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Withdrawal of antiepileptic drugs: Guidelines of the Italian League Against Epilepsy

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Summary

The Italian League Against Epilepsy has issued evidence-based guidelines to help practicing physicians in their decision to stop or withhold antiepileptic drugs (AEDs) in patients achieving a prolonged period of seizure freedom. Six adult and two child neurologists, divided into four pairs, critically appraised 128 published reports and provided graded recommendations answering 15 key questions: length of the seizure-free period after treatment initiation, difference in seizure-free periods in children and adults, electroencephalography (EEG) pattern at the time of discontinuation, etiology of epilepsy, seizure type(s), patient's age and sex, family history of epilepsy, history of febrile seizures, epilepsy syndrome, seizure frequency before entering remission, duration of active epilepsy, tapering period, number and type of AEDs taken at time of discontinuation, combination of risk factors for recurrence, and length of patient monitoring after treatment discontinuation. Based on the available data, the following recommendations can be outlined: (1) antiepileptic treatment might be discontinued after a minimum period of 2 years of seizure freedom; shorter seizure-free periods are associated to a higher risk of relapse; (2) in children, AED discontinuation could be considered after less than two seizure-free years because of a marginally higher risk of relapse for early withdrawal; (3) factors, such as abnormal EEG (including epileptiform abnormalities) at the time of treatment discontinuation, a documented etiology of seizures (including mental retardation, perinatal insults, and abnormal neurologic examination), partial seizures, or an older age at disease onset, enhance the risk of relapse; however, patients should not be encouraged to withhold treatment unless a combination of two or more of these factors is present; (4) female sex, family history of epilepsy, history of febrile seizures, disease length/severity, and number and type of drugs taken should not influence the decision to stop treatment; (5) epilepsy syndrome should be always included in the decision process; (6) slow (at least 6 months) AED discontinuation should be encouraged; in any case the duration of the tapering period should be tailored to the patient's needs and preference; and (7) patient discontinuing treatment should be followed for no <2 years. As a general habit, the decision to stop treatment should be discussed and shared with each patient, taking into account social and personal complications of a seizure relapse and the medical complications of chronic AED treatment.

KEY WORDS: Epilepsy, Antiepileptic drugs, Withdrawal, Seizure, Seizure freedom, Etiology, EEG.

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About 70% of patients with recent-onset epilepsy achieve seizure freedom with adequate antiepileptic drug (AED) treatment (Kwan & Brodie, 2000). For these patients, the questions of whether, when, and how the therapy can be discontinued are as yet largely unresolved. The complexity of the matter relies in a number of aspects waiting for elucidation and/or requiring a careful evaluation of the risk/benefit ratio before the decision to stop or to continue AED therapy is made (Specchio & Beghi, 2004; Schmidt, 2008, 2011; Hixson, 2010; Beghi, 2011). These aspects include the following: (1) the duration of the seizure remission period before starting AED discontinuation, (2) the duration of the AED tapering period, (3) the presence of specific risk factors for relapse and specific types of epilepsy/specific epileptic syndromes, (4) the evaluation of the general conditions of life of a given patient, which include emotional state, job, driving, and other daily activities, and (5) possible age-related differences. Studies have shown that one of three patients, on average, exhibits a relapse within a period of 2 years after AED withdrawal and that the rate of seizure recurrence within the same time period is about two to three times that observed in patients who continue AEDs (Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1991; Berg & Shinnar, 1994; Specchio et al., 2002; Schmidt & Löscher, 2005). The percentage of children who are undergoing AED withdrawal is higher than that of adult patients, that is, nearly 70% versus <50% (Camfield & Camfield, 2005), and the period of seizure remission before considering treatment withdrawal is shorter (1–2 vs. 2–5 years) (Camfield & Camfield, 2005; Schmidt & Löscher, 2005). The decision to stop or continue drug treatment is also influenced by the occurrence of drug-related side effects (Specchio & Beghi, 2004). Some of these effects, which include reduced attention, impaired memory and mood depression, although subtle in their nature, may cause problems during daily activities with consequent impairment of quality of life (Vermeulen & Aldenkamp, 1995). In addition, prolongation of AED therapy exposes patients to other potential risks, like teratogenicity, drug interactions, and long-term development of toxicity. On the other hand, relapse can result in a devastating event in the emotional and social life of patients with possible loss of job and driver's license. Establishing the benefits (Beghi, 2011) or the risks (Schmidt, 2011) of AED discontinuation following a long period of seizure remission is a difficult task and an important challenge for clinicians. The present study is aimed at critically appraising the most relevant literature data on this issue to develop a rational approach to the decision to continue or to stop AED therapy. General guidelines are proposed on the basis of current knowledge.

Procedure for Literature Search

The scientific literature on the discontinuation of epilepsy therapy in seizure-free patients was examined without distinction of period of remission. The databases used were MEDLINE (since 1966) and EMBASE (since 1974), searching for the key words "anticonvulsants," "anticonvulsant agent," "seizure, epilepsy and convulsion," "withdrawal." The literature search was limited to studies in humans.

For each article, the abstract was first examined and then, if the topic was the withdrawal of AEDs in seizure-free patients, the entire publication was obtained and evaluated.

Abstracts, case reports, reviews, editorials, articles in duplicate (i.e., including data from the same cases) except for any additional information, and articles referring to an unscheduled drug withdrawal (e.g., discontinuation of treatment for poor patient compliance) were excluded (Fig. 1). Articles written in languages other than English, Italian, French, and Spanish were also excluded. The literature review was completed by examining also articles found in the reference lists of the eligible articles. This guideline does not include articles referring to treatment discontinuation after epilepsy surgery.

Raters and Items Reviewed

A group of eight experts of the Italian League Against Epilepsy (LICE), six adult and two child neurologists divided into four pairs, examined 128 eligible articles (about 30 per pair). Each article was examined by both components of each pair. For each publication examined, the following variables have been examined: author and year of publication, study design and setting, number of patients, source of patients (general population, specialist clinics, epilepsy centers), patients' age at onset, current patient age, sex, etiology, epileptic syndromes (where indicated), family history of epilepsy, history of febrile seizures, presence of mental retardation, seizure type, number of seizures before treatment, interval between first seizure and treatment start, interval between treatment start and remission, interval between remission and drug withdrawal, tapering period, duration of active disease (i.e., interval between first and last seizure), EEG patterns at time of discontinuation (no EEG, normal, abnormal but without epileptiform abnormalities, with epileptiform abnormalities), duration of remission before drug discontinuation, drugs (number, type and doses), number of patients included, follow-up duration, total number of patients with recurrence after treatment discontinuation, and time of recurrence. Any discrepancies between the components of each pair were solved by discussion and consensus.

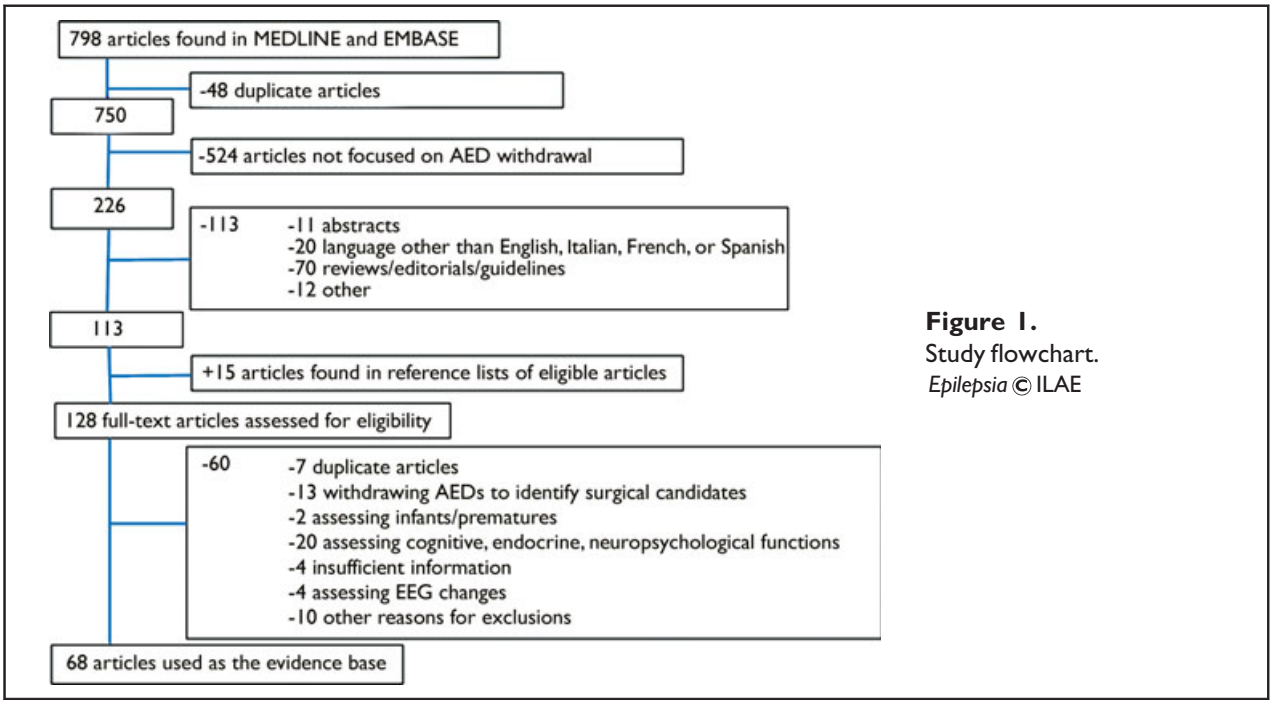

Figure 1.
Study flowchart.
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The definitions of the levels of evidence and the strength of the recommendations used in this guideline are based on the scheme adopted by the U.S. Agency for Health Care and Policy Research (www.ahrq.gov/clinic/cpgsix.htm). According to that scheme, the efficacy of each therapeutic intervention is measured by its ability to modify the prognosis (i.e., the tendency of seizures to relapse).

Levels of Evidence

Level 1: Evidence obtained from prospective cohort studies with adequate design; includes also evidence obtained from meta-analyses of randomized clinical trials and from at least one randomized clinical trial.

Level 2: Evidence obtained from cohort studies with suboptimal design or from case-control studies; includes also evidence obtained from at least one controlled nonrandomized trial and evidence obtained from at least one other well-designed, quasi-experimental study.

Level 3: Evidence obtained from other observational nonexperimental studies.

Level 4: Evidence obtained from expert opinions (including commissions of experts and single authoritative experts). Indicates the absence of good quality studies.

Strength of Recommendations

Grade A: The intervention (whether diagnostic or therapeutic) is to be recommended because it is clearly effective, or to be discouraged because it is ineffective or harmful. The recommendation is based on evidence level 1.

Grade B: The intervention is probably effective, ineffective, or harmful. The intervention may be recommended to specific subgroups of patients. The recommendation is based on evidence levels two and three.

Grade C: The intervention is possibly effective, ineffective, or harmful. The intervention deserves further evaluation before being recommended or discouraged. The recommendation is based on evidence level 4.

The critical appraisal of the literature was performed to provide answers to 15 key questions addressed by the caring physician at the time of treatment discontinuation. The answer to each question has been structured in terms of graded recommendations the strength of which was supported by the levels of the available evidence.

Question 1: What Is the Length of the Seizure-Free Period Required to Start Drug Withdrawal? Should We Consider Different Seizure-Free Periods in Children and Adults?

The minimum period of seizure freedom was indicated by most studies in 2 years. Some studies done in children required a 1-year seizure-free period and occasionally even 6 months. Shorter periods of seizure

freedom in children than in adults were motivated by a lower risk to incur in social complications of seizure relapse. In a Cochrane review comparing early (less than two seizure-free years) versus late (more than two seizure-free years) drug withdrawal in children, the pooled relative risk for seizure relapse for early withdrawal (compared to late withdrawal) was 1.32 (95% confidence interval [CI] 1.02–1.70) (Sirven et al., 2001). On the basis of this estimate, the number needed to harm, that is, the number of individuals to stop early treatment in order for one having a relapse, is 10 [Level of evidence: 3].

Recommendations

Antiepileptic treatment might be discontinued after a minimum period of 2 years of seizure freedom; shorter seizure-free period should be discouraged because of a higher risk of relapse [Strength of recommendation: B].

Discontinuation of treatment could be considered after <2 years in children because of a marginally higher risk of relapse for early withdrawal [Strength of recommendation: B].

Question 2: Should We Consider Withholding Treatment in Patients with an Abnormal EEG at Time of Discontinuation?

A total of 37 studies (mostly done in children) examined the role of EEG as a predictor of seizure recurrence (Table 1). An abnormal EEG at the time of treatment discontinuation predicted a higher risk of relapse in 21 studies. The results were confirmed by multivariate analysis in six studies. AEDs were discontinued prospectively in 88 seizure-free children by Shinnar et al. (1985). The presence of EEG spikes, EEG slowing, EEG persistently abnormal or worsening during the disease course, and the interaction between age at onset and EEG slowing predicted a higher risk of relapse. In a prospective study in 425 children, Matricardi et al. (1989) found an increased relapse risk when the EEG was persistently abnormal during the disease course or was abnormal at time of discontinuation. In a cohort of 200 children, an abnormal postwithdrawal EEG (but not an abnormal EEG preceding withdrawal) was an independent predictor of relapse (Olmez et al., 2009). An abnormal EEG at time of drug withdrawal was the only predictor of seizure recurrence in 80 Ethiopian children who had been seizure free for at least 18 months (Gebremariam et al., 1999). An abnormal EEG predicted an increased risk of relapse in a cohort of 68 children in whom treatment was discontinued after 4 years of seizure freedom (Emerson et al., 1981). In an extended follow-up of a randomized trial of early versus delayed withdrawal in 161 seizure-free children (Geerts et al., 2005), EEG findings were significantly associated with seizure outcome. In the only study assessing the prognostic value of the EEG in adults (Tinuper et al., 1996), 69% of patients with epileptiform abnormalities before reduction relapsed compared to 60% of those with normal EEG. EEG worsening during tapering was associated with an increasing risk of relapse. In a meta-analysis of 25 published studies, Berg and Shinnar (1994) found that patients with abnormal EEG carry a 1.45 higher risk of relapse (95% CI 1.18–1.79). EEG epileptiform abnormalities were found frequently associated with a higher risk of relapse in a systematic review of published reports (Specchio & Beghi, 2004). However, findings are inconsistent regarding the site, type, and density of the recorded abnormalities. Other EEG patterns (background or focal slowing) and their changes were sometimes found to affect the risk of relapse. These results must be, however, interpreted in the light of the published studies and the variability of the methods (definitions used, modalities of EEG recording, interpretation) [Level of evidence: 2].

Recommendations

A patient with abnormal EEG (with or without epileptiform activity) at the time of treatment discontinuation should be informed of an increased risk of relapse but should not be encouraged to withhold treatment if abnormal EEG is the only negative prognostic predictor. This recommendation should also apply to the presence of EEG epileptiform abnormalities or specific EEG patterns. In this case, the decision to stop treatment should be considered in the light of social and personal complications of a seizure relapse [Strength of recommendation: B].

Question 3: Should We Consider Withholding Treatment in Patients with a Documented Etiology of Epilepsy (Including Mental Retardation and Perinatal Insults)?

The role of etiology was assessed in 28 studies (20 done in children) and found significant in 10 (Table 1). Significance was confirmed by multivariate analysis in three studies. In a prospective study in 216 children, remote symptomatic etiology (with global developmental delay/mental retardation, motor deficit and abnormal neuroimaging) was an independent predictor of relapse (Ramos-Lizana et al., 2010). In a randomized trial of early versus delayed discontinuation of treatment in 161 seizure-free children, cryptogenic and remote symptomatic etiology carried a twofold risk of relapse (Peters

et al., 1998). Etiology remained a significant predictor in an extended follow-up of these patients (Geerts et al., 2005). In the prospective study by Shinnar et al. (1994), etiology carried an almost twofold risk of relapse. In the meta-analysis of Berg and Shinnar (1994), patients with remote symptomatic seizures were more likely to relapse than patients with idiopathic seizures (relative risk 1.55, 95% CI 1.21–1.98).

Mental retardation was assessed in 15 studies and resulted in a significantly higher risk of relapse in 10 (multivariate analysis, 3). Mental retardation was one of the independent predictors of seizure relapse in the study of Matricardi et al. (1989). Mental retardation, motor handicap, or both, predicted a higher risk of relapse in 148 children in a model excluding long duration of epilepsy, identified as the variable most highly associated with relapse (Holowach Thurston et al., 1982). In a randomized double-blind study by Lossius et al. (2008), normal neurologic examination predicted seizure freedom after drug withdrawal over 1 year [Level of evidence: 2].

Recommendations

A patient with a documented seizure etiology of his/her seizures should be informed of an increased risk of relapse but should not be encouraged to withhold treatment if this is the only negative prognostic predictor. This recommendation should also apply in presence of mental retardation and/or abnormal neurologic or imaging findings. In this case, as in presence of abnormal EEG, the decision to stop treatment should be considered in the light of the social and personal complications of a seizure relapse. However, a patient with an abnormal EEG pattern and a documented etiology of his/her seizures should be advised not to discontinue the antiepileptic treatment [Strength of recommendation: B].

Question 4: Should We Consider Withholding Treatment in Patients with Partial Seizures?

The prognostic role of seizure type was investigated in 38 studies (children 21; adults 10; mixed 7) (Table 1). Partial seizures carried a higher risk of recurrence in 14 studies (confirmed by multivariate analysis in 7). Jacksonian seizures were found by Holowach Thurston et al. (1982) to be associated with a higher risk of relapse in 148 children followed up to 23 years, when disease duration (indicated by the authors as the most significant predictor of recurrence) was excluded. In contrast, in the study by Pestre et al. (1987), generalized seizures (eventually associated with abnormal EEG) in adolescents carried a higher risk of relapse. Complex partial seizures and atypical febrile seizures were independent predictors of relapse in the study by Shinnar et al. (1985). Dooley et al. (1996), in 97 children free of seizures for 1 year, found partial seizures (along with female sex, age at onset over 120 months, and neurologic abnormalities) as independent predictors of relapse. In the randomized trial by Peters et al. (1998), partial epilepsy was the most important predictor of relapse. Seizure type remained an independent prognostic predictor even in the extended follow-up of that study (Geerts et al., 2005). Seizure type predicted outcome after treatment discontinuation also in the study by Matricardi et al. (1989). In this population, infantile spasms carried the highest risk of a second relapse (29%), followed by absence seizures (17%) and partial or myoclonic seizures (15%). Generalized tonic–clonic seizures with or without myoclonic or absence seizures predicted an increased risk of relapse in a cohort of 59 children and adolescents with idiopathic generalized epilepsy (Pavlovic et al., 2011). The conflicting results on seizure types can be explained

Table 1. Predictors of seizure relapse: Number of studies with results

Variables	No. of studies[a]	Children T/S (M)	Adults T/S (M)	Mixed T/S (M)	Significant (M)
Abnormal EEG	37	24/14 (5)	6/3	7/4 (1)	21 (6)
Etiology	28	20/9 (3)	4/1	4/0	10 (3)
Mental retardation	15	11/9 (2)	3/1 (1)	1/0	10 (3)
Partial seizure	38	21/8 (5)	10/2	7/4 (2)	14 (7)
Age at onset	41	25/11 (4)	8/2	8/5 (2)	18 (6)
Sex	27	17/3 (1)	6/0	4/1	4 (1)
Family history of epilepsy	33	23/3 (1)	3/1	7/1	5 (1)
History of febrile seizure	18	12/4 (1)	2/0	4/2	6 (1)
Epilepsy syndrome	23	11/7 (1)	6/2	6/3 (1)	12 (2)
Epilepsy duration	27	14/4 (1)	6/3	7/4	11 (1)
Seizure frequency	23	16/8 (1)	3/3	4/1	12 (1)
Tapering	10	9/3 (1)	1/1	0/0	4 (1)
Polytherapy	23	14/6 (1)	4/1	5/1 (1)	8 (2)

[a]Total number of studies assessing each predictor
T, total number of studies; S, significant; M, significant in multivariable analysis.
Mixed, children and adults.

by their inclusion in different syndromic patterns [Level of evidence: 3].

Recommendations

The presence of partial seizures should not be considered per se a reason for withholding treatment in a patient who is seizure free and does not have other relevant predictors of relapse (abnormal EEG and documented etiology). Seizure type should be assessed along with other variables when the decision to stop treatment must be taken [Strength of recommendation: B].

Question 5: Should Age at Onset Be a Factor Influencing the Decision to Stop or Withhold Treatment?

Age at onset of seizures was assessed in 41 studies and found to affect the risk of relapse in 18 (Table 1). However, only in 6 studies were the results confirmed by multivariate analysis. Older age at onset was found by Shinnar et al. (1985) to predict higher seizure relapse. However, this finding attained significance only when interacting with slowing on EEG. Age at onset older than 12 years was confirmed by the same author (Shinnar et al., 1994) as an independent predictor of seizure relapse in a cohort of 264 seizure-free children. Age at onset older than 4 years predicted a higher relapse rate in 191 children who were seizure free for at least 2 years and followed by Mastropaolo et al. (1992). Age 6 years or older at onset of seizures predicted a higher relapse rate in 82 seizure-free children with cryptogenic localization-related epilepsies (Ohta et al., 2004). In a cohort of 97 children who were seizure free for 12 months, age at seizure onset over 10 years was associated with a higher risk of seizure recurrence (Dooley et al., 1996). This finding was confirmed by a study in 136 adult patients (Galimberti et al., 1993) in whom age older than 12 years at disease onset was a negative prognostic indicator. The systematic review by Berg and Shinnar (1994) found adolescent-onset epilepsy to carry a higher risk of relapse (relative risk 1.79, 95% CI 1.46–2.19) compared to childhood-onset epilepsy; the corresponding value for adult-onset epilepsy was 1.34 (95% CI 1.00–1.81). These data suggest that epilepsy syndromes occurring in late childhood and adolescence may pose the patient at higher risk of relapse when treatment is discontinued even after long seizure-free periods [Level of evidence: 3].

Recommendations

Age at onset of seizures should be considered along with other factors when deciding to stop or withhold treatment. Older age at onset of seizures should not affect the decision to stop treatment if other negative prognostic predictors are not present [Strength of recommendation: B].

Question 6: Does Sex Matter?

Of the 27 studies investigating the role of sex, four found females at higher risk of relapse than males (Table 1). In the only study adjusting for other covariates, the overall recurrence rate was 48% in female and 28% in male (Dooley et al., 1996) [Level of evidence: 3].

Recommendations

Although a female patient carries a higher risk of relapse than a male patient, the role of sex should not influence the decision to stop or withhold treatment unless other factors (e.g., epilepsy syndrome) are associated [Strength of recommendation: C].

Question 7: Should We Exclude Treatment Withdrawal in Patients with a Family History of Epilepsy?

Family history of epilepsy was investigated in 33 studies (mostly in children) and found associated with an increased risk of relapse in only 5 (Table 1). Adjustment for other confounders was made only by Shinnar et al. (1994), who found family history of seizures carrying a threefold risk of seizure relapse [Level of evidence: 3].

Recommendations

Family history of epilepsy should not be a contraindication to treatment discontinuation when all the other variables have been properly weighted [Strength of recommendation: B].

Question 8: Should We Exclude Treatment Withdrawal in Patients with a History of Febrile Seizures?

Eighteen studies addressed this issue and only six found history of febrile seizures significantly affecting the relapse rate after treatment discontinuation (Table 1). Multivariate analysis confirmed the prognostic role of antecedent febrile seizures in only one report (Ramos-Lizana et al., 2010). In that study, prior febrile seizures predicted a twofold risk of relapse in 216 seizure-free children [Level of evidence: 3].

Recommendations

History of febrile seizures per se should not be a contraindication to treatment discontinuation [Strength of recommendation: B].

Question 9: Should We Exclude Treatment Withdrawal in Patients with Some Epilepsy Syndromes?

Epilepsy type was investigated in 23 studies (two thirds of them in children) and found to be associated with seizure outcome in 12 (multivariate analysis, 2) (Table 1). Specific epilepsy syndromes like juvenile myoclonic epilepsy (associated with an increased risk of relapse) and benign epilepsy with centrotemporal spikes (associated with a reduced risk of relapse) were significant outcome predictors in the study of Shinnar et al. (1994). In the randomized trial of early versus delayed withdrawal (Peters et al., 1998), the risk of relapse in partial epilepsy was increased compared to generalized epilepsy, with symptomatic and cryptogenic partial epilepsy in decreasing order. Epilepsy type was confirmed as an independent outcome predictor in the extended follow-up of that study (Geerts et al., 2005). A population-based study investigating long-term prognosis of epilepsy syndromes in 148 patients with childhood-onset epilepsy found 5-year terminal remission in 59% of patients with symptomatic partial epilepsies and in 13% of patients with symptomatic/cryptogenic generalized epilepsies (Sillanpaa & Schmidt, 2006). These data are consistent with others (Camfield & Camfield, 2007; Geerts et al., 2010) [Evidence level: 3].

Recommendations

Epilepsy syndrome should be always included in the decision process at the time of treatment discontinuation. In this regard, a case should be made to stop treatment in benign epilepsy with centrotemporal spikes and in most idiopathic generalized epilepsies. In contrast, withholding treatment even in seizure-free patients might be an option for cryptogenic or symptomatic generalized epilepsies, juvenile myoclonic epilepsy, and symptomatic partial epilepsies. However, in these latter cases, the patient should be informed of the possibility that on occasion seizures might not occur and treatment stop should not be denied if required [Strength of recommendation: B].

Question 10: Should We Consider Treatment Withdrawal Only in Patients with Lower Seizure Frequency before Entering Remission and/or Shorter Duration of Active Epilepsy and/or Less Difficult Seizure Control?

The duration of active epilepsy was investigated in 27 studies (Table 1). Prolonged disease duration was a predictor of seizure relapse in 11 studies. Only the report by Holowach Thurston et al. (1982) found long duration of active epilepsy before control a predictor of relapse in children, when adjusting for other factors. In another report (Emerson et al., 1981), the number of generalized tonic–clonic seizures before control was an independent predictor of relapse. Longer time before onset of treatment, prolonged duration of the active phase of the disease, and higher seizure frequency are all markers of severity of epilepsy and may explain the higher risk of relapse after drug discontinuation. Nevertheless, the great variability of the definitions used prevent any inference from the available data [Level of evidence: 4].

Recommendations

Prolonged duration of active disease before and during treatment and high seizure frequency should not be a contraindication to treatment discontinuation [Strength of recommendation: C].

Question 11: What Is the Most Appropriate Tapering Period?

The duration of the tapering period was investigated in 10 studies, almost exclusively in children (Table 1). Tapering periods varied between 1 month and >4 years. Significant results in favor of longer tapering periods were obtained in four studies, one of them after adjusting for other factors. In that study (Mastropaolo et al., 1992), sudden discontinuation indicated a higher risk of relapse. In a Cochrane review of randomized trials comparing slow versus rapid taper (Ranganathan & Ramaratnam, 2006) there was only one study (of suboptimal quality) involving 149 children. The rapid taper group consisted in 6 weeks and the slow taper group in 9 months. There were no differences in the number of seizure-free patients at the end of 1, 2, 3, 4, and 5 years of follow-up [Level of evidence: 4].

Recommendations

Slow discontinuation of antiepileptic drugs should be encouraged and the duration of the tapering period should be tailored to the patient's needs and preference [Strength of recommendation: C].

Question 12: Is a Patient Taking Two or More Drugs at Higher Risk of Relapse Compared to a Patient on Monotherapy?

Twenty-three studies investigated the number of drugs taken at time of withdrawal (Table 1). In eight studies, taking two or more drugs carried a higher risk of relapse than taking monotherapy (multivariate analysis, 2). In a study involving 266 children discontinuing treatment after

two or more years of seizure freedom (Vurucu et al., 2010), the total number of antiepileptic drugs taken was the only risk factor for seizure recurrence (odds ratio 30.02; 95% CI 7.42-121-44). The MRC Antiepileptic Drug Withdrawal Study Group (1993) identified several factors increasing the risk of recurrence. These included, among others (see question 14), taking more than one antiepileptic drug [Level of evidence: 4].

Recommendations

The patient should be warned that taking two or more drugs at the time of treatment discontinuation may be associated with an increased risk of relapse. However, discontinuation of AEDs might be considered, in particular when no other concurrent negative prognostic factors occurs [Strength of recommendation: C].

Question 13: Does the Drug Taken at Time of Discontinuation Matter?

There are only few reports (with inconsistent findings) assessing the contribution of individual drugs on the relapse rate after treatment discontinuation with inconsistent findings (Specchio & Beghi, 2004). In the 1,113 children and adults included in the randomized trial comparing slow withdrawal to no withdrawal of AEDs, 83% of patients were receiving monotherapy with carbamazepine, phenobarbital/primidone, phenytoin, or valproate at low doses, and plasma levels were below the usual optimal range (Chadwick, 1999). The most important factor determining seizure recurrence was continued therapy, which was the case for barbiturates, phenytoin, and valproate [Level of evidence; 4].

Recommendations

The decision to stop or withhold treatment in a seizure-free patient is not affected by the type of drug to be removed [Strength of recommendation: C].

Question 14: Which Combinations of Risk Factors Help the Decision to Withhold Treatment?

Several studies using multivariable analysis models identified combinations of risk factors affecting the risk of seizure relapse. Prognostic indexes were also developed. One of them, based on a Cox proportional hazards model, used the data of the MRC Antiepileptic Drug Withdrawal Study Group (1993). The factors included were age 16 years or older, taking more than one AED, experiencing seizures after starting treatment, history of generalized tonic–clonic seizures, history of myoclonic seizures, and having had an abnormal EEG. In a population-based cohort including 504 children followed for an average of 7 years (Camfield et al., 1993), the variables predicting remission at 12 months after treatment start included age <12 years, normal intelligence, prior neonatal seizures, and fewer than 21 seizures before treatment. Prediction was enhanced by including the number of seizures between 6 and 12 months of treatment. The differences in the variables included in these models and the overall methodology of the underlying studies prevent comparisons and inferences [Level of evidence: 4].

Recommendations

A patient who is age 12 years or older and has seizures after treatment start should be cautioned not to stop treatment [Strength of recommendation: C].

Question 15: How long Should We Monitor Patients after Treatment Discontinuation?

The studies investigating the risk of seizure recurrence after drug discontinuation had follow-up periods ranging from few months to >20 years. The relapse rates were highest in the first 6 months after completion of treatment stop and decreased thereafter. As indicated by Specchio and Beghi (2004), the cumulative time-dependent probability of remaining seizure-free at 1, 2, and 3 years or longer was, respectively, 39–95%, 35–91%, and 34–89%. These wide ranges can be explained by the differing populations and study designs. In studies with longer follow-up periods, a further nonsignificant decrease in the chance of remaining seizure-free was detected. In the meta-analysis by Berg and Shinnar (1994), the cumulative probability of relapse at 1 year after initiating AED withdrawal was 25% (95% CI 21–30%) and at 2 years it was 29% (95% CI 24–34%) [Level of evidence: 2].

Recommendations

A patient discontinuing treatment for seizure freedom should be followed for no fewer than 2 years [Strength of recommendation: B].

Discussion

The following issues were addressed as indicators of the risk of seizure recurrence after drug withdrawal in the critical appraisal of published reports: length of the seizure-free period after treatment initiation, difference in seizure-free periods in children and adults, EEG pattern at the time of discontinuation, etiology of epilepsy (including mental retardation and perinatal insults), seizure type (s), patient's age and sex, family history of epilepsy, history of febrile seizures, epilepsy syndromes, seizure

frequency before entering remission, duration of active epilepsy, tapering period, number and type of antiepileptic drug(s) taken at time of discontinuation, combination of risk factors for recurrence, and length of patient monitoring after treatment discontinuation.

Levels of evidence rated 2 for EEG pattern at the time of discontinuation, etiology of epilepsy, and length of patient monitoring after drug discontinuation; 3 for length of seizure-free period after treatment initiation, difference in seizure-free periods in children and adults, patient's age and sex, family history of epilepsy, history of febrile seizures, partial seizure type, and epilepsy syndromes; 4 for seizure frequency before entering remission, prolongation of active epilepsy, difficulty of seizure control, appropriateness of tapering period, number of drugs taken versus monotherapy, antiepileptic drug(s) taken at time of discontinuation, and combination of risk factors.

A grade B recommendation was achieved for EEG pattern at the time of discontinuation, etiology of epilepsy, length of patient monitoring after drug discontinuation, length of seizure-free period after treatment initiation, difference in seizure-free periods in children and adults, patient's age and sex, family history of epilepsy, history of febrile seizures, partial seizure type, epilepsy syndromes, and length of patient monitoring after drug discontinuation. A grade C recommendation was attained for seizure frequency before entering remission, prolongation of active epilepsy, difficulty of seizure control, number and type of antiepileptic drug(s) taken at time of discontinuation, combination of risk factors, and length of tapering period.

Based on the aforementioned levels of evidence and strength of recommendations, the following indications can be given when considering drug withdrawal in seizure-free patients:

1 An abnormal EEG (epileptiform abnormalities or specific EEG patterns) at the time of treatment discontinuation is associated with an increased risk of relapse, although of a limited relevance if the abnormal EEG is the only negative prognostic predictor. The decision to stop treatment should be considered in the light of other (concurrent) predictors of relapse and the social and personal complications of a seizure relapse.

2 A documented etiology of seizures, including the presence of mental retardation and/or abnormal neurologic or imaging findings, is also associated with an increased risk of relapse; however, as with an abnormal EEG, the risk is of a limited relevance if this is the only negative prognostic predictor. The decision to stop treatment should be also considered in the light of the social and personal complications of a seizure relapse. However, an abnormal EEG pattern associated with a documented etiology of seizures warns against treatment discontinuation.

3 A patient discontinuing treatment for seizure freedom should be followed for no fewer than 2 years.

4 A minimum period of 2 years of seizure freedom should precede drug withdrawal.

5 The period of seizure freedom in children can be considerably shorter than that in adults and depends on epilepsy syndrome. This is particularly true for syndromes with a favorable outcome, such as rolandic epilepsy and benign infantile epilepsies (Capovilla & Vigevano, 2001; Hughes, 2010). In these cases, treatment could be withdrawn after a maximum period of 1 year.

6 The presence of partial seizures should not be considered per se a risk factor for relapse, in absence of other relevant seizure predictors (abnormal EEG and/or documented etiology). Seizure type should be assessed along with other variables when the decision to stop treatment must be taken.

7 Age at onset of seizures should be considered along with other factors in the context of an epilepsy syndrome. Older age at onset of seizures does not represent a risk for recurrence if other negative prognostic predictors are not present.

8 Female patients carry a higher risk of relapse than males, but sex should not influence the decision to stop or withhold treatment unless other factors (e.g., epilepsy syndrome) are associated.

9 Family history of epilepsy and history of febrile seizures do not contraindicate treatment discontinuation when all the other seizure predictors have been excluded.

10 Epilepsy syndrome should be always included in the decision process at the time of treatment discontinuation. Treatment can be withdrawn in benign epilepsy with centrotemporal spikes and in most idiopathic generalized epilepsies, but in contrast, withholding treatment even in seizure-free patients might be an option for cryptogenic or symptomatic generalized epilepsies, juvenile myoclonic epilepsy, and symptomatic partial epilepsies. However, even when suggesting treatment maintenance, the patient should be informed of the possibility that on occasional seizures might not occur and treatment stop should not be denied if required.

11 Prolonged duration of active disease before and during treatment and high seizure frequency per se do not contraindicate treatment discontinuation.

12 Slow discontinuation of AEDs should be encouraged and the duration of the tapering period should be tailored to the patient's needs and preferences.

13 Treatment with two or more drugs at the time of discontinuation may be associated with an increased risk of relapse. However, the patient should not be dissuaded from discontinuing treatment if he or she has no other concurrent negative prognostic indicators.

14 The decision to stop or withhold treatment in a seizure-free patient is not based on the type of drug to be removed.

15 A patient discontinuing treatment for seizure freedom should be followed for no fewer than 2 years.

Future Directions

A large multicenter study in newly diagnosed patients followed until prolonged (2 + years) seizure remission should be planned. This is of particular importance in pediatric age for the most common time-limited epilepsy syndromes. Prognostic predictors of seizure relapse (selected among those discussed in the present guideline) should be identified using standard definitions. All factors whose prognostic relevance was confirmed (or excluded) in studies supported by levels of evidence 3 or 4 should be investigated. These include the length of seizure-free period, seizure type, age at onset of seizures, sex, family history of epilepsy and/or febrile seizures, epilepsy syndrome, duration of active disease, seizure frequency before remission, daily dose tapering, and number and type of drugs. The sample should be of sufficient size to consent stratification of patients according to age at treatment discontinuation (children vs. adults) and to assess combinations of prognostic predictors.

An international cohort study with a period of follow-up of 2–5 years should easily meet these requirements and, at the same time, favor the external validity (i.e., generalizability) of the results.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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