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Epilepsy in a rural elderly population

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ABSTRACT – *Purpose*. The first goal of this study was to describe the characteristics of elderly patients with epilepsy and the antiepileptic drugs used to treat them. Next, the factors (such as epilepsy type, seizure frequency, medical comorbidities, etc.) influencing antiepileptic drug choice and living situation were explored. *Methods*. Retrospective chart review of patients older than 70 with epilepsy seen in a rural health care system. This yielded 449 patients with epilepsy, 54 patients with isolated seizures and 38 patients with syncope as the primary diagnosis. *Results*. The most commonly used antiepileptic drug was phenytoin. New generation AED's which had fewer side effects were used much less frequently than old generation AED's but the probability of using new generation AED's was increased in patients with renal failure and congestive heart failure as well as in patients that had seen a neurologist. Patients with acute symptomatic seizures, dementia, chronic obstructive pulmonary disease, frequent seizures and advanced age were less likely to be independent. Patients that had seen a neurologist as an outpatient were more likely to live independently. *Conclusions*. The elderly are a vulnerable population because of difficulty communicating their symptoms and their needs. This leads to the suboptimal use of AED's as well as poor outcomes. Careful attention to seizure control and medication side effects is critical in promoting good outcomes in this patient group. This retrospective study suggests that access of elderly patients with epilepsy to specialty care improves outcomes in terms of living status. This important information needs to be confirmed by prospective studies.

Key words: epilepsy, elderly, rural population, antiepileptic drug, quality of life

The incidence of new epilepsy in the elderly is high (Hauser *et al.* 1993) and, in fact, up to 10% of nursing home residents (Lackner 1998, Garrard *et al.* 2000, Schachter *et al.* 1998) are being treated with an antiepileptic drug (AED). The common choices of antiepileptic drugs in this setting include phenytoin (Schachter *et al.* 1998, Harms *et al.* 2005), carbamazepine (Huying *et al.* 2006, Moran *et al.* 2004), phenobarbital (Galimberti *et al.* 2006) and less frequently valproic acid. The complexity of using antiepileptic drugs in the elderly is further increased because of four factors. First, antiepileptic drug pharmacokinetics are different and not as well studied in the elderly as in younger patients (Perucca *et al.* 1984, Hayes 1975, Bernus, 1997, Battino *et al.* 2003). Second, side effects in the elderly may be different than in younger patients even at the same concentrations (Field *et al.* 2004). Third, the elderly often take a large number of different medications so that the risk of medication interactions is very high (Leppik 2006). In addition, it is not clear at what dosage the balance between control of seizures and the appearance of significant side effects provides for optimal outcomes especially when, because of other medical

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problems, the elderly have difficulty advocating for their own health care. Because of the frequency and expected severity of problems related to antiepileptic drug use in the elderly, it is important to further determine the incidence of AED related side effects in this population. It is also important to understand the factors that are associated with good outcomes in this highly complex group of patients. In particular, it is known that the most commonly used antiepileptic drug in this age group, phenytoin, has many side effects including ataxia, falls and serious medication interactions. It has been proposed that the newer antiepileptic drugs such as levetiracetam (Alsaadi *et al.* 2004, Ferendelli *et al.* 2003), lamotrigine (Mauri Llerda *et al.* 2005, Fife *et al.* 2006, Rowan *et al.* 2005, Giorgi *et al.* 2001) and gabapentin (Martin *et al.* 2001) may cause fewer significant side effects in the elderly and so may be better choices.

The first goal of this project was to define the characteristics of elderly rural epilepsy patients including seizure type, etiology, imaging and EEG findings, and the incidence of significant comorbidities. The second goal was to understand the use of antiepileptic drugs in this population including the factors that influenced the choice of AEDs and the specific side effect profile of the various drugs. The third goal is to identify various factors such as antiepileptic drug use, seizure frequency, seizure type, and coexisting medical problems that affect the ability of patients to live independently.

Methods and materials

This study was a retrospective record review of elderly patients with epilepsy in a rural population. The Geisinger health system (http://www.geisinger.org/professionals/about/stats.html) comprises two main hospitals with a total of 580 beds and roughly 30 000 yearly discharges in 40 counties of rural north central Pennsylvania. Overall, 769 000 outpatients are seen yearly in the health system with all outpatient notes for the five years prior to the study onset kept in an electronic medical record (EMR). After approval from the Geisinger IRRB (protocol 2005-0119) was obtained, an initial list of patients was obtained from the Geisinger decision support system (Eclipsys, Boca Raton, FL).

The following criteria were used to identify patients: 1) patient seen within the Geisinger Health System in the five years period preceding the start of this study;

2) age > 70 years at the start of the study along with ANY of the following: International Classification of Diseases 9th revision (Hart *et al.* 2007) codes 345.xx (comprising the different clinical types of epilepsy), 780.3x ("convulsions"), or an admission under DRG (diagnosis related group) 24 or DRG 25 ("seizure and headache; age > 17 with and without complications").

This search yielded a total of 880 charts. After review of paper and the electronic medical records for these patients, only 680 patient charts had sufficient medical record data for evaluation. On review of the 680 charts, 449 patients had epilepsy, 54 patients had isolated seizures but not epilepsy and 38 patients had syncope as the primary diagnosis. The other patients were thought at one point in their evaluation to have had possible seizures but more complete evaluations yielded other diagnoses that did not include syncope or seizure. This group of patients was not analyzed further so that a total of 531 patients were included.

For each patient, a standard set of data was obtained and was checked by two observers for accuracy. Data was also checked for errors using a number of automated algorithms designed to check for expected relationships between variables. The data recorded included, age, sex, seizure diagnosis, time since first seizure, most significant EEG finding, most significant imaging finding, and seizure frequencies. As there could be multiple findings on EEG studies only the most significant finding in all of the patient's EEG studies was entered. The order of significance from least significant to most significant was: normal, diffuse slowing, focal slowing, focal spikes, generalized spike and wave, and seizures. Similarly there were often multiple abnormalities on imaging studies (either CT or MRI) and only the most significant finding was entered in the order: normal, atrophy, hydrocephalus, white matter abnormalities (typically small vessel ischemic changes in this patient group), large vessel stroke, subdural or epidural hematoma, intracerebral hemorrhage, subarachnoid hemorrhage and brain tumor.

Since antiepileptic drug choice and dose varied from time to time, antiepileptic drug use was studied for up to a five-year study period prior to the time at which the patient's record was reviewed. The doses of each antiepileptic drug at the beginning and end of the study period were documented as well as whether each antiepileptic drug was used at all during the study period. The frequency, type and severity of antiepileptic drug side effects were also tabulated. Severity was graded on a five point scale as none (0) minor (1), moderate (2), life threatening (3) or fatal (4).

Finally, the medical status of each patient including the occurrence of cancer, depression, dementia, stroke, coronary artery disease (CAD), congestive heart failure (CHF), diabetes (DM), hypertension, atrial fibrillation (AFIB), pneumonia, urosepsis, renal failure, chronic obstructive pulmonary disease (COPD), osteoporosis, neuropathy, and peripheral vascular disease (PVD) was also documented. The living status of the patient was classified as: living independently, living in supervised personal care setting, in a nursing home, hospitalized or expired both at the time of the chart review and at the beginning of the 5 year period preceding the time of study onset. For actual analysis of outcomes, this data was transformed into a

4 level variable LIVING STATUS with levels (0-independent, 1-personal care, 2-nursing home, 3-expired, with patients hospitalized at the time of the data collection counted as missing data). A binary variable INDEPENDENCE was taken as 1 if the patient was dependent on others for significant care or 0 if the patient was independent.

A surrogate marker of the level of epilepsy care included whether the patient had seen a neurology specialty practitioner (either MD, DO, or CRNP) within the study period and whether any notes by any practitioner included descriptions of the patient's seizures, seizure frequency or documented discussions of potential medication side effects. The notes of 319 of the 449 epilepsy patients were scrutinized for this information.

Statistics

Data was collected in a Microsoft Access database and then exported to Statistica (Statsoft, Tulsa OK) and SPSS (SPSS Inc, Chicago IL) for analysis. Analysis of crosstabulation tables was performed using a log-linear analysis and significance was assessed from the Pearson χ^2. For 2x2 tables, a two-tailed Fisher's exact test was used to assess the significance of differences and *odds ratio*s were computed.

Testing for associations between a number of factors and a single outcome variable was carried out in a number of ways. Because of the large number of explanatory variables, the first step involved performing univariable Spearman rank correlation analyses between each factor and the outcome variable. Factors with a significant correlation in this analysis ($p < 0.05$) were included in a multivariable analysis. If the outcome variable was binary a forward stepwise logistic regression (SPSS) was employed with $p = 0.01$ to enter and $p = 0.05$ to remove. If the list of variables in the model included any variables with $p > 0.05$ then the analysis was rerun with these variables removed. If the outcome variable was either continuous or had multiple values, the outcome variable was first transformed into a binary value prior to performing the logistic regression analysis. In order to confirm the results obtained with this analysis, a forward stepwise multiple regression linear analysis was performed using the non-transformed outcome measure as the dependent variable. When multiple univariable tests are performed, the level required for statistical significance was derived from the Bonferroni correction and was set at 0.05/number of separate tests.

Analysis of variance (ANOVA) was used to determine whether single or multiple discrete explanatory variables had any effect on a continuous outcome variable.

Results

Basic demographics

The mean age of persons with epilepsy in this study was 79.4 years with a standard deviation of 6 years. The mean age of patients with seizures and not epilepsy was 79 with a standard deviation of 6 years and the mean age of patients with syncope was 80.5 years with a standard deviation of five years, a difference that was not statistically significant. The oldest patients with epilepsy, seizures not epilepsy and syncope were aged 100, 90 and 89 years respectively. Female patients constituted 52% of patients with epilepsy, 45% of patients with seizures and not epilepsy and 53% of patients with syncope ($p > 0.5$).
Table 1 contains a description of the population of patients with epilepsy, seizures not epilepsy and syncope in this study along with univariable measures of significance based on a one-way ANOVA for continuous variables and for binary variables, a log-linear analysis of a 2x3 crosstabulation table produced by counting the number of patients characterized by each variable and by DIAGNOSIS (Epilepsy, Seizures not epilepsy, syncope). After the Bonferroni correction for multiple comparisons, there are *no* significant differences between the listed variables in these three groups.

Characteristics of persons with epilepsy

Of the 449 patients with epilepsy, 24% had acute symptomatic seizures only indicating that seizures occurred only in the setting of an acute neurologic or medical condition such as encephalitis or a new stroke. Forty per cent had chronic stable epilepsy only and 36% had a stable pattern of seizures that substantially worsened due to an acute neurologic or medical condition on at least one occasion. The mean duration of epilepsy was 14+/-17 years.
Table 2 contains a summary of the frequency of various EEG and imaging findings as well as the frequency of various etiologies for seizures in this group.
As expected, stroke is the most common identifiable cause although most etiologies were uncertain. The number of seizures per year of each type was estimated and at both the beginning and the end of the study period.
Table S1 summarizes the frequency of each type of seizure at the end the study period indicating that although one patient experienced extremely frequent seizures, only 38% had any seizures in the last study year and 16% had more than one seizure during this time.

Antiepileptic drug use

The choice and dosing of antiepileptic drugs changed over time in this group of patients. *Table 3* shows the total number of patients that used each AED during the study period. In order to determine how frequently an AED is changed, the percentage of all patients using an AED that

Table 1. Characteristics of patients with different diagnoses
After correcting for multiple comparisons, there are no significant differences in the probability of any patient descriptor in these three groups.
CAD = coronary artery disease, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, PVD = peripheral vascular disease.

Descriptor	Epilepsy	Seizures not epilepsy	Syncope	p
Age	79.6	79.0	80.5	0.49
Female sex	52%	45%	53%	0.72
Any outpatient neurology visit	47%	36%	47%	0.59
Cancer	22%	34%	11%	0.04
Depression	14%	25%	26%	0.04
Dementia	18%	23%	16%	0.66
Stroke	21%	9%	16%	0.14
CAD	43%	41%	45%	0.94
CHF	12%	11%	11%	0.94
Diabetes	8%	16%	8%	0.23
Hypertension	49%	66%	50%	0.09
Atrial fibrillation	18%	11%	16%	0.54
Pneumonia	6%	14%	8%	0.15
Urosepsis	6%	11%	0%	0.08
Renal failure	13%	18%	8%	0.38
COPD	15%	14%	3%	0.1
Osteoporosis	13%	9%	3%	0.13
Neuropathy	8%	5%	8%	0.76
PVD	6%	5%	8%	0.82
Falls	20%	5%	0%	0.14

stopped or started that AED during the study period were tabulated both in all patients and the group in which the study period exceeded three years. Because the electronic and the paper medical records contained information preceding the study period, it was possible to look at AED side effects obtained from both from AED's used during the study period ("strict") and from AED's used at any time in the patient's history ("liberal"). Both are noted in this table.

It is clear that phenytoin was, by far, the most commonly used AED. There were a significant number of medication changes with either old medications being stopped or new medications being started. Each AED except phenobarbital was added during the study period more often than it was discontinued. Significant differences in the rate of discontinuation of different AED's were confirmed by constructing a 13x3 contingency table defined by the 13 level

Table 2. EEG and imaging findings as well as clinical seizure etiologies
This table shows the fraction of persons with epilepsy having each EEG or Imaging finding as the most significant abnormality as described in the text. It also demonstrates the fraction of persons with epilepsy whose seizures were felt to be due to each specific factor. The final column represents the percentage of all patients with the given seizure etiology that had acute symptomatic seizures of any type.

EEG finding	%	Imaging finding	%	Etiology	%	% Acute symptomatic
Normal	26	Normal	8	Stroke	22	68
Diffuse slow	18	Atrophy	11	Head injury	4.6	33
Focal slow	22	Hydrocephalus	1.6	Tumor	9	70
Focal spikes	23	White matter abnormalities	28	Encephalitis	2.4	81
Generalized spike and wave	3	Stroke	30	Intracranial hemorrhage	7.8	71
Seizures	7	Subdural hematoma	4.8	Unknown	42	41
		Intracerebral hemorrhage	3.7	Cerebral palsy	2.8	38
		Subarachnoid hemorrhage	1.4	Other	9.1	76
		Brain tumor	11			

Table S1. ***Seizure types and frequencies seen in epilepsy patients at the end of the study period***

Seizure type	Mean sz/year	Median sz/year	Max sz/year	% at least 1 sz/year	% any seizure in last year
Simple partial	2.8	0	730*	4	8
Complex partial	0.62	0	52*	7	18
Generalized tonic-clonic	0.19	0	4	4	14
Absence	0	0	0	0	0
Status epilepticus	0.018	0	1	1.6	1.7
Total	3.0	0	782	16	38

* both were the same patient.

factor AED-NAME and the three level factor USAGE (continued throughout the study period, started during the study period, stopped during the study period) for which a log-linear analysis demonstrates $p < 0.00001$ (Pearson χ^2=124 df = 24). In order to determine whether there was a difference in the AED discontinuation rate in the new generation AED's (oxcarbazepine, topiramate, gabapentin, zonisamide, lamotrigine, and levetiracetam) and the old generation AED's (phenytoin, phenobarbital, carbamazepine, valproic acid, clonazepam, lorazepam, and primidone) a 2x2 crosstabulation table of NEW-AED (new generation AED used) *versus* AED-STOPPED (whether the AED was stopped during the study period) demonstrates no significant difference (Fisher's exact test p = 0.7) in the rates at which new and older AED's are stopped. However, the 2x2 table of NEW-AED *versus* AED-STARTED reveals (Fisher's exact test $p < 0.00001$) that new generation AED's were roughly five times more likely to be started than old generation AED's.

There were significant differences between the side effect severity with different AED's as determined by analysis of the 13x4 contingency table formed by the variables AED-NAMExSEVERITY (none,mild, moderate, life-threatening) with Pearson chi-square = 91 df = 36 $p < 0.00001$. Despite this, the mean side effect severity values for new and old generation AED's were the same (0.36 for new AED's *versus* 0.54 for old AED's t =-1.5 N = 466 p = 0.125). One possible problem with this analysis could be that patients more likely to have side effects may have been started preferentially on one of the newer AED's so that the side effect estimates may be biased. In order to see if this *was* the case, a similar analysis was carried out in only the

Table 3. Use of antiepileptic drugs in persons with epilepsy

N is the number of patients taking this AED. The next column is the fraction of all persons with epilepsy that took this AED during the study period. Computations of the fraction of users starting and discontinuing any given AED were performed both for patients for whom the study period was > 3 years and for all patients (in parenthesis). Strict assessment of side effects refers only to those side effects occurring in patients that took the given AED during the study period and liberal assessment included side effects occurring prior to the study period.

AED	N	% of pts using this AED	% of users discontinued during study period	% started during study period	Mean of the dose used at end of study period (mg/day)	Fraction any side effect (strict)	Fraction any side effect (liberal)	Mean severity score (strict)	Mean severity score (liberal)
PHT	298	66	16 (15)	24 (25)	340	0.26	0.33	0.37	0.46
PB	64	14	15 (17)	4 (3)	101	0.09	0.15	0.14	0.19
CBZ	46	10	8 (7)	17 (22)	534	0.17	0.42	0.24	0.19
OXC	3	1	0 (0)	100 (66)	700	0.33	0.50	0.67	0.67
VPA	38	8	23 (18)	50 (45)	1177	0.18	0.50	0.29	0.29
TPM	4	1	0 (0)	50 (50)	243	0.25	0.40	0.25	0.80
GBP	40	9	19 (20)	44 (48)	812	0.10	0.12	0.20	0.22
ZNS	2	0.5	0 (0)	100 (100)	250	0	0.33	0	0.33
LTG	9	2	0 (0)	57 (56)	316	0.11	0.20	0.11	0.30
LEV	28	6	0 (7)	88 (82)	1626	0.26	0.33	0.32	0.40
CZP	10	2.0	33 (30)	22 (30)	1.4	0	0.33	0	0.17
LZP	18	4	0 (0)	92 (94)	2.3	0	0.10	0	0.15
PRM	7	1.4	0 (0)	0 (0)	460	0	0	0	0

Table S2. ***Common side effect chart. This table contains the number of occurrences of each side effect found in the medical record ("liberal" assessment). The term "Failure" indicates treatment failure.***

AED	Acute intoxication	Lethargy or confusion	Falls	Neuropathy	Osteoporosis	Rash/ allergy	Hyponatremia	Other
PHT	41	20	9	11	11	28	0	Lft Abn-4 Local Site-2
PB	2	6	0	0	1	3	0	
CBZ	2	6	1	0	0	9	8	PLT-1 WBC-1 Failure-1
OXC	0	0	0	0	0	0	0	Nausea-1
VPA	1	5	0	0	0	4	0	Nausea-2 Tremor-3 Plt-1 Lft-1 Fail-1
TPM	0	1	0	0	0	1	0	
GBP	0	2	1	0	0	1	0	Failure-2
ZNS	0	1	0	0	0	0	0	0
LTG	0	0	0	0	0	0	0	Nausea-1 Failure-1
LEV	0	8	0	0	0	0	0	Nausea-1 Failure-1 Abn WBC-1
CZP	0	0	0	0	0	0	0	0
LZP	0	1	0	0	0	1	0	0
PRM	0	0	0	0	0	0	0	0

smaller (n = 44) group of patients that had taken both a new and an old generation AED. In this group, the mean side effect severity was 0.34 for new generation AED's and 1.18 for old generation AED's ($t = -3.95$; $p < 0.001$) and so when tested in the same patients, new generation AED's did have significantly lower side effects.

It was also possible to look at the factors that influenced the decision to use a new generation AED. The univariable analysis in *table S3* and the subsequent multivariable analysis of *table 4* demonstrate that new generation AED's were much more likely to be used in patients that visited a neurologist as an outpatient, patients that had more changes in AED's and in patients with renal failure or congestive heart failure.

Overall most side effects were classed as mild or moderate. In only one case was there a life threatening side effect. This occurred in a patient quickly switched from and old generation AED to gabapentin and topiramate who developed status epilepticus when treatment with gabapentin and topiramate failed. This was categorized as a life threatening treatment failure of both AED's. There were no fatal side effects. A detailed description of the side effects encountered are found in supplemental *table S2* but the most common side effect of phenytoin was acute intoxication and for carbamazepine it was rash. For all other AED's the most frequent side effect was lethargy/confusion.

In order to get a full picture of the effect of each of the AED's used in this elderly population, it was useful to

Table 4. Factors influencing the choice of new generation AED's

Results of a logistic regression analysis. The analysis is associated with an overall 87.5% correct classification of cases. AEDVAR represents the number of changes in AEDs during the study period

Factor	Risk of using new AED	95% CI	p
Neurology outpatient visit	6.5	3.2-13.2	< 0.001
Polytherapy	4.0	1.9-8.3	< 0.001
Renal failure	3.0	1.3-6.9	0.008
Congestive heart failure	2.4	1.02-5.6	0.04
AEDVAR	2.1	1.3-3.3	0.001

Table S3. ***Spearman R describing correlation between each factor and the use of new generation AED's (Afib = atrial fibrillation)***

Descriptor	Spearman R	Significance
Age	- 0.08	0.1
Sex	0.04	0.40
Modliving3	- 0.04	0.40
Any Neurooutpatient Visit	0.312	< 0.001
Polytherapy	0.376	< 0.001
Cancer	- 0.013	0.78
Depression	- 0.06	0.20
Dementia	- 0.06	0.20
Stroke	0.03	0.83
Coronary artery disease	- 0.05	0.28
Congestive heart failure	0.09	0.06
Diabetes	0.059	0.21
Hypertension	0.069	0.14
Atrial fibrilation	- 0.002	0.96
Pneumonia	0.039	0.41
Urosepsis	0.023	0.62
Renal failure	0.101	0.03
Chronic obstructive pulmonary disease	0.011	0.82
Osteoporosis	- 0.017	0.72
Peripheral vascular disease	- 0.015	0.75
Neuropathy	0.122	0.009
Falls	- 0.07	0.25
Any sz/year	0.101	0.03
AEDVAR	0.36	< 0.001
Acute	- 0.083	0.26
Duration of seizures	- 0.02	0.61

consider the effect of the AED's on seizure frequency. *Table S4* shows the results of univariable analyses and *table 5* the results of a forward stepwise logistic regression of AED use on whether there were any seizures in the last year of the study. Both tables show that the use of phenobarbital is associated with a reduced risk of seizures whereas the use of lamotrigine or lorazepam was associated with a higher risk of seizures. In order to investigate whether the positive effects of phenobarbital were present in both patients with acute symptomatic seizures and chronic seizures, the analysis leading to *table S4* was carried out in only the population with chronic epilepsy. In this analysis no effect of phenobarbital on seizure control was noted.

Role of the neurologist and medical record quality

One surrogate marker for the quality of care provided is the quality of notes in the patient's outpatient medical record. The records of a subgroup of patients in which there were a significant number of outpatient visits documented in the electronic medical record were assessed to see if there was ANY note during the study period that included a description of one of the patient's seizures, a mention of seizure frequency or a note in which any specific discussion of possible medication side effects was documented. *Table 6* shows that patients not seen by a neurologist generally do not contain any of the basic information discussed above while those seen by a neurologist are two to eight times more likely to include this basic information. Even in those patients seen by a neurologist only roughly half of patients have this documentation.

At this point it is also important to note the effects of a neurology outpatient visit on antiepileptic drug management and on seizure frequency. The variable AEDVAR was constructed as the number of antiepileptic drug changes during the study period. A simple t-test reveals that AEDVAR is on average 0.99 in the persons with epilepsy that had seen a neurologist and only 0.62 in patients that has not seen a neurologist a difference that is statistically significant ($t = 5.4$, $df = 447$, $p < 0.001$). This suggests that neurologists are more likely to change a patient's antiepi-

Table S4. *Relationships between the frequency of seizures and the use of each anticonvulsant*
In columns 2, 3 and 4, the data come from an analysis of 2x2 crosstabulation tables created from whether the given AED was used and whether there was more than one seizure in the last year of the study.
Columns 5, 6 and 7 are derived from an analysis of 2x2 crosstabulation tables created from whether the given AED was used and whether there was any seizure in the last year of the study. Larger odds ratio*s imply that use of the anticonvulsant was associated with more seizures.*
Columns 8 and 9 are the Spearman rank correlation coefficient R and its probability describing the correlation between the number of seizures in the last year and whether an anticonvulsant was used. 95% CI is the 95% confidence interval for the estimate of the odds ratio.

AED	Fisher's exact 2tail	*Odds ratio*	95% CI	Fisher's exact 2tail	*Odds ratio*	95% CI	R	p
PHT	0.89	0.95	0.56-1.6	0.68	0.91	0.61-1.4	- 0.03	0.58
PHB	0.10	0.47	0.2-1.14	0.001	0.37	0.19-0.69	- 0.14	0.03
CBZ	0.84	1.05	00.47-20.4	0.15	0.61	0.31-1.2	- 0.054	0.25
OXC	0.42	2.5	00.22-28	0.56	30.3	0.29-36	0.06	0.22
VPA	0.25	1.7	0.76-3.7	0.38	1.4	0.72-20.8	0.06	0.23
TPM	0.02	15.5	10.6-151	0.16	40.9	0.5-47	0.11	0.02
GBP	0.03	2.34	10.1-40.9	0.40	10.4	0.71-20.6	0.07	0.13
ZNS	1	1	0.98-1.003	0.53	0.99	0.98-1.003	- 0.05	0.28
LTG	0.18	2.5	0.62-100.4	0.09	30.3	0.82-130.5	0.09	0.05
LEV	0.80	1.1	0.4-3.0	0.23	1.7	0.78-30.6	0.05	0.25
CZP	0.23	2.2	0.55-80.6	0.51	10.6	0.47-50.7	0.06	0.22
LZP	0.18	2.1	0.73-6.3	< 0.001	8.14	2.3-29	0.16	0.001
ACUTE	0.35	1.35	0.76-2.4	< 0.001	3.9	2.4-6.2	0.23	< 0.001

leptic drugs than other physicians. However, patients that had a neurology outpatient visit did not have improved seizure frequencies. The 2x2 crosstabulation table formed by the two factors NEUROOUTPATIENTVISIT and ANY-SEIZURE (1 if there is any seizure in the last year of the study, 0 otherwise) suggests that the risk of having at least one seizure in year prior to the end of the study period was 1.9 (95% CI: 1.3-2.8; $p < 0.001$) times higher in the group of patients seen by a neurologist. This effect was not present when the same analysis was applied to only patients with acute symptomatic seizures ($p = 0.2$) and was more pronounced (*odds ratio* = 3.17; 95% CI: 2-5; $p < 0.001$) in the group that did not have only acute symptomatic seizures. This suggests that patients with better controlled seizures will not see a neurologist as often as those with more frequent seizures.

What factors predict outcome?

The primary outcome measures in this study are the living situation of the patient at the end of the study and the change in living status during the study period. For the patients with syncope the mean living status at the end of the study was 0.58 (std 1.0) and for the epilepsy patients the mean was 1.0 (std 1.26) and for patients with seizures and not epilepsy 1.63 (std 0.3 $F = 7.51$ $p < 0.001$) and so there is a difference in living status with the persons with epilepsy and patients with seizures and not epilepsy having poorer outcomes than the patients with syncope. One explanation for this phenomenon might be that patients who are extremely medically ill may have seizures as part of their illness and poor outcomes should be expected in this group. In order to test this hypothesis, *table 7* shows

Table 5. Effect of AED use on seizure frequency
Results of logistic regression analysis with dependent variable equaling zero or one depending on whether there were any seizures in the last year of the study.
The dependent factors in the analysis are those significant in the univariable analysis of *table S4* (ACUTE = 1 if acute symptomatic seizures only, 0 otherwise).

Factor	Relative risk	95% CI	p
Phenobarbital	0.45	0.23-0.88	0.02
Lamotrigine	5.2	1.2-22	0.023
Lorazepam	6.7	1.8-25	0.004
ACUTE	3.5	2.1-5.7	< 0.001

Table 6. Quality of the reviewed notes in patients with epilepsy
The p values in this table refer to the hypothesis that the given factor was present with equal probability in patients seen by a neurologist as an outpatient and patients not seen by a neurologist as an outpatient. Larger *odds ratio*s indicated that the factor was more often present in the notes from a neurologist.

Factor	% with this/overall	%with this if no neurologist	% with this if neurologist	p	*Odds ratio* (95% CI)
Any seizure description	34	11	46	< 0.001	6.9 (3.7-13)
Any mention of seizure frequency	58	44	66	< 0.001	2.4 (1.5-3.8)
Any specific discussion of possible side effects	16	3.4	23	< 0.001	8.3 (2.9-24)

that living status is definitely poorer in patients that had acute symptomatic seizures than patients with chronic epilepsy.

It is important to understand those factors that affect outcome in patients with epilepsy. Before proceeding with this, it is useful to see if EEG, etiology and imaging findings correlated with outcome. This information is contained in *table S6*. This table shows that imaging findings were not associated with outcome in epilepsy patients although, there were significant effects of etiology and EEG findings. Based on the results of *table S6*, three additional factors EEGNORMAL, CP (0-etiology of seizures NOT cerebral palsy; 1-cerebral palsy IS etiology of seizures) and HEADINJURY (0-no, 1-yes) were added to the list of factors studied. *Table S7* shows the results of a univariable analysis of the effect of various factors on the living status at the end of the study and the change in living status. Subsequent to this analysis a forward stepwise logistic regression analysis was carried out using the variable INDEPENDENCE as the dependent variable and each factor with $p < 0.05$ in the univariable analysis as dependent factors. The results of this analysis (p to enter 0.01 and p to remove 0.05) which achieves a 70.5% correct classification are shown in *table 8*. This table demonstrates that patients that had seen a neurologist as an outpatient were roughly five times more likely to be independent that patients that had not seen a neurologist as an outpatient. Patients with

Table 7. Effect of seizure type on living status at the end of the study period
Larger values of the living status indicate poorer outcomes.

Type	Mean living status	Standard deviation
Acute symptomatic	1.49	1.36
Chronic stable	0.76	1.16
Both	0.85	1.16

$F(2,382) = 11.3$; $p < 0.001$.

Table S5. *Results of forward stepwise linear regression of various factors on living status at end of study period*
p to enter 0.01 and p to remove 0.05, adjusted $R^2 = 0.31$; $F(11,426)=18.9$, $p < 0.001$ CP = cerebral palsy.

Factor	Slope	Standard deviation	p
Neuro outpatient visit	- 0.57	0.11	< 0.001
Dementia	0.70	0.13	< 0.001
ACUTE	0.63	0.13	< 0.001
Age	0.047	0.009	< 0.001
>0 sz/year at end	0.43	0.11	< 0.001
Neuropathy	- 0.71	0.19	< 0.001
COPD	0.44	0.14	0.002
Urosepsis	0.70	0.22	0.002
Cancer	0.34	0.12	0.003
AEDVAR	0.22	0.07	0.002
CP	0.82	0.30	0.006

Table S6. ***The effect of EEG, imaging findings and etiology on living status at the end of the study period***
The entries under living status are the mean values with the standard deviation in parenthesis. The overall statistical tests are the result of testing the hypothesis that there is no difference between the different factors by ANOVA.

EEG finding	Living status	Imaging finding	Living status	Etiology	Living status
Normal	0.84 (1.2)	Normal	0.86 (1.2)	Stroke	1.2 (1.3)
Diffuse slow	1.5 (1.2)	Atrophy	1.1 (1.2)	Head injury	0.33 (.9)
Focal slow	1.0 (1.3)	Hydrocephalus	1.3 (1.3)	Tumor	1.2 (1.4)
Focal spikes	0.87 (1.2)	White matter abnormalities	0.74 (1.2)	Encephalitis	0.45 (1)
Generalized spike and wave	1.1 (1.1)	Stroke	1.3 (1.3)	Intracranial hemorrhage	1.6 (1.4)
Seizures	1.4 (1.4)	Subdural hematoma	1.2 (1.4)	Unknown	0.8 (1.2)
		Intracerebral hemorrhage	1.4 (1.3)	Cerebral palsy	1.85 (.7)
		Subarachnoid hemorrhage	1.2 (1.6)	Other	1.08 (1.3)
		Brain tumor	1.2 (1.3)		
	F(5,273) = 2.5		**F(8,352) = 1.6**		**F(7,431) = 4.3**
	p < 0.03		**p < 0.15**		**p < 0.001**

neuropathy were also more likely to have good outcomes. Patients with dementia, frequent seizures, increased age, more changes in AED's, chronic obstructive pulmonary disease, urosepsis, and acute symptomatic seizures were all more likely to have poor outcomes. A forward stepwise linear regression analysis of the factors with $p < 0.05$ in the univariable analysis on living status at end of the study period *(table S5)* confirms the above analysis and, in addition, suggests that cancer and cerebal palsy were also associated with a poor outcome. A third statistical look at this relation using a tree classification method is shown in *table S8* of living status on the variables in the significant in the univariable analysis suggested that frequent seizures, age and NEUROOUTPATIENTVISIT were the most important variables in predicting outcome. As shown in *table S9*, similar factors are associated with predicting changes in living status.

Overall, having a neurology outpatient visit and having neuropathy are associated with better outcome. As expected, dementia, urosepsis, COPD and frequent seizures were associated with poor outcomes. The effect of AEDVAR is a simple result of the fact that patients with more severe problems had more medication changes.

Discussion

There are a number of important results that can be drawn from this study. First, as in other studies, the etiology of seizures was not always identifiable but, in those patients with a clearly identifiable cause, stroke was the most likely cause followed by brain tumor and intracranial hemorrhage. This was supported by the fact that stroke was the most common imaging abnormality in this patient group. Consistent with the high likelihood of focal structural injury as the cause of seizures suggested by the clinically determined etiology and imaging studies, there is a high incidence of focal epileptiform abnormalities on the EEG studies and complex partial seizures are the most frequent seizure type.

The elderly persons with epilepsy in this study were more likely to live in supervised care settings than other elderly patients. The overall "living status" was significantly poorer in the elderly group of patients with epilepsy when compared with a group of very similar patients *(table 1)* with syncope. Much of this effect is related to the fact that patients with acute symptomatic seizures due to serious brain injuries have, as expected, poor outcomes. There is some suggestion that patients with only chronic seizures also have worse outcomes than patients with syncope but this effect is very much smaller. In this study, roughly 40% of elderly persons with epilepsy lived in settings where they were dependent on others for care, placing them in an especially vulnerable position. This is much more of a significant problem for persons with epilepsy than for patients with other medical problems because, for most other medical conditions such as hypertension, diabetes or coronary artery disease, there is a simple objective test that can be used to assess the patient. In patients with epilepsy, a good history documenting the number and type of seizures and the presence of medication side effects is still critical to appropriate management. The fact that the medical record infrequently contains critical historical information about the patients' seizures although it contains much information about other medical problems is symptomatic both of the fact that these patients have difficulty communicating information and of the fact that other more common medical problems are often given

Table S7. ***Effect of various factors on the living status at the end of the study and the change in living status.***
Columns 2 and 3 present univariable analyses of the correlation between each factor and the living status of the patient at the end of the study period using the Spearman rank correlation.
Columns 4 and 5 present the correlation between each factor and the change in living status during the study period for those patients with epilepsy in which the study duration was longer than three years. The change in living status is the difference in living status between that at the beginning and the end of the study period so that a negative value indicates that the patient's living status deteriorated during the study period.

Factor	Living status at end of study		Change in living status	
	R	p	R	p
Age	0.194	< 0.001	- 0.18	0.002
Female	0.08	0.11	0.03	0.58
PHT	0.07	0.18	- 0.12	0.04
PHB	- 0.12	0.02	0.15	0.01
CBZ	- 0.05	0.30	0.04	0.5
OXC	- 0.003	0.95	0.03	0.55
VPA	- 0.015	0.75	0.09	0.12
TPM	- 0.011	0.82	0.09	0.11
GBP	0.012	0.8	0.01	0.81
ZNS	- 0.056	0.24	0.03	0.55
LTG	- 0.017	0.72	0.05	0.39
LEV	- 0.06	0.22	0.05	0.34
CZP	- 0.004	0.94	0.09	0.12
LZP	0.165	0.001	- 0.06	0.28
Neuro outpatient visit	- 0.246	< 0.001	.21	< 0.001
Cancer	0.096	0.04	- 0.09	0.12
Depression	0.015	0.76	- 0.04	0.5
Dementia	0.237	< 0.001	- 0.03	0.55
Stroke	0.062	0.19	- 0.07	0.22
CAD	- 0.063	0.19	- 0.04	0.52
Congestive heart failure	0.07	0.14	- 0.09	0.13
Diabetes	0.05	0.28	- 0.09	0.13
HTN	- 0.03	0.57	- 0.07	0.23
AFIB	0.11	0.03	- 0.20	< 0.001
Pneumonia	0.12	0.01	- 0.06	0.33
Urosepsis	0.16	0.001	- 0.06	0.26
Renal failure	0.12	0.02	- 0.21	< 0.001
COPD	0.10	0.03	- 0.10	0.07
Osteoporosis	- 0.06	0.23	0.05	0.40
Neuropathy	- 0.20	< 0.001	.14	.02
PVD	0.023	0.63	- 0.07	0.24
Polytherapy	- 0.03	0.56	0.11	0.06
ACUTE	0.20	< 0.001	- 0.28	< 0.001
Duration of epilepsy (years)	- 0.17	0.001	0.22	< 0.001
More than 1sz/year at end	0.09	0.06	- 0.1	0.08
More than 0sz/year at end	0.19	< 0.001	- 0.12	0.04
Total number of seizures/year at end of study	0.17	< 0.001	- 0.12	0.04
Falls	0.14	0.02	- 0.10	0.11
AEDVAR	0.11	0.02	- 0.08	0.16
EEGNORMAL	0.10	0.09	0.04	0.55
HEADINJURY	- 0.13	0.01	0.14	0.01
CP	0.14	0.003	0.18	0.001
NEWAED	- 0.04	0.37	0.08	0.15

Table 8. Results of logistic regression of factors on the outcome variable INDEPENDENCE
A relative risk > 1 indicates that the factor decreases the chance that the patient is independent (Hosmer-Lemeshow χ^2=11.4, df = 8, p = 0.2; 75% correct classification).

Factor	Relative risk	95% CI	p
Age	1.1/year	1.05/year-1.14/year	< 0.001
NEUROOUTPATIENTVISIT	0.31	0.19-0.51	< 0.001
Dementia	6.9	3.5-13.3	< 0.001
Urosepsis	4.0	1.4-11.5	0.01
COPD	2.6	1.4-4.8	0.003
Neuropathy	0.09	0.02-0.36	0.001
ACUTE	2.9	1.6-5.1	< 0.001
ANYSEIZURE	2.65	1.6-4.4	> 0.001
AEDVAR	1.54	1.1-2.1	0.009

priority in dealing with the elderly person with epilepsy because objective data is easier to obtain.

Associated with this barrier to care, the current study has demonstrated that patients who had seen a neurologist on an outpatient basis had a better "living status" than patients that did not. The reason for this relationship was explored in a number of analyses. First, the relationship between outcome and an outpatient neurology visit persisted in three different multivariable analyses in which acute symptomatic seizures was also a variable. Hence, this effect is unlikely to be explained by the fact that the more acutely ill patients with a higher mortality were less likely to have neurology outpatient visits. The next question is whether the positive effect of a neurology outpatient visit could be explained by the fact that patients seen by neurologists on an outpatient basis were more likely to receive one of the new generation antiepileptic drugs. This depends, in part, on whether there are any advantages in this elderly population to the use of new generation AED's. In regard to side effects, a direct comparison of the side effects of the new and old generation AED's in this study showed no statistical difference. However, new generation AED's were more likely to be prescribed in more medically ill patients (*i.e.* those with CHF and renal failure) than old generation AED's. When this factor was eliminated by comparing side effects in the group of patients that had taken both new and old generation AED's, the new generation AED's were associated with a significantly lower side effect profile. Despite the difference in side effects, there was no difference in seizure frequency in patients taking different antiepileptic drugs with one exception. Patients taking phenobarbital had lower seizure frequencies than other patients. This may be the result of its effects in patients with acute symptomatic seizures or it may be the result of the fact that patients were only continued on phenobarbital and not switched to another antiepileptic drug with fewer side effects if seizure control was excellent. Also, as a group, patients taking new generation antiepileptic drugs were not more likely to have improved seizure control. This suggests that it is not seizure frequency but management of side effects that is associated with the improved outcomes in patients seen by a neurologist on an outpatient basis. This suggestion is reinforced by the fact that patients seeing neurologists as an outpatient actually had more frequent seizures than patients that did not see an outpatient neurologist. This complex set of data along with the fact that changes in antiepileptic drugs were much more common when the patient was seen by a neurologist as an outpatient suggests that the most important role of the outpatient neurologist is to collect information on seizure type and frequency and to find a medication regimen which provides the best balance between eventual side effects and seizure control. The role of the neurologist is *not* simply to optimize seizure control in this patient population.

The fact that patient access to specialty care improves outcomes has not been previously demonstrated in elderly seizure patients. However, this effect has been demonstrated in other areas of medicine such as in the management of myocardial infarction (Nash *et al.* 1999, Casale *et al.* 1998) and in the management of asthma (Wu *et al.* 2001).

In regard to pharmacologic management of seizures in this elderly population, it should be noted that 66% of patients had taken phenytoin during the study period, 14% had taken phenobarbital and less than 10% of patients took any other antiepileptic drug. Although the high prevalence of phenytoin utilization in American elderly patients has been previously documented (Schachter *et al.* 1998, Harms *et al.* 2005), this study suggests that this trend may be changing since (*table 3*) most patients taking phenytoin and phenobarbital were started on these prior to the study period and most patients taking other antiepileptic drugs were started on them during the study period. For phenytoin the most common side effect was acute intoxication, and for carbamazepine it was rash or allergy. Lethargy/confusion was the most common side effect in the other antiepileptic drugs.

Table S8. ***Analysis of the factors associated with changes in living status at the end of the study period***

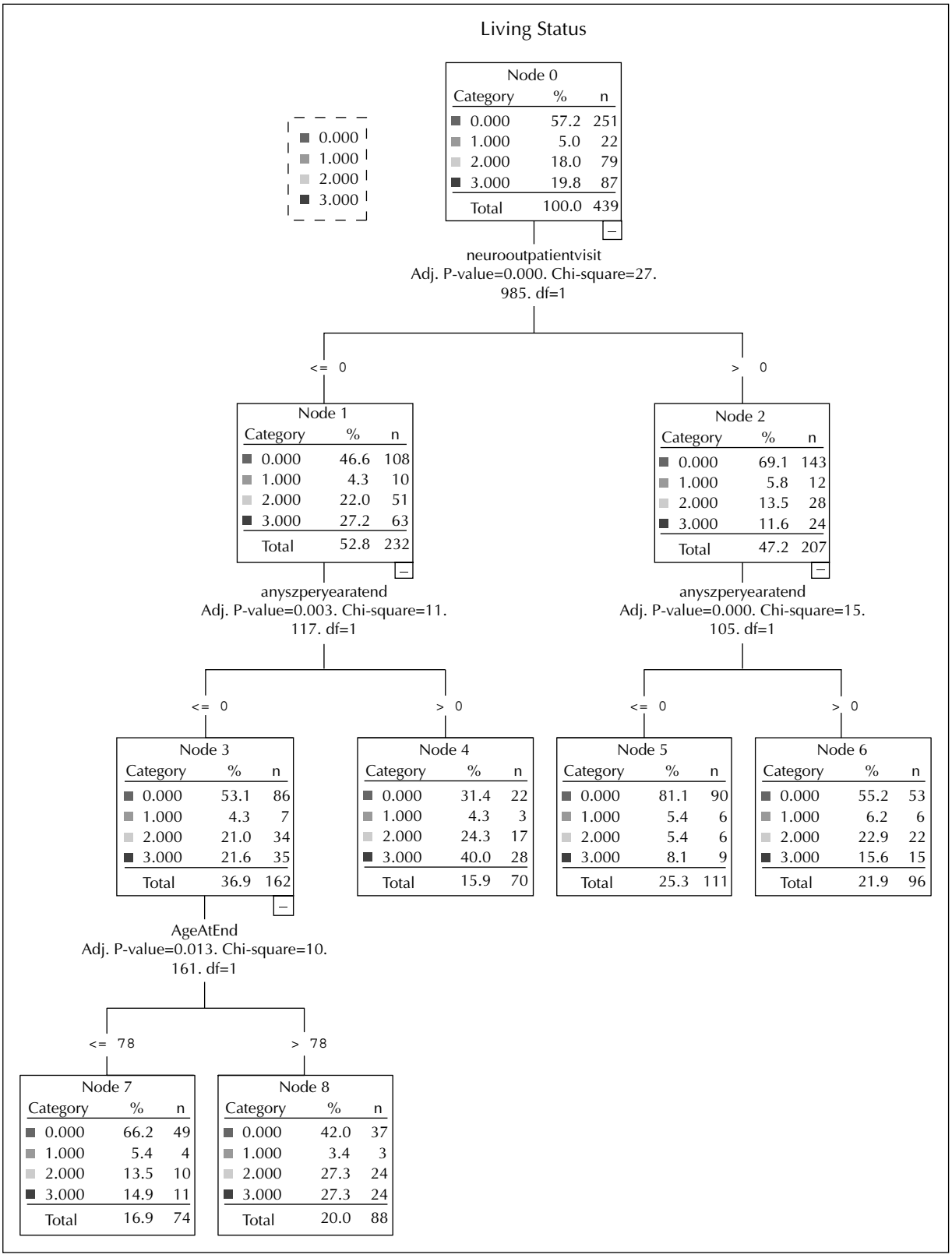

Table S9. ***Results of logistic regression of factors on the outcome variable describing whether the patient's living status deteriorated or not during the study period***
Relative risks < 1 indicate the factor produces worse outcomes (only patients with study duration > 3 years). p to enter 0.01 p to remove 0.05; 74% correct classification.

Factor	Relative risk	95% CI	p
Age	0.90/year	0.86-0.95/year	< 0.001
Neuro outpatient visit	3.2	1.7-5.8	< 0.001
Renal	0.26	0.12-0.56	0.001
Neuropathy	13.7	1.6-116	0.016
Acute	0.24	0.12-0.49	< 0.001
>0 sz/year at end	0.40	0.21-0.26	0.005

There are a number of limitations inherent in this study. One is the lack of complete information describing the patient's seizures in the medical record. Despite this, elements of the patient history such as living status, medications, allergies, listings of general medical problems and physician visits are all very well documented in the electronic medical record. This may lead to an underestimate of AED side effects and problems with seizure frequency assessment but would have only minor effects on the relationship between subspecialty care and patient outcome.

Another major problem lies in the complexity of the data set. Because there are a large number of possible complex interrelations between the factors in this study, it is possible that statistical studies may reveal relationships between two factors that are not due to the direct influence of one factor on the other but related to the effect of a third factor on the other two factors. For example, the relationship between the presence of neuropathy and improved outcomes may be related to the fact that patients with neuropathy and epilepsy were more likely to have seen a neurologist than patients with epilepsy or it may be that patients with neuropathy are more likely to have chronic epilepsy (if the neuropathy is induced by long term exposure to antiepileptic drugs) and hence have better outcomes. Another explanation is that patients who saw a neurologist were more likely to be diagnosed with neuropathy. Multivariable analyses such as logistic regression, multiple linear regression and the classification tree analysis do account in some ways for the relationships between the dependent variables and hence provide better measures of true dependence than univariable analyses such as the Spearman rank correlation. Although these methods cannot completely control for all of effects discussed above, the best insight into the factors responsible for an effect comes when there is an agreement between the results obtained using different types of analysis. For this reason, more sophisticated analyses applied to this and other data sets would be helpful in confirming the results suggested in this study. Yet another issue is the age range chosen in this study. Choosing a lower age cutoff could substantially change the "living status" of the patient group and the number of patients in supervised care settings.

The effect of the retrospective nature of this study also needs to be addressed. Clearly a prospectively designed study will have significant advantages over a retrospective study in terms of a developing a clearer understanding of why certain AED changes were made, rather than just using statistical relations to suggest causation. It would also be helpful in extracting those specific elements in the clinical care decisions that lead to better outcomes. This retrospective study provides the essential framework needed to design further studies to address these important questions. It is also important to note that there could also be limitations in a prospective study. One of the critical elements of this study involves the practice patterns of physicians taking care of complex patients with epilepsy. These practice patterns since they are not standardized can vary substantially in response to various factors such as patient load, physician interest, and physician education. Involving the treating physicians in a prospective study might change practice patterns and hence change the outcome under study. □

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