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Remission of epilepsy after 2 drug failures in children: a prospective study

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Abstract

Objective—Determine the probability of ≥ 1 year remission after failure of a second drug in children prospectively followed from initial diagnosis of epilepsy and then from time of second drug failure. Identify prognostic factors for remission after second drug failure.

Methods—Of 613 children, 128 failed 2 drugs, had a trial of at least a third drug (median=3) and were followed ≥ 1 year (median= 10.1 years) since second drug failure. Product-limit and proportional hazards techniques were used to analyze predictors of any 1 year remission (Rem1) and 1 and 3-year remission at last contact (Rem1/3-LC).

Results—73 (57%) had a remission. Repeated remissions and relapses were common. Only 48 (37.5%) achieved Rem1-LC and 28 (23%) Rem3-LC. Idiopathic epilepsy (Rem1: rate ratio(RR)= 3.64, $p < 0.0001$; Rem1-LC: RR=2.57, $p = 0.008$) and seizure frequency (Rem1: RR= 0.76, $p = 0.003$; Rem1-LC: RR=0.82, $p = 0.04$ per increase in category) were the most robust predictors. Symptomatic cause was the only correlate of Rem3-LC. Remission before second drug failure did not predict remission after second drug failure.

Interpretation—Remission after second drug failure is common but often temporary.. Children who have failed two appropriate drugs should be carefully evaluated to maximize therapy and, possibly considered for more aggressive treatments.

Pharmacoresistance in epilepsy is a serious problem, yet it is often only studied years after it first occurs, frequently in the context of epilepsy surgery evaluations or randomized trials of new drugs. Even in most available cohort studies, intractability is only defined at an arbitrary point in time (e.g. at last contact or five years after diagnosis) ^{1–3}.

Several studies have attempted to study the risk and predictors of pharmacoresistance; however, only two (including ours) have prospectively applied definitions of pharmacoresistance and identified pharmacoresistance as it occurred ^{4, 5}. Early prospective identification of intractability, as soon as it can be recognized, is increasingly important in light of the growing interest in the earlier use of more invasive therapies, particularly surgery when medications fail to work, ^{6–9}.

At the same time, early identification of intractability runs the risk of being overly sensitive and perhaps including individuals whose epilepsy may respond to another drug or resolve on its own. Consequently, before any early definition of intractability is employed, especially for purposes such as surgical intervention, the seizure course once patients meet specified

criteria should be examined. Several studies, including our own, have documented brief, sometimes temporary remissions in patients who have met various criteria for intractable epilepsy ^{4, 5, 10–14}.

We have previously reported on the prediction ¹⁵ and time course ⁴ of intractability in this cohort. Here we focus on the long-term outcomes in those cohort members who met minimum criteria for pharmacoresistance, failure of adequate trials of two appropriate antiepileptic drugs (AED).

Methods

Data are from a prospective study of children (age 1 month – 16 years) with newly diagnosed epilepsy who were recruited from the offices of 16 of the 17 practicing pediatric neurologists in the State of Connecticut from 1993–1997. Detailed methods have been previously published ^{4, 16}.

This analysis focuses on those individuals whose seizures did not come under control (remission for ≥ 1 year) after two trials of AED therapy appropriate for the seizure and epilepsy type and pushed to maximum tolerated or recommended limits and taken as prescribed. AEDs discontinued because of side-effects or other concerns without adequate evidence to determine efficacy for seizure control were not considered as failures. Information about drug doses, levels, compliance, growth spurts, and seizures was obtained through ongoing review of medical records and telephone calls with parents. All of this information was taken into account when evaluating AED failure. In these analyses, subjects were further limited to those followed at least one year after the second drug failure and who also received an informative trial of at least one further AED. As a simplifying convention, a drug added to a failed drug regimen which was then associated with a period of remission ≥ 1 year was credited with the success. The failed drugs were often stopped, allowing a clearer test of the added drug's effect; however, the treating neurologists had sole control over how the AEDs were used and many patients received multiple drugs simultaneously.

Specific epilepsy syndromes were identified at initial diagnosis according to published criteria ^{17, 18} and revised throughout follow-up as new information (e.g. a more informative EEG or MRI) became available, or as the syndrome evolved (e.g. West to Lennox-Gastaut). A simplified grouping of syndromes (based on syndromic diagnosis as determined nine years after initial study entry) was used for these analyses: traditional idiopathic syndromes ¹⁷, epileptic encephalopathies/secondary generalized epilepsies, and other focal or undetermined epilepsies. If a child at any point in the course of his epilepsy expressed a syndrome considered to be an epileptic encephalopathy (e.g. West syndrome evolving to focal epilepsy) the syndrome was still grouped with the epileptic encephalopathies.

Data analysis

Chi-square and t-tests were used as appropriate for bivariate comparisons. Survival analysis with the product-limit methods and associated Kaplan-Meier curves was used for examining the occurrence of remission (≥ 1 year) ever and 1 and 3-year remission at last contact. The Cox proportional hazards model was employed for multivariable analyses ¹⁹.

Surgery

Because one of the purposes in performing this analysis was to provide information relevant to surgical decisions, individuals who had resective or disconnection surgical procedures were censored at the time of surgery. Their post-surgical outcomes are described.

Ethics

All procedures were approved by the Institutional Reviews Boards of all institutions involved. Written informed assent of the child and written permission of the parent were obtained. Written informed consent of subjects when they attained the age of majority was obtained.

Results

As of 8–2008, a total of 140 subjects had failed trials of at least 2 different AEDs considered appropriate for their seizures and type of epilepsy. Twelve were excluded from analysis for having less than 1 year of follow-up since second drug failure (N=2), no additional drug trials after second drug failure (N=8), or both (N=2). Descriptive information for the total group and those included versus excluded is provided in table 1.

The 128 included study subjects have been followed a median 11.8 years since initial diagnosis of epilepsy (maximum 15.4y, inter-quartile range (IQR) =11.0 to 13.1). Since second AED failure, they have been followed a median of 10.1 years (maximum 14 years, IQR=6.7 to 11.7). Ten subjects have died. Of the other 118, 106 (90%) are actively followed.

Because children were enrolled and initially treated in 1993–1997, the choice of first drugs was strongly weighted toward the drugs considered first-line at the time (table 2). The use of newer agents as second and third drugs reflects the increasing availability of newer drugs towards the end of the recruitment period and, to a certain extent, the tendency of some individuals to have a delayed expression of their intractability and not to be treated with these drugs until later ^{4, 5}.

Responses to additional drug trials and other treatments

All subjects included in these analyses had tried 1 to 15 additional different AEDs (median=3). For each of the additional drugs tried, only a small proportion became seizure free for at least one year and continued seizure-free at last contact or had periods of nonresponsiveness to the drug mixed in with at least one period seizure-free lasting ≥ 1 year (table 3).

Remission after second drug failure (figure 1)

Seventy-three (57%) individuals experienced at least one period of remission ≥ 1 year. The cumulative probability (with 95% confidence intervals (CI)) of entering remission 2, 5, 10 and 12 years after second drug failure was 27.3% (19.4, 35.1%), 47.1% (38.1, 56.2%), 64.5% (54.8, 74.2%), and 68.6% (58.5, 78.9%) (figure 1). The median time to first remission was 2.3 years (range 1 to 11.3; inter-quartile range (IQR) = 1.4 to 4.5 years). Relapses occurred in 50 (68%) of those who had a 1-year remission. Repeated remissions and relapses were common; 37 individuals had a second remission period, of whom 19 relapsed. Of those 19, 15 remitted for a third time with 11 subsequently relapsing. Of those 11, four regained remission (1 after relapsing then remitting for a fifth time).

Forty-eight (38%) patients were in remission ≥ 1 year at last contact, 20 of whom were no longer taking AEDs. The proportion entering and remaining in 1-year remission at 2, 5, 10 and 12 years after a second drug failure was 8.8% (3.9, 13.8%), 18.6% (11.5, 25.6%), 40.1% (30.2, 49.9%), 47.3% (36.2, 58.3) (figure 1). Of those who failed 0, 1–2, 3–5, 6–9, and 9–15 trials of additional drugs, 71%, 54%, 21%, 24%, and 0% were in 1-yr remission at last contact. For those in 1-year remission at last contact, the median time to achieve that remission was 5.3 years (range 1.1 to 12.7, IQR=2.3 to 8.1).

Only 28 (22%) subjects were ≥ 3 years seizure-free at last contact. The proportion entering and remaining in 3-year remission at 5, 10 and 12 years after a second drug failure was 10.0% (4.4, 15.6%), 24.5% (15.5, 33.5%), and 26.3% (16.8, 35.7%). Of those who failed 0, 1–2, 3–5, 6–9, and 9–15 trials of additional drugs, 48%, 38%, 9%, 6%, and 0% were in 3-yr remission at last contact

Thirteen patients who had epilepsy surgery were censored at the time of surgery. Five of them entered remission and were seizure-free at last contact. If their post-surgical time and remissions were included, the figures above would remain essentially unchanged. In addition, vagal nerve or brain stimulators were used in 14, and the ketogenic diet in 24. Observations were not censored for these therapies. Had they been, the results would not have been appreciably different.

Predictors of remission after a second drug failure

We selected potential predictive factors based on their associations with seizure outcomes in other studies and settings (Table 4). In a multivariable proportional hazards model, idiopathic syndromes and lower frequency of days with seizures remained as independent predictors of entering remission (Table 5). After adjustment for these factors, the RR for underlying symptomatic cause was 0.63 ($p=0.08$). Epileptic encephalopathies/other secondary generalized epilepsies and remission prior to second drug failure did not further contribute to predicting remission. For patients with focal epilepsy ($N=70$), symptomatic cause ($p=0.04$) and seizure frequency ($p=0.03$) were independently associated with remission. Remission prior to second drug failure ($p=0.35$, figure 2a) was not substantially associated with subsequent remission in this subset.

For 1-year remission at last contact, similar associations were found. Idiopathic forms of epilepsy and prior seizure frequency were the only independent predictors (Table 5). Remission prior to second drug failure (figure 2b), symptomatic cause, and the epileptic encephalopathy/secondary generalized epilepsies were not associated with remission at last contact. Within the focal epilepsies, only prior seizure frequency attained marginal significance ($p=0.02$) on its own.

By contrast, only symptomatic cause was associated (negatively) with 3-year remission ($RR=0.33$, $p=0.02$). Exploratory analyses suggested a higher risk of relapse after remission associated with idiopathic versus other forms of epilepsy (57% vs. 40%, $p=0.25$). Prior seizure frequency was strongly correlated with relapse after remission, from lowest to highest seizure frequency category, 56%, 52%, 39%, 24% ($p=0.005$, trend).

Any remission >1 year prior to second drug failure was not predictive of later remission (figure 3c). Prior remissions lasted an average of 3.1 years (range 1.2 to 8.5). The duration of prior remission was not correlated with remission at last contact.

Discussion

Our data present a long-term view of seizure outcomes after a second drug failure, a criterion for pharmacoresistance that has been adopted (with or without further specifications) in this and several other studies^{1, 3–5, 12}. More than half of patients subsequently experienced significant periods of seizure freedom. We found this was often not a lasting remission. Although it is common to refer to remission at last contact as “terminal,” in fact, we do not know what the future outcomes will be in those last known to be in remission. Those who were last in 1-year remission took many years to reach that point. Fewer were in a longer-term (≥ 3 year) remission.

Some of the newer drugs may explain some of the high remission rates that we saw. Schiller and Najjar clearly demonstrated in patients ≥ 12 years old that after each successive drug failure, a proportion of previously pharmacoresistant patients would become seizure-free with the introduction of the next drug²⁰. We too found a large proportion that attained remission, some after repeated drug failures. Whether remission was in response to a new drug or for reasons related to the natural history of the disease, or to other unidentified factors we do not know.

Although our evidence does not suggest that the newer drugs were dramatically more successful at controlling seizures than were the older drugs, these data must be viewed in context. The newer drugs were just being released when the children in our study were first being treated. This is also true of some of the other studies cited above. By the time a child received some of these newer drugs, he had often failed multiple trials of the other drugs. Thus, due to secular trends, those who received newer drugs were somewhat selected for being particularly difficult to treat, and the number of previous drug failures tends to predict response to the next therapeutic agent tried^{10, 11, 20}.

The findings of brief remission after meeting criteria for pharmacoresistance has been reported by ourselves and others in prospective^{4, 5} and retrospective^{10, 11, 13, 14} studies. The Dutch investigators discussed the variability over time in seizure outcomes as well³. While these brief remissions may encourage optimism, in fact, they are often not enduring. To the extent they are, they appear to take many years to achieve. Subjects with infrequent seizures were more likely to experience remission. They were also more likely to relapse after remission. Possibly, in these patients, AEDs were partially effective and reduced their break-through seizure rate to such a low point that they experienced 1-year seizure-free periods, thus appearing to be well-controlled when, in fact, they were not fully controlled. There are no standards or guidelines in the literature for handling this situation. Potentially, such patients would have to be seizure-free for many years before drug effectiveness could be reliably determined.

We also note that remission period before the appearance of pharmacoresistance has been reported previously^{4, 25}. Our findings suggest that remission before a second drug failure did not substantially improve the likelihood of attaining remission after a second drug failure. Thus, prior remission probably should not be a major consideration in management decisions after a second AED failure.

The recent studies of this issue^{10, 11} were quite different from ours. We focused on an exclusively pediatric population in which the forms of epilepsy are quite diverse. Interestingly, we did not find that the most aggressive pediatric syndromes (epileptic encephalopathies) behaved differently than focal epilepsies once they became intractable. Instead, it appeared that the seizure frequency prior to second drug failure was a more reliable determinant of later 1-year remission. This was also associated with early appearance of intractability in this cohort¹⁵. The finding of a relatively better seizure prognosis for those with traditional idiopathic syndromes is not surprising and others have reported similar results^{10, 11, 20}. These developmental syndromes are often self-limiting and the seizure propensity resolves on its own; however, some in our study have clearly not fully resolved at this point. Of these, all had idiopathic generalized syndromes, which occasionally may persist long after childhood or for life. The recent studies of Callaghan¹¹ and Luciano¹⁰ were quite different from our own both in methods and purpose. These studies were both retrospective and sampled prevalent cases, most with epilepsy ≥ 10 years duration when they entered the observation periods reported in those articles. Prevalence sampling is known for over-sampling cases with the longest course of the disorder (milder for diseases that are rapidly fatal and severe for diseases that tend to remit, or are perhaps

inoperable as with epilepsy). Ours by contrast involved incident cases of epilepsy prospectively identified and followed from initial diagnosis and, for this analysis, from date of second AED failure. This is the preferred method for assessing prognosis as the observation period begins at a defined moment, as soon as the second drug has failed. Our study directly addresses the question of prognosis after second AED failure, a point identified as a time when a comprehensive epilepsy evaluation should be obtained both for children and adults ^{6, 8}.

Although a first remission is achieved fairly rapidly in some and the cumulative proportion experiencing remission is quite high, the proportion attaining a 3-year remission as of last contact is substantially lower. It takes several years to achieve this longer-term remission, during which time, the individual must live with all of the consequences of uncontrolled epilepsy including the consequences of the seizures, the side-effects and costs of medications, and the increased risk of mortality ²¹. Our finding that relatively few subjects rapidly attained seizure control emphasizes the recommendations of the ILAE's subcommission for pediatric epilepsy surgery: children whose seizures are not controlled after reasonable trials of two or three agents should be evaluated at a comprehensive epilepsy center ⁸.

Referral for a comprehensive evaluation may not be enough though. In the last decade we have seen an explosion in the number of pharmacologic and other therapeutic options available for the treatment of epilepsy. Two recent surveys of experts in Europe ²² and the US ²³, indicated that, although there was excellent consensus on the initial approach to treatment of epilepsy in children and very good agreement on the second therapeutic choice if the first failed, after that, there was increasing divergence regarding what constitutes appropriate third, fourth, fifth and subsequent therapies ²⁴. Thus we have the therapies, but not a strong evidence base or consensus to guide their most effective and rational use.

Strengths of our study include that it is prospective, community-based, and with considerable follow-up. We also prospectively assessed AED failure and distinguished failure from discontinuation due to adverse events prior to achieving an informative trial and from other reasons a trial might not be adequate, distinctions not always clearly made by other studies. Limitations include a limited sample size for complex multivariable analyses and somewhat limited power to provide definitive identification or exclusion of prognostic factors. We encourage others to examine these issues in larger prospective studies and to extend prospective investigations into adult populations as well.

How best to define pharmacoresistance is still a matter for debate ^{26–28}. Increasingly, the failure of two appropriate drugs pushed to maximum limits is considered a basic threshold which should generally trigger specific actions, referral for comprehensive evaluation. Our data show that many patients who pass this threshold have periods of seizure-freedom, but substantial and perhaps lasting remission, to the extent we can measure it over the course of 10 years, is more elusive. The implications of this varying course are profound for defining drug refractoriness, understanding treatment response, recommendations for surgical evaluation, and design of drug trials ²⁶.

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Figure 1. Overall cumulative probability of any remission and of 1 and 3 year remission at last contact.

Figure 2. Cumulative probability of (a) any remission after second AED failure (b) 1-year remission at last contact, and (c) 3-year remission at last contact as a function of remission prior to second AED failure.

Table 1

Characteristics of subjects who failed at least two AEDs overall and by inclusion or exclusion in the analyses.

	Failed 2 AEDs (N=140)	Included (N=128)	Excluded (N=12)
Time to second drug failure (years, SD)	2.4 (2.9)	2.3 (2.9)	3.8 (2.5)
Time followed since second drug failure (Years, SD)	8.4 (3.6)	9.3 (3.1)	4.6 (2.8)
Any period 1-year seizure free since meeting criteria	76 (55.9)*	73 (57.0%)	3 (37.5%)*
In 1-year remission at last contact	50 (36.8)*	48 (37.5%)	2 (25.0%)*
Deceased**	11 (7.9%)	10 (7.8%)	1 (8.3%)
Surgery***	13 (9.3%)	13 (10.2)	0
VNS	14 (10%)	14 (10.9%)	0
ketogenic diet	24 (17.1%)	24 (18.8%)	0
Nature of underlying cause of epilepsy			
Idiopathic (generalized or focal)	16 (11.4)	14 (10.9)	2 (16.7%)
Other focal/undetermined	79 (56.4%)	72 (56.3%)	7 (58.3%)
Epileptic encephalopathy/other secondary generalized	45 (32.1%)	42 (32.8%)	3 (25.0%)

Excluded individuals included 7 who did not have a trial of at least one further AED (N=8) those followed <1 year after second AED failure (N=2), and both (N=2). As part of ongoing monitoring of the data, six cases previously considered to have failed two drugs were reclassified due to incorrect drug for the epilepsy syndrome (recognized only later in the course) and drug failures for indications other than seizures per se (e.g. AED given for migraine).

* 4 individuals followed <1 year were not classified with respect to 1-year remission and are removed from the denominator for calculating percents.

** Other deaths occurred in this cohort, however the individuals had not failed 2 or more drugs and therefore are not included here.

*** Other neurosurgical procedures were performed, typically for tumors, prior to the individual having failed 2 AEDs. Those are not tabulated in this table.

Table 2

First two drugs failed, most common combinations of first two AEDs failed, and third drugs failed for those failing another AED by grouped type of epilepsy.

	Focal & other undetermined epilepsies (N=70 subjects)		Epileptic encephalopathies and secondary generalized epilepsies (N=44 subjects)		Idiopathic epilepsies (N=14 subjects)	
	Failed as 1 st or 2 nd AED*	3 rd AED failed**	Failed as 1 st or 2 nd AED*	3 rd AED failed**	Failed as 1 st or 2 nd AED*	3 rd AED failed**
First line AEDs in common use in 1993 when recruitment began						
ACTH	0	0	10	4	0	0
Carbamazepine	56	0	10	5	1	0
Clonazepam	5	3	14	7	1	0
Diazepam	0	1	0	0	0	0
Ethosuximide	0	0	3	0	8	1
Phenobarbital	12	5	19	4	1	0
Phenytoin	26	4	8	5	2	0
Prednisone	0	0	0	1	0	0
Valproate	18	15	18	6	10	0
Newer generation of drugs released in the US starting in the early 1990s.						
Felbamate	1	1	1	1	0	0
Gabapentine	8	3	0	2	3	0
Levetiracetam	3	4	0	1	0	0
Lamotrigine	2	11	0	1	0	2
Oxcarbazepine	4	0	0	0	0	0
Tiagabine	1	2	0	0	0	0
Topiramate	4	5	0	2	0	2
Vigabatrin	0	0	2	0	0	0
Zonisamide	0	3	0	0	1	0

	Focal & other undetermined epilepsies (N=70 subjects)		Epileptic encephalopathies and secondary generalized epilepsies (N=44 subjects)		Idiopathic epilepsies (N=14 subjects)	
	Failed as 1 st or 2 nd AED*	3rd AED failed**	Failed as 1 st or 2 nd AED*	3rd AED failed**	Failed as 1 st or 2 nd AED*	3rd AED failed**
Older and less commonly used drugs.						
Acetazolamide	0	1	0	1	1	0
Clonazepam	0	0	1	0	0	0
Ethotoin	0	0	0	1	0	0
Methsuximide	0	1	0	0	0	0
Nitrazepam	0	0	1	0	0	0
Primadone	0	1	1	0	0	0
Most common combinations of first 2 AEDs that were failed***	CBZ&PHT (N=18) CBZ&VPA (N=12) CBZ&PB (N=7)		VPA&CZP (N=5)		VPA&ESM (N=6)	

* Totals equal twice the number of subjects as each one contributed two drug failures.

** The total is less than the number of subjects as not all failed a trial of a third AED.

*** CBZ=carbamazepine, PHT=phenytoin, VPA=valproate, PB=Phenobarbital, CZP=clonazepam, ESM=ethosuximide

Table 3

Results for additional drugs tried after failure of the second AED

	N patients who tried AED (noninformative)*	≥1 year remission on drug**	Mixed***	Failure (% of informative trials)
First line AEDs in common use in 1993 when recruitment began				
ACTH	10 (0)	2	0	8 (80%)
Carbamazepine	24 (2)	3	3	16 (73%)
Clonazepam	42 (1)	1	0	40 (98%)
Clobazam	3 (0)	0	0	3 (100%)
Diazepam	3 (0)	0	0	3 (100%)
Ethosuximide	10 (1)	1	0	8 (89%)
Lorazepam	8 (1)	1	1	5 (71%)
Phenobarbital	28 (2)	1	0	25 (96%)
Phenytoin	33 (3)	1	1	28 (93%)
Prednisone	8 (1)	0	0	7 (100%)
Valproate	62 (2)	15	6	39 (63%)
Newer generation of drugs released in the US starting in the early 1990s.				
Felbamate	16 (5)	0	0	11 (100%)
Gabapentine	25 (2)	2	0	21 (91%)
Levetiracetam	43 (4)	2	1	35 (90%)
Lamotrigine	73 (7)	4	8	54 (82%)
Oxcarbazepine	23 (3)	2	0	18 (90%)
Pregabalin	2 (0)	0	0	2 (100%)
Tiagabine	9 (1)	0	1	7 (88%)
Topiramate	55 (7)	4	7	37 (77%)
Vigabatrin	12 (0)	1	2	9 (75%)
Zonisamide	37 (3)	2	5	27 (79%)
Older and less commonly used drugs.				
Acetazolamide	9 (0)	1	0	8 (89%)
Clorazepate	9 (0)	0	0	9 (100%)
Ethotoin	2 (0)	0	0	2 (100%)
Methsuximide	5 (0)	0	0	5 (100%)
Nitrazepam	5 (0)	0	0	5 (100%)
Primadone	12 (0)	1	1	10 (83%)

* Total number of patients is given as N with the number who had noninformative trials in parentheses. Noninformative trials were trials in which the drug was stopped, usually for side-effects, before its effectiveness on seizures could be reasonably ascertained. For Felbamate, several trials were abruptly stopped secondary to the FDA warning. Subjects had trial of 1–15 (median=3) additional different AEDs each

** Relapse for discontinuation or noncompliance or in association with a low level for other reasons did not preclude classifying the outcome in this category.

*** A mixed outcome indicates that the drug was associated with a minimum 1-year period of remission but that at some point was also considered to have failed to control seizures at maximum tolerated doses, either before or after the remission period was achieved.

Table 4

Bivariate association of any remission and remission at last contact with potential prognostic factors

		Any remission since second AED failure	≥1 year remission at last contact	≥3 year remission at last contact
Factor	N	N (%) remission	N (%) remission	N (%) remission Total=124*
Total	128	73 (57%)	48 (38%)	28 (23%)
"Symptomatic" cause				
None identified	69	46 (67%)	33 (48%)	22 (33%)
Present	59	27 (46%)	15 (25%)	6 (11%)
p-val		0.02	0.009	0.003
Type of epilepsy				
Traditional idiopathic syndrome	14	14 (100%)	11 (79%)	7 (50%)
Other focal/undetermined	70	40 (57%)	24 (34%)	12 (18%)
Epileptic encephalopathy/other secondary generalized	44	19 (43%)	13 (30%)	9 (21%)
p-val		0.0009	0.003	0.03
Age at onset				
< 5 years	77	40 (52%)	27 (35%)	16 (22%)
5–9 years	30	18 (60%)	13 (43%)	9 (31%)
≥10 years	21	15 (71%)	8 (38%)	3 (14%)
p-val		0.10 (trend)	0.63 (trend)	0.77 (trend)
Age at second AED failure				
< 5 years	55	25 (45%)	15 (27%)	10 (19%)
5–9 years	31	21 (68%)	17 (55%)	13 (42%)
≥10 years	42	27 (64%)	16 (38%)	5 (13%)
p-val		0.05 (trend)	0.22 (trend)	0.69 (trend)
Intelligence				
IQ≥80	56	39 (70 %)	26 (46%)	17 (31%)
IQ<80	72	34 (47%)	22 (31%)	11 (16%)
p-val		0.01	0.07	0.05
History of febrile seizures				
No	109	61 (56%)	39 (36%)	21 (20%)
Yes	19	12 (63%)	9 (47%)	7 (37%)
p-val		0.56	0.34	0.11
Status by time of initial epilepsy diagnosis				
No	111	66 (59%)	44 (40%)	25 (23%)
Yes	17	7 (41%)	4 (24%)	3 (19%)
p-val		0.16	0.20	0.70
Any status epilepticus				

		Any remission since second AED failure	≥1 year remission at last contact	≥3 year remission at last contact
No	83	52 (63%)	36 (43%)	21 (26%)
Yes	45	21 (47%)	12 (27%)	7 (16%)
p-val		0.08	0.06	0.19
Any remission prior to failure of second AED				
No	99	55 (56%)	38 (38%)	26 (27%)
Yes	29	18 (62%)	10 (34%)	2 (7%)
p-val		0.53	0.70	0.04
Seizure frequency (days on which seizures occurred) at time of second drug failure				
< 1 day /month**	25	19 (76%)	11 (44%)	3 (13%)
≥1 day/month – <1/week	29	19 (66%)	13 (45%)	9 (32%)
≥1 day/week - < daily	28	17 (61%)	12 (43%)	7 (25%)
Daily seizures	46	18 (39%)	12 (26%)	9 (20%)
p-val		0.002 (trend)	0.13 (trend)	0.69 (trend)

* 4 subjects followed <3 years after second drug failure are dropped from analyses of 3-year remission

** Frequency in this group ranged from 3 to 11 seizure days per year in the year prior to second drug failure.

Table 5

Results of multivariable proportional hazards models

Model & Factors	Rate Ratio	95% CI	p-value
First remission after second AED failure (N=128)			
Idiopathic syndrome	3.65	1.97, 6.76	<0.0001
Seizure frequency*	0.75	0.65, 0.87	0.0002
Symptomatic cause**	0.63	0.38, 1.05	0.08
Remission prior to second AED failure**	1.25	0.71, 2.18	0.44
Epileptic** encephalopathy/secondary generalized epilepsy	0.77	0.40, 1.46	0.42
First remission after second AED failure, focal epilepsy only (N=70)			
Symptomatic cause	0.48	0.25, 0.92	0.04
Seizure frequency*	0.80	0.65, 0.97	0.03
Remission prior to second AED failure**	1.39	0.69, 2.80	0.35
1 year Remission at last contact after second AED failure (N=128)			
Idiopathic syndrome	2.67	1.31, 5.24	0.007
Seizure frequency*	0.82	0.67, 0.99	0.04
Symptomatic cause**	0.67	0.35, 1.29	0.23
Remission prior to second AED failure**	1.19	0.56, 2.52	0.65
Epileptic encephalopathy/secondary generalized epilepsy**	0.80	0.37, 1.72	0.56
1-year Remission at last contact after second AED failure, focal epilepsy only (N=70)			
Symptomatic cause**	0.54	0.23, 1.28	0.16
Seizure frequency*	0.71	0.54, 0.95	0.02
Remission prior to second AED failure**	1.63	0.66, 4.03	0.29
3-year Remission at last contact after second AED failure (N=124) ⁺			
Symptomatic cause	0.33	0.14, 0.82	0.02
Idiopathic syndrome**	2.14	0.86, 5.34	0.10
Seizure frequency*, **	0.97	0.74, 1.28	0.84
Remission prior to second AED failure**	0.45	0.11, 1.92	0.28
3-year Remission at last contact after second AED failure, focal epilepsy only (N=65) bivariate results***			

Model & Factors	Rate Ratio	95% CI	p-value
Symptomatic cause	0.22	0.05, 1.02	0.053
Seizure frequency*	0.90	0.59, 1.35	0.60
Remission prior to second AED failure**	0.36	0.04, 2.85	0.33

* The remission rate decreases with each increase in the frequency of days on which seizure occurred, "seizure frequency."

** Estimates for factors with p-values >0.05 are after adjustment for those that remained statistically significant in the multivariable model.

+ 4 subjects who were followed <3 years were dropped for analyses of 3-year remission.