EARLY IDENTIFICATION OF REFRACTORY EPILEPSY

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ABSTRACT

Background More than 30 percent of patients with epilepsy have inadequate control of seizures with drug therapy, but why this happens and whether it can be predicted are unknown. We studied the response to antiepileptic drugs in patients with newly diagnosed epilepsy to identify factors associated with subsequent poor control of seizures.

Methods We prospectively studied 525 patients (age, 9 to 93 years) who were given a diagnosis, treated, and followed up at a single center between 1984 and 1997. Epilepsy was classified as idiopathic (with a presumed genetic basis), symptomatic (resulting from a structural abnormality), or cryptogenic (resulting from an unknown underlying cause). Patients were considered to be seizure-free if they had not had any seizures for at least one year.

Results Among the 525 patients, 333 (63 percent) remained seizure-free during antiepileptic-drug treatment or after treatment was stopped. The prevalence of persistent seizures was higher in patients with symptomatic or cryptogenic epilepsy than in those with idiopathic epilepsy (40 percent vs. 26 percent, $P=0.004$) and in patients who had had more than 20 seizures before starting treatment than in those who had had fewer (51 percent vs. 29 percent, $P<0.001$). The seizure-free rate was similar in patients who were treated with a single established drug (67 percent) and patients who were treated with a single new drug (69 percent). Among 470 previously untreated patients, 222 (47 percent) became seizure-free during treatment with their first antiepileptic drug and 67 (14 percent) became seizure-free during treatment with a second or third drug. In 12 patients (3 percent) epilepsy was controlled by treatment with two drugs. Among patients who had no response to the first drug, the percentage who subsequently became seizure-free was smaller (11 percent) when treatment failure was due to lack of efficacy than when it was due to intolerable side effects (41 percent) or an idiosyncratic reaction (55 percent).

Conclusions Patients who have many seizures before therapy or who have an inadequate response to initial treatment with antiepileptic drugs are likely to have refractory epilepsy. (N Engl J Med 2000;342: 314-9.)

EPILEPSY is estimated to affect approximately 50 million people worldwide.[1] Although the prognosis for the majority of patients is good,[2] up to 30 percent do not have remission despite appropriate therapy with antiepileptic drugs[3-5]; the results are substantial deleterious effects on individual health and quality of life and a heavy burden on society.[6] The characteristics of this group of patients are ill defined, but possible unfavorable prognostic factors include an early onset of epilepsy and the presence of symptomatic or cryptogenic epilepsy, multiple types of seizures, large numbers of seizures before treatment, complex febrile seizures or febrile status epilepticus, and generalized epileptiform activity on surface electroencephalography.[7,8] In the 1990s, eight new antiepileptic drugs were licensed worldwide,[9] some of which are now available for monotherapy. We conducted a prospective observational study of patients who were given a diagnosis of epilepsy, treated, and followed up at a single center in which we evaluated their response to antiepileptic-drug therapy and attempted to determine the factors associated with a poor response to therapy.

METHODS

Patients

The study included 525 consecutive unselected children, adolescents, and adults in whom epilepsy was diagnosed and antiepileptic-drug therapy begun at the Epilepsy Unit of the Western Infirmary in Glasgow, Scotland, between January 1, 1984, and December 31, 1997. Most of the patients were referred to the unit by primary care physicians, but a minority (8 percent) were referred from the hospital's accident and emergency department.[10] During the first visit, we used a structured questionnaire to collect demographic and clinical information from the patients and any witnesses to the seizures and performed a general physical and neurologic examination.[11] Additional studies were carried out as clinically indicated. A neurophysiologist performed surface electroencephalography, either using a standard approach or testing the patients after sleep deprivation, to look for interictal changes that might aid in the diagnosis, help to identify the seizure focus, and facilitate the classification of the epilepsy. Neuroimaging, particularly computed tomography or magnetic resonance imaging, was performed by a neuroradiologist to screen for underlying structural abnormalities that might have caused the epilepsy. Information obtained from the history, physical examination, and other studies was used to classify the patient's epilepsy, since the type of epilepsy has implications for prognosis and the approach to treatment.

Approach to Treatment

For all patients who were given a diagnosis of epilepsy, the appropriate antiepileptic drug was chosen after discussion among the clinicians, taking into account the type of seizures and other characteristics and the efficacy, side effects, and interaction profiles of the available drugs.[12] Some patients volunteered to participate in randomized studies, in which case the antiepileptic drug administered remained unknown to both the clinicians and the patients during the study period. Protocols for all drug trials were

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approved by the ethics committee of the Western Infirmary, and all patients or their parents or legal guardians provided written informed consent.

Patients were subsequently evaluated at the epilepsy clinic every four to six weeks for the first six months and at least every four months thereafter. If medical attention was necessary between scheduled appointments, the patients or their primary care physicians could call the epilepsy unit by using a dedicated telephone line. At each follow-up visit, clinical information and the response to antiepileptic-drug therapy were recorded. Compliance was monitored at the clinic,[13] since poor compliance is a common cause of treatment failure in patients with epilepsy.[8] Patients who persistently did not comply with the treatment regimen were excluded from the study at the time of analysis.

Drug doses were adjusted as clinical circumstances dictated, with particular attention paid to efficacy and tolerability. Patients were treated with a single drug when possible, as is recommended practice.[5] Treatment was changed to another drug if seizures remained uncontrolled or if the patient had an idiosyncratic reaction or intolerable side effects. A combination of drugs was used in patients whose epilepsy remained uncontrolled despite treatment with two or three single drugs. Patients whose epilepsy was the result of a possibly remediable lesion, such as mesial temporal sclerosis, a tumor, or arteriovenous malformation, were referred for surgery.[14,15]

Definitions

The types of seizures and epileptic syndromes were classified according to the guidelines of the International League against Epilepsy.[5,16-19] Seizures were classified as generalized convulsive (e.g., tonic, clonic, or tonic–clonic) or nonconvulsive (e.g., absence or myoclonic) or as partial (focal), depending on the clinical presentation and the results of the studies described above. The epilepsy was classified as idiopathic, symptomatic, or cryptogenic, according to the putative cause and depending on such factors as the age of the patient, the type of seizure, the presence or absence of a family history of epilepsy, and the presence or absence of an underlying neurologic lesion. Patients with a particular type of epilepsy may have more than one type of seizure. Idiopathic epilepsy, such as childhood absence epilepsy and juvenile myoclonic epilepsy, is presumed to have a genetic origin. Symptomatic epilepsy is considered to be the consequence of a known structural abnormality, such as mesial temporal sclerosis, cortical dysplasia, arteriovenous malformation, stroke, or cerebral palsy. Cryptogenic epilepsy is presumed to be due to an underlying but unidentified focal abnormality on the basis of clinical information and study results.

Patients were considered to be free of seizures if they had not had seizures of any type for a minimum of one year while receiving the same dose of antiepileptic drug or while not taking any medication. Patients who had seizures were, by definition, considered to have refractory epilepsy. The extent of control of seizures was assessed at the time of the patient's last clinic visit.

Statistical Analysis

Patients were divided into two groups for purposes of comparison according to whether or not they were seizure-free during follow-up. We used the chi-square test for comparisons of categorical data and the Mann–Whitney test for comparisons of nonparametric continuous data. We used the chi-square test for trend to assess the effect of the number of seizures before treatment on the outcome. Potential interaction between factors was examined by logistic-regression analysis. All statistical tests were two-tailed. Statistical calculations were performed with use of Minitab for Windows software (version 11.21).

RESULTS

Characteristics of the Patients

Overall, 629 of the 3209 patients who were referred to the clinic between January 1, 1984, and December 31, 1997, were not being treated at the time of referral. They included patients who had not previously been given a diagnosis of epilepsy and those in whom antiepileptic-drug treatment had been withdrawn. Eight patients died from a variety of causes during treatment, 74 did not return for follow-up after treatment with the first antiepileptic drug was started, and 22 were excluded because of uncertainty about the diagnosis or persistent noncompliance with treatment. The remaining 525 patients (52 percent of whom were male) constituted the study group. Among them, 470 patients had never received antiepileptic-drug therapy (Fig. 1). The median duration of follow-up was 5 years (range, 2 to 16), and 90 percent of the patients attended the clinic for at least 3 years. The median age at referral was 29 years (range, 9 to 93), and the median age at the onset of epilepsy was 26 years (range, <1 to 92) (Table 1). There was no significant difference in sex, age at referral or the onset of seizures, prevalence of a family history of epilepsy, or prevalence of a history of febrile convulsions between the group that became seizure-free and the group with uncontrolled epilepsy (Table 1).

Effects of Treatment

At the time of the last clinic visit, 333 patients (63 percent) were seizure-free (Fig. 1). Among the 55 patients who had previously received one or more antiepileptic drugs, 56 percent became seizure-free, as compared with 64 percent of the patients who had not been previously treated. Among the previously treated patients, the prognosis was better in the 38 patients whose previous antiepileptic-drug therapy had been withdrawn after a seizure-free period of at least two years (66 percent were seizure-free at the end of the study) than in the 17 patients in whom therapy was discontinued for other reasons (35 percent were seizure-free at the end of the study), such as lack of efficacy or intolerable side effects. The 55 patients who had previously received antiepileptic drugs were included in the analysis of other factors associated with refractory epilepsy, with the exception of the analysis of the response to the first antiepileptic drug.

Classification of Epilepsy

One hundred forty patients (27 percent) were classified as having idiopathic epilepsy, 150 (29 percent) as having symptomatic epilepsy, and 235 (45 percent) as having cryptogenic epilepsy. A higher proportion of patients with symptomatic or cryptogenic epilepsy continued to have seizures during treatment than of patients with idiopathic epilepsy (40 percent vs. 26 percent, $P=0.004$; relative risk, 1.5; 95 percent confidence interval, 1.1 to 2.1). There was no significant difference between the proportion of patients with symptomatic epilepsy and the proportion with cryptogenic epilepsy who continued to have seizures (43 percent vs. 39 percent). There was a sig-

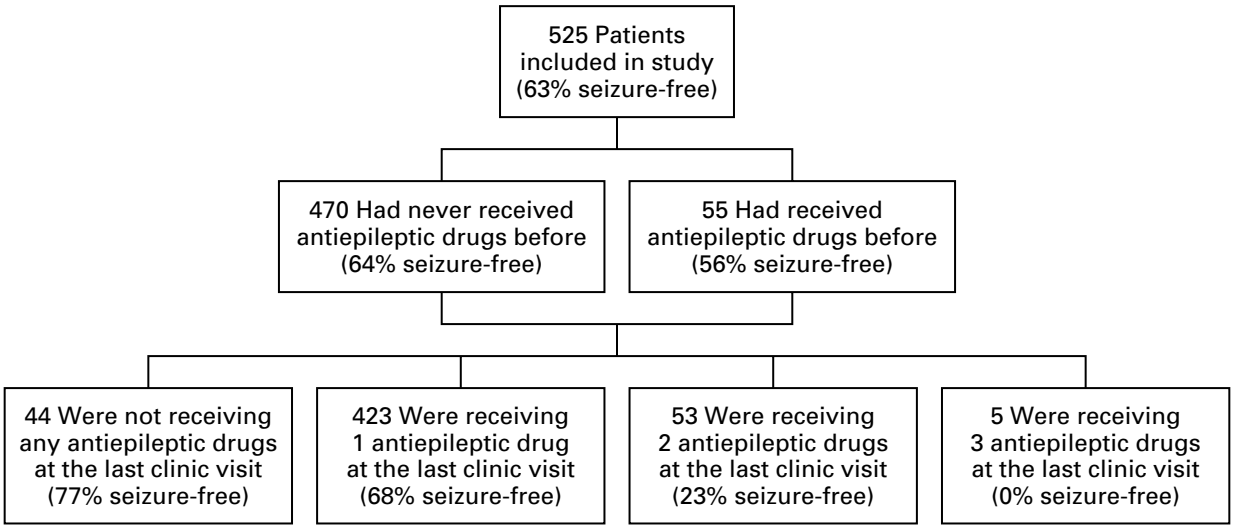

Figure 1. Outcome in 525 Children, Adolescents, and Adults Who Received Antiepileptic-Drug Therapy.
The status of patients at the time of the last clinic visit is given in parentheses.

TABLE 1. CLINICAL CHARACTERISTICS OF 525 PATIENTS WITH EPILEPSY ACCORDING TO WHETHER THEY BECAME SEIZURE-FREE OR HAD PERSISTENT SEIZURES WHILE RECEIVING ANTIEPILEPTIC DRUGS.

CHARACTERISTIC	PATIENTS WHO WERE SEIZURE-FREE (N=333)	PATIENTS WITH UNCONTROLLED EPILEPSY (N=192)
Sex — no. (%)		
Male	157 (47)	102 (53)
Female	176 (53)	90 (47)
Age at onset — yr		
Median	25	26
Range	<1–92	1–75
Age at referral — yr		
Median	27	31
Range	9–93	13–76
Family history of epilepsy — no. (%)		
Yes	74 (22)	44 (23)
No	259 (78)	148 (77)
History of febrile convulsions — no. (%)		
Yes	16 (5)	10 (5)
No	317 (95)	182 (95)
Type of epilepsy — no. (%)		
Idiopathic	103 (31)	37 (19)
Symptomatic	86 (26)	64 (33)
Cryptogenic	144 (43)	91 (47)
No. of seizures at base line — no. (%)		
≤20	242 (73)	98 (51)
>20	91 (27)	94 (49)

nificant linear trend in the proportion of patients with uncontrolled epilepsy in relation to the number of seizures before treatment ($P<0.001$) (Fig. 2), even after the exclusion of patients who had only one seizure before treatment ($P<0.001$). Epilepsy was uncontrolled in 94 of the 185 patients (51 percent) who reported having more than 20 seizures before the initiation of therapy, as compared with 98 of the 340 patients (29 percent) who had 20 seizures or fewer ($P<0.001$; relative risk, 1.8; 95 percent confidence interval, 1.4 to 2.2). Logistic-regression analysis revealed no significant interaction between the type of epilepsy and the number of seizures before treatment.

Antiepileptic-Drug Therapy

Four hundred twenty-three patients (81 percent) were being treated with a single antiepileptic drug at the last clinic visit; 289 were receiving an established drug (155 were receiving carbamazepine, 125 valproate sodium, 8 phenytoin, and 1 ethosuximide), and 134 were taking one of the newer antiepileptic drugs (99 were receiving lamotrigine, 15 gabapentin, 7 oxcarbazepine, 9 tiagabine, 3 topiramate, and 1 vigabatrin). There was no significant difference in seizure-free rates between the groups (67 percent vs. 69 percent). Overall, 70 patients tried combination therapy. Fifty-three were being treated with two antiepileptic drugs at the time of the last clinic visit, of whom only 12 (23 percent) were seizure-free (Fig. 1). None of the five patients who were receiving three antiepileptic drugs at the time of the last clinic visit were seizure-free. Forty-four patients had chosen not to continue treatment with antiepileptic drugs, some after a period of remission (39 percent), some because of side

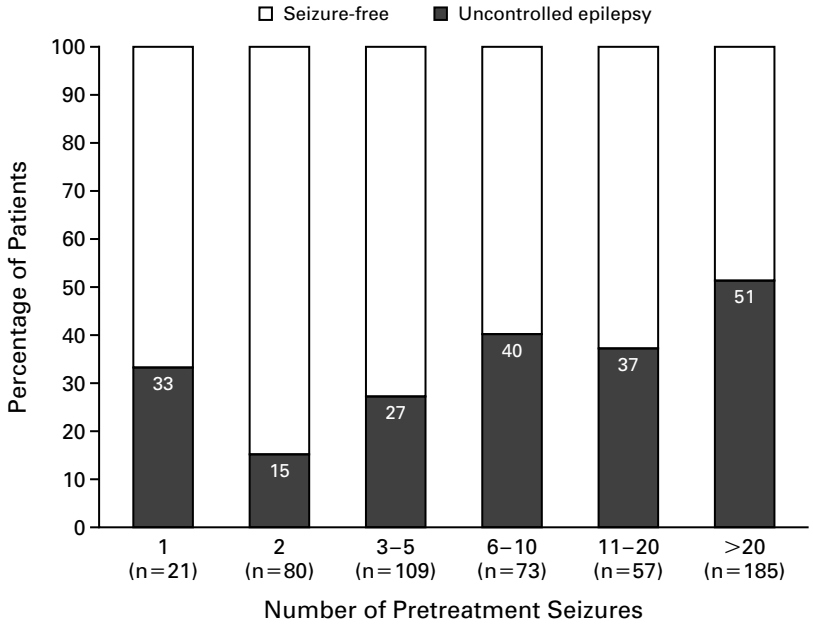

Figure 2. Outcome in Patients According to the Number of Seizures before Treatment.
The percentages of patients with uncontrolled epilepsy are shown within the bars ($P<0.001$ for the comparison with patients who were seizure-free).

effects (48 percent), and the remainder for personal reasons (13 percent). Thirty-four of these patients (77 percent) had been seizure-free for more than a year.

One hundred ninety-five patients were enrolled in double-blind studies comparing an established antiepileptic drug with a new drug. Of the 104 patients (53 percent) who completed such a study (38 received carbamazepine, 13 valproate sodium, 30 lamotrigine, 5 gabapentin, 5 oxcarbazepine, 12 tiagabine, and 1 felbamate), there was no significant difference in the seizure-free rate between the patients who received an established drug and those who received a new drug (71 percent vs. 66 percent). All but four of the patients continued to be seizure-free while receiving the same drug after the study ended. The majority of the 91 patients who did not complete those studies (59 percent) withdrew because of side effects. The interpretation of data on outcomes was limited by the fact that the assigned drug remained unknown in the case of some of these patients. However, 62 percent of the patients (120 of 195) who participated in studies of single drugs became seizure-free, a value that was similar to that for the rest of the cohort, suggesting that there was no bias in the selection of patients for these studies.

Efficacy of First Drug

Among the 470 patients who had never before received an antiepileptic drug, 301 (64 percent) became seizure-free during treatment. In 222 patients (47 percent), epilepsy was controlled by the first antiepileptic drug, which was an established drug in the case of 151 patients and a new drug in the case of 71 patients (Fig. 3 and Table 2). Fifteen of these 222 patients remained seizure-free after the discontinuation of the drug. The seizure-free rates were the same whether a new or an established drug was given. Sixty-seven of the 470 patients (14 percent) became seizure-free during treatment with a second or third drug. In 12 patients (3 percent of the total population) epilepsy was controlled by treatment with two drugs (Table 2).

One hundred thirteen patients discontinued their first drug because of lack of efficacy; 69 because of intolerable side effects; 29 because of idiosyncratic reactions, such as rash and hepatotoxicity; and 37 for other reasons, including concern about potential adverse effects, planning a pregnancy, and a change of mind about drug treatment (Fig. 3). Only 79 of these 248 patients (32 percent) subsequently became seizure-free. The outcome among these patients was strongly associated with the reason for the failure of treatment with the first drug ($P<0.001$) (Fig. 3). Sixteen of the patients with an idiosyncratic reaction (55 percent) subsequently became seizure-free, as did 28 of the patients with intolerable side effects (41 percent), but only 12 of the patients in whom treatment with the first drug was ineffective (11 percent) subsequently became seizure-free.

DISCUSSION

In our study, the overall rate of remission of seizures of 63 percent was similar to that in several hos-

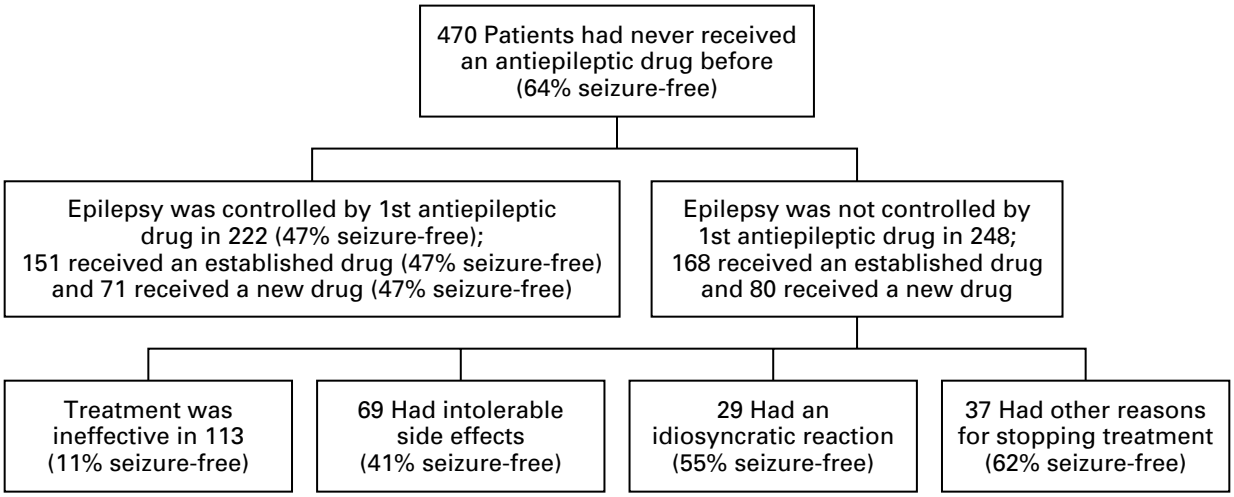

Figure 3. Outcome in 470 Previously Untreated Patients.
The status of patients at the time of the last clinic visit is given in parentheses.

TABLE 2. SUCCESS OF ANTIEPILEPTIC-DRUG REGIMENS IN 470 PATIENTS WITH PREVIOUSLY UNTREATED EPILEPSY.

VARIABLE	NO. (%)
Response to first drug	222 (47)
Seizure-free during continued therapy with first drug	207 (44)
Remained seizure-free after discontinuation of first drug	15 (3)
Response to second drug	61 (13)
Seizure-free during monotherapy with second drug	41 (9)
Remained seizure-free after discontinuation of second drug	20 (4)
Response to third drug or multiple drugs	18 (4)
Seizure-free during monotherapy with third drug	6 (1)
Seizure-free during therapy with two drugs	12 (3)
Total	301 (64)

pital-based studies.[20-25] As in previous studies,[21,24-28] patients in our study who had a known or probable structural cerebral abnormality were 1.5 times as likely to have refractory disease as those with idiopathic epilepsy. A large number of seizures before treatment was a poor prognostic indicator, an observation that has also been made previously.[20,28] It is tempting to attribute the association between a high number of pretreatment seizures and later intractability to the experimental phenomenon of kindling, whereby electrical stimulation at what is initially a subconvulsive level in an animal subsequently becomes sufficient to induce seizures.[29] However, in a recent multicenter Italian study, initiation of treatment after the first seizure did not improve the long-term prognosis.[30] In addition, in a study of children with epilepsy, the initiation of treatment after 10 or fewer seizures did not influence the remission rate.[31] It seems more likely, therefore, that a large number of seizures before treatment is the result, rather than the cause, of the pathophysiologic changes that are later manifested as refractory epilepsy.[32]

Our finding that many patients were seizure-free while taking a single antiepileptic drug is in agreement with the consensus that monotherapy is a realistic goal for most patients[5] and, indeed, that the overall prognosis of epilepsy is good.[2,33-35] It is reinforced by the observations that 47 percent of the patients who had not previously received an antiepileptic drug became seizure-free during treatment with the first drug and that 77 percent of those who stopped treatment remained seizure-free.

The rates of remission were similar in patients who received an established antiepileptic drug and those who were treated with a new antiepileptic drug. In randomized, double-blind trials comparing carbamazepine with lamotrigine, there was no difference in efficacy between the two drugs, although fewer side effects and lower dropout rates were reported among patients who were treated with lamotrigine.[36,37]

An early response to drug therapy confers a favorable prognosis.[20,21,27,33] Our results suggest that the response to the first antiepileptic drug is also a powerful prognostic factor. This factor was particularly useful among patients in whom treatment with the first drug was ineffective; only 11 percent of such pa-

tients subsequently became seizure-free, as compared with 41 percent of the patients who had intolerable side effects and 55 percent of those with an idiosyncratic reaction. Among the patients who had no response to the first antiepileptic drug, 14 percent became seizure-free when treatment was changed to another drug, but only 3 percent became seizure-free while taking two drugs.

Our observations may be useful in devising more effective therapy for patients with refractory epilepsy. They reinforce the assertion that for patients with correctable structural abnormalities, surgery should be considered as soon as treatment with two first-line drugs fails.[14,15] In selected groups of patients, this approach can render up to 80 percent of patients seizure-free. For the majority of patients, in whom epilepsy cannot be cured by surgery, antiepileptic drugs remain the mainstay of treatment. Our finding that only 3 percent of patients became seizure-free while taking more than one drug highlights the need to combine drugs in a more rational fashion by taking into consideration their mechanisms of action.[38,39]

Our findings offer support for the hypothesis that some patients have refractory epilepsy at the outset. Refractory epilepsy may be present from the beginning rather than evolve over time, since the clinical characteristics of this type are apparent early in the course of disease. Such patients are more likely to have underlying structural cerebral abnormalities, to have had more than 20 seizures before treatment is initiated, and to have an inadequate response to the first antiepileptic drug prescribed. Perhaps the drug has limited access to the epileptic focus but not to the rest of the brain, as a result of the differential expression of drug transporters at the blood–brain barrier,[40,41] and thus cannot fully exert the desired pharmacologic effect without neurotoxicity.

In conclusion, our findings indicate that some patients with refractory epilepsy can be identified early in the course of disease and can thus be targeted for rational combination therapy or surgery.

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