



Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz



Stopping epilepsy treatment in seizure remission: Good or bad or both?

Dieter Schmidt^{a,*}, Matti Sillanpää^{b,c}

^a Epilepsy Research Group, Berlin, Germany

^b Departments of Public Health and Child Neurology, University of Turku, and Department of Child Neurology, Turku University Hospital, Turku, Finland

^c Department of Public Health, University of Turku, Turku, Finland

ARTICLE INFO

Article history:

Received 15 August 2016

Received in revised form 1 September 2016

Accepted 4 September 2016

Keywords:

Drug-treated epilepsy

Stopping AEDs

AED withdrawal: long-term seizure prognosis

Natural course

Relapse seizures

Pitfalls in stopping AEDs

ABSTRACT

Purpose: To review the outcome of epilepsy after stopping antiepileptic drugs in remission.

Results: Stopping antiepileptic drugs (AEDs) in remission is routinely done in many patients. Although the consequences of an unexpected relapse seizure in the 2 years after stopping AEDs may cause anguish and social issues, the impact on the long term seizure outlook of the epilepsy is minimal, if any. Discontinuation of drug treatment does not seem to affect the long-term prognosis but exposes patients who were seizure-free for years to a transient two-fold risk of seizures for the first 2 years after stopping AEDs. In addition, 20% of patients who were seizure-free for years, do not become seizure-free immediately after restarting AED treatment after relapse. The list of potential pitfalls is long. Patients with juvenile myoclonic epilepsy, those with prior withdrawal attempts and late remission have a higher risk of relapse.

Conclusion: Stopping AEDs in remission does not affect the long-term patterns of epilepsy and some patients report a better general health in a life without AEDs. High-risk patients should not be generally encouraged to stop their AEDs in remission. We need new drugs that combine anti-seizure and antiepileptogenic effects to prevent seizure relapse and flare up of epilepsy after stopping AEDs in remission.

© 2016 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.

1. Introduction

The ideal objective of treating a person with epilepsy is of course to induce remission by usage of antiepileptic drugs (AEDs) and ultimately stop the AEDs without causing seizure recurrence [1]. Nearly 70% of patients with new-onset epilepsy eventually enter prolonged terminal seizure remission during treatment with AEDs [2,3]. The continued use of AEDs in children and adults may be associated with adverse effects in a substantial fraction of the exposed population, including behavioral and cognitive and other chronic side effects [1]. Further disadvantages of continuing treatment indefinitely include a higher risk of teratogenicity, drug interaction with concurrent medications, and, last not least, the concern that treatment may be unnecessary. Understandably, many patients wish to lead a life without taking drugs and plan to stop their AEDs drugs after being seizure free for a while [1]. As a consequence, AEDs are routinely withdrawn in the majority of

patients entering prolonged seizure remission during drug treatment [3,4]. Surprisingly, class I evidence on the consequences of stopping versus continuing treatment on seizure outcome and general health are rather limited and the list of potential pitfalls when attempting to stop AEDs is long [1]. The decision to continue or to stop AED treatment in patients with prolonged seizure remission is a difficult one and requires a full assessment of the risk-benefit balance of drug discontinuation for the individual patient. In this brief overview, we discuss the best available evidence on outcome after stopping treatment of epilepsy in remission during drug treatment and how to avoid common pitfalls with an emphasis on more recent data. For a review of the earlier literature including stopping AEDs after surgical remission see [4]. We will not be able to discuss stopping AEDs following surgical remission or in cases of a misdiagnosis of epilepsy.

2. Seizure outcome in patient populations after stopping AEDs in remission

The short-term recurrence risk after stopping AEDs in seizure free patient populations is well established. Three major lines of evidence exist. However, there is only one small randomized

* Corresponding author at: Epilepsy Research Group, Goethestr. 5, D-14163 Berlin, Germany. Fax: +49 30 8017679.

E-mail address: dbschmidt@t-online.de (D. Schmidt).

<http://dx.doi.org/10.1016/j.seizure.2016.09.003>

1059-1311/© 2016 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.

double-blind trial for AED withdrawal of selected adults becoming seizure-free on AEDs [5]. The best evidence from the earlier literature comes from a large unblinded randomized trial in patients who became seizure-free on AED treatment [6], and several non-randomized observational studies [e.g., 7–10]. Finally, a number of reviews offer valuable information [4,11,12].

2.1. The Akershus double-blind randomized study

The Akershus study is the first double-blind, randomized trial of AED withdrawal in remission [5]. In this study, 15% of patients randomized to treatment withdrawal and 7% of those randomized to remain on treatment had a recurrence at 12 months, a non-significant difference. However, those who stopped AEDs improved significantly in their neuropsychological performance. In this benchmark study, Lossius and colleagues [5] randomized carefully chosen adult patients, who were seizure-free for more than 2 years on AED monotherapy, to AED withdrawal ($n = 79$) or no withdrawal ($n = 81$), and followed them up for 12 months, or until seizure recurrence. After withdrawal, recurrence rates were 27% after a median of 41 months off medication. Adverse effects including behavioral and cognitive side effects have been shown to improve after drug withdrawal [5]. Withdrawal did however not affect general health measured as quality of life and the EEG findings. Predictors for remaining seizure-free after AED withdrawal over 1 year were normal neurological examination at presentation and, in the view of the authors, use of carbamazepine prior to withdrawal.

Although the Akershus study is first in class, and the authors are to be commended for this, it needs to be considered in the light of several limitations as any study however good it may be. One weakness is the limited generalizability of the findings as the study excluded patients with a high risk of seizure relapse after withdrawal, for example, patients with idiopathic generalized epilepsy showing epileptiform discharges and those with juvenile myoclonic epilepsy, patients seizure-free on polytherapy, and those with a history of two prior withdrawal attempts were not eligible. The restricted access unfortunately introduced a substantial bias toward lowering the risk of seizure relapses, obviously in both arms. Another limitation is that patients were not randomized on prior AED use, thus the better outcome of withdrawal observed in those withdrawn from carbamazepine, may, in part, reflect a selection bias when treatment was started, and at least in our view, should not be taken as evidence that withdrawing patients from carbamazepine is more successful than withdrawal from other AEDs. Finally, the AED treatment, if any, and prognosis of seizures occurring after a relapse, if any, have not been included in the results. It would have been informative to learn if most patients had one seizure and remained seizure free after relapse or how often treatment was restarted and how successful it was in terms of regaining remission. This information would have been valuable for patient counseling.

What are the implications of this important study? Foremost, AED withdrawal in adults is associated with a considerable risk of seizure-recurrence in one of six low-risk patients, more than double the risk in those who remain on drug. (Though the difference was not significant, possibly due to the limited power of the small number of patients in the trial.) Although some patients had improved neuropsychological outcome, general health, measured as quality of life was not better after withdrawal. This important finding is in general agreement with the benchmark MRC AED withdrawal study [6] (see below), although Jacoby et al. [13] found a benefit in a subgroup of patients of the MRC study who had a low risk of recurrence. Another important result of the Akershus study was that remaining on AEDs did not fully protect from seizure recurrence. In fact, 2 years after withdrawal, there

was no difference in recurrence rate between the withdrawal and the no withdrawal group. This shows that stopping AEDs in remission does not seem to influence the long-term seizure outcome of epilepsy. The Akershus study provided robust class I evidence about the benefits and risks of withdrawing AEDs in low-risk seizure-free adults that we did not have before. Patients and physicians are now better equipped to make the difficult decision to withdraw AEDs, after taking into account the individual risk profile of the patients regarding relapse and other important factors, such as the preference of the patient and consideration of the sometimes grave social consequences of a seizure relapse in patients who had been seizure free for years.

2.2. MRC antiepileptic drug withdrawal study and subsequent reports

The MRC study is an unsurpassed benchmark study because it is the first in class to uniquely assess the risk of seizures after stopping AEDs compared to continued treatment in a pragmatic trial conducted in 1013 patients who had been free of seizures for at least 2 years and were undecided whether to stop AEDs or not [6]. The MRC AED withdrawal study provided unique evidence about the risk of seizures despite continued AED treatment. AED discontinuation doubles the risk of seizures for up to 2 years after stopping AED compared to continued treatment [14]. By 2 years after randomization, 78% of patients in whom treatment was continued and 59% of those in whom it was withdrawn remained seizure free, but thereafter the differences between the two groups diminished. This suggests that the long-term seizure outcome is not affected by drug discontinuation. The main result of the MRC study was that AED discontinuation doubles the risk of seizures for up to 2 years after stopping AED compared to continued treatment [14]. Non-compliance with continued treatment apparently accounted for only a small proportion of the risk to the group continuing with treatment. The most important factors determining outcome were longer prior seizure-free periods (reducing the risk) and more than one antiepileptic drug and a history of tonic-clonic seizures (increasing the risk of relapse). Other factors (e.g., history of neonatal seizures, specific electroencephalographic features) seemed to have smaller effects, but even in such a large study the confidence intervals for these observations were wide [6,15]. The failure to predict the risk of recurrence for the individual patient even in this large study creates uncertainty and anguish and is a matter of concern. The study group has since provided very useful information to delineate the individual risk which will be discussed below. Although both studies, the MRC study and the Akershus study, are most valuable, however both included subpopulations of patients by either excluding those with a high risk of relapse as in the Akershus study or excluding those who unambiguously wished to stop their AEDs. Additional valuable information on the risk of relapse, albeit in a lower evidence class is available from selected reviews.

2.3. Selected reviews

The overall quite substantial risk of seizure relapse after treatment discontinuation has been well reviewed in the literature (Table 1).

The proportion of patients with relapses during or after treatment withdrawal ranges from 12 to 66% (see Table 1). Using life-table analysis, the cumulative probability of remaining seizure-free in children was 66–96% at one year and 61–91% at two years (adults 39–74% and 35–57% respectively). The relapse rate was highest in the first 12 months (especially in the first 6 months) and tended to decrease thereafter. A review of the impact of planned discontinuation of AEDs in seizure-free patients on seizure recurrence yielded 14 observational studies of seizure

Download English Version:

<https://daneshyari.com/en/article/4935531>

Download Persian Version:

<https://daneshyari.com/article/4935531>

[Daneshyari.com](https://daneshyari.com)