



Prediction of risk of seizure recurrence after a single seizure and early epilepsy: further results from the MESS trial

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Summary

Background The MRC Multicentre trial for Early Epilepsy and Single Seizures (MESS) showed a reduced risk of further seizures in patients, for whom treatment with antiepileptic drugs was uncertain, who were randomly assigned immediate treatment compared with delayed treatment. However, there was no evidence of long-term remission rates. This study was undertaken to assess the role of patient characteristics and treatment in the prediction of seizure recurrence. This will enable decision-making on the basis of the perceived risk of treatment compared with the benefit of reducing the risk of further seizures in the initial years after diagnosis.

Methods A prognostic model was developed based on individual patient data from MESS to enable identification of patients at low, medium, or high risk of seizure recurrence. A split-sample approach was used in which the model was developed on a subsample of the full data and validated on the remainder of the sample. Distinction of the prognostic groups and predictive accuracy of the model were assessed.

Findings Number of seizures of all types at presentation, presence of a neurological disorder, and an abnormal electroencephalogram (EEG) were significant factors in indicating future seizures. Individuals with two or three seizures, a neurological disorder, or an abnormal EEG were identified as the medium-risk group, those with two of these features or more than three seizures as the high-risk group, and those with a single seizure only as the low-risk group.

Interpretation The model shows that there is little benefit to immediate treatment in patients at low risk of seizure recurrence, but potentially worthwhile benefits are seen in those at medium and high risk.

Introduction

Epilepsy is a common and diverse disorder with many different causes. Outcomes are varied with 60–70% of newly diagnosed people rapidly entering remission after starting treatment, and 20–30%¹ developing a drug-resistant epilepsy with consequent clinical and psychosocial distress. Treatment for most patients is with antiepileptic drugs, which carry risks of acute idiosyncratic reactions, dose-related and chronic toxic effects, and teratogenicity. For most patients diagnosed with epilepsy, the benefits of treatment will far outweigh the risks associated with treatment. However, for those who have had a single seizure and for those who have seizures with minor symptoms, this risk to benefit ratio is more finely balanced.

A large, multinational, randomised trial (the MRC Multicentre trial for Early Epilepsy and Single Seizures; MESS) was undertaken to assess the benefits of starting or delaying treatment after the first reported epileptic seizure.² The study showed that although immediate versus delayed treatment with the commonly used antiepileptic drugs carbamazepine and valproic acid reduced the risk of further seizures (hazard ratio for time to first seizure 1.4 [95% CI 1.2–1.7]), there was no evidence of an effect on long-term remission rates (absolute difference in percentage seizure free between 3 and 5 years –0.2% [95% CI –5.8% to 5.5%]). Decisions on starting treatment should therefore be affected by the perceived risk of antiepileptic drug treatment compared with the benefit of reducing the risk of further seizures

in the first 2–3 years after diagnosis. Data from MESS and from other studies^{3–8} indicate that the risk of further seizures on or off treatment depends on a number of individual characteristics. The decision-making process for embarking on immediate treatment after diagnosis would therefore benefit from a more formal analysis of the importance of these features.

In this study, we used data for individual patients from the MESS trial to develop a prognostic model for the risk of seizures, and to assess the role of patient characteristics and treatment in this prediction. The model is lent support by a cross-validation sample, enabling assessment and calibration of the model developed.

Methods

Patients and procedures

The MESS trial (ISRCTN 98767960) randomised 1443 patients in 13 countries worldwide (50% from the UK). The detailed methods and primary results have been described elsewhere,² but a brief summary is provided here. Eligibility for the trial was determined by at least one recent epileptic seizure and by the clinician and patient being uncertain whether to proceed with immediate treatment. Patients were randomly assigned either immediate treatment with an antiepileptic drug or delayed treatment after a time when the clinician and patient agreed treatment was necessary. Whenever antiepileptic drug treatment was given, the choice of drug and treatment regimen was made according to the clinician's usual practice. The MESS trial was approved

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	Baseline data (n=1420)*
Number of seizures before randomisation	3.6 (13.5)
Neurological disorder	254 (18%)
Abnormal EEG	618 (44%)
Epilepsy syndrome	63 (4%)
Tonic-clonic seizures only (including secondary generalised)	1231 (87%)
Simple or complex partial seizures only	103 (7%)
Age at randomisation, years	31.2 (19.1)
Age at first seizure, years	30.0 (19.1)
Years between most recent seizure and randomisation	0.23 (0.91)
Men	815 (57%)
Febrile convulsions	105 (7%)
Family history of epilepsy (primary relatives)	162 (11%)

Data are mean (SD) or number (%). *Data are not provided for 23 individuals who had no baseline seizure data.

Table 1: Baseline characteristics of randomised patients

by the northwest multicentre research ethics committee in the UK and by the ethics committees for participating non-UK centres.

Information about past seizures and neurological and family history, in addition to demographic information and findings of neurological examination, was gathered at baseline. The median age at randomisation was 25.3 years (IQR 17.4–43.4) and the median age reported for first seizure was 24.3 years (16.1–41.9). Electroencephalogram (EEG) and CT scan data were also collected where available. Follow-up information was obtained at 3 months, 6 months, 1 year, and successively at yearly intervals after randomisation, for a median of 4.4 years (3.0–6.3). Details of antiepileptic drug treatment, seizures, and other adverse events were recorded.

Statistical analysis

The complete sample of 1443 individuals was split into a test sample and a validation sample in the ratio 6:4 using a random number generator (Stata 8), stratified by randomised treatment. The test sample was used to develop a prognostic model for the interval from randomisation to first seizure based on Cox regression stratified by treatment allocation. Stepwise regression

was used to assess the predictive value of baseline covariates of interest with exclusion at $p \geq 0.1$ and inclusion at $p \leq 0.05$. The numbers of patients with a neurological disorder, neurological deficit or impairment, delayed development, or learning disability were small; hence a single variable was used to represent patients with any of these neurological conditions. An abnormal EEG was defined as specific focal or generalised epileptiform or slow wave abnormality. This definition excluded non-specific abnormality. Missing values of covariates were imputed using the mean of remaining observations in the sample (mode for categorical variables). Transformation of continuous variables was assessed with Martingale residuals.

Sensitivity analyses were done for only those individuals with complete covariate data, and for only those with an EEG in the interval from 9 months prerandomisation to 3 months post-randomisation (excludes 7% of the test sample with no EEG data and 5% with an EEG outside of this interval). The proportion of individuals who had a further seizure was similar among those with an EEG in and outside of the time period (48%), but was lower in those with missing EEG data (33%). Application of a shrinkage factor⁹ to the regression coefficients was also considered, to compensate for over-fitting in the validation sample.

A prognostic index was defined as the linear predictor resulting from the final model. The predictive value of this prognostic index is assessed by calculation of a separation statistic, D , which indicates the predictive ability of the index.¹⁰ An optimism-adjusted version of the statistic, D_{adj} , was used to correct for bias when fitting the model and estimating the separation statistic on the same dataset.

Risk group classifications were assigned by use of tertiles of the prognostic index distribution obtained from the model, and probabilities of seizure recurrence by 1, 3, and 5 years then calculated for each of these groups. The prognostic index constructed from the test sample was then applied to the validation sample, enabling assignment of each individual to a specific risk group. The predicted risk (as observed in the test sample) of seizure recurrence in each of these groups was compared with the observed seizure recurrence in the validation sample. Kaplan-Meier plots were used to assess the differences across risk groups in both the test (predicted risk) and validation (observed risk) samples. The predictive accuracy of the prognostic index in the validation sample was also assessed more formally by use of a censoring adjusted Brier score.¹¹

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.

	Model 1	p	Model 2	p
Neurological disorder	1.35 (1.07–1.72)	$p=0.013$	1.36 (1.07–1.73)	$p=0.012$
Abnormal EEG	1.54 (1.27–1.86)	$p<0.0001$	1.53 (1.26–1.86)	$p<0.0001$
Number of seizures prerandomisation (log transformation)	1.56 (1.42–1.72)	$p<0.0001$	1.61 (1.46–1.77)	$p<0.0001$
Years between most recent seizure and randomisation	0.92 (0.84–1.02)	$p=0.10$
First degree relative with epilepsy	1.27 (0.96–1.70)	$p=0.10$

Data are hazard ratios (95% CI), interpretable as the relative change in risk for a one unit increase in the prognostic factor; for log seizures, one unit refers to $\exp(1)=2.718$ seizures. Regression coefficients as used in the calculation of the prognostic index can be calculated from hazard ratios as the natural logarithm of the hazard ratio.

Table 2: Final model resulting from backward stepwise regression from full model

Results

Table 1 summarises the baseline characteristics of interest for the prognostic modelling. Means for the whole sample are given, including items recoded from missing to the mean or mode. Randomisation of trial individuals to the test or validation samples resulted in 885 and 535 in each sample respectively (excluding 23 individuals with no seizure data recorded at randomisation). Backward stepwise regression (stratified by treatment) investigating the first set of variables in table 1 (those significant in univariate analysis at $p \leq 0.10$) on the test sample resulted in the identification of three potentially important prognostic factors (model 1): neurological disorder, total number of seizures of all types prerandomisation, and abnormal EEG (as defined above). Epileptiform abnormality on the EEG (paroxysmal slow-wave abnormality with spiking) added no greater specificity than the variable “any abnormality”, which included also slow-wave disturbance without spikes or sharp waves. Forward stepwise regression was then undertaken to establish the importance of the second set of variables (those significant in univariate analysis at $p > 0.10$), together with interaction terms using the terms identified in model 1 and reconsidered variables excluded from the first set. This resulted in the identification of two further predictive factors: a borderline significant increase in seizure recurrence with a history of epilepsy in a primary relative and a borderline significant decrease with an increasing interval between most recent seizure before randomisation and randomisation itself (model 2). However, this latter association was largely due to two extreme outliers with 13 and 23 years between most recent seizure and randomisation; exclusion of these individuals resulted in this factor not being added to the model. Both models are described in table 2. Sensitivity analysis restricted to individuals with complete covariate information, and to individuals with EEG data from 9 months prerandomisation to 3 months post-randomisation resulted in no change to the models.

A prognostic index was calculated, on the basis of model 1, as the sum of the covariate values for a particular patient, weighted by the corresponding estimated regression coefficients. So, for an individual with two seizures, an abnormal EEG, and no neurological disorder, the prognostic index (as calculated from table 2) is: $(\log_2 \times \log_e 1.56) + (1 \times \log_e 1.54) + (0 \times \log_e 1.35) = (\log_2 \times 0.44) + (1 \times 0.43) + (0 \times 0.30) = 0.74$

Since the two variables added at the forward stepwise regression phase were both of borderline significance (model 2), it was decided to omit these from the final prognostic index for simplicity. The separation statistic D_{adj} was 0.77 (95% CI 0.36–0.90). Since the confidence interval excludes zero, this suggests that the prognostic index has acceptable ability to discriminate between patients' risks of seizure recurrence. The D statistic can also be used to provide guidance on the largest number of prognostic groups that would (with 90% power)

maintain significant separation. For our prognostic model, the maximum number of groups likely to maintain reasonable separation is three.¹⁰

Tertiles of the continuous prognostic index described correspond to values of <0.30 , <0.50 , and ≥ 0.50 —ie, group 1 (low risk) includes individuals with a prognostic index of <0.30 , group 2 (medium risk) includes individuals with a prognostic index of 0.30 – 0.49 , and group 3 (high risk) includes individuals with a prognostic index of ≥ 0.50 . Table 3 shows the probabilities of a further seizure by 1, 3, and 5 years in each of these risk groups. No significant difference is observed between treatments for low-risk individuals (Log-rank test $\chi^2=1.7$, $p=0.2$), but there is an indication of improvement with immediate antiepileptic-drug treatment for medium-risk and high-risk individuals (7.0, $p=0.008$; 21.9, $p<0.0005$, respectively; overall likelihood ratio test for interaction between risk group and treatment 13.27, $p=0.001$). The risk group for each individual in the validation sample can be calculated by first calculating the prognostic index with their baseline characteristics, then assigning them to a risk group on the basis of the cut-off values identified in the test sample above. Figure 1 shows the observed proportions seizure-free among individuals in each of these predicted risk groups.

Predictive accuracy of the prognostic model in the validation sample was examined by plotting observed proportions of individuals with seizure recurrence within six groups of predicted seizure recurrence (bandwidths 0.2, 0.1, 0.1, 0.1, 0.1, and 0.4) based on the continuous prognostic model 1 in table 2 at 1 and 3 years post-randomisation (figure 2). These plots suggest that some shrinkage remains despite adjustment for this, with observed proportions experiencing seizure recurrence less extreme than predicted at very high and very low predicted proportions of seizure recurrence. The censoring adjusted Brier score suggests a degree of success of the model, with a score of 0.23 at 1 year, 0.24 at 3 years, and 0.25 at 5 years (the Brier score ranges from 0 to 1, with a large score indicating poorer predictive accuracy of the model).

Use of the prognostic index in practice requires some simplification; it is useful to rewrite the final model using integer values as shown in table 4. This is derived from the continuous prognostic index obtained from model 1

	Treatment allocation	Probability of seizure by 1 year	Probability of seizure by 3 years	Probability of seizure by 5 years
Low risk	Start	0.26	0.35	0.39
	Delay	0.19	0.28	0.30
Medium risk	Start	0.24	0.35	0.39
	Delay	0.35	0.50	0.56
High risk	Start	0.36	0.46	0.50
	Delay	0.59	0.67	0.73

Table 3: Risk classification groups based on prognostic index separation, showing stratified Kaplan-Meier estimates of the probability of a future seizure

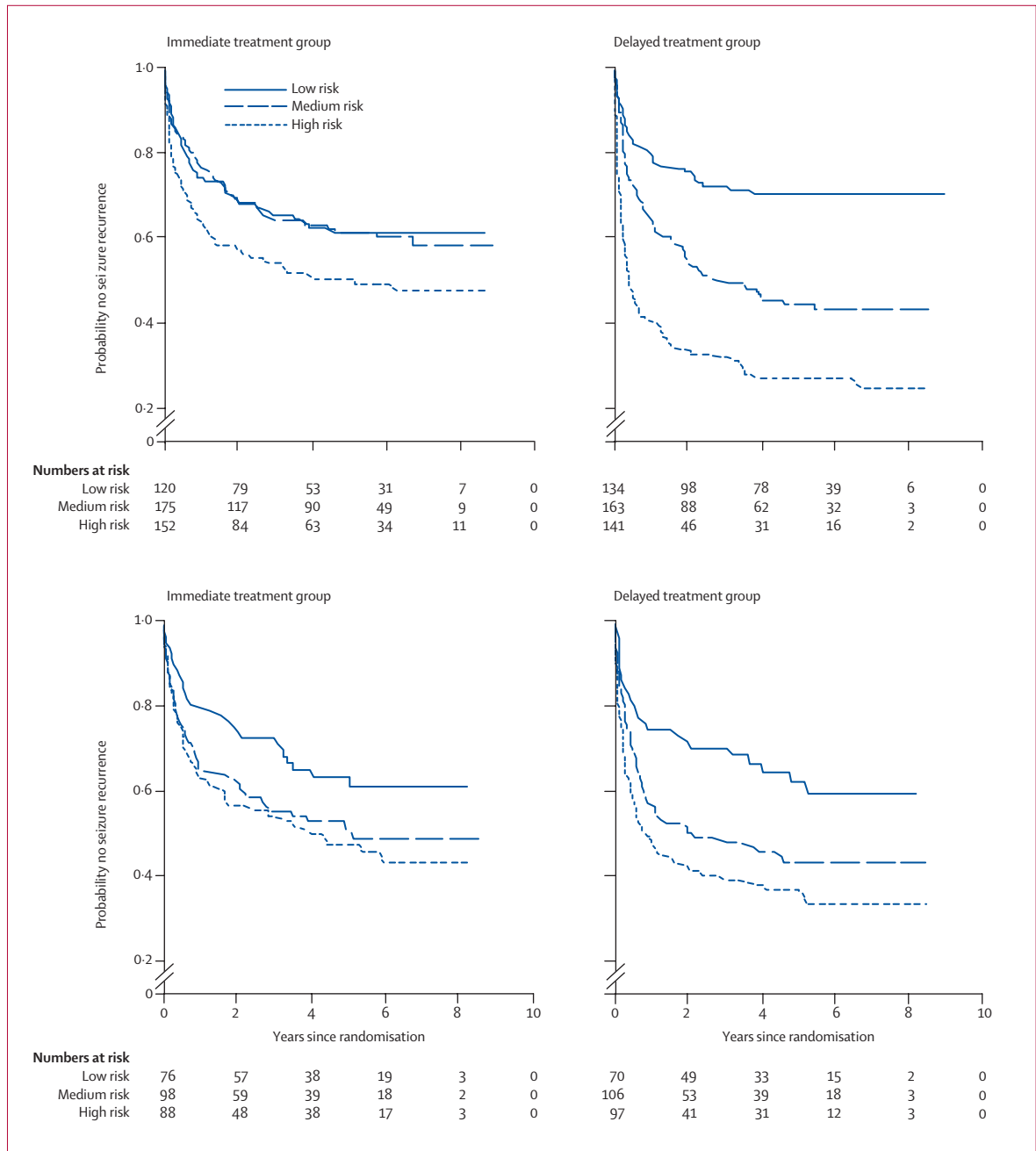


Figure 1: Kaplan-Meier plots of time to first seizure, stratified by risk group, in the test (top) and validation (bottom) samples, by treatment group

(table 2). Given the risk group cut-offs at <0.30 (low risk), <0.50 (medium risk), and ≥ 0.50 (high risk), and prognostic index given by $[(\log_e \text{ seizures} \times 0.44) + (\text{neurological condition} \times 0.30) + (\text{abnormal EEG} \times 0.43)]$, an individual can only be low risk if all the prognostic factors are 0 (ie, where the number of seizures is 1, hence $\log_e \text{ seizures}$ is 0). The starting value for the look-up table is therefore given as 0 for all individuals with one seizure. One point is added to the score for individuals with two to three seizures and 2 points are added for individuals with four

or more seizures. Similarly 1 point is added to the score for individuals with an abnormal EEG and 1 point is added for individuals with a neurological disorder. Individuals with a low risk of recurrence are those with a prognostic index score of 0—ie, those with a single seizure, a normal EEG, and the absence of a neurological disorder. Individuals with a prognostic index score of 1 have a medium risk of recurrence—ie, those with two to three seizures, a normal EEG, and no neurological abnormality, or individuals with a single seizure and an

abnormal EEG or a neurological disorder. Individuals with a prognostic index score of 2–4 have a high risk of recurrence—ie, those with a single seizure, abnormal EEG, and a neurological disorder; those with two to three seizures, an abnormal EEG, or neurological disorder; and any individual with four or more seizures.

Once a risk category has been assigned, estimates of the risk of recurrence can be taken from table 3. For example, an individual in the high-risk category has around a 50% chance of seizure recurrence within both 3 and 5 years if antiepileptic drug treatment is started immediately, compared with around a 65% chance of seizures within 3 years (70% within 5 years) if treatment is delayed. By contrast, an individual in the low-risk category has around a 30% chance of seizure recurrence by 3 years (35% by 5 years) under both treatment policies, bearing in mind that there is no significant difference between them within the low-risk group.

Discussion

The MESS trial² gathered information about a range of clinical factors previously identified as potentially affecting seizure recurrence.¹² Our model indicates that risk of seizure recurrence increases with number of seizures at presentation, abnormal EEG, and presence of a neurological disorder. The identification of these factors as the most important in relation to seizure recurrence is lent support by other published work.¹³ These findings enabled the development of a relatively simple model, which identifies patients with low, medium, and high risk of seizure recurrence. The low-risk group comprises only those presenting with a single seizure, no neurological disorder, and a normal EEG. For those in this low-risk group, there is little benefit to immediate treatment, but potentially worthwhile benefits are seen in the medium and high-risk groups.

Internal validation has been investigated using a split-sample approach. Adequate separation of risk groups and reasonable predictive accuracy has been shown, giving some confidence in the clinical accuracy of the model. External validation on other datasets is needed to provide a more rigorous test of model validity. The model should be used with caution in populations not represented in MESS, and thus should not be relied on in patients with frequent seizures who would generally be advised to start treatment. The model might also be unreliable in patients seen very quickly after a first definite seizure.

Our model indicates that individuals with more than one seizure at presentation are at a higher risk of seizure recurrence than those with only one seizure. Among patients with one seizure at randomisation in MESS, the actuarial cumulative percentages having had seizure recurrence at 2 years were 39% and 32% for those randomly assigned delayed and immediate treatment, respectively; for patients with more than one seizure at presentation, these percentages were 61% and 43%,

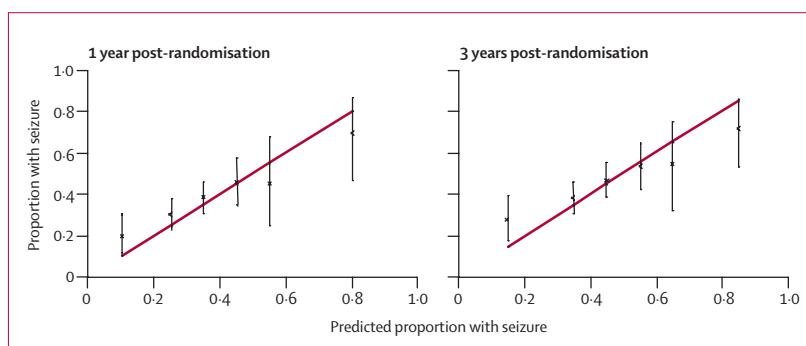


Figure 2: Plots of observed proportions (95% CI) with seizure recurrence according to categories of predicted proportions with seizure recurrence occurring at 1 and 3 years post-randomisation. Confidence intervals were calculated from a binomial distribution for the proportion observed.

respectively.² Trials of antiepileptic-drug treatment versus no treatment after a single tonic-clonic seizure have reported that treatment with carbamazepine or valproic acid reduced the risk of seizure recurrence by 2 years from approximately 60% to 20% ($n=91$)⁷ and that antiepileptic-drug treatment (most commonly phenobarbital) reduced the 2-year risk from 40% to 32% in those randomly assigned immediate treatment ($n=419$).⁸ The risk reduction in MESS is relatively small, and a large proportion of patients with single seizures remained seizure-free at 2 years, even without treatment. This finding could be due to differences in the inclusion criteria; MESS is unusual in that it included patients with infrequent or minor seizures. Furthermore, non-compliance in the group randomised to no immediate treatment (and the consequent dilution of the observed treatment effect) could have varied between trials. Randomisation might also have been relatively delayed in MESS, with 26% randomised within 1 week of the last seizure. By comparison, in the FIRST study,⁸ all patients were randomised within a week of the index seizure.

The decision to start antiepileptic-drug treatment after diagnosis of single seizures or epilepsy can be complex because it is affected by many social and psychological

Prognostic index	
Starting value	
One seizure prior to presentation	0
Two or three seizures prior to presentation	1
Four or more seizures prior to presentation	2
Add if present	
Neurological disorder or deficit, learning disability, or developmental delay	1
Abnormal EEG	1
Risk classification group for seizure recurrence*	Final score
Low risk	0
Medium risk	1
High risk	2–4

*See table 3 for probabilities of no seizure recurrence at specific time points for each of these subgroups.

Table 4: Prognostic index, with integer values

factors that are extraneous to the basic risk–benefit assessment. Avoidance of further seizures might be paramount in someone whose employment is dependent on their ability to drive, whereas a woman of child-bearing age might be unwilling to accept risks to future pregnancies from drug treatment. For these reasons, the main clinical input is the provision of appropriate information to allow informed decision-making by the patient. Indeed, in the absence of this guidance there is unlikely to be good adherence to any policy of immediate drug treatment.

Although patients with frequent seizures at diagnosis are often easy to advise given the risk of further seizures is high, this is not the case for patients with few or infrequent seizures, or seizures with minor symptoms. Here, the risk of future clinically significant seizures is lower and more closely matched by the risks of adverse effects associated with antiepileptic-drug treatment. MESS has provided evidence for a significant benefit in terms of time to first seizure on immediate treatment compared with delayed treatment.² Results from MESS also suggest there is no clinically important benefit from immediate treatment on late outcomes such as terminal remission of 2 years at 3 and 5 years after starting therapy.² For this reason, decision-making should be dominated by the degree to which risk of seizures will be reduced by immediate treatment in the first 2 or 3 years after diagnosis.

There is a need to assess the external validity and usefulness of the model in assisting everyday decision-making for relevant patients in a new unselected population. The model is, however, consistent with and supportive of current clinical practice. Patients who present with single or infrequent seizures should not be prescribed an antiepileptic drug, but should be referred to a specialist. The predictive model may be a useful adjunct to individual counselling, but will need the support of appropriate expertise to answer any patient questions that might arise from its predictions.

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Authors' contributions

LGK and TLJ carried out the modelling and analysis; LGK, DWC, TLJ, and AGM wrote and commented on the text.

Conflicts of interest

We have no conflicts of interest.

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