NEUROLOGY MS ID#: NEUROLOGY/2017/869974

**Title: Identification of patients who will not achieve seizure remission within 5 years on AEDs.**

David M. Hughes (PhD)1, Laura J Bonnett (PhD)1, Gabriela Czanner (PhD)1,2, Arnošt Komárek (PhD)3, Anthony G Marson (MD)4, Marta García-Fiñana (PhD)1

1. Department of Biostatistics, Institute of Translational Medicine, University of Liverpool, Liverpool, UK.

2. Department of Eye and Vision Science, Institute of Ageing & Chronic disease, University of Liverpool, Liverpool, UK.

3. Department of Probability and Mathematical Statistics, Faculty of Mathematics and Physics, Charles University, Prague, Prague, Czech Republic.

4. Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK.

Title Character Count: 95

Number of References: 24/50

Number of Tables: 4

Number of Figures: 3

Word count abstract: 228/250

Word Count Introduction 231/250

Word count paper: 4382/4500

Correspondence to:

Dr. Marta García-Fiñana,

Department of Biostatistics,

Institute of Translational Medicine,

University of Liverpool,

Block F, Waterhouse Bld.

1-5 Brownlow Street

Liverpool,

L69 3GL,

UK

[martaf@liv.ac.uk](mailto:martaf@liv.ac.uk)

0151 794 9755

Statistical Analysis was conducted by David M. Hughes, University of Liverpool

Search terms: All Epilepsy/seizures; All Clinical Neurology; Prognosis; Epilepsy Monitoring

David M Hughes: [dmhughes@liverpool.ac.uk](mailto:dmhughes@liverpool.ac.uk)

Laura J Bonnett: [ljbcmshe@liverpool.ac.uk](mailto:ljbcmshe@liverpool.ac.uk)

Gabriela Czanner [czanner@liverpool.ac.uk](mailto:czanner@liverpool.ac.uk)

Arnošt Komárek [arnost.komarek@mff.cuni.cz](mailto:arnost.komarek@mff.cuni.cz)

Anthony G Marson: [marjon01@liverpool.ac.uk](mailto:marjon01@liverpool.ac.uk)

Marta García-Fiñana: [martaf@liv.ac.uk](mailto:martaf@liv.ac.uk)

**Author contributions:**

David M Hughes: Study Design, analysis and interpretation of the data, wrote the first draft of the manuscript.

Laura J. Bonnett: Study Design, interpretation of the data, critical revision of the manuscript.

Gabriela Czanner: Study Design, interpretation of the data, critical revision of the manuscript.

Arnošt Komárek: Software for statistical methods. Analysis and interpretation of the data, critical revision of the manuscript.

Anthony G. Marson: Study Design, data acquisition, close supervision regarding the clinical aspects of the work, clinical interpretation of the analysis, critical revision of the manuscript.

Marta García-Fiñana: Study Design, supervision of the analysis and interpretation of the data, critical revision of the manuscript.

Author Disclosures:

Dr. David M Hughes: Reports no disclosures.

Dr. Laura J. Bonnett: Reports no disclosures.

Dr. Gabriela Czanner: Reports no disclosures.

Dr. Arnošt Komárek: Reports no disclosures.

Prof. Anthony G. Marson: Reports no disclosures.

Dr. Marta García-Fiñana: Reports no disclosures.

Study funded by the MRC (Research project MR/L010909/1), the EPSRC grant EP/N014499/1 and the NIHR (PDF-2015-08-044). TGM is part-funded by The National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North West Coast (NIHR CLAHRC NWC). The views expressed here are those of the authors and not necessarily those of the EPSRC, the MRC, the NHS, the NIHR, or the Department of Health and Social Care.

“The Article Processing Charge was funded by**the Medical Research Council (RCUK)"**

**Abstract**

**Objective:** Our aim was to identify people with epilepsy who will not achieve a 12-month seizure remission within 5-years of starting treatment.

**Methods:** The Standard and New Antiepileptic Drug study (SANAD) is the largest prospective study in patients with epilepsy to date. We applied a recently developed multivariable approach to the SANAD dataset that takes into account not only baseline covariates describing a patient’s history prior to diagnosis, but also follow-up data as predictor variables.

**Results:** Changes in number of seizures and treatment history were the most informative time-dependent predictors, and were associated with history of neurological insult, epilepsy type, age at start of treatment, sex, and having a first degree relative with epilepsy.

Our model classified 95% of patients. Of those classified, 95% of patients observed to not achieve a remission at 5 years were correctly classified (95%CI: 89.5-100%), with 51% identified by three years, and 90% within four years of follow-up. 97% of patients observed to achieve a remission within 5 years were correctly classified (93.3-98.8%). Of those predicted not to achieve remission, 76% (58.5-88.2%) truly did not achieve remission (Positive Predictive Value). The predictive model achieved similar accuracy levels via external validation in two independent UK-based datasets

**Conclusions:** Our approach generates up-to-date predictions of the patient’s risk of not achieving seizure remission whenever new clinical information becomes available which could influence patient counselling and management decisions.

**Introduction**

Epilepsy is a heterogeneous disorder with respect to aetiology, seizures types, and outcome. Although for most patients, seizures can be controlled using antiepileptic drugs (AED), around 30% never enter a sustained remission from seizures, despite multiple treatment changes. Patients typically undergo years of treatment before the clinician is confident that their epilepsy is drug-resistant.1, 2 Uncontrolled seizures during this time can have a pronounced reduction in quality of life, education and employment prospects. The ability to reliably predict earlier that seizure remission will not occur would offer the opportunity of more effective management and better patient counselling in an attempt to minimise adverse effect on quality of life.

The focus of our paper is to predict patients who will not achieve a 12 month remission by 5 years of follow up using covariates collected at baseline and during follow-up. Several studies have assessed prognostic factors for outcomes in newly diagnosed epilepsy3-10 but prediction of drug-resistant epilepsy based on baseline (or early follow-up) prognostic factors has only achieved area under curves of between 61-78%. This work is different, since we use data collected during follow-up (referred to as longitudinal variables) in addition to baseline covariates that describe a patient’s history prior to diagnosis. Our approach generates up to date predictions of the patient’s risk of not achieving seizure remission whenever new clinical information becomes available, providing a framework to aid decision making.

**Methods**

**Patients and Procedures**

The Standard and New Antiepileptic Drugs (SANAD) trial 11, 12 is a randomised controlled trial that recruited 2437 people with epilepsy assigned to one of two arms of the trial. Arm A included those for whom carbamazepine was considered the first line standard treatment, primarily patients with focal epilepsy, who were randomised to treatment with carbamazepine, gabapentin, lamotrigine, oxcarbazepine or topiramate. Arm B included those for whom sodium valproate was considered the first line standard treatment, primarily those with generalised or unclassified epilepsy, who were randomised to lamotrigine, topiramate or valproate. Clinicians recruiting patients into SANAD were primarily neurologists with expertise in epilepsy. This dataset contains a large, heterogeneous group of patients with epilepsy, many of whom are observed over at least five years, and provides the opportunity to investigate the individual profiles of patients in order to predict those who will not achieve a 12-month continuous seizure remission during follow-up. Our multivariate analysis includes data from both arms of the SANAD study simultaneously. Previous analysis of the SANAD data used only baseline covariates to identify prognostic factors influencing a patient’s time to remission from seizures or treatment failure, and the development of a clinical classification tool was not addressed.13, 14

This analysis considers 1577 patients who achieved at least one continuous period of 12-month remission within five years from starting treatment and 175 patients who did not. Patients were included in our analysis if they had experienced at least two clinically definite unprovoked seizures, were at least 5 years old, and had been followed up either to first remission or for 5 years. Our aim was to correctly identify patients who did not achieve remission as early as possible in their treatment journey by looking at the individual profiles (using both baseline and longitudinal data), and our primary outcome was a binary variable indicating whether the patient achieves remission within five years of starting treatment.

For the purposes of external validation the Multicentre Study of Early Epilepsy and Single Seizures (MESS)15 and National General Practice Study of Epilepsy (NGPSE)16 datasets were used, which come from a UK-based randomised controlled trial and the UK primary care system, respectively.

**Standard Protocol Approvals, Registrations, and Patient Consents**

SANAD received appropriate multicentre and local ethics and research committee approvals, and was managed according to the Medical Research Council’s Good Clinical Practice Guidelines. Patients gave informed written consent to inclusion and to long-term follow-up. SANAD is registered as an International Standard Randomised Controlled Trial, number ISRCTN38354748.17

**Predictive Models and follow-up data**

Two models are fitted, one for the remission group and one for the no-remission group. These models are then used to predict for a new patient the likelihood of not achieving remission by assessing which of the two models the new patient’s profile is *closer* to. Predictions are updated each time new information becomes available for a patient. The model does not need to be refitted, and the new patient’s data is used to generate a patient-specific prediction of their risk of not achieving remission.

In this study, four follow-up variables were considered for inclusion in the final model based on clinical consensus. These were (1) whether a patient experienced seizures (of any type) since their last clinic visit, (2) the total number of seizures experienced since the last clinic visit, (3) whether or not treatment was changed at the last visit and (4) the number of adverse events experienced by the patient since the last visit. Common adverse events experienced included depression, dizziness, allergic reactions, headaches, tiredness, pins and needles and weight gain.18 Treatment change could include the addition or removal of an antiepileptic drug or a change in the dose of a drug.

The list of potential baseline covariates considered were: age at start of treatment, sex, type of epilepsy, electroencephalogram (EEG) results, Computerized Tomography/Magnetic Resonance Imaging (CT/MRI) results, first degree relative with epilepsy, neurological insult and total number of seizures experienced before starting treatment. Patients were classified as having a neurological insult if they had learning disabilities or a neurological deficit. Epilepsy type was classed as focal, generalised or unclassified, and is highly correlated with the randomisation arm the patient was recruited to. EEG and CT/MRI results were defined as normal, not clinically indicated or abnormal. Previous analysis of the SANAD dataset used these baseline covariates to identify prognostic factors influencing a patient’s time to remission.13 In this analysis, they are used to model the evolution over time of the longitudinal variables that predict no-remission, and only indirectly influence the classification procedure, through their influence on the longitudinal variables.

Models also accounted for time since starting treatment and also for time since last follow up to account for the fact that clinic visits were not equally spaced.

**Statistical Methods**

Multivariate generalised linear mixed modelling (MGLMM) was applied to model the longitudinal variables in each prognostic group separately (patients who achieved 12-month remission and patients who did not).19 Multivariate models account for the correlation between repeated measurements over time, as well as for the dependence of the longitudinal variables on baseline covariates.

Multivariate models were built by first considering the subset of baseline covariates that best described the changes over time of each of the four longitudinal variables listed above. Models were compared using penalised expected deviance (PED)20 alongside a forward selection approach. PED is a loss function that penalises for model complexity and that is suitable for complex hierarchical models. These models were then used to assess the probability that new patients would not achieve remission within five years of starting treatment in a discriminant analysis. The best combination of longitudinal variables was determined by probability of correct classification (PCC). Training sets consisting of data from 70% of patients in each group were used to build the model and data from the remaining 30% were used to test the model. Training and test sets were randomly generated 100 times and the results were averaged.

**Dynamic Classification Scheme**

To classify patients as remission or no remission we used the following procedure. Firstly, the risk of not achieving remission for each patient was predicted using the multivariable model. Secondly, we stated a threshold for the predictive risk. The threshold chosen in this paper is 0.64, which was associated with the point on the Receiver Operator Characteristic (ROC) curve nearest to the top left corner (i.e., it provides the best balance in terms of number of patients correctly identified as no-remission, and those correctly identified as 12-month seizure free patients). Thirdly, the uncertainty of the risks predicted by the model varies across patients (and over time). To account for this uncertainty, credible intervals (Bayesian equivalent of confidence intervals, an interval in which we are 99% confident that the true probability of not achieving remission during five years lies) were used to assess the confidence in the assigned risk.21

We applied the following allocation scheme:

1. We consider the first visit of a patient and calculate both the probability of the patient to not achieve remission during five years after starting treatment and a 99% credible interval around this probability.
2. If the credible interval is entirely above the threshold of 0.64, we assign the patient to the no-remission group. Prediction now stops for this patient since they show a high risk of not achieving remission.
3. If the credible interval is entirely below 0.64, we temporarily assign the patient to the remission group, and update the patient’s risk at the next visit.
4. If the credible interval contains 0.64, the patient remains unclassified (due to the level of uncertainty in the estimated risk the patient is not yet assigned to a group). Their risk is updated at the next visit.

**Data Availability**

Anonymized data used in this study is available upon request from Professor Anthony Marson.

**Results**

Figure 1 shows the disposition of patients recruited to SANAD and who were included in the analyses reported here, for whom Table 1 shows baseline variables.

FIGURE 1 ABOUT HERE

TABLE 1 ABOUT HERE

The best multivariate models consisted of two longitudinal variables; whether the patient experienced seizures since the last clinic visit and whether the patient’s treatment was changed at the last clinic visit. The baseline covariates included in each model, along with their odds ratios are described in Table 2.

Having focal epilepsy increases the risk of experiencing seizures, regardless of whether the patient will ultimately experience remission or not (Table 2). Having a first-degree relative with epilepsy or neurological insult increases the risk for patients who will ultimately achieve remission. These variables were not selected in the model for patients who do not achieve remission, although this could be due to smaller sample size.

TABLE 2 ABOUT HERE

Figure 2 describes how the assigned probability of not achieving remission changes according to follow-up factors. Patients who experienced seizures or whose treatment was changed since the previous visit tend to be assigned higher probabilities of not achieving remission. These assigned probabilities increase as the length of observation increases for a patient. In general, patients with a history of neurological insult are assigned lower probabilities of ultimately being no-remission compared to patients with similar seizure and treatment history but without neurological insult, especially early in their observation history (e.g. 1 year), reflecting the fact that patients with neurological insult are more likely to experience seizures13, at least initially, regardless of whether they will ultimately achieve remission or not.

FIGURE 2 ABOUT HERE

Figure 3 illustrates the allocation scheme for four real scenarios. Patient (A) initially has a low probability of not achieving remission because, despite having experienced seizures, the time of observation is still short. At the next visit the risk drops since a treatment change led to a short period free from seizures. As more information is gathered on the patient, their probability of not achieving remission increases, but only after the fifth visit is the entire 99% credible interval above the chosen threshold of 0.64. At this point we are more confident this patient is not going to achieve remission because they have changed treatment three times and are still experiencing seizures. This patient is classified as no-remission within two years, a much earlier time point than the decision might otherwise be taken in clinical practice.

FIGURE 3 ABOUT HERE

Patient (B) takes longer to be classified as no-remission. After two years the patient changed treatment and it resulted in a period without seizures, which caused the assigned probability of not achieving remission to decrease dramatically offering hope that this patient may achieve remission. Unfortunately for this patient, the seizures returned causing a steady increase in the probability of being in the no-remission group, until the patient is confidently predicted to be no-remission after just over four years.

Patient (C) achieves remission immediately after 12 months. This is accurately predicted by the model since the patient experiences no seizures following the start of treatment and the clinicians felt no need to change treatments. By contrast, patient (D) experienced seizures for a longer period. They had focal epilepsy, a high number of seizures before starting treatment and were relatively young, which meant that although the patient continued experiencing seizures for over two years, their risk of not achieving remission was not initially high because seizures were likely to occur according to these baseline characteristics. Just over three years after starting treatment, the patient is observed to have changed onto a treatment that appears to give adequate seizures control and is correctly classified as remission.

The overall accuracy of our predictive model is assessed by considering how many patients from the test sample, were correctly classified (Table 4). Using the selected threshold of 0.64 and excluding patients left unclassified by the model, 95% of patients who truly did not achieve remission were identified as such (sensitivity, 95% confidence interval: 89.6-100%), whilst 97% of patients who achieved remission were correctly classified (specificity, 95% confidence interval 93.3-98.8%). Overall, 97% (93.4-98.5%) of patients were correctly classified (PCC). For patients predicted by the model as not achieving remission, 76% (58.5-88.2%) truly did not achieve remission (Positive Predictive Value=PPV). The area under ROC curve (AUC) was 94.5% (90.9.0-96.7%).

A randomly chosen split of the data into training and test sets achieved a calibration slope of 0.922, suggesting the model is well calibrated (calibration slopes close to one show well calibrated models with observed and expected risks matching well), in addition to providing good discrimination between patients who achieve remission and those who do not.22

There were 5% of patients who were left unclassified and, including these patients, the model achieved overall sensitivity of 78%, specificity of 93% with a PCC of 91%.

The average time at which a patient was correctly identified as not achieving remission was 36.4 months (just over three years). In fact, 51% of patients who were correctly identified as not achieving remission were identified within 3 years, whilst only 10% required a visit in their fifth year after starting treatment to be correctly classified (Table 3). For most patients who will not achieve remission, our model can identify them between one and three years. Our model is patient specific. A patient’s classification as no-remission is not made at the same time for all patients (unlike the previously published predictive models8-10) but only when their individual risk is high enough.

By using the dynamic classification scheme with 99% credible intervals, only 5% of patients were left unclassified and would require further follow up in clinical practice to determine their classification. The time of prediction is less important for patients who achieve remission since these patients would in practice remain under observations until remission is observed. Nevertheless, 973/1577 patients (62%) who achieve remission can be correctly identified using only observations from their first year of follow up.

TABLE 3 ABOUT HERE

**External Validation**

We conducted an external validation study of our predictive model using two additional datasets MESS15, 23 and NGPSE (See Table 1 for descriptive details).16 MESS was a UK based randomised control trial comparing immediate and deferred treatment for patients who experienced a first unprovoked seizure or had epilepsy. NGPSE is an unselected cohort from the UK primary care system of people with newly diagnosed seizures. We used the model built using all the SANAD data to predict the status of patients in MESS and NGPSE and assessed the accuracy of the predictions. In the NGPSE data, all counts of eleven or more seizures were recorded as more than 10. This only affected a relatively small number of patients (9/45 no-remission patients and 57/586 remission patients). Following previous examples24 we used various missing data imputation methods to assign values greater than 10 for the total number of seizures before starting treatment to the relevant patients in NGPSE. The different imputation methods employed gave almost identical results and so only the hot deck imputation is reported here.

The accuracy in terms of sensitivity and specificity of the classified patients when the predictive model is applied to MESS and NGPSE is high (Table 4, i.e., with sensitivity >90% and specificity >95% for classified patients, and only 1% of patients left unclassified) and comparable to the prediction accuracy within SANAD (obtained by splitting the data into training and test sets). In both the MESS and NGPSE cohorts, very high AUC values demonstrate excellent model discrimination. For the MESS data set, PPV was lower, although we suspect this is due to the low proportion of patients who do not achieve remission.

The NGPSE cohort was well calibrated, achieving a calibration slope of 0.95, suggesting that the SANAD model is well calibrated and discriminates well even in this external dataset. The MESS cohort achieved, on the other hand, a calibration slope of 0.52. Calibration slopes in external datasets are often worse than in the dataset used to train the model. In the case of the MESS cohort, the worse calibration slope is likely to be also influenced by the low proportion of patients who do not achieve remission as was seen in the PPV value for MESS.

This external validation shows that the SANAD model was able to correctly identify people with epilepsy who would not achieve remission from seizures within 5 years of commencing treatment with a high degree of accuracy.

TABLE 4 ABOUT HERE

Differences are nevertheless expected due to the fact that the datasets are not identical in purpose or form, but can be considered to come from the same “super population” as required for external validation.22

**Discussion**

Our dynamic prediction approach allows identification of patients who will not achieve remission within 5 years of starting treatment. The time at which non-remission is identified is different among patients, reflecting the heterogeneous nature of epilepsy and patient trajectories. For classified patients, 95% of no remission cases are correctly identified and the majority of these patients are identified within the first 3 years from commencing treatment. Some patients are clearly missed by remaining unclassified, and the overall sensitivity would be reduced to 78% by taking into account unclassified patients.

The most informative evidence in terms of predicting a patient’s epilepsy status is the combination of treatment changes and seizure history together with baseline factors that accurately predicts a patient’s prognosis. Note that these results do not imply that changing treatment causes an increased likelihood of not achieving remission, since changing treatment has been shown to be usually beneficial.25 Instead, the fact that a clinician felt the need to change the dose or type of AED at the previous visit is used as an indicator that something was not going well.

Whilst clinicians may at first be concerned about choice of drug and dosing, and the effect that choice might have on prognosis, it is important to consider that RCTs in epilepsy have largely failed to find important differences among antiepileptic drugs. This was exemplified by the use of non-inferiority designs in the European Union and historical controlled withdrawal to monotherapy trials in the USA. In contrast, we have clearly demonstrated the effect of clinical factors on outcome.

The International League Against Epilepsy (ILAE) proposed a definition of drug resistant epilepsy as the failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.2 This definition is however of little use in clinical practice (e.g., *adequate* or *appropriately chosen* are subject to interpretation and the choice of two AEDs is arbitrary) and patients currently wait years before clinicians are confident that they will not achieve remission. In contrast, our analysis includes dose and drug changes, thereby using information about treatment in a more quantifiable and informative way, avoiding any need to make judgements about adequacy and appropriateness.

In our dataset, a total of 600 (out of 1752) patients stopped taking their randomised drug (34%). However, 413 of these 600 patients were changed to a different drug and 187 received no AEDs (of whom 159 achieved remission, 85%).

Patients who did not achieve remission from seizures within 5 years of starting treatment had an average of 5.2 treatments changes (either a change in dose, or addition or removal of an AED) over the duration of the five years for which they were observed. Patients who were correctly identified as not achieving remission by our model had undergone an average of 3.9 treatment changes at the point at which they were correctly identified. The ILAE definition of drug-resistance requires only two changes in treatment to classify a patient as drug-resistant. Our analysis suggests that, in practice, more treatment changes occur before we can be confident a patient will not achieve remission.

Previous models have defined remission/no-remission differently to us so a direct comparison is not possible. However, when predicting terminal remission at 5-years post diagnosis using baseline characteristics8, sensitivity of 65%, specificity of 64%, PPV of 36%, NPV of 85% and AUC of 0.7 was achieved. When the prediction used data collected during a 6-month follow up period,8 these values increased slightly to 69%, 71% 43%, 88% and 77%, respectively. A model that was built to predict drug-resistance after 10 years (based on values at one year of follow up) reported AUCs between 61% and 76%.10 Finally, a model developed to predict 2-year status after 6 months of follow up reports an AUC of 77.97%.9 The predictive accuracies from our model reported above are higher than these values (even when sensitivity/specificity accounts for the unclassified patients).

The optimal threshold should be selected according to the clinical objective. A higher threshold will produce greater specificity and greater PPV, but a longer time is required on average to identify patients who will not achieve remission. Conversely, a lower threshold will reduce the time required to identify patients who will not achieve remission, increasing the sensitivity of the test will increase but at the cost of a reduction in specificity.

The baseline characteristics influence the time at which a patient’s status can be confidently predicted, whilst seizure and treatment history have the largest influence on the predicted status. This discovery is illustrated by comparing the first visits of patients (A) and (B) in Figure 3. Patient (B) has characteristics at the start of treatment that are associated with an increased likelihood of experiencing seizures for at least some time, whereas patient (A) has characteristics that would not lead a clinician to expect the patient would experience seizures. Their first visits occur at approximately the same time, and they both have experienced seizures, and are still on the first treatment assigned. But at baseline patient (A) is assigned a probability of not achieving remission that is 5% higher when compared to patient (B) since it is expected that patient (B) experienced seizures. Because patient (A) continues to experience seizures the estimated risk that they will ultimately not achieve remission increases much more quickly than for patient (B).

A limitation of the model is that patients who achieve remission are only considered up to the point at which they first achieve remission. In the SANAD data, 532 patients out of 1577 patients who were observed to achieve a 12-month remission went on to have further seizures (34%) whilst under observation. Of these, 183 (34%) experienced one further seizure only and 236/532 patients (44%) were observed to achieve 12-month remission again.

A number of patients with insufficient follow-up time to determine their five-year status were excluded from the analysis (n=545, mostly administrative censoring). In addition, 34 patients dropped out of the study before it was possible to determine their status and therefore it was not possible for these patients to be included in the analysis. The omission of this group of patients may have an influence on the model parameters for each MGLMM, and hence also on the discriminant analysis. However, given that this exclusion is mainly dictated by time of starting treatment, we don’t expect this led to biased results.

Although a group of patients has been excluded from this analysis, the proportions of patients achieving a 12-month remission within 5 years of follow up is comparable to previous studies, suggesting that the included cohort is reasonably representative of people with epilepsy. Previous estimates suggest that 60 to 70% of people will achieve a remission from seizure, defined as a 5-year period of continuous remission within 9 years of follow up.26 In Table 1 they report that after 5 years of follow up, 93% (91%-95%) of patients had achieved a 12-month remission interval, which is comparable to the 90% observed in this study.

Although possible, we do not expect that the imputation of the number of seizures in the NGPSE dataset have dramatically increased the degree of agreement with SANAD given that this was applied to only a relatively small number of patients (10%).

This is a step towards a clinical tool for identifying patients who will not achieve remission from seizures. The model has been internally and externally validated and it has the potential to be used in clinical practice to aid stratification of patient management and influence patient counselling.

Patients who will not achieve remission can be identified by recording at baseline (commencement of treatment on AEDs) the following information: patient’s age, sex, type of epilepsy, the number of seizures they had experienced prior to treatment, whether they had a first degree relative with epilepsy and whether or not they had a neurological insult, and by monitoring over time whether the patient had experienced seizures since their last clinic visit, and whether the clinician had felt it necessary to change treatment at the last visit. By leaving a small group of patients unclassified, increased confidence is obtained in the predictions of those patients who are classified as not likely to achieve remission. This selection of baseline and longitudinal variables, along with the times of the clinic visits post baseline are sufficient to classify patients with high levels of accuracy.

**Acknowledgements**

We are grateful to Dr Ley Sander for permission to use the NGPSE dataset and to Dr. Rebecca Bromley for reading and discussing the manuscript.

**Role of the funding source**

The sponsor of the study had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**References**

1. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. New England Journal of Medicine 2011;365:919-926.

2. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069-1077.

3. Kwan P, Brodie MJ. Early identification of refractory epilepsy. New England Journal of Medicine 2000;342:314-319.

4. Hitiris N, Mohanraj R, Norrie J, Sills GJ, Brodie MJ. Predictors of pharmacoresistant epilepsy. Epilepsy research 2007;75:192-196.

5. Sillanpää M, Schmidt D. Predicting antiepileptic drug response in children with epilepsy. Expert review of neurotherapeutics 2011;11:877.

6. Wassenaar M, Leijten FS, Egberts TC, Moons KG, Uijl SG. Prognostic factors for medically intractable epilepsy: a systematic review. Epilepsy research 2013;106:301-310.

7. Sillanpää M, Schmidt D. Long-term outcome of medically treated epilepsy. Seizure 2016.

8. Arts WF, Brouwer OF, Peters AB, et al. Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. Brain 2004;127:1774-1784.

9. Huang L, Li S, He D, Bao W, Li L. A predictive risk model for medical intractability in epilepsy. Epilepsy & Behavior 2014;37:282-286.

10. Sillanpää M, Schmidt D. Early seizure frequency and aetiology predict long-term medical outcome in childhood-onset epilepsy. Brain 2009;132:989-998.

11. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. The Lancet 2007;369:1016-1026.

12. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. The Lancet 2007;369:1000-1015.

13. Bonnett L, Smith CT, Smith D, Williamson P, Chadwick D, Marson AG. Prognostic factors for time to treatment failure and time to 12 months of remission for patients with focal epilepsy: post-hoc, subgroup analyses of data from the SANAD trial. The Lancet Neurology 2012;11:331-340.

14. Bonnett LJ, Smith CT, Smith D, Williamson PR, Chadwick D, Marson AG. Time to 12-month remission and treatment failure for generalised and unclassified epilepsy. Journal of Neurology, Neurosurgery & Psychiatry 2013:jnnp-2013-306040.

15. Marson A, Jacoby A, Johnson A, et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. The Lancet 2005;365:2007-2013.

16. Hart Y, Sander J, Sharvon S. National General Practice Study of Epilepsy and Epileptic Seizures: objectives and study methodology of the largest reported prospective cohort study of epilepsy. National General Practice Study of Epilepsy and Epileptic Seizures (NGPSE). Neuroepidemiology 1988;8:221-227.

17. Vere D. MRC guidelines for good clinical practice in clinical trials. Journal of medical ethics 1999;25:280.

18. Shukralla AA, Tudur-Smith C, Powell GA, Williamson PR, Marson AG. Reporting of adverse events in randomised controlled trials of antiepileptic drugs using the CONSORT criteria for reporting harms. Epilepsy Research 2011;97:20-29.

19. Hughes DM, Komárek A, Czanner G, Garcia-Fiñana M. Dynamic longitudinal discriminant analysis using multiple longitudinal markers of different types. Statistical Methods in Medical Research 2016:DOI: 10.1177/0962280216674496.

20. Plummer M. Penalized loss functions for Bayesian model comparison. Biostatistics 2008;9:523-539.

21. Hughes DM, Komárek A, Bonnett LJ, Czanner G, García‐Fiñana M. Dynamic classification using credible intervals in longitudinal discriminant analysis. Statistics in medicine 2017;36:3858-3874.

22. Steyerberg E. Clinical prediction models: a practical approach to development, validation, and updating: Springer Science & Business Media, 2008.

23. Kim LG, Johnson TL, Marson AG, Chadwick DW, group MMS. Prediction of risk of seizure recurrence after a single seizure and early epilepsy: further results from the MESS trial. The Lancet Neurology 2006;5:317-322.

24. Bonnett LJ, Marson AG, Johnson A, et al. External Validation of a Prognostic Model for Seizure Recurrence Following a First Unprovoked Seizure and Implications for Driving. PloS one 2014;9:e99063.

25. Szaflarski JP, Martin RC, Faught E, et al. Quality Indicator for Epilepsy Treatment 15 (QUIET-15): Intervening after recurrent seizures in the elderly. Epilepsy & Behavior 2017;70:253-258.

26. Cockerell OC, Sander J, Hart YM, Shorvon SD, Johnson A. Remission of epilepsy: results from the National General Practice Study of Epilepsy. The Lancet 1995;346:140-144.

Table 1: Baseline Characteristics of patients included in SANAD, MESS and NGPSE.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dataset | **SANAD** | | **MESS15, 23** | | **NGPSE16** | |
| Patient Group | **Remission within 5 years** | **No Remission within 5 years** | **Remission within 5 years** | **No Remission within 5 years** | **Remission within 5 years** | **No Remission within 5 years** |
| Number of Patients | 1577 (90%) | 175 (10%) | 753 (98%) | 12 (2%) | 586 (93%) | 45 (7%) |
| Males | 911 (58%) | 95 (54%) | 411 (54%) | 9 (75%) | 298 (51%) | 19 (42%) |
| Median Age at start of treatment (years) | 32 | 31 | 22 | 34 | 26 | 22 |
| Focal Epilepsy | 957 (61%) | 136 (78%) | 306 (41%) | 6 (50%) | 247 (42%) | 29 (64%) |
| Generalised Epilepsy | 376 (24%) | 24 (14%) | 432 (57%) | 6 (50%) | 157 (27%) | 10 (22%) |
| Neurological Insult | 155 (10%) | 35 (20%) | 45 (6%) | 2 (17%) | 234 (40%) | 21 (47%) |
| First Degree relative with epilepsy | 298 (13%) | 25 (14%) | 91 (12%) | 2 (17%) | 68 (12%) | 4 (9%) |
| Total number of seizures before start of treatment (Median) | 8 | 50 | 2 | 1.5 | 1 | 1 |

Table 2: Covariates selected in the multivariate models. Odds ratios, along with their 95% credible intervals, are shown for the covariates of the models of both remission and no-remission patients. Blank entries show that the parameter was not selected.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | Longitudinal Variable | | | |
| Seizures since last visit | | Treatment Changed at last visit | |
| Group | Variable | Odds Ratio | 95% CI | Odds Ratio | 95% CI |
| Patients who achieve remission | Number of Seizures before start of treatment (per 10 seizures) | 1.010 | (1.007,1.014) | 1.005 | (1.003,1.007) |
| Neurological Insult Present | 1.576 | (1.097,2.288) |  |  |
| Focal epilepsy (vs Generalised) | 1.755 | (1.281,2.461) |  |  |
| Unclassified epilepsy (vs Generalised) | 0.903 | (0.582,1.394) |  |  |
| Age at start of treatment (per 10 years) | 0.861 | (0.802,0.924) |  |  |
| First degree relative with epilepsy | 1.804 | (1.218,2.693) | 1.178 | (0.957,1.462) |
| Male |  |  | 0.996 | (0.878,1.139) |
| Time since last follow up (months) | 0.989 | (0.963,1.017) | 0.963 | (0.945,0.981) |
| Time since start of treatment (months) | 0.900 | (0.889,0.911) | 1.003 | (0.995,1.010) |
| Patients who do not achieve remission | Number of Seizures before start of treatment (per 10 seizures) | 1.005 | (0.999,1.011) |  |  |
| Focal epilepsy (vs Generalised) | 1.900 | (0.982,3.637) |  |  |
| Unclassified epilepsy (vs Generalised) | 0.624 | (0.271,1.460) |  |  |
| Time since last follow up (months) | 1.399 | (1.263,1.544) | 0.967 | (0.942,0.994) |
| Time since start of treatment (months) | 1.018 | (1.004,1.032) | 1.014 | (1.007,1.022) |
| The model included a patient specific random intercept for each longitudinal variable.   1. For patients who achieve remission, the risk of experiencing seizures increases by more than 50% in patients with a history of neurological insult (OR=1.58), increases by approximately 75% in patients with focal epilepsy (OR=1.76) and also in patients with a first degree relative with epilepsy (OR=1.80), and it decreases by about 14% by every 10 years of age (OR=0.86). The risk of experiencing seizures decreases by 10% per month since starting treatment (OR=0.90). The number of seizures before start of treatment, although statistically significant, was not clinically relevant (1% increase in risk per 10 seizures). For patients who do not achieve remission, the risk of experiencing seizures almost doubles in patients with focal epilepsy (OR=1.9, although the result is not statistically significant) and increases by about 2% per month since the start of treatment (OR=1.02) | | | | | |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Patients who do not achieve remission (n=175) | | | | Patients who achieve remission (n=1577) | | | |
| Correctly classified as no-remission |  | n=138 (79%) | 138 (95%) | Correctly classified as remission |  | n=1467 (93%) | 1467 (97%) |
| Less than 1 year | 0 (0%) | Less than 1 year | 973 (66%) |
| 1-2 years | 9 (7%) | 1-2 years | 395 (27%) |
| 2-3 years | 61 (44%) | 2-3 years | 72 (5%) |
| 3-4 years | 54 (39%) | 3-4 years | 26 (2%) |
| More than 4 years | 14 (10%) | More than 4 years | 1 (<1%) |
| Misclassified as remission | | 7 (4%) | 7 (5%) | Misclassified as no-remission | | 47 (3%) | 47 (3%) |
| Unclassified | | 30 (17%) |  | Unclassified | | 63 (4%) |  |

Table 3: Summary of the classification accuracy of the model showing the number of patients correctly identified as no-remission or remission by yearly intervals. The percentages were calculated as averages across 100 test sets, but are reported also as numbers out of the whole data set to give an overall impression.

Table 4: Summary of the predictive accuracy for SANAD, MESS and NGPSE. The SANAD results report the averages over 100 splits of the data into 70% training sets and 30% test sets.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Data and Modifications** | **Sensitivity** | **Specificity** | **PCC** | **PPV** | **AUC** | **% Unclassified** | **Mean Prediction Time (months)** |
| SANAD | 0.95 | 0.97 | 0·97 | 0.76 | 0.94 | 5 | 36.4 |
| MESS | 0.91 | 0.98 | 0·98 | 0.36 | 0.98 | 1 | 37.9 |
| NGPSE (Hot Deck) | 0.93 | 0.97 | 0·96 | 0.67 | 0.98 | 1 | 35.6 |

Figures and Legends:

**Figure 1**: SANAD Trial Profile

**Figure 2**: Probability of no remission within five years of starting treatment for combinations of risk factors at three chosen time points.

Figure 2 Legend: The box represents the point estimate average of the predicted probability of being no-remission for patients with the given characteristics, whilst the line represents the 99% credible interval. The Seizures and Treatment Change columns refer to the period since the last clinic visit, whilst neurological insult and Total Seizures are recorded at baseline. The risks are calculated at 1, 2 and 3 years after starting treatment.

**Figure 3**: Profiles of risk for two no-remission patients correctly classified two years (A) and just over four years (B) after starting treatment, and for two remission patients correctly classified soon after (C) and approximately three years after (D) starting treatment.

Figure 3 Legend: The points represent the probability assigned to the patient whilst the bars show the 99% credible interval around each probability of no-remission. The observations recorded along the top of each plot indicate whether the patient experienced seizures (SZ) since last visit and whether or not treatment was changed at last visit (TC), whilst the information to the left of each plot describe some baseline characteristics for each patients (Type=epilepsy type, F=Focal, U= Unclassified). The solid horizontal lines show the selected threshold of 0.64. The grey box shows the remaining period of the five years since starting treatment once a patient’s status has been predicted.