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Drug Resistant Epilepsy in Adults: Outcome Trajectories after Failure of Two Medications

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OBJECTIVE: To examine the seizure trajectories of adults with epilepsy developing drug-resistant epilepsy (DRE) and to identify the predictors of seizure trajectory outcome.

METHODS: Adult patients failing two antiepileptic drugs (AEDs) due to inefficacy and starting their 3rd AED at a tertiary epilepsy center were followed for seizure trajectory outcome during medical management. Seizure trajectories were categorized into one of 5 patterns: (1) constant, sustained seizures; (2) delayed, sustained seizures; (3) unclear trajectory; (4) delayed, sustained remission; (5) early, sustained remission. Sustained seizure remission was defined as no seizures for ≥12 months. Multiple ordinal logistic regression models were used to estimate the association between trajectory categories and clinical factors and specific AEDs.

RESULTS: 466 adult patients met the eligibility criteria. Of them, 264 (57%) never achieved a seizure remission. The trajectories of 37 (8%) patients had delayed, sustained seizures, 45 (10%) had a delayed, sustained remission, and 83 (18%) had an early, sustained remission. An additional 37 (8%) patients had a complex and fluctuating trajectory that did not fit within any of the previous groups. Independent predictors of ordinal trajectory categories included older age of epilepsy onset and epilepsy type. Specifically, compared to patients with focal epilepsy of temporal lobe, patients with focal epilepsy of occipital lobe (OR=4.08, 95% CI: [1.05, 14.5], p= 0.03), primary generalized (OR=2.84, 95% CI: [1.61, 5.01], p<0.001), unclear epilepsy type (OR=4.0, 95% CI: [1.68, 9.34], p=0.003), and both focal and generalized epilepsy(OR=8.75, 95% CI: [1.25, 61.0], p=0.03) were significantly more likely to experience a better trajectory pattern. Conversely, the trajectory of patients with symptomatic generalized were no better than focal epilepsy of temporal lobe (non-significant: OR=0.50; p-value=0.49).

SIGNIFICANCE: Examination of patterns of seizure trajectory of patients with incident DRE showed that 28% were in a sustained seizure freedom at the end of observation period.

Key Words: Prognosis; Incidence studies; All Epilepsy/Seizures; Antiepileptic drugs

INTRODUCTION

In 2009, the International League Against Epilepsy (ILAE) issued a report addressing the longstanding controversy over how to define drug-resistant epilepsy (DRE).[1] The ILAE definition specifies "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, which could be either 3 times the prior inter-seizure interval or 1 year, whichever is longer". This new definition, focusing on failure of adequate antiepileptic drug (AED), specifies a point at which consideration of alternative treatment options or re-evaluation of diagnosis is warranted. Prior to the ILAE definition, uncertainty and variability existed over what constituted drug-resistance.[2]

The new ILAE definition allows for selecting a subgroup of patients to study the trajectory of DRE (i.e., incident cohort). Previous natural history studies of DRE in adults have examined prevalent cohorts. Differences in prognosis can exist between incident and prevalent cohorts even when derived from the same population.[3] Thus, there is a need for long-term outcome of incident DRE patients.

We conducted a study of adult patients with incident DRE using retrospective design. To capture the complex fluctuations in seizure trajectories, including multiple relapses, we classified the trajectories of each patient into one of several different trajectory patterns. Additionally, we identified the clinical predictors and specific antiepileptic medication associated with various outcome trajectory patterns.

METHODS

Sample and procedure

The Columbia Comprehensive Epilepsy Center (CCEC) has an ongoing longitudinal observational study of antiepileptic drug response and tolerability.[4-6] The study is based on medical chart review of 3,410 adult outpatients (at the time of this study). Inclusion criteria includes that patients have treatment outcome available for at least one AED trial. Data collection began on January 1, 2000 and is ongoing. Data abstraction of the existing longitudinal study at CCEC is based on retrospective review of medical records and includes patient characteristics, medical and psychiatric history, concomitant medications and dosages, laboratory test results, side effects, and efficacy measures. Data are entered into an electronic database by trained research assistants. The database is designed to reflect the medical chart, so that for each patient appointment at CCEC, an entry is made into the database. That is, for each visit, information about seizure occurrence, medication change, and presence of side effects since the last visit are included. Treatment efficacy measures include average monthly seizure frequency and seizure freedom since the last visit.

In August, 2012, from the existing longitudinal ongoing study at CCEC, we identified "incident" DRE adult patients (≥16 years old), defined as failing two trials of AEDs due to lack of seizure control and initiation of the 3rd AED while being treated by an epileptologist at CCEC (i.e., persistent seizures despite 2nd AED) regardless of how many AEDs were failed previously for intolerable side effects. The two failed AEDs may have been discontinued prior to administration of the 3rd (i.e., sequential monotherapy) or continued with 3rd (i.e., polytherapy), consistent with the ILAE definition.(1) Any prior AED failures due to side effects were not counted towards requirement of two AED failures due to inefficacy. As an example, a patient who failed two AEDs due to inefficacy and three other AEDs due to intolerability met our

inclusion criteria. Two failed AEDs due to inefficacy could have started prior to medical care at CCEC as long as transitioning to the 3rd AED occurred at CCEC. We excluded (1) patients with a diagnosis of non-epileptic psychogenic seizures, as determined by the treating doctor at CCEC, (2) patients who did not fail the second AED but started third for other reasons, such as to reduce the risk of fetal malformation or to reduce the risk of long-term side effect such as bone loss, and (3) patients who failed less than 2 AEDs due to inefficacy. When AED failures occurred prior to medical care at CCEC, attribution of reason for failure (whether due to inefficacy or intolerability) was made based on CCEC physician note, if available. If CCEC physician note did not provide reasons for failure of AEDs that occurred prior to CCEC, those patients were not included in the study. Observation time began at the start of the third AED while being seen at CCEC and ended at the time of last visit at CCEC. If patients received epilepsy surgery (including vagus nerve stimulator) after meeting the inclusion criteria, their observation data were censored on the date of epilepsy surgery since our main interest of this study is outcomes during medical management.

Outcome variable

The outcome variable, seizure trajectory over time, was an ordinal measure based on a physician assessment of a patient's seizure history. This ordinal variable was based on a simple, yet novel graphical depiction for each patient's seizure history. The graphical displays were constructed as follows: The x-axis represented seizure history over the observation period, beginning with the start of third AED at CCEC, and ending with the last observed visit time. The y-axis represented the amount of time a patient was in seizure remission since the most recent previous seizure occurrence (See Figure 1). The 5-point ordinal scale described in Table 1 (and illustrated in Figure 1) was developed by four epilepsy attending physicians (CB, HC, LJH, and

AM). A definition for each category was developed by two epilepsy attending physicians (HC and LJH). Next, inter-rater reliability was assessed. A random sample of 26 patients was selected to be assessed using this scale and two epilepsy attending physicians (HC, LJH) reviewed graphical displays. After completing assessments independently, HC and LJH compared results. For discordant ratings, HC and LJH discussed the cases and came to a consensus. The iterative discussions led to further modification of the category definitions. At the conclusion of this process, four epilepsy attending physicians unanimously agreed that the outcome categories accurately reflected all possible outcomes. All subjects were then assessed using the ordinal categories by an epilepsy attending physician (HC).

Measures

Study endpoints

- Trajectory of seizure outcomes based on the 5-point ordinal scale

Independent variables

- Months using each AED medication (25 AEDs, as listed in Supplementary Table 1), sex, age at start of observation, age at seizure onset, epilepsy duration, epilepsy type, status epilepticus, side of seizure onset, static encephalopathy, status epilepticus, family history of epilepsy, presence of etiology (binary), observation time, and receiving treatment for depression with medication during observation period.

Statistical Analysis

Study measures were summarized using appropriate descriptive statistics. Ordinal logistic regression was used to model the 5-point ordinal outcome measure as a function of demographic variables, patient characteristics, and treatment factors. Data on the age of epilepsy onset were missing for 3.6% (17/466) of the patients. Missing data were handled with multiple imputation

and use of 5 imputed values. Imputations were generated using linear regression with covariates strongly associated with the age of epilepsy onset. Complete information was available for all other study measures.

Evaluation of agreement between the two raters (HC, LH) was made based on their initial classification of seizure outcome categories of 26 randomly chosen patients from the cohort prior to consensus meetings using the kappa statistic (k), a measure of inter-rater agreement between two raters.[7]

Bivariate ordinal logistic regression models were fit for each covariate for association with ordinal outcome. Variables with an $\alpha \leq 0.1$ were tested in the multiple ordinal logistic regression model for consideration in the final model. Because duration of epilepsy has been previously associated with DRE[8], this variable was included in the multiple ordinal logistic regression model regardless of statistical significance. Multiple ordinal logistic regression models were also adjusted for age, given the wide age range of the cohort, and sex, given that sex may play a role in treatment (particularly with respect to AEDs), and observation time (given the wide range of follow up time in months). Multiple ordinal logistic regression model building was accomplished with a twofold approach, based on statistical significance and Akaike Information Criterion (AIC).[9] AIC is a method for developing a parsimonious statistical model which balances providing a good fit to the data with the complexity of the model. Since AEDs are often given in combination (i.e., polytherapy), we tested for statistical interactions between any AEDs remaining in the multivariate model.

The level of significance in this study was $\alpha \leq .05$. The SAS software for Windows, version 9.3, was used for statistical analyses.

RESULTS

Of the 3,410 patients in the ongoing longitudinal CCEC study, 466 patients met inclusion criteria for this study. A description of the demographics of the sample is displayed in Table 2. There were more females (54%) and the mean age of epilepsy onset was 24.5 years (SD=18.5). At the beginning of the observation period, the mean age of this cohort was 42.5 years (SD=16.6; range of [16, 94] years) and mean duration of epilepsy (or time to DRE onset) was 18 years (SD=15.7). The mean observation time was 58 months (range of [12,198] months).

Of the initial 26 randomly selected patients (out of 466) for developing the ordinal trajectory scale, "almost perfect agreement" between the two independent reviewers (HC, LJH) resulted with a kappa of .84 ($p<.0001$).[7]

As shown in Table 3, 57% (n=264) patients never achieved a 12-month seizure remission (Category 1). The outcome trajectories of 8% (n=37) of patients had a delayed, sustained relapse (Category 2), 10% (n=45) had a delayed, sustained remission (Category 4), and 18% (n=83) had an early sustained remission (Category 5). An additional 8% (n=37) had a complex trajectory that did not fit within any of the previous groups (Category 3). Thus, 28% of patients were in a sustained remission at the end of the study (Category 4 and 5).

In the bivariate analysis (Table 4), we found statistically significant associations ($\alpha \leq 0.1$) between ordinal trajectory category and age of seizure onset, epilepsy type, static encephalopathy, etiology, observation time (i.e., follow up time in months), and month of use of several AEDs (valproate, lamotrigine, lacosamide).

In our final multiple ordinal logistic regression model adjusted for age, sex, and observation time, the following variables were included: (1) Age of epilepsy onset, (2) epilepsy type (categorized according to lobe of onset in focal onset epilepsy), (3) static encephalopathy, (4) presence of etiology of epilepsy, (5) epilepsy duration, (6) months of valproate use, (9)

months of lamotrigine use, and (10) months of lacosamide use. Based on statistical significance and AIC values, only 3 AEDs were included in the final model. No statistical interaction terms between these three AEDs were included in the final model since models with interaction terms resulted in less desirable AIC values.

From our multiple logistic regression analysis, we identified several independent predictors of ordinal trajectory categories. As seen in Table 4, observation time in the study (measured in follow-up months) was significantly associated with ordinal outcome categories (OR=1.01, 95% CI: [1.01, 1.02], p<0.001), indicating that the longer the follow up time, more likely the patients were to experience better trajectory patterns. Adjusting for this confounder and other variables in the multiple logistic regression model, patients with older age of epilepsy onset had a better trajectory pattern (OR=1.02 for one-year increase of epilepsy onset, 95% CI: [1.00, 1.03], p=0.01). Additionally, epilepsy type was also significantly associated with trajectory outcome. Specifically, compared with focal epilepsy with temporal onset, focal epilepsy with occipital lobe onset (OR=4.08, 95% CI: [1.05, 14.5], p= 0.03), primary generalized (OR=2.84, 95% CI: [1.61, 5.01], p<0.001), unclear epilepsy type (OR=4.0, 95% CI: [1.68, 9.34], p=0.003), and those who had both focal and generalized epilepsy (OR=8.75, 95% CI: [1.25, 61.0], p=0.03) were more likely to have better trajectory pattern. Conversely, compared to focal epilepsy of temporal onset, patients with symptomatic generalized epilepsy had a two-fold worse outcome pattern (non-significant: OR=0.50; p-value=0.49).

To assess if the results are consistent across a broader age range, we re-ran the analyses, adding 84 additional patients who met the inclusion criteria of AED failure but who were younger than 16 years of age at the beginning of the observation period to our cohort (for a total

N=550). The results of final multiple ordinal logistic regression analysis did not differ considerably in terms of effect size and significance level.

DISCUSSION

Delineating the natural history of DRE can facilitate patient treatment and counseling by helping clinicians determine the point at which continuing trials of various AED treatments may no longer yield additional benefit and begin to consider alternative treatments (e.g., resection, vagus nerve stimulation, responsive neurostimulation device, etc.). To assist in prognostication, we defined long-term seizure trajectories into five categories in a cohort of adult patients with incident DRE (i.e. followed from the time of failure of 2nd AED due to inefficacy, operationalized as the start time of 3rd AED). We found that approximately two thirds of patients never achieved a 12-month remission or had early remission followed by a sustained period of seizures before the end of observation. In contrast, slightly more than a quarter of our patients had favorable trajectories, characterized by an early or delayed sustained remission which persisted until the end of observation period.

To date, different temporal patterns of seizure outcome have been described in the context of understanding outcome in newly diagnosed epilepsy patients.[10] The temporal patterns of seizure outcome in newly diagnosed patients were nearly the inverse of our findings, with the majority of newly diagnosed patients attaining seizure freedom that persisted throughout observation period. A small group of the newly diagnosed cohort had a fluctuating course characterized by a "remitting-relapsing" course. Small groups of patients with "remitting-relapsing" course have been reported in the literature in other cohorts.[11-12] What distinguishes patients with fluctuating course from individuals with stable/constant course remains unclear.

Natural history studies of adult patients with DRE have provided much needed data of seizure outcome to help counsel patients, but those studies used different set of outcomes as well as patient cohorts.[8, 13-17] In those previous DRE studies, sustained period of seizure remission (>12 months) was seen in about 4% of patients per year, but most of those patients went on to relapse subsequently.[16-17] While informative, the previous studies are not necessarily applicable in counseling patients newly developing drug-resistance, because previous DRE studies included (1) a mixture of prevalent cases with longstanding history of drug-resistance as well as patients with more recent onset of drug-resistance, and (2) required monthly seizures prior to study, which we did not. This current study ascertained a group of patients at the time of failure of second AED (defined as start of 3rd AED at CCEC), which, to our knowledge, is the first to examine the seizure trajectory in adults using the newly adopted ILAE definition of incident DRE in adults. In children, a population-based, prospective study has examined outcome among 128 patients who failed 2 AEDs.(18) Although 57% (73/128) of the patients experienced a remission, only 23% were in remission for 3 years at last contact, similar in proportion to our cohort (Category 4 and 5).

Slightly more than a quarter of our incident adult DRE patients experienced favorable trajectory patterns of sustained seizure remission (Category 4 and 5). This provides a hopeful outlook that not all DRE patients are destined to be in a state of persistent seizures. However, among focal epilepsy patients (Table 5), particularly in patients with temporal and parietal epilepsies, higher percentage of them tended to experience less favorable outcome trajectory patterns (Category 1 and 2) compared to patients with other focal onset epilepsies. Additionally, although the total number of patients with symptomatic generalized epilepsy was small, the majority experiencing the poorest category was notable. Information such as these may help with

decision-making process for clinicians and patients at the juncture of deciding further medication adjustment versus alternative treatment options.

To fully describe the natural history and the effects of medical management, this study captured the entire course of each patient by graphically depicting the multiple changes in seizure outcome throughout the observation period. Our novel graphical representation allows for a user-friendly method of assessing the entire trajectory in one visual display. Previous studies have made use of a time to event analysis,[14-15] estimating the annual probability of *first* >12 months seizure remission with Kaplan-Meier analysis.[19] Our approach offers distinct advantages over this other approach, since we account for all available historical seizure data for each patient. This graphical representation of patient's course could also be useful in clinic setting. At an individual patient level, the graphical summary can help patients visualize their course which may prompt deeper discussions about management.

We attempted to identify a clinical profile that predicts progression into one of five clinical trajectories from the point of failing second AED. Significant predictors of our five clinical trajectories were age of epilepsy onset and epilepsy types. We found that older the age of onset, more likely that a patient would experience more favorable outcome trajectory pattern. For those with focal epilepsy, we were able to further stratify epilepsy type based on lobe of onset. Compared to focal epilepsy of temporal onset, patients with focal epilepsy of occipital onset, primary generalized epilepsy, patients with unclear epilepsy type, and patients who had both focal and primary generalized epilepsy were significantly more likely to experience better outcome trajectory patterns. Interestingly, patients with symptomatic generalized epilepsy had a two-fold worse outcome pattern. Although the association was not significant, this finding suggests that individuals with symptomatic generalized epilepsy should be considered to have at

least a similar poor trajectory outcome as focal epilepsy of temporal onset. Interestingly, the results did not change when we additionally included children (<16 years old) in our additional analysis. This could suggest that the factors leading to different trajectory outcomes do not depend on the age at DRE. However, further studies with larger sample sizes are needed to confirm.

Previous prevalent cohort studies of DRE did not identify independent predictor of seizure remission or relapse. This discrepancy may be due to a larger sample size of this study, compared to previous studies that ranged between cohorts of 155 to 246 patients. Another explanation for the differences in findings may be that our incident cohort cases were more homogeneous than patients ascertained at different disease stages as in previous prevalent cohort studies. For examination of trajectory outcome of a disease, patients in an incident cohort are more homogeneous than those of a prevalent cohort in terms of disease stage.[3]

Months of use of valproate, lamotrigine, and lacosamide were all individually associated with our ordinal outcome categories in bivariate ordinal logistic regression analyses. However, we found that these associations were likely confounded by observation time. When adjusted for observation time as well as other variables in multiple ordinal logistic regression model, no AED was significantly associated with our ordinal outcome categories. Previous prevalent DRE studies also did not find significant association between seizure remission and specific AED.[14-15] However, in a prior study, we reported that the majority of patients with ≥12 months of seizure remission had a medication change within the 3 months preceding the start of the seizure remission.[15] Callaghan et al found that almost all of their subjects with seizure remission had a medication change.[14] In the study by Luciano and Shorvon, each seizure remission was preceded by the addition of a previously untried drug.[8]

This study had some limitations. First, as our goal was to delineate individual patient's trajectory into one of several unique patterns and identify factors associated with those patterns, we did not use one aspect of ILAE definition of treatment success (i.e., "the individual has remained without seizures for either 3 times the prior inter-seizure interval or 1 year, whichever is longer"). That is, we did not assess the binary occurrence of "treatment success" by examining whether every new AED initiation for a given individual patient resulted in a sustained period of seizure freedom as compared to before the AED initiation, considering the prior inter-seizure interval. Second, a convenience sample from a single tertiary care center setting was used for this study, limiting the generalization of results. Third, this was a cohort study in which outcome data were abstracted from medical charts retrospectively. We found a long delay (mean of 18 years, SD 15.7) before failure of 2nd AED. This variable, time to failure of 2nd AED (operationalized as start time of 3rd AED at CCEC), was calculated as the difference in years between age of epilepsy onset and age at starting 3rd AED. Upon further examination, we found that most of the 18 years was spent outside of CCEC, as evidenced by the mean time between age of epilepsy onset and age at first visit to CCEC of 17 years (SD=15.7). Once patients started their care at CCEC, the time it took to transition from 2nd to 3rd AED due to inefficacy was on average 1 year (SD=1.7). This intriguing finding raises two possibilities. One, for many patients, the onset of drug resistance was indeed delayed by more than a decade after the onset of epilepsy. However, a prior pediatric prospective study showed that time to failure of two AEDs occurred about 3 years after initial diagnosis for a substantial proportion of children.[20] Two, AED changes were not necessarily considered in a timely fashion despite incomplete seizure control. In the case of latter, the primacy of attaining complete seizure freedom over just reducing seizures to affect quality of life[21-22] needs to be emphasized. For many patients who presented to CCEC after

many years after the onset of epilepsy, recall bias may be an issue. To minimize recall bias, patients who had unclear reasons for failure of AEDs that occurred prior to CCEC were not included in this cohort.

Our findings suggest that a favorable long-term seizure outcome could be seen in about a quarter of adult patients meeting the new ILAE criteria for drug-resistance, providing a hopeful outlook. However, the long interval between onset of epilepsy and failure of 2nd AED is compelling, and calls for further study to understand possible variability in treatment goals and practice patterns.

Table 1. Definitions for 5-point ordinal trajectory categories*

Category	Description
1	Constant sustained seizures: -Patient never experience a sustained period (i.e., ≥12 months) of seizure remission during study follow up
2	Delayed, sustained seizures: -Patient can have multiple brief or sustained periods of remissions but is in a sustained period of recurrent seizures at the end of follow-up.
3	Unclear/not classifiable: -Patient has a change of status from sustained remission to brief relapse or from sustained relapse to brief remission at the end of follow-up, meaning there hasn't been 12 months of time elapsed since the status change to know which way patient will go, and therefore cannot qualify for another category
4	Delayed, sustained remission: -Patient can have multiple sustained periods of seizure recurrence but is in a sustained period of seizure remission (>12 months) at the end of follow-up The start of sustained remission occurs after the first 12 months of study (i.e. still having seizures for the first year or longer)
5	Early, sustained remission: -Patients may have brief relapse(s) in the first 12 months (after the start of the study) but is in a sustained period of seizure remission (>12 months) at the end of follow-up -The start of sustained remission occurs within (or at) 12 months from the time of index date (i.e. seizure freedom begins before the end of the first year)

* "Sustained" means 12 months or longer. "Brief" means <12 months.

Table 2. Demographics of cohort

Characteristics	
	Mean (SD)
Age of onset (years)	24.5 (18.5)
Observation time (months)	58 (40.8)
Time to drug resistance (years)*	18 (15.7)
	Count (%)
Female	252 (54)
Epilepsy classification	
Focal	329(71)
Primary generalized	94 (20)
Symptomatic generalized	16 (3)
Focal and primary generalized	4 (1)
Unclassifiable	23 (5)
History of status epilepticus	25 (5)
Static encephalopathy	30 (6)

*Time to drug resistance is the difference in years between onset of epilepsy and start of this study

Table 3. Seizure outcome trajectories

Categories		Count (%)
1	Sustained seizures	264 (57)
2	Delayed, sustained relapse	37 (8)
3	Unclear/not classifiable	37 (8)
4	Delayed, sustained remission	45 (10)
5	Early, sustained remission	83 (18)

Table 4. Ordinal Logistic Regression Analyses of Predictors of Seizure Outcome Trajectory Categories

Variable		Unadjusted Odds Ratio	p-value	Adjusted Odds Ratio	p-value	CI
Age of Seizure Onset		1.01	0.03	1.02	0.01	1.00, 1.03
Epilepsy Type			<0.001		<0.001	
	Focal epilepsy with temporal (referent)	--	--	--	--	
	Focal epilepsy with frontal onset	1.55	0.15	1.63	0.13	0.87, 3.05
	Focal epilepsy with occipital onset	3.24	0.06	4.08	0.03	1.15, 14.5
	Focal epilepsy with parietal onset	0.57	0.34	0.60	0.40	0.18, 1.97
	Focal epilepsy with multiple onset	2.34	0.23	3.00	0.14	0.69, 13.00
	Focal epilepsy with unknown lobe of onset	1.24	0.43	1.50	0.16	0.85, 2.60
	Primary generalized	2.73	<0.001	2.84	<0.001	1.61, 5.01
	Symptomatic generalized	0.28	0.09	0.50	0.49	0.07, 3.49
	Unclear epilepsy type	3.20	0.005	4.00	0.003	1.68, 9.34
	Focal and generalized	6.16	0.05	8.75	0.03	1.25, 61.00
Static Encephalopathy	(present=1, absent=0)	2.63	0.027	0.57	0.26	0.16, 1.65
Etiology	(present=1, absent=0)	1.49	0.03	0.81	0.24	0.53, 1.18

Epilepsy Duration			0.51		0.97	
	<10 years (referent)	--	--	--	--	
	10-19 years	1.31	0.25	1.06	0.81	0.56, 1.61
	≥20 years	1.24	0.37	1.03	0.89	0.60, 1.69
Sex		0.96	0.82	0.82	0.30	0.56, 1.20
Observation time in months during study		1.01	<0.001	1.01	<0.001	1.01, 1.02
Each month of valproate use		1.01	<0.01	1.00	0.54	1.00, 1.01
Each month of lamotrigine use		1.01	0.02	1.00	0.40	1.00, 1.01
Each month of lacosamide use		0.89	0.06	0.90	0.08	0.80, 1.01

Table 5. Individual outcome category by epilepsy type (stratified by lobe for those with focal epilepsy)

Classification	focal frontal	Focal temporal	Focal occipital	Focal parietal	Focal multiple	Focal unknown	Primary generalized	Symptomatic generalized	unclear	Focal&generalized	Total
Sustained seizures	29 (54%)	102 (65%)	2 (22%)	13 (76%)	3 (43%)	53 (62%)	37 (39%)	14 (88%)	10 (44%)	1 (25%)	264
Delayed, sustained relapse	5 (9%)	15 (10%)	2 (22%)	1 (6%)	0 (0)	3 (4%)	10 (11%)	0 (0)	1 (4%)	0 (0)	37
Unclear/not classifiable	6 (11%)	5 (3%)	2 (22%)	1 (6%)	1 (14%)	7 (8%)	11 (12%)	1 (6%)	2 (9%)	1 (25%)	37
Delayed, sustained remission	5 (9%)	18 (11%)	1 (12%)	1 (6%)	2 (29%)	7 (8%)	10 (11%)	0 (0)	1 (4%)	0 (0)	45
Early, sustained remission	9 (17%)	17 (11%)	2 (22%)	1 (6%)	1 (14%)	15 (18%)	26 (27%)	1 (6%)	9 (39%)	2 (50%)	83
Total	54	157	9	17	7	85	94	16	23	4	466

Figure 1. X-axis represents seizure history over the observation period. Y-axis represents the amount of time a patient was in seizure remission since the most recent previous seizure occurrence (with dots representing clinic visits). Category 1- Patients never experience a sustained (i.e.≥12 months) remission; Category 2 - Patients experience a 12-month remission but that is followed by sustained period of seizure recurrence. In a state of seizure recurrence at end of observation period; Category 3 - Patients experience a change of status at the end of observation period (for less than 12 months), so trajectory is uncertain; Category 4 - Patients experience a delayed onset (>12 months from start of study) of sustained remission. In remission at end of observation period; Category 5 - Patients experience an early onset (<12 months from start of study) of sustained remission. In remission at the end of observation period.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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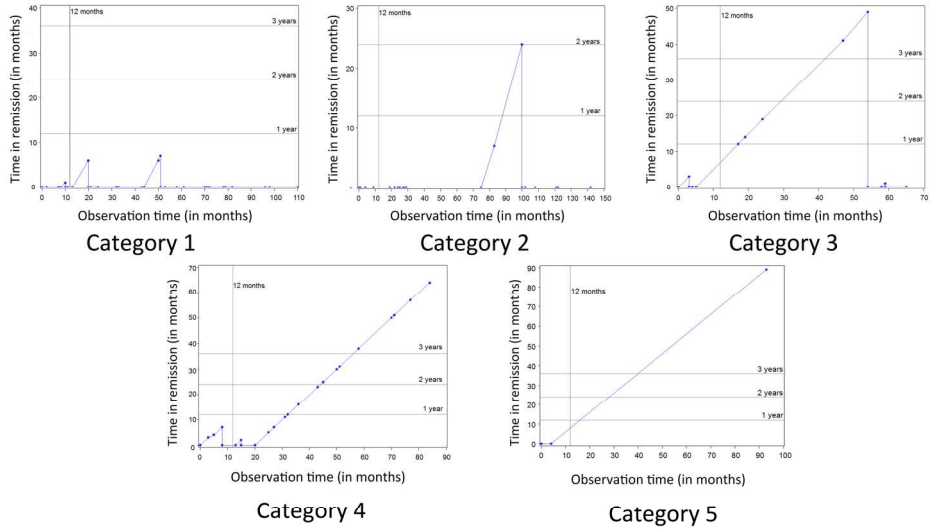
Figure 1. Graphs of ordinal outcome trajectories



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