Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis

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Summary

Background People with epilepsy who became seizure-free while taking antiepileptic drugs might consider discontinuing their medication, with the possibility of increased quality of life because of the elimination of adverse events. The risk with this action, however, is seizure recurrence. The objectives of our study were to identify predictors of seizure recurrence and long-term seizure outcomes and to produce nomograms for estimation of individualised outcomes.

Methods We did a systematic review and meta-analysis, and identified eligible articles and candidate predictors, using PubMed and Embase databases with a last update on Nov 6, 2014. Eligible articles had to report on cohorts of patients with epilepsy who were seizure-free and had started withdrawal of antiepileptic drugs; articles also had to contain information regarding seizure recurrences during and after withdrawal. We excluded surgical cohorts, reports with fewer than 30 patients, and reports on acute symptomatic seizures because these topics were beyond the scope of our objective. 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 a web-based tool to determine individual risks.

Findings We identified 45 studies with 7082 patients; ten studies (22%) with 1769 patients (25%) were included in the meta-analysis. Median follow-up was 5·3 years (IQR 3·0–10·0, maximum 23 years). Prospective and 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 1769 patients; 136 (9%) of 1455 for whom data were available had seizures in their last year of follow-up, suggesting enduring seizure control was not regained by this timepoint. Independent predictors of seizure recurrence were epilepsy duration before remission, seizure-free interval before antiepileptic drug withdrawal, age at onset of epilepsy, history of febrile seizures, number of seizures before remission, absence of a self-limiting epilepsy syndrome, developmental delay, and epileptiform abnormality on electroencephalogram (EEG) before withdrawal. Independent predictors of seizures in the last year of follow-up were epilepsy duration before remission, seizure-free interval before antiepileptic drug withdrawal, number of antiepileptic drugs before withdrawal, female sex, family history of epilepsy, number of seizures before remission, focal seizures, and epileptiform abnormality on EEG before withdrawal. Adjusted concordance statistics were 0·65 (95% CI 0·65–0·66) for predicting seizure recurrence and 0·71 (0·70–0·71) for predicting long-term seizure freedom. Validation was stable across the individual study populations.

Interpretation We present evidence-based nomograms with robust performance across populations of children and adults. The nomograms facilitate prediction of outcomes following drug withdrawal for the individual patient, including both the risk of relapse and the chance of long-term freedom from seizures. The main limitations were the absence of a control group continuing antiepileptic drug treatment and a consistent definition of long-term seizure freedom.

Funding Epilepsiefonds.

Introduction

Antiepileptic drugs suppress seizures in 65% to 85% of people with epilepsy.[1] Because of the fear of seizure relapse many people with epilepsy continue antiepileptic drug treatment even when free from seizures and despite the side-effects of the drugs. Up to 88% of patients often have several adverse effects from antiepileptic drugs.[2,3] As a result, quality of life for seizure-free patients is significantly better when antiepileptic drugs are discontinued,[4] provided they remain seizure free.

Results from a meta-analysis estimated that the cumulative seizure recurrence rate after antiepileptic

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Research in context

Evidence before this study

We did a systematic review of the English-language scientific literature in PubMed and Embase published up to Nov 6, 2014, using the search terms "antiepileptic", "withdrawal", "recurrence", and "seizure-free", and their synonyms. Overall risk of bias for separate studies was low for study participation, study attrition, prognostic factor measurement, and outcome measurement. 25 variables were identified as significant predictors of seizure recurrence in at least one peer-reviewed article. However, differences in study design, population, and methods limited the possibility to determine which were the strongest predictors, and how to combine those predictors to identify risks for the individual patient.

Added value of this study

This individual participant data meta-analysis of information from 1769 patients identified independent predictors of seizure relapse and eventual seizure freedom after antiepileptic drug withdrawal, and enabled the computation of individualised outcome risks. Our nomograms are validated across various populations and can be applied in all seizure-free patients, both children and adults, for whom antiepileptic drug withdrawal is being considered.

Implications of all the available evidence

The nomograms have the potential to improve patient consultations by providing evidence-based estimates of risk for antiepileptic drug withdrawal. Furthermore, future studies on prognostic factors for the outcome of antiepileptic drug withdrawal should correct for those identified as predictors in this paper.

drug withdrawal is around 34%.[5] For those who have seizure recurrence, about 80% will be able to control their seizures by reinstating antiepileptic drug treatment.[6] The remaining 20% will develop treatment-refractory epilepsy, although there is no convincing evidence that this refractoriness occurs as a consequence of antiepileptic drug withdrawal. Nonetheless, there is some debate around whether antiepileptic drug withdrawal is safe at all.[7,8]

The dilemma between overtreatment and side-effects of antiepileptic drugs on the one hand, and the risk of seizure recurrence on the other should be considered with every seizure-free patient. However, a robust tool to guide the decision to withdraw antiepileptic drugs is not available. 25 predictors of seizure outcome have been identified, but the published populations, methods, and results were too variable to distil a definitive set of independent predictors.[5] Although many studies have focused on predictors of seizure recurrence, only a few have studied factors related to refractory epilepsy.[6] A major limitation of prognostic meta-analyses that have used published aggregate data is that effect sizes associated with individual predictors cannot be produced because of 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 for a large dataset.[9]

In this IPD meta-analysis we aimed to identify independent predictors of seizure recurrence and long-term seizure outcome, and ultimately provide an evidence-based tool using nomograms to predict the short-term and long-term seizure outcomes for individual seizure-free patients who face the decision of whether to withdraw antiepileptic drugs.

See Online for appendix

Methods

Search strategy and selection criteria

To select articles eligible for this study, we did a systematic search of PubMed and Embase on Nov 6, 2014 (with no date restrictions). Inclusion criteria were that they had to be original full-text articles reporting on a cohort of seizure-free patients who started antiepileptic drug withdrawal and containing information regarding seizure recurrences during and after antiepileptic drug withdrawal. We excluded surgical cohorts, reports with fewer than 30 patients, and reports on acute symptomatic seizures because these topics were beyond the scope of our objective. Unpublished data were not explored. Search queries are in the appendix (p 11). We checked reference lists for missed articles. Two independent researchers (HJL and KG) selected the studies and differences in article inclusion were solved through discussion. After selecting eligible articles, contact details of authors were gathered from recent articles or the internet and authors were asked to collaborate with us. A second request was sent to non-responders 6 weeks later. Authors who agreed to collaborate were requested to provide anonymous IPD for baseline, outcome, and candidate predictor variables. Aggregate data from studies for which IPD were not available were not used.

Outcome and predictor variables

We used two distinct outcome variables corresponding with the two main research questions. The first was the occurrence and timing of seizure recurrence at 2 and 5 years after initiation of antiepileptic drug 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 antiepileptic drug withdrawal and seizure recurrence; for seizure-free patients at last follow-up, irrespective of the presence of seizure recurrence, censoring time was the maximum follow-up duration.

The selection of candidate predictors was based on a systematic review of the predictors of seizure recurrence after antiepileptic drug withdrawal,[5] 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 (table 1). Information on variable definitions is in the appendix.

The quality of data presented in the original publications was previously assessed in a systematic review[5] with an adjusted version of the Quality in Prognosis Studies system.[10] Potential for bias was classified as low, moderate, or high for the categories of study participation, study attrition, prognostic factor measurement, and outcome measurement.

Data analysis

A detailed overview of statistical methods is in the appendix (p 12). Briefly, missing data were dealt with by multiple imputations. Random-effects proportional hazards regression was done to study prognostic factors. A selection of the strongest contributing predictors was made through backward selection of variables using the Akaike information criterion combined with manual removal of the least contributing predictors, until the most optimum 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 done to assess the validity of the model across the different populations.

Role of the funding source

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. 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

We identified 45 reports as eligible for inclusion; 33 authors were ultimately contacted and invited to collaborate, of whom ten agreed to participate and provide IPD (appendix p 1). 1771 (25%) of 7082 patients were included in the initial analysis. 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 IPD from contributing cohorts. The cohorts consisted of a variety of populations (table 2),[11–20] some with selected populations, such as children with cryptogenic focal epilepsies,[15] patients only on monotherapy,[19] and patients older than 13 years on monotherapy with exclusion of idiopathic generalised epilepsies,[11] and others with mostly unselected populations of children,[12,16–18,20] adults,[14] or both.[13] The maximum follow-up after start of antiepileptic drug withdrawal was 23 years (median 5·3, IQR 3·0–10·0) and for the patients with a seizure recurrence the follow-up after the recurrence was a median of 3·7 years (range 0–20·0, IQR 1·0–7·0). The median time to antiepileptic drug withdrawal after the last seizure was 33 months (range 3–385, IQR 24–48).

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 antiepileptic drug withdrawal. The appendix (p 2) shows the survival curve split by electroencephalogram (EEG) results. The overall recurrence rate was higher than the average reported in the literature;[5] when only published data were considered, the median of published seizure recurrence estimates of the ten included papers was 40% (IQR 36–48), whereas the median of the 35 papers that were not included was 28% (22–37; appendix p 3). Another difference between included and excluded papers was the high percentage of randomised controlled trials in the current analysis (50%) compared with 11% in non-included papers (appendix p 3). 136 (9%) of 1455 patients were not seizure-free in the last year of follow-up (table 2), although some of those patients might have had a period of seizure freedom before this point. Of the patients with seizure recurrence and maximum follow-up between 1 and 5 years after recurrence, 202 (72%) of 280 were seizure-free in the last year of follow-up. The proportions of patients with seizure recurrence who were seizure free at final follow-up were 121 (80%) of 152 patients, 65 (81%) of 80, and 50 (88%) of 57 for the maximum follow-up durations of 5–10 years, 10–15 years, and more than 15 years after seizure recurrence, respectively.

Five variables had missing values in between 30% and 45% of patients (appendix pp 4–5). Imputation was not possible for two cases because of too much missing information; these cases were removed from further analysis, which was thus done for 1769 patients. The risk of bias based on the published papers in the ten selected cohorts was scored as low to partly present (appendix p 6).[5]

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 of failure of previous antiepileptic drug withdrawal, baseline characteristics between positive and negative cases were investigated; this analysis showed no large differences

between the groups besides a longer duration of epilepsy (median 61 months [IQR 19–116] *vs* 24 months [5–68]), and a longer seizure free interval (median 41 [IQR 48–62] *vs* 31 months [24–48]; appendix p 7) in the group of patients who had a previous relapse after withdrawal.

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 (appendix p 8). 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 in the appendix (p 9). A visual representation of the models is 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 timepoints in each individual patient. Independent predictors of seizure recurrence were epilepsy duration before remission, seizure-free interval before antiepileptic drug withdrawal, age at onset of epilepsy, history of febrile seizures, number of seizures before remission, absence of a self-limiting epilepsy syndrome, developmental delay, and 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 antiepileptic drug withdrawal, number of antiepileptic drugs before withdrawal, female sex, family history of epilepsy, number of seizures before

	n (%)* or median (IQR)	Seizure recurrence†		Seizures in last year of follow-up‡	
		HR (95% CI)	p value	HR (95% CI)	p value
Female sex	842/1769 (48%)	1·08 (0·94–1·24)	0·2745	1·43 (1·02–2·01)	0·0391
Age at onset of epilepsy (years)					
Childhood (0–10)	1087/1769 (61%)	0·75 (0·60–0·92)	0·0064	1·31 (0·80–2·16)	0·3069
Adolescent(11–17)	387/1769 (22%)	1·15 (0·93–1·42)	0·2008	1·41 (0·84–2·36)	0·1769
Adult age (≥18)	295/1769 (17%)	Ref	..	Ref	..
Age at withdrawal of antiepileptic drugs (years)	15 (0–84)	1·01 (1·01–1·02)	<0·0001	1·00 (0·98–1·01)	0·5155
Family history of epilepsy	365/1735 (21%)	1·16 (0·98–1·38)	0·0828	1·55 (1·04–2·30)	0·0311
History of neonatal seizures	53/1601 (3%)	1·30 (0·91–1·84)	0·1440	1·77 (0·77–4·07)	0·1792
History of febrile seizures	199/1765 (11%)	1·27 (1·03–1·56)	0·0250	1·06 (0·61–1·85)	0·8424
At least ten seizures before remission	573/1446 (40%)	1·52 (1·29–1·81)	<0·0001	2·21 (1·15–3·37)	0·0003
Epilepsy duration before remission (years)	1 (0–5)	1·04 (1·03–1·05)	<0·0001	1·03 (1·01–1·06)	0·0118
Seizure-free interval before withdrawal of antiepileptic drugs (years)	3 (2–4)	0·94 (0·91–0·98)	0·0022	0·85 (0·76–0·95)	0·0057
Number of antiepileptic drugs before withdrawal	1 (1–2)	1·15 (1·05–1·26)	0·0035	1·51 (1·24–1·83)	<0·0001
Failure of previous antiepileptic-drug withdrawal	126/1246 (10%)	1·13 (0·89–1·44)	0·3268	1·15 (0·68–1·95)	0·5954
Focal seizures	833/1652 (50%)	1·13 (0·97–1·32)	0·1162	1·81 (1·26–2·56)	0·0015
Generalised tonic–clonic seizures	1141/1652 (69%)	1·51 (1·25–1·83)	<0·0001	1·07 (0·69–1·66)	0·7470
Multiple seizure types	254/1089 (23%)	1·24 (1·02–1·51)	0·0334	0·94 (0·55–1·59)	0·8088
Remote symptomatic causes	468/1649 (28%)	1·45 (1·24–1·70)	<0·0001	1·80 (1·26–2·56)	0·0011
Self-limiting epilepsy syndrome§	183/978 (19%)	0·51 (0·39–0·68)	<0·0001	0·48 (0·25–0·92)	0·0266
History of epileptic encephalopathy	24/1142 (2%)	0·82 (0·60–1·12)	0·2201	0·79 (0·29–2·12)	0·6365
Juvenile myoclonic epilepsy	30/978 (3%)	1·27 (0·87–1·86)	0·2116	0·91 (0·29–2·87)	0·8663
Developmental delay	262/1742 (15%)	1·52 (1·27–1·82)	<0·0001	1·30 (0·82–2·04)	0·2622
Motor deficit	163/1736 (9%)	1·23 (0·97–1·54)	0·0850	0·90 (0·47–1·72)	0·7515
Imaging					
Normal	774/1061 (73%)	Ref	..	Ref	..
Abnormal	210/1061 (20%)	1·32 (1·08–1·62)	0·0076	1·66 (0·93–2·98)	0·0877
Not done	77/1061 (7%)	0·86 (0·66–1·13)	0·2861	0·71 (0·37–1·36)	0·2996
Electroencephalogram before withdrawal					
Normal	1207/1536 (79%)	Ref	..	Ref	..
Epileptiform abnormality	283/1536 (18%)	1·50 (1·25–1·79)	<0·0001	1·68 (1·11–2·54)	0·0144
Not done	46/1536 (3%)	0·71 (0·39–1·27)	0·2446	1·14 (0·27–4·78)	0·8562

Data are n (%), median (IQR), or hazard ratios (HR [95% CI]). Analysis was done with proportional hazards regression that included a random-effects term to correct for heterogeneity between populations. *Based on available information before imputations; the denominator indicates total number of complete cases. †Heterogeneity: relative risk between studies ranged between 1·29 and 1·45. ‡Heterogeneity: relative risk between studies ranged between 1·95 and 2·66. §Formerly called benign course—eg, absence epilepsy, benign epilepsy with centrotemporal spikes (Rolandic epilepsy), and Panayiotopoulos syndrome.

***Table 1*: Univariable predictors of seizure recurrence and the presence of seizures in the last year of follow-up**

	Total (n=1769)	Cardoso[11] (n=99)	Geerts[12] (n=133)	MRC[13] (n=510)	Overweg[14] (n=65)	Pavlovic[15] (n=52)	Ramos-Lizana[16] (n=216)	Serra[17] (n=57)	Shinnar[18] (n=264)	Specchio[19] (n=256)	Tennison[20] (n=119)
Year of publication	..	2003	2005	1991	1987	2012	2010	2005	1994	2002	1994
Study design	..	RCT*	RCT†	RCT‡	Prospective	Retrospective	Prospective	RCT§	Prospective	Prospective	RCT¶
Country	..	Brazil	Netherlands	UK	Netherlands	Serbia	Spain	Brazil	USA	Italy	USA
Follow-up (years)	5·3 (3·0–10·0)	9·0 (7·3–13·3)	10·9 (10·0–11·3)	5·0 (4·0–5·9)	3·0 (2·7–3·3)	3·0 (2·0–6·0)	4·5 (2·3–7·5)	2·3 (1·8–5·0)	16·1 (15·3–17·7)	2·0 (0·7–4·0)	2·4 (1·3–4·2)
Follow-up after seizure recurrence (years)	3·7 (0·6–6·8)	7·8 (5·4–11·9)	9·4 (7·7–10·4)	3·9 (2·6–4·9)	2·5 (1·8–2·8)	2·0 (1–5·2)	4·0 (2·6–5·9)	3·9 (2·2–5·7)	14·8 (11·3–16·9)	0 (0–0)	0 (0–1·8)
Female sex	842/1769 (48%)	46/99 (46%)	69/133 (52%)	260/510 (51%)	25/65 (38%)	16/52 (31%)	96/216 (44%)	25/57 (44%)	128/264 (48%)	130/256 (51%)	47/119 (39%)
Polytherapy	464/1753 (26%)	47 (47%)	22 (17%)	86 (17%)	46 (71%)	10 (19%)	40 (19%)	29 (51%)	13 (5%)	130 (51%)	41 (34%)
Remote symptomatic causes	468/1649 (28%)	72 (73%)	42 (32%)	134 (26%)	13 (20%)	0/52	55 (25%)	18 (32%)	97 (37%)	37 (14%)	0/0
Age at onset of epilepsy (years)	8 (4–14)	14 (9–22)	7 (4–10)	14 (7–24)	10 (6–14)	7 (5–9)	5 (1–8)	4 (1–8)	5 (2–9)	12 (7–17)	3 (1–6)
Age at withdrawal of antiepileptic drugs (years)‖	15 (10–26)	26 (21–36)	8 (5–11)	27 (18–43)	29 (22–24)	14 (11–16)	8 (4–10)	10 (7–13)	12 (8–16)	22 (17–30)	11 (8–14)
Epilepsy duration before remission (months)	23 (4–72)	8 (3–15)	19 (5–43)	53 (10–143)	157 (94–240)	1 (0–12)	0 (0–6)	23 (10–46)	21 (5–55)	47 (11–108)	35 (12–74)
Seizure-free interval before withdrawal of antiepileptic drugs (months)	33 (24–48)	40 (27–38)	6 (6–12)	41 (29–70)	63 (48–85)	48 (36–60)	25 (23–27)	24 (24–33)	30 (26–42)	36 (36–60)	24 (24–48)
Previously failed attempt at withdrawal of antiepileptic drugs**	126/1246 (10%)	27/99 (27%)	0/133	60/510 (12%)	4/51 (8%)	0/52	0/0	3/57 (5%)	22/264 (8%)	0/0	10/80 (13%)
Epileptiform electroencephalogram before withdrawal of antiepileptic drugs**	283/1536 (18%)	12/99 (12%)	72/133 (54%)	85/457 (19%)	31/64 (48%)	0/41	0/171	0/41	0/158	55/256 (21%)	28/116 (24%)
Number of seizure recurrences	812/1769 (46%)	53/99 (54%)	71/133 (53%)	235/510 (46%)	39/65 (60%)	19/52 (37%)	56/216 (26%)	23/57 (40%)	110/264 (42%)	160/256 (63%)	46/119 (39%)
Seizures in last year of follow-up**	136/1455 (9%)	16/98 (16%)	17/129 (14%)	60/495 (12%)	12/60 (20%)	0/47	6/211 (3%)	9/56 (16%)	11/258 (4%)	5/101 (5%)	No value††

Data are n (%) or median (IQR). RCT=randomised controlled trial. .. =not applicable. *Randomly assigned to either reduction of antiepileptic drugs or complete discontinuation of antiepileptic drugs. Seizure-free patients from the reduction group later completely withdrew from antiepileptic drugs. †Randomly assigned to withdrawal of antiepileptic drugs after either 6 or 12 months of freedom from seizures. ‡Patients in this study were randomly assigned to either withdrawal or no withdrawal from antiepileptic drugs; in this analysis, we included only patients assigned to withdrawal. §Randomly assigned to tapering from antiepileptic drugs for a duration of either 1 month or 6 months. ¶Randomly assigned to tapering from antiepileptic drugs for a duration of either 6 weeks or 9 months. ‖988 patients (56%) were younger than 18 years at withdrawal.**Incomplete cases; the denominator shows the number of patients with available information ††In most cases follow-up was ceased after seizure recurrence, so that the final seizure outcome could not be reported.

***Table 2*: Characteristics of individuals from included studies**

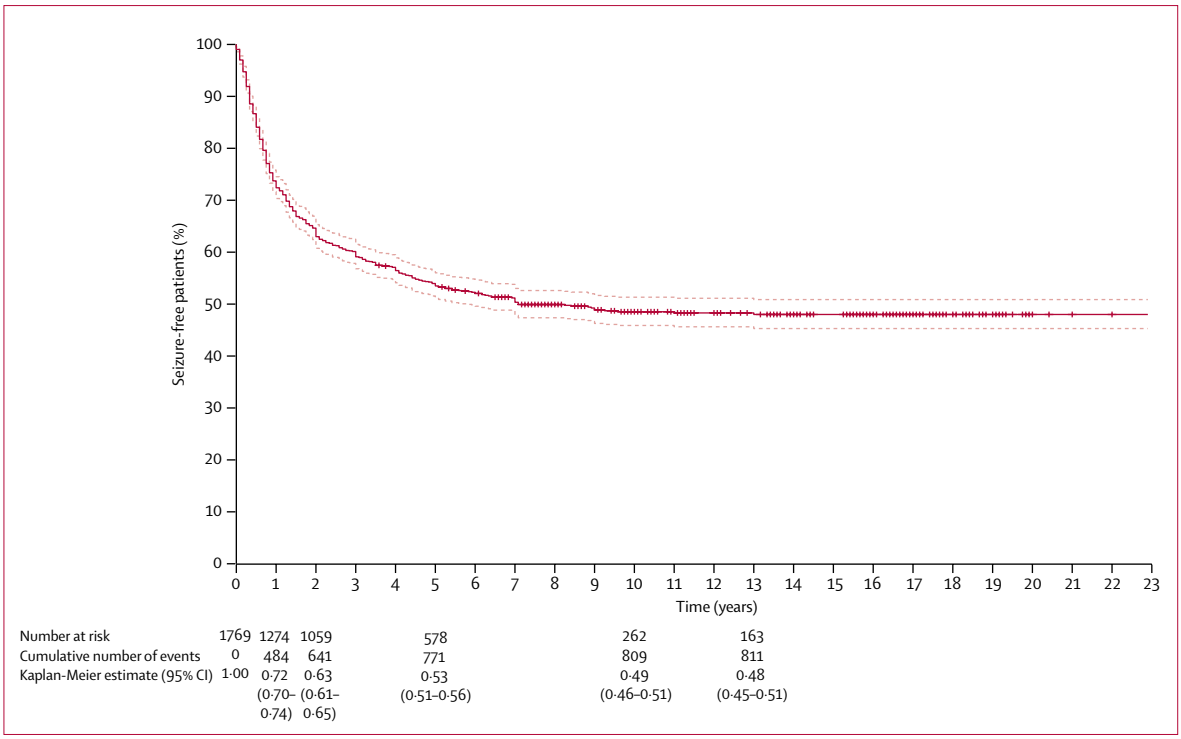

***Figure 1*: Seizure-free patients after initiation of antiepileptic drug withdrawal**
Survival curve of seizure-free patients over time with Kaplan-Meier estimates at 1, 2, 5, 10, and 13 years (time of last event in this dataset), with seizure recurrence taken as event. Time 0 equals the start of antiepileptic drug withdrawal.

For the **web-based tool for antiepileptic drug withdrawal** risk see http://epilepsypredictiontools.info

remission, focal seizures, and epileptiform abnormality on EEG before withdrawal. For practical purposes the nomograms were translated into a web-based tool for risk calculation.

The adjusted c statistic for predicting seizure recurrence was 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 (appendix p 10). For predicting long-term seizure freedom, the adjusted c statistic was 0·71 (0·70–0·71), which varied in the validation procedure between 0·68 and 0·79 (appendix p 10). Lastly, plotting the predicted probabilities against the observed proportions showed good calibration for both models (figures 2, 3).

Discussion

This prognostic IPD meta-analysis of the risks of antiepileptic drug withdrawal in 1769 seizure-free people with epilepsy yielded clinically useful nomograms to predict individual seizure outcome. Relapse occurred in 812 (46%) patients, while only 136 (9%) of 1455 in the cohort of patients with available information had seizures in the last year of follow-up. The proportion of relapsing patients who did not regain freedom from seizures decreased with longer follow-up times. The strongest predictors included in the nomograms for seizure recurrence were 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), intelligence quotient (IQ) below 70, and epileptiform abnormality on EEG before antiepileptic drug withdrawal. For predicting long-term seizure outcome, the eight selected independent predictors were duration of epilepsy, duration of the seizure-free interval, number of antiepileptic drugs before withdrawal, female sex, family history of epilepsy in first or second degree relatives, ten or more seizures before remission, the presence of focal seizures, and epileptiform abnormality on EEG before antiepileptic drug withdrawal. Validation, or assessment of how well a prediction works on data other than those on which the model was built, is arguably the most important issue in prognostic modelling;[21] internal–external cross validation within the available data was done through IECV[22] with good and stable performance across all cohorts.

Several clinically important implications can be drawn from the presented data. The first is that although the 22 candidate predictors had all been reported as significant predictors in at least one peer-reviewed article,[5] eight of these have now been 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 findings from a publication by Wolf and colleagues,[23] seizure recurrence

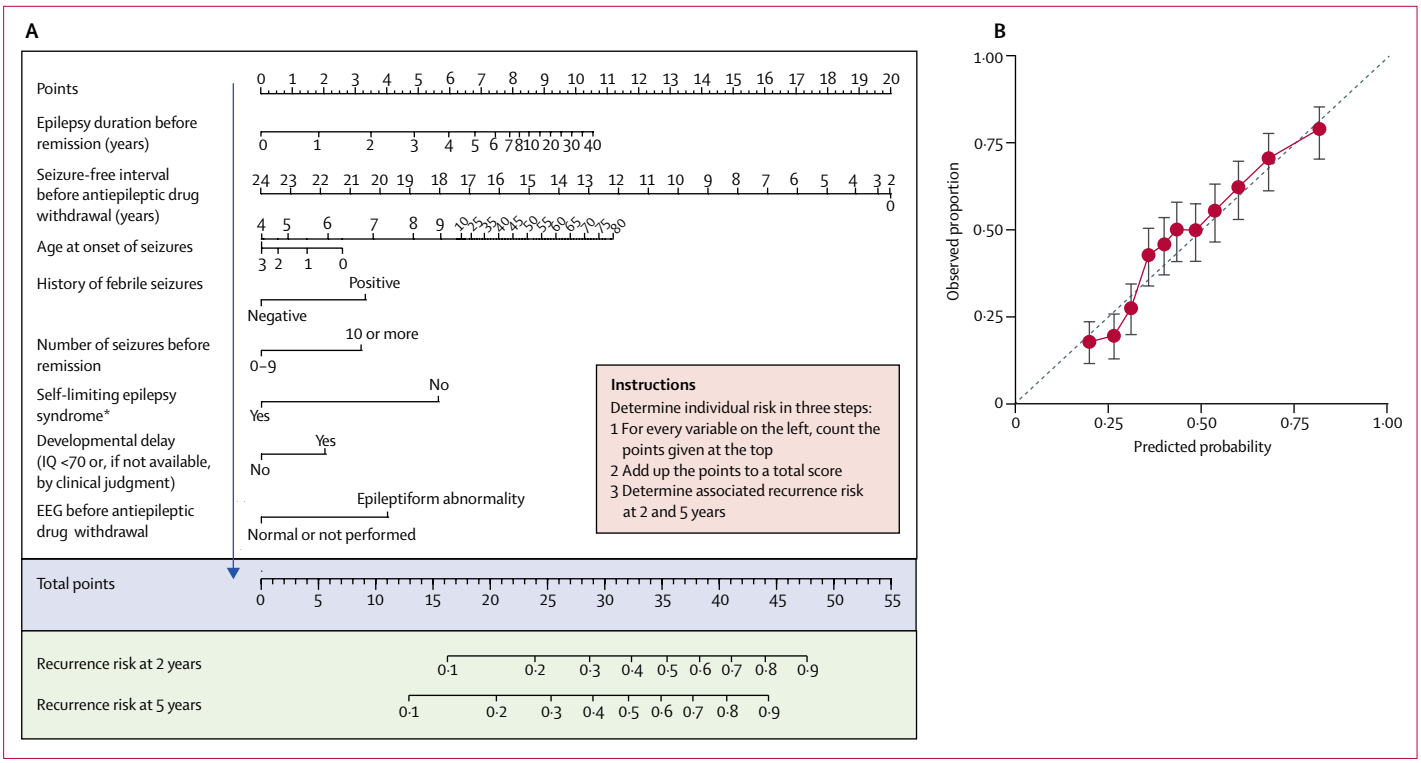

***Figure 2*: Prediction of seizure recurrence after antiepileptic drug withdrawal**

(A) Nomogram to predict seizure recurrence after antiepileptic drug withdrawal, validated in the ten cohorts summarised in table 1 (see also appendix). For example, a child whose seizures started at the age of 3 years (0 points) who had active epilepsy for 1 year (2) and has been free from seizures for 2 years (20), with no history of febrile seizures (0), less than ten seizures (0), no self-limiting epilepsy syndrome (5·5), no developmental delay and a normal electroencephalogram (EEG; 0), has a total of 27·5 points, which corresponds to a risk of seizure recurrence of 28% and 36% at 2 and 5 years respectively. (B) Calibration plot for the prediction of seizure recurrence 5 years after the start of antiepileptic drug withdrawal, as modelled in part A and appendix. *For example, absence or Rolandic epilepsy, or Panayiotopoulos syndrome.

after previous antiepileptic drug withdrawal is not related to the outcome of a second (or third) attempt. This finding is unlikely to be the result of selection bias because none of the included cohorts excluded patients with a previous failure of antiepileptic drug withdrawal and the baseline characteristics of patients with a failed previous antiepileptic drug withdrawal attempt were very similar to patients attempting withdrawal for the first time.

Another observation is the effect of epileptiform activity on EEG before antiepileptic drug withdrawal, a factor which has been debated in the past.[24] EEG abnormalities were significantly associated with outcome, but in the absence of other predictive factors they only slightly increased the risks. EEG abnormalities alone should thus not prevent withdrawal of medication, a notion which was already stated in 1987[19] and is in agreement with, for example, the 2013 Italian guideline on antiepileptic drug withdrawal.[25]

The age at onset of epilepsy is an important predictor for seizure recurrence but not for long-term freedom from seizures. Its association with seizure recurrence is U-shaped, with an elevated risk at birth that falls to a nadir by about age 3–4 years when it begins to rise again until age 10 years and plateaus until age 25 years; 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 antiepileptic drug withdrawal assess the dichotomy of early versus late antiepileptic drug withdrawal, as meta-analysed in a Cochrane review,[26] our analysis showed that the risk decreases with every additional year of seizure freedom. The common understanding that it is advisable to wait for at least 2 years is based on an artificial threshold and the rule should at least be complemented by adding that every added seizure-free year reduces the risk. The nomograms will provide insight into the best timing for the individual patient.

As a general caveat, in addition to likelihood of the outcome, there are many more considerations in the decision to withdraw antiepileptic drugs in seizure-free patients. When counselling patients with the use of these prediction models, a physician should be aware of the way the risks are presented as it can steer the patient towards a certain choice.[27] Other factors such as the fear of losing a driver's licence or even a job,[28] the social stigma around seizures,[29,30] and the quality of the patient's

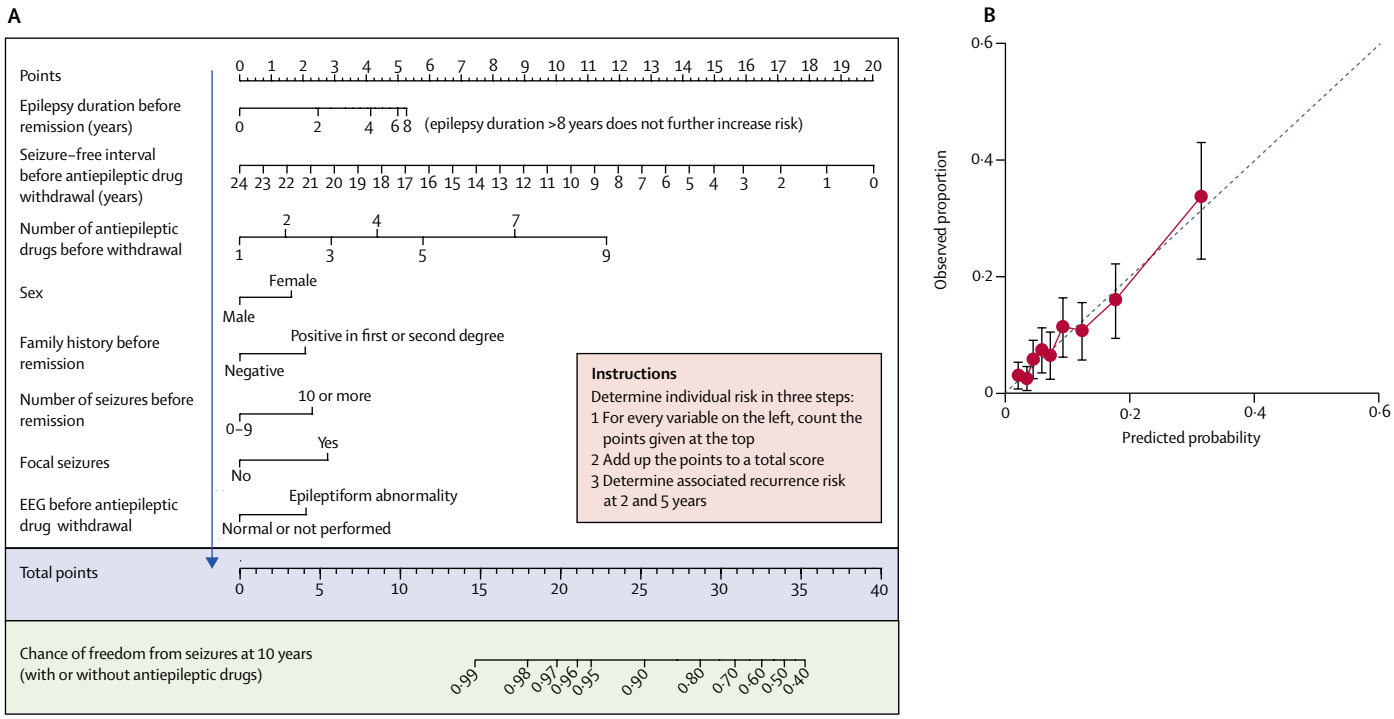

***Figure 3*: Prediction of seizure freedom (for at least 1 year) at 10 years of follow-up**

(A) Nomogram to predict long-term outcome after antiepileptic drug withdrawal, validated in the ten cohorts summarised in table 1 (see also appendix). For example, a female patient (1·5 points) who had active seizures for 1 year (1), has been seizure free for 2 years (17), is using one antiepileptic drug (0), has no family history of epilepsy (0), had fewer than ten seizures in total (0), only had generalised seizures (0), and has no abnormalities on electroencephalogram (EEG) before withdrawal (0), has a total of 19·5 points, which corresponds to the chance to be seizure-free in the long term of 97%. (B) Calibration plot for the prediction of long-term seizure freedom, as modelled in part A and appendix.

life[2] are important considerations. The nomograms only provide individualised statistical chances and should be applied when balancing benefits and risks within the context of all these factors.

Our models might appear to be restricted to populations with relatively high recurrence rates, with an estimated 52% of patients having seizure recurrence within 23 years after antiepileptic drug withdrawal. However, the ten included studies contained many different populations, from strictly selected to population based, with recurrence rates between 26% and 63%. In the internal–external cross-validation procedure the effect of the separate populations was 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 generalisability of the models.

One limitation of our analysis was that the study population contained only people who made an attempt to withdraw antiepileptic drugs, since maintaining antiepileptic drugs still carries the risk of seizure recurrence and refractory epilepsy. The findings from the only two randomised trials of antiepileptic drug withdrawal showed that continued antiepileptic drug treatment is related to 7% seizure recurrence at 1 year after withdrawal[31] and 22% at 2 years,[13] compared with 15% and 41% for the withdrawal groups, respectively. The development of refractory epilepsy might not be related to antiepileptic drug withdrawal: a follow-up study of the UK Medical Research Council antiepileptic drug withdrawal trial showed no differences between the two randomisation groups in terms of seizure control after relapse.[32]

For two predictors, few cases were provided: history of epileptic encephalopathy (24 cases) and juvenile myoclonic epilepsy (JME; 30 cases). Because of these low patient numbers it cannot be concluded that these factors are not predictors of outcome. For patients with JME, 26 (87%) of 30 had seizure relapse but all were seizure free at last follow-up. This finding suggests that few patients can be successful at antiepileptic drug withdrawal.[33,34] However, although most patients relapse, the eventual rate of regaining freedom from seizures 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 noted (appendix). The self-limiting epilepsy syndromes were strictly defined in our protocol and not subject to different interpretation.

Another limitation was the quantification of long-term seizure freedom chosen in the analysis. From most studies, only two outcome measures were available:

seizure recurrence and seizure status in the last year of follow-up, both dichotomised as 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 were helpful to calculate an individualised risk of antiepileptic drug withdrawal and the chance of long-term favourable seizure outcomes. They might therefore help to guide individual-tailored choices by the physician and patient.

Contributors

HJL, WMO, DS, SS, KG, and KPJB contributed to the study design. HJL and KG did the literature search. Data were obtained by HJL, ATG, MP, JR-L, AGM, JO, LS, LMS, MT, TMOC, and SS. HJL and WMO analysed the data 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.

Declaration of interests

We declare no competing interests.

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