Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2020;9(4):1065-71

Factors associated with seizure recurrence after antiepileptic drug withdrawal

Asli Ece Cilliler, Bulent Guven

Ankara Diskapi Yildirim Beyazit Training and Research Hospital, Faculty of Health Sciences, Department of Neurology, Ankara, Turkey

Received 06 July 2020; Accepted 23 August 2020
Available online 25.11.2020 with doi: 10.5455/medscience.2020.07.127

Abstract

In seizure-free patients, there are difficulties in deciding to discontinue treatment and optimal timing of withdrawal. We aimed to investigate the disease characteristics associated with recurrence of seizures after discontinuation of antiepileptic drugs (AEDs), as well as the factors affecting the time to seizure recurrence. Patients with epilepsy who had seizure recurrence after withdrawing AED treatment for at least 2 years of the seizure-free period included. The demographic and clinical characteristics of the patients were recorded. Of the 107 patients included, time to recurrence of seizures after AED withdrawal was 18 (1-188) months. Univariate cox regression analysis showed that later onset of epilepsy, older age at AED withdrawal, discontinuation of treatment by the patient, and shorter AED withdrawal periods were associated with recurrence (p=0.041, p=0.028, p<0.001, and p=0.001, respectively). In the multivariate analysis, discontinuation of therapy by the patient (HR 0.491; 95% CI 0.266-0.906; p=0.023) and shorter AED withdrawal periods (HR 0.938; 95% CI 0.888-0.991; p=0.022) were independently associated with recurrence. Earlier seizure recurrence was associated with later onset of epilepsy, fewer seizures in the first 6 months, higher age at AED withdrawal, discontinuation of treatment by the patient, shorter AED withdrawal period, and monotherapy in univariate linear regression analysis (p=0.021, p=0.032, p=0.012, p=0.008, p=0.001, and p=0.042, respectively). In multivariate analysis, the AED withdrawal period was found to be associated with early recurrence (SE 0.968; 95% CI for B 0.721-4.561; p=0.008). Our results indicate that a shorter AED withdrawal period is the most important factor related to increased and earlier seizure recurrence. Older age either at the onset of disease or at the withdrawal of AEDs seems to be related to the risk of earlier recurrence.

Keywords: Epilepsy; seizure recurrence; antiepileptic drug withdrawal; seizure-free

Introduction

The main purpose of epilepsy treatment is to ensure that patients live a seizure-free life. Approximately 70% of patients diagnosed with epilepsy become seizure-free after using antiepileptic drugs (AED), although some drugs have different side effects, and some are serious [1-3]. The withdrawal of AEDs after seizure control is controversial, and there is disagreement on issues such as the time of drug discontinuation, how to use a protocol upon discontinuation, and in which patients' discontinuation is appropriate.

The risk of seizure recurrence is higher in the first year after the discontinuation of AED [2]. However, it has been suggested that the difference in seizure recurrence rates gradually decreases over time between patients who withdraw from treatment and those who continue, and there is no deterioration in the long-term prognosis with drug discontinuation [2].

***Coresponding Author:** Bulent Guven, *A*nkara Dışkapı Yıldırım Beyazıt Training and Research Hospital, Faculty of Health Sciences, Department of Neurology, Ankara, Turkey. E-mail: bulentcanguven@gmail.com

Also, cognitive functions improve significantly when AED treatment is withdrawn successfully [4-6]. In a study evaluating AED withdrawal, it was found that discontinuation of drugs and the lack thereof did not provide a clear gain in the overall quality of life of patients [7]. On the other hand, the discontinuation of AEDs may have serious psychosocial benefits in patients with low recurrence risk [2,8].

AEDs can have serious side effects and costs, and the life-long absence of seizures is not guaranteed with continuous AED treatment. Thus, it is often referred to as discontinuing AEDs after a seizure-free period. Medications may sometimes be discontinued by the patient or even under unfavorable conditions. On the other hand, the high likelihood of having an early seizure following withdrawal from AEDs may create concerns for both patients and physicians about discontinuing the medication.

In recent years, studies have focused on determining the appropriate time point for AED withdrawal [8-11]. However, the results of these studies are contradictory, and there is no definite seizure-free time recommended for the termination of treatment [2,9,12,13]. Studies have shown that longer seizure-free time before AED withdrawal is associated with more likelihood for patients to

develop remission, at least for adults [8,9]. Recent studies have shown that seizure recurrence risk is lower among patients who have discontinued AEDs after a seizure-free period of at least 5 years [10,11]. In this study, we aimed to determine the predictive factors associated with seizure recurrence and recurrence duration after AED discontinuation among patients with epilepsy who had no seizures for 2 years or more.

Material and Methods

The study included 107 patients who were followed up in the epilepsy outpatient clinic between 2009 and 2017. The patients' treatment was either discontinued by the doctor, or they chose to discontinue the treatment on their own after a seizure-free period of at least 2 years. In both cases, all included patients later had seizure recurrence. Patients were excluded from the study if they had acute symptomatic seizures, seizures due to external factors such as alcohol deprivation, malignancy, progressive neurodegenerative disease, or severe systemic disease. Also, patients were excluded if they had conditions with a high or low risk of recurrence of seizures such as Lennox-Gastaut Syndrome, West syndrome, juvenile myoclonic epilepsy, benign childhood epilepsy with centrotemporal spikes, cluster seizures (at least three seizures within 24 hours), or a history of status epilepticus.

The information recorded comprised demographic features, type, and etiology of seizures, age of onset of seizures, number of seizures in the first 6 months after diagnosis, frequency of seizures while under AED treatment, mono- or polytherapy treatment, duration of the disease until AED discontinuation, duration of AED use and drug withdrawal period, a seizure-free time before and after AED treatment, electroencephalography (EEG) at the time of the diagnosis of epilepsy and after AED treatment, and brain magnetic resonance imaging (MRI) findings. The data also included patients' family history of epilepsy and history of febrile seizures, mental retardation, and the presence of additional factors (insomnia, hunger, infection, emotional stress, and pregnancy) that could trigger seizure recurrence after AED withdrawal.

The type of seizure was evaluated and classified according to the ILAE criteria as focal, generalized, or focal to bilateral tonic-clonic seizures [14]. The etiology of epilepsy was determined as idiopathic, cryptogenic, or symptomatic. EEG findings were classified as epileptiform activity (focal or generalized spike or spike-wave complexes) or normal (normal, abnormal focal or generalized background pattern). Brain MRI was classified as abnormal if there was a lesion that could be considered as the cause of epilepsy. The occurrence of a non-provoked seizure history among first and second-degree relatives of the patient was accepted as a positive family history. The frequency of seizures was determined by the number of seizures before the seizure-free period of at least 2 years before discontinuation of AED therapy (<1 / month, ≥1/month).

The study was carried out according to the Helsinki Declaration and was approved by the Institutional Ethics Committee. All patients participating in the study provided written informed consent.

Statistical Analysis

Statistical analyses were performed using statistical software (Statistical Package for the Social Sciences, version 23.0 for Windows, SPSS Inc., Chicago, IL, U.S.A.).The distributions of continuous variables were evaluated for normal behavior with the Kolmogorov-Smirnov test. Descriptive statistics were reported as mean ± SD or median (range, minimum to maximum) for continuous variables and number (%) for categorical variables.

A univariable Cox regression analysis was used to identify factors associated with the recurrence of seizures. Variables with a p-value of less than 0.05 in the univariable analysis were accepted as candidates for the multivariable model along with all variables of known clinical importance. Hazard ratios (HR) and 95% confidence intervals (CI) for each independent variable were also calculated.

The best predictors that influenced the time of seizure recurrence were analyzed by a univariable linear regression method. Any variable with a p-value less than 0.05 in the univariable test was accepted as a candidate for the multivariable model. Multivariate linear regressions were performed on univariate variables with a p-value < 0.05 to determine their effect on the time of seizure recurrence. The standard error (SE) and 95% confidence intervals (CI) were also calculated for each independent variable. Statistical significance was defined as $p<0.05$.

Results

A total of 107 patients (64 females, 43 males) were included in the study. The duration of AED use was 55 (24-228) months, the duration of the AED withdrawal period was 5 (0-24) months, and the time for recurrence of seizures after AED withdrawal was 18 (1-188) months. MRI abnormalities detected were namely; cortical dysplasia in 7 (28%), hippocampal sclerosis in 5 (20%), focal encephalomalacia in 5 (20%), giant arachnoid cyst in 3 (12%), leukomalacia due to perinatal injury in 1 (4%), an arteriovenous malformation in 1 (4%), corpus callosum agenesis in 1 (4%), pachygyria in 1 (4%), and double cortex in 1 (4%). The demographic and clinical characteristics of the patients are shown in Table 1.

The univariate Cox regression analysis showed that older age of epilepsy onset, older age of the patient when AED was discontinued, discontinuation of treatment by the patient, and shorter AED withdrawal periods were associated with seizure recurrence after AED withdrawal (p=0.041, p=0.028, p<0.001 and p=0.001, respectively). In the multivariate analysis, withdrawal of treatment by the patient and shorter AED withdrawal periods were found to be independent factors associated with the risk of recurrence (p=0.023 and p=0.022, respectively) (Table 2).

The factors affecting the time to seizure recurrence following AED withdrawal were examined, and the factors associated with earlier recurrence were late-onset of epilepsy, lower number of seizures in the first 6 months, older age when AED was discontinued, discontinuation of treatment by the patient, shorter AED withdrawal period, and treatment with monotherapy (p=0.021, p=0.032, p=0.012, p=0.008, p=0.001, and p=0.042, respectively). In the multivariate analysis, only shorter AED withdrawal periods were associated with early seizure recurrence (p=0.008) (Table 3).

Table 1. Demographic and disease characteristics of patients with recurrent seizures following AED withdrawal.

	n = 107
Age (years)	22 (16-70)
Sex (female/male)	43 (40.2)/64 (59.8)
Duration of epilepsy (years)	12 (3-42)
Age at onset (years)	12 (1-59)
Seizure type	
Focal seizures	11(10.3)
Generalized seizures	75 (70.1)
Focal to bilateral tonic-clonic seizures	21 (19.6)
Etiology	
Idiopathic	79 (73.8)
Symptomatic/cryptogenic	28 (26.2)
Mental retardation	10 (9.3)
History of febrile seizures	17 (15.9)
Family history of epilepsy	21 (19.6)
Number of seizures in the first 6 months of disease	1.4 (0-10)
Seizure frequency before epilepsy withdrawal (number of patients)	
<1/month	85 (79.4)
≥1/month	22 (20.6)
Epilepsy duration at the time of AED withdrawal (months)	60 (36-240)
The seizure-free time before AED withdrawal (months)	42 (24-150)
Duration of AED treatment (months)	55 (24-228)
Age at time of AED withdrawal (years)	17 (5-64)
AED withdrawal period (months)	5 (0-24)
AED treatment was withdrawn by doctor/patient	90 (84.1)/17 (15.9)
The seizure-free time following AED withdrawal (months)	18 (1-188)
Presence of triggering factor before seizure recurrence *	33 (41.2)
Triggering factors	
Sleep deprivation	11 (33.3)
Hunger	7 (21.2)
Infection	7 (21.2)
Emotional stress	7 (21.2)
Pregnancy	1 (3)
Epileptiform EEG abnormality	
Epileptiform EEG at diagnosis	48 (44.9)
Epileptiform EEG following AED withdrawal†	53 (58.9)
Brain MRI abnormalities	25 (23.4)
Treatment type before AED withdrawal	
Monotherapy	96 (89.7)
Polytherapy	11 (10.3)

Data are presented as mean ± SD, median (range, minimum to maximum), or number (%).
AED: Antiepileptic drug, EEG: Electroencephalography, MRI: Magnetic resonance imaging.
* Seizure triggering factors were evaluated in 80 patients.
† EEG was evaluated in 90 patients following AED withdrawal.

Table 2. Factors affecting seizure recurrence following AED withdrawal.

		Univariate regression			Multivariate regression		
		HR	**95% CI**	**p**	**HR**	**95% CI**	**p**
Sex	Male (ref. female)	1.224	0.828-1.811	0.311			
Age at onset (years)		1.015	1.001-1.030	**0.041**	0.972	0.922-1.025	0.289
Seizure type (ref. focal)	Generalized	1.363	0.720-2.579	0.341			
	Focal to bilateral tonic clonic	1.231	0.584-2.594	0.585			
Etiology Idiopathic (ref. Symptomatic/cryptogenic)		1.183	0.766-1.827	0.450			
Mental retardation No (ref. yes)		1.016	0.529-1.953	0.962			
History of febril convulsion No (ref. yes)		1.167	0.690-1.974	0.565			
Family history of epilepsy No (ref. yes)		1.234	0.757-2.014	0.399			
Number of seizures in the first 6 months of disease		0.891	0.785-1.012	0.075			
Seizure frequency before epilepsy withdrawal (number of patients) <1/month (ref. ≥1/month)		1.494	0.928-2.405	0.099			
Duration of epilepsy at time of AED withdrawal (years)		1.004	0.954-1.057	0.866			
Seizure-free time before AED withdrawal (months)		1.003	0.995-1.012	0.417			
Duration of AED treatment (months)		1.001	0.997-1.005	0.694			
Age at time of AED withdrawal (years)		1.017	1.002-1.033	**0.028**	1.047	0.990 – 1.107	0.108
AED withdrawal period (months)		0.916	0.870-0.965	**0.001**	0.938	0.888 - 0.991	**0.022**
AED withdrawn by doctor (ref. patient)		0.360	0.210-0.618	**<0.001**	0.491	0.266 - 0.906	**0.023**
EEG at diagnosis Not epileptiform (ref. epileptiform)		1.054	0.717-1.549	0.789			
EEG following AED withdrawal* Not epileptiform (ref.epileptiform)		1.238	0.808-1.897	0.328			
Brain MRI abnormalities No (ref. Yes)		1.122	0.715-1.761	0.615			
Treatment type before AED Withdrawal Monotherapy (ref. polytherapy)		1.609	0.856-3.025	0.140			

Bold indicates statistical significance.
AED: Antiepileptic drug, EEG: Electroencephalography, MRI: Magnetic resonance imaging, ref.: reference,
HR: Hazard ratio, CI: Confidence interval.
* EEG was evaluated in 90 patients following AED withdrawal.

Table 3. Factors affecting the time to first seizure recurrence following AED withdrawal.

		Univariate regression					Multivariate regression				
		B	**SE**	**95% CI for B**	**β**	**p**	**B**	**SE**	**95% CI for B**	**β**	**p**
Sex, Male (ref. female)		-12.949	8.510	-29.823 - 3.926	-0.147	0.131					
Age at onset (years)		-0.853	0.363	-1.573 - -0.133	-0.224	**0.021**	1.430	1.073	-0.699-3.559	0.375	0.186
Seizure type (ref. focal)	**Generalized**	-7.981	9.180	-26.184 - 10.221	-0.085	0.387					
	Focal to bilateral tonic-clonic	-0.884	10.620	-21.942 - 20.174	-0.008	0.934					
Etiology, Idiopathic (ref. symptomatic/cryptogenic)		-6.519	9.575	-25.505 - 12.467	-0.066	0.497					
Mental retardation, No (ref. yes)		-3.103	14.489	-31.831- 25.625	-0.021	0.831					
History of febril convulsion, No (ref. yes)		-10.548	11.493	-33.336 - 12.240	-0.089	0.361					
Family history of epilepsy, No (ref. yes)		-9.899	10.577	-30.870 - 11.073	-0.091	0.351					
Number of seizures in the first 6 months of disease		5.362	2.469	0.466 - 10.258	0.207	**0.032**	3.910	2.431	-0.913-8.733	0.151	0.111
Seizure frequency before epilepsy withdrawal (number of patients) <1/month (ref. ≥1/month)		-18.933	10.272	-39.301 - 1.435	-0.177	0.068					
Duration of epilepsy at time of AED withdrawal (years)		-0.212	1.125	-2.442 - 2.019	-0.018	0.851					
Seizure-free time before AED withdrawal (months)		-0.121	0.150	-0.418 - 0.176	-0.079	0.420					
Duration of AED treatment (months)		-0.034	0.096	-0.225 - 0.157	-0.034	0.728					
Age at time of AED withdrawal (years)		-0.964	0.378	-1.715 - 0.214	-0.241	**0.012**	-2.121	1.102	-4.308-0.065	-0.531	0.057
AED withdrawal period (months)		3.126	0.877	1.386 - 4.865	0.328	**0.001**	2.641	0.968	0.721-4.561	0.277	**0.008**
AED withdrawn by doctor (ref. patient)		30.294	11.154	8.179 - 52.410	0.256	**0.008**	10.513	11.895	-13.086-34.111	0.089	0.379
EEG at diagnosis, Not epileptiform (ref. epileptiform)		0.452	8.481	-16.364 - 17.269	0.005	0.958					
EEG following AED withdrawal*, Not epileptiform (ref. epileptiform)		0.706	8.868	-16.879 - 18.290	0.008	0.937					
Brain MRI abnormalities No (ref. Yes)		-4.140	9.960	-23.890 - 15.609	-0.041	0.678					
Treatment type before AED withdrawal Monotherapy (ref. polytherapy)		-28.062	13.616	-55.060 - 1.063	-0.197	**0.042**	-22.228	12.854	-47.730-3.275	-0.156	0.087
							R=0.469	**R2=0.220**	**F=4.710**	**p=0.000**	

Bold indicates statistical significance. AED: Antiepileptic drug, EEG: Electroencephalography, MRI: Magnetic resonance imaging, ref.: reference, SE: Standard error, CI: Confidence interval.
* EEG was evaluated in 90 patients following AED withdrawal.

Discussion

Our results indicated that a short AED withdrawal period is the most important independent factor associated with increased seizure recurrence risk and early seizure recurrence. It is controversial whether the rate of drug reduction affects the success or failure of AED withdrawal. Furthermore, the relationship between the length of the drug withdrawal period and seizure recurrence remains unclear. A drug reduction period of fewer than 6 months has been reported to be a negative prognostic factor [15-17]. On the other hand, a randomized study comparing 6-week and 9-month AED withdrawal schedules found no difference in recurrence rates [18].

It has been suggested that slow AED reduction should be encouraged and that AED withdrawal should be tailored to the needs and preferences of patients [19,20]. In our study, the withdrawal of AED treatment by the patient instead of a doctor was found to be a factor that increased the risk of seizure recurrence and recurrence within a shorter period. If a patient decides to cease his/her treatment often stops drugs without reducing the dose and so it is understandable to predict that the risk of recurrence of seizures may increase. This is also the case when AEDs are discontinued by the patient in a short time or even suddenly and is consistent with the effect of shorter drug withdrawal periods on seizure recurrence.

In our study, patients whose seizures started at an older age had a higher risk of seizure recurrence following the withdrawal of AED treatment. Also, seizure recurrence was found to have occurred earlier following AED withdrawal among patients with late-onset of epilepsy. The age of onset of epilepsy is one of the most frequently investigated risk factors for seizure recurrence. Earlier disease onset age has been associated with higher recurrence rates [21,22], while other studies suggest that early disease onset is predictive of lower recurrence rates [21,23-25].

The onset of seizures before the age of 10 to 12 years suggests a favorable prognosis, and the recurrence rates are higher among epilepsy patients who have had seizures after this age range [15,23-25]. Studies linking the late onset of epilepsy with lower recurrence rates were conducted with pediatric age groups. In these studies, the groups with early onset of epilepsy were selected mostly from patients under 2 years of age. It is thought that the high incidence of recurrence may be because epilepsy is often accompanied by mental retardation or symptomatic or cryptogenic etiology, which is more frequent in this age group. Also, these patients may have a higher number of seizures, EEG abnormalities, and a need for longer and multiple AED usage before the seizure-free period, which may affect increasing seizure recurrence [21,22].

Certain epilepsy etiologies and syndromes should also be considered. Examples include benign childhood epilepsy with centrotemporal spikes with a low risk of seizure recurrence after drug withdrawal, as well as juvenile myoclonic epilepsy having a high risk of seizure recurrence after drug withdrawal. Such patients with epileptic disorders that are known to have a high or low risk of recurrence of seizures were excluded from the study, and their effects on the outcomes were avoided.

Withdrawal of AED at an older age was associated with both the risk of recurrence of seizures and the recurrence of seizures in a shorter period following drug withdrawal. Other studies have also shown that discontinuation of AEDs at an older age increases the risk of relapse [7,21,25-27]. However, it has been reported that recurrence is more frequent following drug discontinuation among whose AEDs are withdrawn earlier [21,28]. There few and partly contradictory results on the prognostic significance of age at the time AED is withdrawn, which can be explained by the fact that it largely reflects the patient's characteristics and preferences and the physician's decision to stop treatment, regardless of the age of the patient. On the other hand, a higher incidence of recurrence was found among patients with delayed onset of the disease in our study, which may result in increased seizure risk among patients whose AEDs were withdrawn at a later age.

A lower number of seizures in the first 6 months of the disease and monotherapy were not associated with an increased risk of seizures following AED withdrawal. However, they were associated with the recurrence of seizures in a shorter period, but they did not have a significant effect on the multivariate model. It was not expected that seizures would recur earlier after discontinuation of the drug among patients with low seizure frequency in the first 6 months of the disease. However, in our study, patients with epileptic syndromes with poor prognosis in terms of seizure recurrence were excluded, and the number of patients with seizures with symptomatic etiology was not high, which could have affected the results.

Among patients receiving polytherapy, the decision to discontinue medication may often result in the withdrawal of AEDs in a certain order, which may prolong the duration of discontinuation and lead to longer antiepileptic efficacy. This might be a possible explanation for the shorter duration of seizure recurrence among patients receiving monotherapy before AED withdrawal, which is one of the results in this study. On the other hand, patients treated with polytherapy may have more refractory seizures and increased risk of seizure recurrence [29].

Studies have suggested that longer seizure-free time before AED withdrawal is associated with more likelihood for patients to develop remission, at least for adults [8,9]. One study was reported that patients with idiopathic generalized epilepsy and those without seizures for <5 years had more frequent seizure recurrence than those without seizures for ≥5 years [10]. In another study evaluating adult patients with focal epilepsy, the risk of seizure relapse associated with AED withdrawal was much lower after at least 5 years of remission [11]. In our study, no correlation was found between the seizure-free period before AED withdrawal and seizure recurrence. This may have been an effect of the fact that the patients included in the study were seizure-free for at least 2 years under AED treatment, and perhaps because we did not assess the duration of seizure-free periods at specific time intervals, such as 5 years.

Our study has some limitations. Because of the retrospective design, randomization could not be performed, and there was no control group. Although patient interviews were used, there may be data loss because file records were the main source of information. Another limitation is that the data evaluated belong to both child and adult periods. Problems that may arise from this have been

partially addressed by excluding patients with childhood or juvenile epilepsies that are known to have a good or bad prognosis for seizure relapse.

Conclusion

It is not yet clear when it is appropriate to withdraw AED after seizure control is achieved and which patients have a higher risk for recurrence of seizures. These issues remain an important problem for those dealing with epilepsy treatment. We still do not have any predictors of seizure recurrence following the withdrawal of AED treatment. This study investigated seizure recurrence following AED withdrawal and the factors that may affect the duration of this recurrence. Our results indicated that a shorter AED withdrawal period was the most important predictor of increased seizure recurrence risk and early seizure recurrence. Also, our results suggest that the risk of seizure recurrence may be higher, and the seizures may recur in a shorter period among patients with seizures starting at an advanced age and discontinuing AED treatment at an older age.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
No financial support is received.

Ethical approval
The study was carried out according to the Helsinki Declaration and was approved by the Institutional Ethics Committee (University of Health Sciences, Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital, Clinical Researches Ethics Committee, 23.12.2019, 78/11).

References

1. 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;20:790-4.
2. Lossius MI, Hessen E, Mowinckel P, et al. Consequences of antiepileptic drug withdrawal: a randomized double-blind study (Akershus Study). Epilepsia. 2008;49:455-63.
3. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342:314-9.
4. Meador KJ. Cognitive and memory effects of the new antiepileptic drugs. Epilepsy Res. 2006;68:63-7.
5. Hessen E, Lossius MI, Reinvang I, et al. Slight improvement in mood and irritability after antiepileptic drug withdrawal: a controlled study in patients on monotherapy. Epilepsy Behav. 2007;10:449-55.
6. Hessen E, Lossius MI, Reinvang I, et al. Influence of major antiepileptic drugs on neuropsychological function: results from a randomized, double-blind, placebo-controlled withdrawal study of seizure-free epilepsy patients on monotherapy. J Int Neuropsychol Soc. 2007;13:393-400.
7. Medical Research Council Antiepileptic Drug Withdrawal Group. Randomized study of antiepileptic drug withdrawal in patients in remission. Lancet. 1991;337:1175-80.
8. Jacoby A, Johnson A, Chadwick D. Psychosocial Outcomes of Antiepileptic Drug Discontinuation. Epilepsia. 1992;33:1123-31.
9. Specchio LM, Tramacere L, La Neve A, et al. Discontinuing antiepileptic drugs in patients who are seizure free on monotherapy. J Neurol. 2002;72:22-5.
10. Vorderwülbecke BJ, Kirschbaum A, Merkle H, et al. Discontinuing antiepileptic drugs in long-standing idiopathic generalised epilepsy. J Neurol. 2019;266:2554-9.
11. Wang X, He R, Zheng R, et al. Relative seizure relapse risks associated with antiepileptic drug withdrawal after different seizure-free periods in adults with focal epilepsy: a prospective, controlled follow-up study. CNS Drugs. 2019;33:1121-32.
12. Strozzi I, Nolan SJ, Sperling MR, et al. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. Cochrane Database Syst Rev. 2015;11:001902.
13. Verrotti A, Morresi S, Basciani F, et al. Discontinuation of anticonvulsant therapy in children with partial epilepsy. Neurology. 2000;55:1393-5.
14. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE commission for classification and terminology. Epilepsia. 2017;58:512-21.
15. Britton JW. Antiepileptic drug withdrawal: literature review. Mayo Clin Proc. 2002;77:1378-88.
16. Altunbaşak S, Artar O, Burgut R, et al. Relapse risk analysis after drug withdrawal in epileptic children with uncomplicated seizures. Seizure. 1999;8:384-9.
17. Todt H. The late prognosis of epilepsy in childhood: results of a prospective follow-up study. Epilepsia. 1984;25:137-44.
18. Tennison M, Greenwood R, Lewis D, et al. Discontinuing antiepileptic drugs in children with epilepsy. A comparison of a six-week and a nine-month taper period. N Engl J Med. 1994;330:1407-10.
19. He RQ, Zeng QY, Zhu P, et al. Risk of seizure relapse after antiepileptic drug withdrawal in adult patients with focal epilepsy. Epilepsy Behav. 2016;64:233-8.
20. Beghi E, Giussani G, Grosso S, et al. Withdrawal of antiepileptic drugs: guidelines of the Italian league Against epilepsy. Epilepsia. 2013;54:2-12.
21. Specchio LM, Beghi E. Should antiepileptic drugs be withdrawn in seizure-free patients? CNS Drugs. 2004;18:201-12.
22. Emerson R, D'Souza BJ, Vining EP, et al. Stopping medication in children with epilepsy: predictors of outcome. N Engl J Med. 1981;304:1125-9.
23. Peters ACB, Brouwer OF, Geerts AT, et al. Randomized prospective study of early discontinuation of antiepileptic drugs in children with epilepsy. Neurology. 1998;30:724-30.
24. Dooley J, Gordon K, Camfield P, et al. Discontinuation of anticonvulsant therapy in children free of seizures for 1 year: a prospective study. Neurology. 1996;46:969-74.
25. Shinnar S, Berg AT, Moshé SL, et al. Discontinuing antiepileptic drugs in children with epilepsy: a prospective study. Ann Neurol. 1994;35:534-45.
26. Matricardi A, Bertamino F, Risso D. Discontinuation of antiepileptic therapy: a retrospective study of 86 children and adolescents. Ital J Neurol Sci, 1995;16:613-22.
27. Overweg J, Binnie CD, Oosting J, et al. Clinical and EEG prediction of seizure recurrence following antiepileptic drug withdrawal. Epilepsy Res. 1987;1:272-83.
28. Donati F, Hassink RI, Jung H, et al. Factors predicting the risk of relapse after antiepileptic drug discontinuation in children with partial seizures. Eur J Pediatr. 1995;154:44-7.
29. Ou S, Xia L, Li R, et al. Long-term outcome of seizure-free patients and risk factors of relapse following antiepileptic drug withdrawal. Epilepsy Behav. 2018;88:295-300.