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

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Summary

Background Epilepsy is a heterogeneous disorder, with outcomes ranging from immediate remission after taking a first antiepileptic drug to frequent unremitting seizures with multiple treatment failures. Few prognostic models enable prediction of outcome; we therefore aimed to use data from the SANAD study to predict outcome overall and for patients receiving specific treatments.

Methods The SANAD study was a randomised controlled trial in which standard antiepileptic drugs were compared with new treatments. Arm A included patients for whom carbamazepine was considered the first-line treatment, most of whom were newly diagnosed with focal epilepsy. Patients were randomly assigned to receive carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate. Outcomes were time to treatment failure overall, because of inadequate seizure control, and because of adverse events, and time to 12 months of remission from seizures. In this post-hoc study we used regression multivariable modelling to investigate how clinical factors affect the probability of treatment failure and the probability of achieving 12 months of remission.

Findings For time to treatment failure, we identified several significant risk factors: sex (male vs female, hazard ratio [HR] 0·86, 95% CI 0·75–0·99), treatment history (taking non-SANAD antiepileptic drugs [other than those listed above] vs treatment naive, 1·27, 1·05–1·53), age (eg, older than 71 years vs 10 years or younger, 0·68, 0·51–0·91), total number of seizures (eg, four to 11 seizures vs two or fewer, 1·08, 1·05–1·11), electroencephalogram results (epileptiform abnormality vs normal, 1·26, 1·07–1·50), seizure type (eg, secondary generalised vs simple or complex partial only, 0·78, 0·66–0·91), site of onset (not localised vs temporal lobe, 1·25, 1·06–1·47), and treatment (lamotrigine vs carbamazepine, 0·76, 0·61–0·95). Significant factors for time to 12 months of remission were sex (male vs female, 1·19, 1·05–1·35), treatment history (taking a non-SANAD antiepileptic drug vs treatment naive, 0·64, 0·52–0·78), age (eg, older than 71 years vs 10 years or younger, 1·60, 1·26–2·03), time from first seizure (60–239 months vs ≤2 months, 1·41, 1·01–1·92; >240 months vs ≤2 months, 1·39, 1·04–1·86), neurological insult (present vs absent, 0·75, 0·61–0·93), total number of seizures before randomisation (eg, four to 11 vs two or fewer, 0·87, 0·85–0·90), and treatment (gabapentin vs carbamazepine, 0·71, 0·59–0·86; topiramate vs carbamazepine, 0·81, 0·68–0·98).

Interpretation We present a thorough investigation of prognostic factors from a large randomised controlled trial in patients starting antiepileptic monotherapy. If validated, our models could aid in individual patient risk stratification and the design and analysis of epilepsy trials.

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Introduction Few epilepsy trials have been designed to be pragmatic, to recruit a broad heterogeneous population representative of clinical practice, and to provide data that will inform everyday decision making. Arm A of the Standard and New Antiepileptic Drug (SANAD) trial recruited 1721 patients for whom clinicians considered carbamazepine to be the first-line standard treatment, 89% of whom had a focal epilepsy. Patients were randomly assigned to receive treatment with carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate. The results showed that lamotrigine was a potential first-line treatment because it was significantly superior to carbamazepine for time to treatment failure (hazard ratio [HR] 0·78, 95% CI 0·63–0·97), but not significantly different to carbamazepine for time to 12 months of remission. Gabapentin and topiramate were identified as unsuitable first-line treatments, gabapentin because of poor efficacy and topiramate because of poor efficacy and poor tolerability. Oxcarbazepine was not significantly different from carbamazepine for either outcome.

The epilepsies are a heterogeneous group of disorders, which consist of numerous seizure types and epilepsy syndromes with differing causes, severities, and ages of onset. Although the SANAD results provide overall estimates of treatment effect, a large heterogeneous group of patients was recruited, providing an opportunity to use prognostic modelling to investigate which clinical factors might affect outcome. Previous prognostic models have been derived from the National General Practice Survey of Epilepsy, the Medical Research Council antiepileptic drug...
withdrawal study, and the multicentre study of early epilepsy and single seizures. These models identified patient characteristics that modify seizure recurrence risks, informing decisions about whether to stop antiepileptic drug treatment for patients with seizures in remission or whether to start antiepileptic drug treatment for patients with one or few seizures. However, few prognostic models based on data from prospective cohorts or randomised controlled trials have been published, and none represent an epilepsy cohort accrued at the start of antiepileptic drug treatment. In this Article we have modelled data from SANAD arm A to identify clinical factors that affect outcome when antiepileptic drug treatment is started.

**Methods**

**Patients and procedures**

Patients were eligible for inclusion in arm A of the SANAD study if, in the previous year, they had had at least two clinically definite unprovoked epileptic seizures, if they were at least 5 years old, and if the recruiting clinician deemed carbamazepine, not valproate, to be the optimum standard treatment. Between Dec 1, 1999, and June 1, 2001, patients were allocated in a ratio of 1:1:1:1 to receive carbamazepine, gabapentin, lamotrigine, or topiramate. From June 1, 2001, to Aug 31, 2004, an oxcarbazepine group was added to the trial and patients were randomly allocated in a ratio of 1:1:1:1:1 to receive carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate.

SANAD had two primary outcomes. The first was time to treatment failure from randomisation. Treatment failure can be split into two categories: inadequate seizure control for which the randomly assigned drug might be withdrawn or a second treatment added, or failure because of unacceptable adverse events. Patients were categorised into these two main failure groups as was done in the original SANAD analyses. The second outcome was time to the first period of 12 months of remission from seizures. The methods for the SANAD study have been published in full.

SANAD received appropriate multicentre research committee approvals, and was managed according to the Medical Research Council good clinical practice guidelines. Patients provided informed written consent for inclusion and long-term follow-up. SANAD is registered with the International Standard Randomized Controlled Trial Number Register, number ISRCTN38354748.

**Prognostic modelling**

Our aim was to identify two sets of factors—one that predicted time to 12 months of remission, and one that predicted time to treatment failure. On the basis of clinical consensus and our knowledge of previous prognostic studies in epilepsy, we compiled a list of potential prognostic factors: sex, febrile seizure history, first degree relative with epilepsy, CT or MRI scan results, treatment history, age, time from first seizure to randomisation, neurological insult (eg, hemiparesis), total number of seizures before randomisation, electroencephalogram (EEG) results, seizure type, and epilepsy type. For the CT and MRI scans, results were classified as normal, abnormal, or not done. Patients were classified as having had a neurological insult if they had learning disabilities or a neurological deficit. EEGs were classified as normal, not done, non-specific

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**Figure 1: Trial profile**

*Patients with a time from first seizure to randomisation in the first or last 1% of the variable were removed from the data set. Patients with generalised epilepsy were removed from analyses.
abnormality, or epileptiform abnormality (focal or generalised spikes or spike and slow wave activity).

Seizure types were classified according to the International League Against Epilepsy seizure classification. Epilepsy type was first classified as focal, generalised, or unclassified. When there was uncertainty between focal onset and generalised onset seizures, patients were recorded as having had unclassified convulsive or other unclassified seizures. Focal epilepsy was further classified as temporal lobe, frontal lobe, parietal lobe, occipital lobe, benign focal epilepsy, or focal epilepsy not localised. For the regression modelling, because of the small numbers of participants, occipital lobe, parietal lobe, and benign focal epilepsy were combined into one group (“other”). Only 29 patients were classified as having generalised epilepsy; hence, they were removed from the dataset.

Variables associated with an increased chance of treatment failure and an increased chance of achieving 12 months of remission were determined after adjustment for multiple variables with Cox proportional hazards modelling. Because oxcarbazepine was included only after June 1, 2001, all analyses were stratified by randomisation period to account for the reduced number of patients who took this drug. Variables were centred to reduce multicolinearity and tested with the likelihood ratio test. Best-fitting, parsimonious, multivariable models were produced with backwards elimination. From the multivariable model we calculated the probability of the event for combinations of risk factors of age, sex, and total number of seizures. The proportional hazards assumption was tested with Schoenfeld residual plots and incorporation of time-dependent covariate effects. Internal validity was

| Table 1: Baseline characteristics of patients included in the analysis of time to treatment failure |
|-----------------------------------------------|
| **Carbamazepine (n=355)** | **Gabapentin (n=356)** | **Lamotrigine (n=357)** | **Oxcarbazepine (n=193)** | **Topiramate (n=347)** | **Total (n=1608)** |
|---|---|---|---|---|---|
| Males | 195 (55%) | 197 (55%) | 199 (55%) | 102 (53%) | 191 (56%) | 887 (55%) |
| History of febrile seizures | 24 (7%) | 15 (4%) | 22 (6%) | 7 (4%) | 13 (4%) | 81 (5%) |
| First degree relative with epilepsy | 36 (10%) | 41 (12%) | 33 (9%) | 21 (11%) | 34 (10%) | 165 (10%) |
| Treatment history | | | | | | |
| Treatment naive | 290 (82%) | 289 (81%) | 292 (82%) | 167 (87%) | 282 (81%) | 1320 (82%) |
| Taking non-SANAD antiepileptic drug* | 57 (16%) | 56 (16%) | 58 (16%) | 23 (12%) | 57 (16%) | 251 (16%) |
| Seizures after remission | 8 (2%) | 11 (3%) | 7 (2%) | 2 (1%) | 9 (3%) | 37 (2%) |
| Age at randomisation (years; median [IQR]) | 38 (25-53) | 36 (24-50) | 34 (22-51) | 40 (27-56) | 37 (25-52) | 38 (24-52) |
| Time from first seizure to randomisation (years; median [IQR]) | 1.4 (0.5-4.9) | 1.3 (0.6-6.0) | 1.4 (0.5-4.7) | 1.3 (0.5-4.0) | 1.4 (0.5-5.3) | 1.4 (0.5-5.1) |
| Neurological insult | 42 (12%) | 41 (12%) | 41 (11%) | 16 (8%) | 43 (12%) | 113 (7%) |
| Total seizures before randomisation (median [IQR]) | 12 (4-75) | 14 (4-70) | 12 (4-60) | 11 (4-53) | 12 (4-100) | 12 (4-70) |
| Seizure type | | | | | | |
| Simple or complex partial only | 122 (34%) | 112 (31%) | 105 (29%) | 55 (28%) | 116 (33%) | 510 (32%) |
| Secondary generalised tonic-clonic | 202 (57%) | 209 (59%) | 216 (61%) | 117 (61%) | 191 (55%) | 937 (58%) |
| Uncertain | 31 (9%) | 35 (10%) | 36 (10%) | 21 (11%) | 38 (11%) | 161 (10%) |
| Epilepsy type | | | | | | |
| Focal | 325 (92%) | 323 (91%) | 321 (90%) | 173 (90%) | 311 (90%) | 1453 (90%) |
| Temporal | 150 (46%) | 120 (37%) | 107 (33%) | 56 (32%) | 114 (37%) | 547 (38%) |
| Frontal | 20 (6%) | 17 (5%) | 34 (11%) | 5 (3%) | 31 (10%) | 107 (7%) |
| Other | 20 (6%) | 28 (9%) | 17 (5%) | 13 (8%) | 21 (6%) | 99 (7%) |
| Not localised | 135 (42%) | 158 (49%) | 163 (51%) | 99 (57%) | 145 (47%) | 700 (48%) |
| Unclassified | 30 (8%) | 33 (9%) | 36 (10%) | 20 (10%) | 36 (10%) | 155 (10%) |
| EEG results | | | | | | |
| Normal | 150 (42%) | 177 (50%) | 169 (47%) | 84 (44%) | 144 (41%) | 724 (45%) |
| Non-specific abnormality | 59 (17%) | 48 (13%) | 56 (16%) | 32 (17%) | 59 (17%) | 254 (16%) |
| Epileptiform abnormality | 133 (32%) | 100 (28%) | 100 (28%) | 54 (28%) | 104 (30%) | 471 (29%) |
| Not done | 33 (9%) | 31 (9%) | 32 (9%) | 23 (12%) | 40 (12%) | 159 (10%) |
| CT or MRI results | | | | | | |
| Normal | 205 (58%) | 225 (63%) | 207 (58%) | 109 (56%) | 188 (54%) | 934 (58%) |
| Abnormal | 99 (28%) | 82 (22%) | 83 (23%) | 53 (27%) | 102 (30%) | 420 (26%) |
| Not done | 51 (14%) | 49 (14%) | 67 (19%) | 31 (16%) | 56 (16%) | 254 (16%) |

Data are n (%), unless otherwise stated. EEG=electroencephalogram. SANAD=Standard and New Antiepileptic Drug trial. *Antiepileptic drugs other than those that were randomly allocated in SANAD.
Table 2: Multivariable model hazard ratios for time to overall treatment failure, treatment failure because of inadequate seizure control, and treatment failure because of unacceptable adverse events, by prognostic factor

| Sex | Overall HR (95% CI) | Inadequate seizure control HR (95% CI) | Unacceptable adverse events HR (95% CI) |
|-----|---------------------|--------------------------------------|--------------------------------------|
| Female | 1.00 | 1.00 | 1.00 |
| Male | 0.86 (0.75–0.99) | 1.06 (0.86–1.31) | 0.81 (0.66–0.98) |
| Treatment history | | | |
| Treatment naive | 1.00 | 1.00 | 1.00 |
| Seizures after remission | 1.35 (0.87–2.0) | 0.48 (0.19–1.23) | 2.13 (1.22–3.73) |
| Taking non-SANAD antiepileptic drugs | 1.27 (1.05–1.53) | 1.56 (1.20–2.03) | 1.00 (0.75–1.33) |
| Age (years) | | | |
| ≤20 | 1.00 | 1.00 | 1.00 |
| 21–24 | 0.95 (0.91–0.99) | 0.85 (0.79–0.90) | 1.06 (1.00–1.12) |
| 25–36 | 0.88 (0.80–0.97) | 0.68 (0.58–0.78) | 1.14 (1.01–1.20) |
| 37–49 | 0.82 (0.71–0.96) | 0.55 (0.44–0.69) | 1.23 (1.01–1.49) |
| 50–70 | 0.76 (0.61–0.94) | 0.42 (0.30–0.58) | 1.35 (1.02–1.79) |
| ≥71 | 0.68 (0.51–0.91) | 0.31 (0.19–0.48) | 1.50 (1.02–2.20) |
| Total number of seizures before randomisation | | | |
| ≤2 | 1.00 | 1.00 | 1.00 |
| 3 | 1.02 (1.01–1.03) | 1.04 (1.03–1.05) | 1.00 (0.99–1.01) |
| 4–11 | 1.08 (1.05–1.11) | 1.14 (1.09–1.18) | 0.99 (0.95–1.04) |
| 12–50 | 1.17 (1.10–1.23) | 1.29 (1.19–1.39) | 0.99 (0.91–1.07) |
| 51–299 | 1.28 (1.17–1.40) | 1.51 (1.33–1.71) | 0.98 (0.86–1.12) |
| ≥300 | 1.52 (1.31–1.76) | 2.00 (1.62–2.47) | 0.97 (0.77–1.21) |
| EEG result | | | |
| Normal | 1.00 | 1.00 | 1.00 |
| Not done | 1.25 (0.96–1.61) | 0.79 (0.51–1.22) | 1.34 (0.95–1.88) |
| Non-specific abnormality | 1.20 (0.98–1.47) | 1.01 (0.74–1.38) | 1.21 (0.91–1.61) |
| Epileptiform abnormality | 1.26 (1.07–1.50) | 1.21 (0.94–1.55) | 1.11 (0.87–1.41) |
| Seizure type | | | |
| Simple or complex partial only | 1.00 | 1.00 | 1.00 |
| Secondary generalised tonic-clonic | 0.78 (0.66–0.91) | 1.01 (0.79–1.28) | 0.69 (0.55–0.86) |
| Uncertain | 0.33 (0.05–2.37) | 0.76 (0.08–7.29) | Could not be estimated |
| Focal epilepsy site of onset | | | |
| Temporal | 1.00 | 1.00 | 1.00 |
| Not localised | 1.25 (1.06–1.47) | 1.18 (0.92–1.51) | 1.17 (0.93–1.48) |
| Frontal | 1.18 (0.88–1.58) | 1.04 (0.69–1.59) | 1.24 (0.81–1.90) |
| Other | 0.92 (0.66–1.28) | 1.04 (0.66–1.66) | 0.76 (0.45–1.26) |
| Unclassified | 2.69 (0.37–19.74) | 1.28 (0.13–12.72) | Could not be estimated |
| Treatment | | | |
| Carbamazepine | 1.00 | 1.00 | 1.00 |
| Gabapentin | 1.23 (1.00–1.51) | 2.45 (1.80–3.34) | 0.59 (0.43–0.80) |
| Lamotrigine | 0.76 (0.61–0.95) | 1.05 (0.75–1.48) | 0.62 (0.46–0.85) |
| Oxcarbazepine | 0.94 (0.72–1.23) | 1.12 (0.73–1.73) | 0.84 (0.59–1.20) |
| Topiramate | 1.23 (1.00–1.52) | 1.44 (1.03–2.00) | 1.01 (0.77–1.32) |

HR=hazard ratio. SANAD=Standard and New Antiepileptic Drug. EEG=electroencephalogram.

Table 2: Multivariable model hazard ratios for time to overall treatment failure, treatment failure because of inadequate seizure control, and treatment failure because of unacceptable adverse events, by prognostic factor

Role of the funding source

The sponsor of the study 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

Figure 1 shows the flow of the 1721 patients recruited into arm A of SANAD. 1608 patients were included in the analysis of time to treatment failure and 1588 were included in the analysis of time to 12 months of remission. The baseline demographic data for patients included in the analysis of time to treatment failure are summarised in table 1. Data were much the same for time to 12 months of remission (data not shown).

The parsimonious model for overall treatment failure included variables for sex, treatment history, age, total number of seizures before randomisation, EEG result, seizure type, focal epilepsy site of onset, and treatment, which was forced in the model regardless of significance, using the backward elimination process. Table 2 shows the multivariable HRs (see appendix for regression coefficients and standard errors); HR greater than 1 indicates that treatment failure is more likely. The χ statistic for the model was 0.6, indicating that the model accurately discriminates patients 60% of the time. Because the aim is to predict patients with poor outcomes, our χ statistic suggests that the internal validation of the model is acceptable.

Treatment failure decreased as age increased and patients aged 10 years or younger were significantly more likely to have treatment failure. Treatment failure increased as the total number of seizures before randomisation increased and patients with two or fewer seizures before randomisation were significantly less likely to experience treatment failure. Treatment failure was significantly more likely in women than in men, in patients taking a non-SANAD antiepileptic drug (ie, not carbamazepine, gabapentin, lamotrigine, oxcarbazepine, gabapentin, lamotrigine, oxcarbazepine, carbamazepine, lamotrigine, oxcarbazepine, gabapentin, lamotrigine, oxcarbazepine, gabapentin, lamotrigine, oxcarbazepine,

See Online for appendix assessed by the χ statistic, which assesses the discriminatory power and the predictive accuracy of nonlinear statistical models.19

Assessment of the different reasons for treatment withdrawal requires a competing risks analysis that includes the probability of one of several different events occurring. Therefore, we did cumulative incidence analyses to assess the probability of one of the two treatment failure events occurring (inadequate seizure control and unacceptable adverse events), with covariates tested by Gray’s method.18

We investigated continuous variables with log and fractional polynomial transformations.16–18 The results for the continuous variables are presented as categorical variables defined post hoc with categories chosen according to knot positions for a spline model fit to the data.20 The time from first seizure to randomisation includes extreme values. Therefore people with a time from first seizure to randomisation in the first or last 1% of the variable were removed from the dataset—this applied to 34 patients.
or topiramate) immediately before randomisation than in patients who were treatment naive, in patients with an epileptiform EEG abnormality than in patients with a normal EEG, in patients with simple or complex partial seizures without secondary generalisation than in patients with secondary generalised tonic-clonic seizures, in patients with epilepsy that was not localised than in patients with temporal lobe epilepsy, and in patients taking carbamazepine than in patients taking lamotrigine (table 2). To show the range of treatment failure rates predicted by the multivariable model, figure 2 shows estimates of the proportion of patients treated with either carbamazepine or lamotrigine having treatment failure 1 year and 3 years after randomisation (see appendix for numerical results). 1 year and 3 years were chosen to represent medium-term and long-term timepoints. Patients were assumed to be treatment naive and to have normal EEG results, simple or complex partial seizures, and temporal lobe epilepsy, which were the most common characteristics in the SANAD dataset. The other variables were altered according to categories of interest (eg, age as 10 years, 40 years, and 75 years; figure 2). Lamotrigine and carbamazepine were chosen because carbamazepine is the standard treatment for focal epilepsy and lamotrigine was suggested by the results of the SANAD trial as a potential first-line treatment after the publication of the initial results of SANAD. Generally, overall treatment failure rates were lower in patients treated with lamotrigine (figure 2). The risk of failure decreased slightly with an increase in age and men had a slightly lower chance of treatment failure than did women. An increase in total number of seizures before randomisation also slightly increased the chance of treatment failure.

The competing risks model has been fitted to match the model for overall time to treatment failure results (table 2). The appendix includes regression coefficients and results for the multivariable model including all variables—ie, without variable selection.

The significant variables in the model for treatment failure because of inadequate seizure control were treatment history, age, total number of seizures before randomisation, and treatment. Compared with treatment naive patients, patients already taking a non-SANAD antiepileptic drug had a high rate of treatment failure because of inadequate seizure control (table 2). Figure 3 shows relative hazard plots for the continuous

| Age (years) | Sex | Seizures (n) | Treatment |
|------------|-----|-------------|-----------|
| 10         | M   | 2           | Carbamazepine |
| 10         | F   | 2           | Carbamazepine |
| 10         | M   | 2           | Lamotrigine  |
| 10         | F   | 2           | Lamotrigine  |
| 10         | M   | 10          | Carbamazepine|
| 10         | F   | 10          | Carbamazepine|
| 10         | M   | 10          | Lamotrigine  |
| 10         | F   | 10          | Lamotrigine  |

Figure 2: Combination of risk factors for time to treatment failure
Bars show 95% CIs. M=male. F=female.
variables (for associated regression coefficients, see appendix). A linear effect was noted for age, with older patients significantly less likely to have a treatment failure because of inadequate seizure control than were younger patients. The number of seizures before randomisation was positively associated with the overall risk of treatment failure, which was largely caused by an increasing chance of failure because of inadequate seizure control.

The significant variables in the model of treatment failure because of unacceptable adverse events were sex, treatment history, age, seizure type, and treatment (table 2). Women were more likely to have treatment failure than were men. Patients restarting treatment after remission had a higher treatment failure rate than treatment naive patients. A linear effect was noted for age, with older patients significantly more likely to have a treatment failure because of unacceptable adverse events than were younger patients (figure 3). Patients with simple or complex partial seizures were significantly more likely to have a treatment failure attributable to adverse events than were patients with secondary generalised tonic-clonic seizures (table 2).

Although the chance of treatment failure for any reason decreased with age, in the competing risks analysis an X-shaped relation was seen (figure 3), in which younger patients have a higher chance of treatment failure because of inadequate seizure control and a lower chance of treatment failure because of adverse events than do older patients, who have a lower chance of treatment...
failure because of inadequate seizure control and a higher chance of treatment withdrawal because of unacceptable adverse events.

Table 3 and the appendix show results for time to 12 months of remission. The factors significantly associated with time to 12 months of remission were sex, treatment history, age, time from first seizure to randomisation, neurological insult, total number of seizures before randomisation, CT or MRI scan results, and treatment. The c statistic for the model is 0·7, indicating that the model accurately discriminates patients 70% of the time, which is an acceptable internal validation.22,23

For age, the relation is U-shaped with patients aged 10 years or less, or more than 71 years, having a significantly higher chance of remission than that of patients in the middle of the age range (figure 4). Time to 12 months of remission was higher for men than for women, and for treatment naive patients than for patients already taking a non-SANAD antiepileptic drug (table 3). Time to 12 months of remission decreased with increasing number of seizures before randomisation (figure 4, table 3). Figure 4 shows relative hazard plots for the continuous variables (for associated regression coefficients, see appendix). Rates of 12 months of remission were significantly higher for patients on carbamazepine than for those on gabapentin or topiramate (table 3). To show the range of rates of 12 months of remission predicted by the model, figure 5 shows estimates of the proportion of patients achieving a remission 1 year and 3 years after randomisation for patients treated with either carbamazepine or lamotrigine (see appendix for numerical results). Patients were assumed to be treatment naive, to have been randomised 6 months after their first seizure, to not have neurological insult, to have normal CT or MRI results, and to have temporal lobe epilepsy, because those were the most common patient characteristics. In the subset of combinations included, remission rates were highest in older patients. Men were slightly more likely to achieve remission than were women, as were patients with fewer seizures compared with patients with many seizures. The probability of remission in patients taking carbamazepine increased slightly compared with those taking lamotrigine, but not all the comparisons were significant.

Discussion

Treatment failure because of unacceptable adverse effects was significantly less likely in men than in women, but no significant difference existed for failure because of inadequate seizure control. This finding could explain the lower time to 12 months of remission in women, if women are less likely to remain on treatment for long enough to achieve therapeutic doses. Further analyses of dose data in SANAD show no difference between the mean doses of carbamazepine, oxcarbazepine, or topiramate taken by men and women, but women did receive lower doses of gabapentin and lamotrigine (data not shown). Baseline bodyweight was not measured in SANAD and therefore cannot be adjusted for.
Patients with an abnormal EEG were more likely to experience treatment failure than were those with a normal EEG, predominantly because of inadequate seizure control. Patients who did not have an EEG done had a lower chance of treatment failure because of inadequate seizure control and a higher chance of failure because of unacceptable adverse events. Patients who did not have an EEG tended to be older (mean age 42 years vs 38 years) and therefore there might have been more clinical certainty that they had focal epilepsy.
Men were more likely to achieve 12 months of remission than were women, which might be because women had a higher rate of treatment withdrawal because of adverse events, which precedes a change in treatment and a delay in controlling seizures.

The relation between age and 12 months of remission is U-shaped—the chance of 12 months of remission is higher in children and elderly people than in those in the mid-age range (approximately 20–50 years old). This relation might be because of the different aetiologies in different age groups, pharmacokinetics, or other factors, and should be investigated further. As might be anticipated, patients who were already taking an antiepileptic drug but needed to change treatment had a lower chance of having 12 months of remission than did treatment naive patients. The chance of remission that lasted 12 months increased with time between first seizure and randomisation but decreased with increasing number of seizures before randomisation, indicating that patients with a larger number of seizures over a shorter period before starting treatment had a reduced chance of remission. Of the antiepileptic drugs, carbamazepine was associated with the highest rates of remission that lasted for 12 months.

The SANAD study is the largest randomised controlled trial in epilepsy and includes data for long-term treatment outcomes, which is essential to inform the management of this chronic condition (panel). A heterogeneous group of patients was recruited, which some have criticised but we argue that this is a strength, as shown by this Article, because such a group enables thorough investigation of the factors that affect treatment outcome; the multivariable models in this Article include up to nine clinical factors. The SANAD investigators were not masked to treatment allocation, which could have affected outcome assessment—for example, decisions about whether a treatment had failed—although dosing data indicate that reasonable doses were tried to give each treatment the best chance before it was decided that treatment had failed. Although randomised controlled trials are the best method for assessing treatment outcomes, they recruit a selected population, which might affect estimates of prognosis. Ideally SANAD would have recruited a greater proportion of children and elderly patients; nonetheless, the analysis has clearly shown the effect of age on outcome. Participants were predominantly examined by neurologists experienced at identifying and classifying seizures, but a further challenge in outpatient studies of seizures and epilepsy, such as SANAD, is that seizures are reported to the clinician by the patient, and patients might under-report the occurrence of seizures. Validation of patient reporting in an outpatient population with infrequent seizures is difficult and has not been done to date. Recruiting clinicians were asked to estimate the likely site of seizure onset or if uncertain they were able to categorise the patient as such. This approach might lead to some imprecision, although it does allow patients to be categorised in a way that clinicians are familiar with and allows assessment of whether this categorisation is of prognostic value.

We have presented models that have the potential to inform patient counselling and treatment decisions, and internal validation of our two models suggests an adequate model fit. However, these models should be validated in other similar datasets and their predictive power should be tested. Unfortunately, no other datasets that are similar to SANAD exist. The best match is a set of individual participant data we have collected. However, these data do not include covariates that are significant in the multivariable model and the treatments to which patients were randomly allocated do not always coincide with the drugs tested in SANAD. Therefore more work should be done to determine how best to overcome these difficulties. Our results show the heterogeneity of outcome in epilepsy and the complex interplay between the factors that affect the condition. Patients with different risks of treatment failure and achieving 12 months of remission could be identified when antiepileptic drug treatment is initiated. If validated, our results might improve predictions of outcome for patients and enable identification of patients more likely to have a poor treatment outcome, who might need to be followed up more regularly. The models might also help with identification of patients with poor seizure control outcomes who might be eligible to participate in trials of new treatments, particularly treatments that might have a greater risk of adverse events than do conventional antiepileptic drugs, such as anti-inflammatory and other potential disease-modifying treatments.

Panel: Research in context

Systematic review

We identified studies published between Dec 1, 1946, and Jan 20, 2012, by searching Medline with the terms “prognostic model”, “prognostic factor”, “predictive model”, “predictive factor”, “epilepsy”, and “seizures”. Searches were restricted to human studies. Any prognostic factor studies or prognostic models reporting a seizure outcome were included. All included clinical trials were assessed by LB for methodological quality for randomisation, masking, and proportion of patients lost to follow-up.

Interpretation

Although other prognostic models have been constructed for epilepsy no other epilepsy monotherapy trial has had sufficient power to investigate prognostic factors thoroughly. Analysis of the National General Practice Study of Epilepsy—a large prospective population-based observational study—identified only one independent predictor of 1 year and 2 year remission: the number of seizures the patient had had in the 6 months after the first seizure. However, many patients in the National General Practice Study of Epilepsy were not prescribed antiepileptic drugs. Our Article extends previous studies because it is a thorough investigation of prognostic factors with data from a large randomised controlled trial in which patients were prescribed antiepileptic drugs. We have identified numerous prognostic factors for treatment failure and 12 months of remission from seizures and have produced models that should enable the estimation of these outcomes for individual patients.
Although we have identified clinical predictors of outcome, the mechanism by which these factors affect outcome are still poorly understood and some variability is unexplained. Personalised medicine and pharmacogenetics hold much interest and predictors of rare hypersensitivity reactions have been identified, but predictors of seizure control or common adverse effects have not yet been established.

Contributors
LJB analysed the data and drafted and revised the Article. CTS and PRW provided support for statistical analyses and drafted and revised the Article. AGM, DFS, and DWC coordinated the SANAD trial, provided clinical input, and drafted and revised the Article.

Conflicts of interest
We declare that we have no conflicts of interest.

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