**Individualised prediction model of seizure recurrence and long-term outcome after antiepileptic drug withdrawal – an Individual Participant Data meta-analysis.**

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Number of pages: 17

Number of words: 3051 (excluding “Research in context” box)

Number of figures: 3

Number of tables: 2

Supplementary figures: 3

Supplementary tables: 10

Key words: antiepileptic drug withdrawal; prediction; prognosis; seizure recurrence; long-term seizure-freedom; nomogram

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**Abstract**

**Background**. People with epilepsy who became seizure-free while taking antiepileptic drugs (AEDs) may consider discontinuing their medication, with the possibility of increased quality of life due to the elimination of adverse events. The risk, however, is seizure recurrence. Factors related to long-term seizure outcome have not been studied widely. The objective of the study was to identify predictors of both outcomes, and produce nomograms for individualised outcome estimation.

**Methods**. A systematic review identified candidate predictors and eligible articles, using PubMed and EMBASE databases with a last update in November 2014. Eligibility criteria were: cohort with seizure-free patients with epilepsy, AED withdrawal, information regarding seizure recurrences during and after withdrawal. Risk of bias was assessed using the Quality in Prognosis Studies system. Data analysis was based on individual participant data. Survival curves and proportional hazards were computed. The strongest predictors were selected with backward selection. Models were converted to nomograms and an Excel tool to determine individual risks.

**Findings**. Forty-five studies with 7082 patients were identified; ten studies (22%) - with 1769 patients (25%) were included. Median follow-up was five years (interquartile range 3-10, maximum 23 years). Prospective, retrospective studies and randomised controlled trials were included, covering non-selected and selected populations of both children and adults. Relapse occurred in 812 (46%) of patients, 9% had seizures in their last year of follow-up suggesting enduring seizure control was not (yet) regained. Independent predictors of seizure recurrence were: epilepsy duration before remission, seizure-free interval before AED withdrawal, age at onset of epilepsy, history of febrile seizures, number of seizures before remission, absence of a self-limiting epilepsy syndrome, developmental delay, epileptiform abnormality on EEG before withdrawal. Independent predictors of seizures in the last year of follow-up were: epilepsy duration before remission, seizure-free interval before AED withdrawal, number of AEDs before withdrawal, female sex, family history of epilepsy, number of seizures before remission, focal seizures, epileptiform abnormality on EEG before withdrawal. Adjusted concordance-statistics were 0·65 (95% CI 0.65-0.66) and 0·71 (95% CI 0.70-0.71), respectively. Validation was stable across the individual study populations.

**Interpretation**. Presented nomograms are evidence-based tools with robust performance across populations of children and adults. The nomograms allow for predicting the outcome of drug withdrawal for the individual patient, including both the risk of relapse and the chance of long-term seizure-freedom. Main limitations are the absence of a control group continuing AED treatment and the definition of long-term seizure freedom.

**Funding**. Dutch National Epilepsy Fund (NEF 08-10).

**INTRODUCTION**

Antiepileptic drugs (AEDs) suppress seizures in 65-85% of people with epilepsy1. Because of the fear of seizure relapse many people continue AED treatment even when free from seizures and despite the side effects. Up to 88% of patients experience – often multiple – adverse effects from AEDs2,3. As a result, quality of life of seizure-free patients is significantly better when AEDs are discontinued4, provided they remain seizure-free.

A meta-analysis estimated that the cumulative seizure recurrence rate after AED withdrawal is around 34 percent5. From those who experience seizure recurrence, about 80% will be able to control seizures by reinstating AED treatment6. The remaining 20% of people will develop treatment refractory epilepsy, although there is no convincing evidence that this refractoriness occurs as a consequence of AED withdrawal. Nonetheless, some have debated whether AED withdrawal would be safe at all7,8.

The dilemma between overtreatment and side effects on the one hand, and the risk of seizure recurrence on the other, is one that should be considered with every seizure-free patient. However, a robust tool to guide the decision to withdraw AEDs is missing. Twenty-five predictors of seizure outcome have been identified in the past, but the published populations, methods and results were too variable to distil a definite set of independent predictors5. While many studies focused on predictors of seizure recurrence, only a few studied factors related to refractory epilepsy6. A major limitation of prognostic meta-analysis using published aggregate data is that effect sizes associated with individual predictors cannot be produced due to different methods and reporting of the original studies. A method to overcome this issue is through a meta-analysis of Individual Participant Data (IPD) in which the original data from previous studies are combined and more accurate, adjusted, statistics can be computed on a large dataset9.

In this IPD meta-analysis of 1769 patients we aimed to (1) identify independent predictors of seizure recurrence and (2) long-term seizure outcome, and ultimately, (3) provide an evidence-based tool, using nomograms, to predict the short-, and long-term seizure outcome in an individual seizure-free patient who faces the decision to withdraw AEDs.

**METHODS**

### Article selection

To select articles eligible for this study, a systematic search of the databases of PubMed and EMBASE was employed on 6-11-2014. Inclusion criteria for articles were: original full-text article of a cohort of seizure free patients who started AED withdrawal, information regarding seizure recurrences during and after AED withdrawal. Surgical cohorts and reports with <30 patients have been excluded, as well as publications on acute symptomatic seizures because this is beyond the scope of the objective. No limitation concerning the year of publication was used. Unpublished data were not explored. Search queries are presented in Appendix 1. Reference lists were checked for missed literature. Two independent researchers (HJL and KG) selected the studies. Differences in article inclusion were solved through discussion. After selecting eligible articles, contact details of authors were gathered from recent articles or Internet. Authors were asked to collaborate. A second request was sent to non-responders six weeks later. Authors who agreed to collaborate were requested to provide anonymous individual participant data concerning baseline, outcome and candidate predictor variables. Aggregate data from non-included studies were not used. The Dutch Medical Research Involving Human Subjects Act did not apply and ethical approval and informed consent was not needed.

### Outcome variables

Two distinct outcome variables were used, corresponding with the two main research questions. The first was the occurrence and timing of seizure recurrence, at two and five years, after initiation of AED withdrawal. The second was long-term seizure outcome, with favourable outcome defined as complete seizure-freedom in the last year of follow-up, suggesting either no recurrence, or recurrence with subsequent regain of seizure control. For those with unfavourable long-term outcome, time to event was defined as the interval between initiation of AED withdrawal and seizure recurrence; for patients seizure-free at last follow-up, irrespective of the presence of seizure recurrence, censoring time was the maximum follow-up duration.

### Predictor variables

The selection of candidate predictors was based on a systematic review on the predictors of seizure recurrence after AED withdrawal5, which identified 25 significant predictors. Three pairs of variables measured similar constructs and were therefore reduced to three single variables, resulting in a final list of 22 variables for the analysis. All studied variables are listed in table 1. Information on variable definitions can be found in Appendix 2.

### Quality assessment

The quality of data as presented in the original publication of the collaborators was previously assessed in a systematic review5, with an adjusted version of the Quality in Prognosis Studies system10. Potential for bias was classified as low, moderate or high for the categories ‘study participation’, ‘study attrition’, ‘prognostic factor measurement’, and ‘outcome measurement’.

### Statistical analysis

A detailed overview of statistical methods can be found in Appendix 2.

In short: missing data were dealt with by multiple imputations. Random-effects proportional hazards regression was performed to study prognostic factors. A selection of strongest contributing predictors was made through backward selection of variables using Akaike information criterion combined with manual removal of least contributing predictors, until the most optimal model was selected. Calibration plots were created, and for validation a concordance statistic (c-statistic) was computed and adjusted for optimism by using 200 bootstrap samples. Internal-external cross-validation (IECV) was performed to assess validity of the model across the different populations.

The funding source was the National Epilepsy Fund, which provided a grant for the doctoral studies of the first author. They had no influence on the design, execution or publication of this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**RESULTS**

Forty-five publications were identified as eligible for inclusion, 33 authors were ultimately contacted and invited to collaborate of which ten agreed to participate and provide individual participant data (flow-chart, supplementary figure 1). A total of 1771 of 7082 patients were included (25%). Many authors provided additional, unpublished details on the cohorts, such as longer follow-up durations. No important issues that could compromise the analysis were identified in checking individual participant data from contributing cohorts. Details on the separate cohorts are given in table 2, showing a variety of populations, some with selected populations such as children with cryptogenic focal epilepsies11, patients only on monotherapy12, patients on monotherapy older than 13 years with exclusion of idiopathic generalised epilepsies13, others with mostly unselected populations of children14–18, adults19, or both20. The maximum follow-up after start of AED withdrawal was 23 years, and for the patients with a seizure recurrence, the follow-up after the recurrence was a median of 3·7 years (range 0-20 years, interquartile range (IQR) 1-7 years). The median time to AED withdrawal after the last seizure was 33 months (range 3-385 months, IQR 24-48 months).

### Seizure-freedom after initiation of AED withdrawal

Seizure recurrence occurred in 812 patients (46%, table 2). Figure 1 shows the survival curve for time to seizure recurrence, with an ultimate Kaplan Meier estimate of 48% seizure-free patients. The last seizure recurrence was 13 years after starting AED withdrawal. Supplementary figure 2 shows the survival curve split by EEG results. The overall recurrence rate is higher than the average reported in the literature5; when only published data are considered, the median of published seizure recurrence estimates of the 10 included papers was 40%, where the median of the 35 papers, which were not included, was 28% (suppl. table 1). The only other difference between included and excluded papers was the high percentage of randomised controlled trials in the current analysis (50%) compared to 11% in non-included papers (suppl. table 1). Nine percent of patients were not seizure-free in the last year of follow-up (table 2), although some of those may have had a period of seizure-freedom prior to that. Of the patients with seizure recurrence and maximum follow-up between 1 and 5 years after recurrence, 202/280 (72%) were seizure-free in the last year of follow-up. The rates were 121/152 (80%), 65/80 (81%) and 50/57 (88%) for those who relapsed and were followed 5-10 years, 10-15 years and more than 15 years after seizure recurrence, respectively.

### Missing data and quality appraisal

Supplementary table 2 and suppl. figure 3 provide information on missing data. Five variables had missing values in between 30-45% of patients. Imputation was not possible for two cases because of too much missing information; these cases have been removed from further analysis, thus performed on 1769 patients. The risk of bias based on the published papers in the ten selected cohorts was scored as low to ‘partly present’ (suppl. table 3)5.

### Univariable proportional hazards

### Univariable predictors of seizure recurrence are presented in table 1, showing 14 significant variables. With respect to the long-term outcome, defined as the presence of seizures in the last year of follow-up, ten variables were significantly related in univariate analysis.

### To investigate a possible selection bias for the variable ‘failure of previous AED withdrawal’, baseline characteristics between positive and negative cases were investigated which showed no large difference between the groups besides a longer duration of epilepsy (median 61 vs. 24 months), and a longer seizure free interval (median 41 vs. 31 months, suppl. table 4) in the group of patients who had a previous relapse after withdrawal.

### Predicting outcome by multivariable analysis

### For the risk of seizure recurrence and the chance of long-term seizure-freedom, respectively, 13 and 12 independent predictors were identified in multivariable modelling (suppl. tables 5 and 6 resp.). It was possible to reduce the number of variables in each model to eight, without having an effect on the calibration plots or the validation statistics. The final reduced models with hazard ratios are found in supplementary tables 7 and 8. Independent predictors of seizure recurrence were: epilepsy duration before remission, seizure-free interval before AED withdrawal, age at onset of epilepsy, history of febrile seizures, number of seizures before remission, absence of a self-limiting epilepsy syndrome, developmental delay, epileptiform abnormality on EEG before withdrawal. Independent predictors of seizures in the last year of follow-up were: epilepsy duration before remission, seizure-free interval before AED withdrawal, number of AEDs before withdrawal, female sex, family history of epilepsy, number of seizures before remission, focal seizures, epileptiform abnormality on EEG before withdrawal.

A visual representation of these models is provided in figures 2a and 3a, which are nomograms that can be applied for direct use in clinical practice to calculate the chance of both outcome measures at specific time points in each individual patient.

For practical purposes the nomograms were translated into an Excel tool for risk calculation. It is available via the URL <https://github.com/epilepsypredictions/AED-withdrawal>

### Validation and calibration

The adjusted c-statistic for predicting seizure recurrence is 0·65 (95% CI 0·65-0·66). In the validation procedure, the c-statistic varied between 0·64 and 0·67, thus showing stability across all populations (suppl. table 9). For predicting long-term seizure-freedom, the adjusted c-statistic is 0·71 (95% CI 0·70-0·71), which varied in the validation procedure between 0·68 and 0·79 (suppl. table 10). Lastly, plotting the predicted probabilities against the observed proportions shows good calibration for both models (figures 2b and 3b; note the change of scale on both axes for figure 3b).

**DISCUSSION**

This prognostic IPD meta-analysis of the risks of AED withdrawal in 1769 seizure-free people with epilepsy yields clinically useful nomograms to predict individual seizure outcome. Relapse occurred in 812 (46%) of patients, while only 9% of the total cohort had seizures in the last year of follow-up. The proportion of relapsing patients that did not regain seizure-freedom decreased with longer follow-up times. The strongest predictors, included in the nomograms, were for seizure recurrence: duration of epilepsy, duration of the seizure-free interval, age at onset of seizures, history of febrile seizures, ten or more seizures before remission, the absence of a self-limiting epilepsy syndrome (such as absence-, or Rolandic epilepsy or Panayiotopoulos syndrome), IQ below 70, and epileptiform abnormality on EEG before AED withdrawal. For predicting long-term seizure outcome, the eight selected independent predictors were: duration of epilepsy, duration of the seizure-free interval, number of AEDs before withdrawal, female sex, family history of epilepsy in first or second degree, ten or more seizures before remission, the presence of focal seizures, and epileptiform abnormality on EEG before AED withdrawal. Validation -or assessment how well a prediction works on data other than that on which the model was built- is arguably the most important issue in prognostic modelling21, and “external” validation within the available data was done through IECV22 with good and stable performance across all cohorts.

Several clinically important implications can be drawn from the presented data. The first observation is that, although the 22 candidate predictors had all been reported as significant predictors in at least one peer-reviewed article5, eight of these were now shown to have no consistent significant association with the outcome. The most striking example is the failure of a previous attempt to withdraw from medication. In line with a recent publication from Wolf23, a prior seizure recurrence after AED withdrawal is not related to the outcome of a second (or third) trial. This finding is not the result of a selection bias, because (a) none of the included cohorts excluded patients with a previous failure of AED withdrawal, and (b) the baseline characteristics of those with a failed previous AED withdrawal attempt were very similar to those attempting for the first time.

Another observation is the effect of epileptiform activity on EEG before AED withdrawal, a factor which has been debated in the past24. Based on the analyses, EEG abnormalities are significantly associated with outcome, but in the absence of other predictive factors only increase the risks mildly. EEG abnormalities alone should thus not prevent withdrawal of medication, a notion which was already stated in 198719 and is in agreement with for example the 2013 Italian guideline on AED withdrawal25.

The age at onset of epilepsy is an important predictor for seizure recurrence, but not for long-term seizure-freedom. Its association with seizure recurrence is U-shaped, with an elevated risk at  birth which falls to a nadir by about 3-4 years when it begins to rise again until age 10 and plateaus until age 25; subsequently the risk continues to rise further with older ages of onset. No clear explanation for the U-shaped relation between age at onset and seizure recurrence could be found.

The duration of the seizure-free interval is negatively correlated to both seizure outcomes. Where most studies on the timing of AED withdrawal study the dichotomy “early versus late AED withdrawal”, as meta-analysed in a Cochrane review26, our analysis shows that in fact the risk decreases with every additional year of seizure-freedom. The common understanding that it is advisable to wait for “at least two years” is based on an artificial threshold, and the rule should at least be complemented by stating, “every added seizure-free year reduces the risk”. The nomograms will provide insight in the best timing for the individual patient.

As a general caveat, in addition to likelihood of the outcome, there are many more considerations to be made in the decision to withdraw AEDs in seizure-free patients. When counselling patients with the use of these prediction models, a physician should be aware of the way risks are presented, as it can steer the patient towards a certain choice27. Other factors like fear of losing a driver’s license or even a job28, the social stigma around seizures29,30, and the quality of life2 are important considerations. The nomograms only provide individualised statistical chances, and can only be applied when balancing benefits and risks within the context of all these factors.

### Limitations

It may appear that our models are restricted to populations with relatively high recurrence rates, with an estimated 52% of patients with seizure recurrence within 23 years after AED withdrawal. However, the ten included studies contain many different populations, from strictly selected to population-based, with recurrence rates between 26% and 63%. In the internal-external cross-validation procedure the influence of the separate populations is tested by omitting them one by one. For both the populations with low and high recurrence risks the model performance remained stable. Therefore, the high average recurrence rate is no limitation to the generalizability of the models.

A limitation is that the study population contains only people who made an attempt to withdraw AEDs, and maintaining AEDs still carries the risk of seizure recurrence and refractory epilepsy. The only two randomised AED withdrawal trials showed that continued AED treatment is related to 7% seizure recurrence at one year31 and 22% at two years20, compared with 15% and 41% for the withdrawal groups, respectively. The development of refractory epilepsy may not at all be related to AED withdrawal: a follow-up study of the MRC AED withdrawal trail showed no differences between the two randomisation arms in terms of seizure control after relapse32.

For two predictors a low number of cases were provided: (history of) epileptic encephalopathy (24 cases) and juvenile myoclonic epilepsy (JME, 30 cases). Due to the low patient numbers it cannot be concluded that these factors are not predictors of outcome. For JME patients, 26/30 experienced seizure relapse (87%) but all were seizure free at last follow-up. This suggests that only few patients can be successful at AED withdrawal (see also 33,34). However, although most relapse, the eventual rate of regaining seizure freedom is high.

A limitation of using IPD from previously executed studies is that prognostic factors can be defined differently. For the included variables, some variation in the measurement of developmental delay and the definition of epilepsy duration was found, as described in Appendix 2. The variable “self-limiting epilepsy syndromes” was strictly defined in our protocol and not subject to different interpretation.”

A last limitation is the quantification of long-term seizure-freedom chosen in the analysis. From most studies, only two outcome measures were available: seizure recurrence, and the seizure status in the last year of follow-up, both dichotomised in seizures being present or not. Although the presence of seizures in the last year of follow-up does not fully cover long-term outcome, it is the most accurate approximation of seizure control after seizure recurrence currently available.

In conclusion, the presented nomograms are helpful to calculate an individualised risk of AED withdrawal and the chance of long-term favourable seizure outcome. They may therefore help to guide person-tailored choices by the physician and patient.

**Conflicts of interest**

All authors declare that they have no conflicts of interest.

**Acknowledgements**

This study was funded by the Dutch National Epilepsy Fund (NEF 08-10)

**Authors’ contributions**

HJL, WMO, DS, SS, KG and KPJB contributed to the design of the study. HJL and KG performed the literature search. Data collection was performed by HJL, ATG, MP, JR-L, AGM, JO, LS, LMS, MT, TMOC, and SS. HJL and WMO performed data analysis and created the figures. All authors contributed to the interpretation of results, reviewed and critically revised the article, and approved the final version for submission.

**Research in context (box)**

**Evidence before this study**

A systematic review of available literature was performed which identified all significant predictors of AED withdrawal outcome previously reported. A total of 25 variables were identified as significant predictor of seizure recurrence in at least one peer-reviewed article. However, differences in study design, population, and methods limited the possibility to determine which are the strongest predictors, and how to combine those to predict risks for the individual patient.

**Added value of this study**

This IPD meta-analysis of 1769 patients identified independent predictors of seizure relapse and eventual seizure freedom after AED withdrawal, and enabled the computation of individualized outcome risks. The nomograms are validated across various populations, and can be applied in all seizure-free patients, children and adults, in whom AED withdrawal is considered.

**Implications of all the available evidence**

The nomograms will improve patient consultation by providing insight in the risks of AED withdrawal, providing the patient with evidence-based risk estimates. Furthermore, future studies on prognostic factors for the outcome of AED withdrawal should correct for those found in this paper.

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