure relapse after AEDs withdrawal [8]. This finding is consistent with Italian League Guidelines, according to which treatment with two or more drugs at the time of withdrawal may be associated with an increased risk [14]. On the contrary, according to Su et al. polytherapy is weakly associated with relapse [12].

Blood level of drugs at the time of suspension: In literature there are no recent studies assessing the role of blood level of AEDs at the time of suspension as risk factor for seizure recurrence.

When to stop AEDs

In literature, the optimal duration of the seizure-free period before AEDs withdrawal is controversial. Most studies indicate the minimum period of seizure freedom in 2 years [15,16]. Some studies, conducted on children, considered a 1-year seizure-free period and even 6 months [17], because of the lower risk to incur in social complications in case of seizure relapse, than in adults [4]. According to Italian League guidelines, seizure-free period shorter than 2 years can be considered in children because of a marginally higher risk of seizure recurrence [4]. Some Authors state that stopping AEDs early is not recommended as a standard practice in children, even in those children who rapidly respond to treatment [10]; whereas others believe that it is necessary to stop medication after a 2-years seizure-free period [18].

According to Schmidt et al. [5], continuing AED treatment after a seizure-free period of 2 years, does not guarantee lifelong seizure remission not only in adults but also in children; in addition, stopping AEDs exposes patients to a transient two-fold risk of seizures for the next 2 years. Authors argue that the decision to withdraw or to withhold treatment should be individualized and, in a conservative approach, withdrawal should be encouraged only in children with benign idiopathic epilepsy and absence epilepsy.

Lamberink et al. recently stated that the usual practice of stopping AEDs after 2 years without seizures is an outdated and artificial construct and should be discarded in favour of an individualized approach, only after a thorough examination of all risks and benefits for each patient [19].

How to stop AEDs

In literature there is also controversy about how to stop AEDs in children, especially about the optimal duration of the tapering period [6]. Few studies focused on the mechanism for withdrawing AEDs. In clinical practice it is relatively

intuitive that to abruptly discontinuing AEDs can cause an increased risk of seizure recurrence or even status epilepticus [17]. In the 2010 Cochrane review, the range of tapering period for children was from 4 weeks to 1 year [16-19]. According to Italian League guidelines [4], clinicians should encourage slow discontinuation of AEDs and the duration of tapering period should be tailored to the patient's needs and preferences.

Conclusion

The decision to withdraw AEDs in seizure-free patients is a difficult one and must be based on a full balanced view of the overall risk of seizure relapse. A thorough review of the medical record and history is necessary to identify all risk factors present for a patient. The patient and family should be informed regarding the patient's individual risk, but also reassured about the good prognosis of their children. In daily clinical practice, AEDs discontinuation is usually done very gradually, over several months, also based on parental anxiety and always prescribing also Micropam or Buccolam in case of unexpected recurrence of a seizure.

References

- French JA. Withdrawal of anti-epileptic drugs: An individualized approach. *Lancet Neurol.* 2017; 16: 493-494.
- Shorvon SD, Goodridge DMG. Longitudinal cohort studies of the prognosis of epilepsy: Contribution of the National General Practice Study of Epilepsy and other studies. *Brain.* 2013; 136: 3497-510.
- Incecik F, Herguner OM, Altunbasak S, et al. Risk of recurrence after discontinuation of antiepileptic drug therapy in children with epilepsy. *J Pediatr Neurosci.* 2014; 9: 100-104.
- Beghi E, Giussani G, Grosso S, et al. Withdrawal of antiepileptic drugs: Guidelines of the Italian League against epilepsy. *Epilepsia.* 2013; 54: 2-12.
- Schmidt D, Sillanpa M. Stopping epilepsy treatment in seizure remission: Good or bad or both? *Seizure.* 2017; 44: 157-161.
- Ramos-Lizana J, Aguirre-Rodríguez J, Aguilera-López P, et al. Recurrence risk after withdrawal of antiepileptic drugs in children with epilepsy: A prospective study. *Eur J Paediatr Neurol.* 2010; 14: 116-124.
- Olmez A, Arslan U, Turanli G, et al. Risk of recurrence after drug withdrawal in childhood epilepsy. *Seizure.* 2009; 18: 251-256.
- Vurucu S, Saldır M, Unay B, et al. Determination of Risk Factors Associated with Seizure Relapse after Antiepileptic Drug Withdrawal. *Cent Eur J Med.* 2010; 5: 251-256.
- Geerts A, Arts WF, Stroink H, et al. Course and outcome of childhood epilepsy: A 15-year follow-up of the Dutch study of epilepsy in childhood. *Epilepsia.* 2010; 51: 1189-1197.
- Lee IC, Li SY, Chen YJ. Seizure recurrence in children after stopping antiepileptic medication: A 5-year follow-up. *Pediatr Neonatol.* 2017; 58: 338-343.
- Pavlovic M, Jovic N, Pekmezovic T. Antiepileptic drugs withdrawal in patients with idiopathic generalized epilepsy. *Seizure.* 2011; 20: 520-525.
- Su L, Di Q, Yu N, et al. Predictors for relapse after antiepileptic drug withdrawal in seizure-free patients with epilepsy. *J Clin Neurosci* 2013; 20: 790-794.
- Tang L, Xiao Z. Can electroencephalograms provide guidance for the withdrawal of antiepileptic drugs: A meta-analysis. *Clin Neurophysiol.* 2017; 128: 297-302.
- Lossius MI, Hessen E, Mowinckel P, et al. Consequences of antiepileptic drug withdrawal: A randomized, double-blind study (Akershus Study). *Epilepsia.* 2008; 49: 455-463.
- Camfield P, Camfield C. When is it safe to discontinue AED treatment? *Epilepsia.* 2008; 49: 25-28.
- Sirven J, Sperling MR, Wingerchuk DM. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. *The Cochrane Library.* 2010; 4: 1.
- Hixson JD. Stopping antiepileptic drugs: When and why? *Current Treatment Options in Neurology.* 2010; 12: 434-442.
- Li W, Si Y, Zou XM, et al. Prospective study on the withdrawal and reinstitution of antiepileptic drugs among seizure-free patients in west China. *J Clin Neurosci.* 2014; 21: 997-1001.
- Lamberink HJ, Otte WM, Geerts AT, et al. Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of anti-epileptic drugs in seizure-free patients: A systematic review and individual participant data meta-analysis. *Lancet Neurol.* 2017; 16: 523-531.

Correspondence to:

Francesca Felicia Operto,
Child Neuropsychiatry Unit,
Department of Basic Medical Sciences,
Neuroscience and Sense Organs,
University of Bari "Aldo Moro";
Piazza Giulio Cesare 11,
Bari, Italy
Tel: +39 080/5592829
Fax: +39 080/5595260
E-mail: operto francesca@gmail.com