

INTRACTABLE EPILEPSY: RELAPSING, REMITTING, OR PROGRESSIVE?

Seizure Remission and Relapse in Adults with Intractable Epilepsy: A Cohort Study. Choi H, Heiman G, Pandis D, Cantero J, Resor SR, Gilliam FG, Hauser WA. *Epilepsia* 2008;49(8):1440–1445. **PURPOSE:** To investigate the cumulative probabilities of ≥ 12 month seizure remission and seizure relapse following remission, and to test the associations of clinical characteristics with these two study end points in a prevalence cohort of intractable adult epilepsy patients during medical management. **METHODS:** A retrospective cohort study of intractable epilepsy patients seen in 2001 at a single center was conducted. Kaplan–Meier analysis was used to estimate the cumulative probabilities of seizure remission and subsequent seizure relapse. Cox proportional hazards models were used to estimate the association (1) between clinical factors and ≥ 12 month seizure remission and (2) between clinical factors and seizure relapse following remission. **RESULTS:** One hundred eighty-seven subjects met the eligibility criteria for intractable epilepsy. The estimate of probability of remission was about 4% per year. Seizure remission was temporary for some individuals, as 5 out of 20 subjects with remission ultimately relapsed. No clinical factors predicted the likelihood of achieving ≥ 12 month seizure remission or subsequent seizure relapse. **DISCUSSION:** Some people with intractable epilepsy achieve ≥ 12 month seizure remission during medical treatment. Remission, however, is only temporary for some individuals. We were unable to identify clear predictors for remission.

Quantifying the Response to Antiepileptic Drugs: Effect of Past Treatment History. Schiller Y, Najjar Y. *Neurology* 2008;70(1):54–65. **OBJECTIVE:** To quantify the response to treatment with antiepileptic drugs (AEDs) as a function of the past treatment history and identify additional prognostic factors for predicting the response to newly administered AED treatments. **METHODS:** A cohort of 478 consecutive patients who received newly administered AED treatments between January 1999 and December 2004 and were followed prospectively for 1.5 to 7.5 years in a single epilepsy clinic. **RESULTS:** The response to newly administered AED treatments was highly dependent on the past treatment history. The seizure-free rates decreased from 61.8% for the first AED to 41.7%, 16.6%, and 0% after one, two to five, and six to seven past AEDs proved inefficient. This response curve corresponded to a mono-exponential function with a maximal response of 61.8% and half-decay constant of 1.5 AEDs. Likewise the response curve describing a greater than 50% reduction in seizure frequency corresponded to a mono-exponential function with a maximal response of 85.3% and half-decay constant of two AEDs. Three additional independent prognostic factors for predicting the response to AEDs were identified: type of epilepsy, duration of epilepsy, and number of seizures in the 3 months prior to AED initiation. **CONCLUSION:** Drug resistance is a graded process that follows a mono-exponential course with a half-decay constant of 1.5 to two antiepileptic drugs (AEDs). Although relative drug-resistant epilepsy can be diagnosed after failure of two past AEDs, absolute drug resistance requires failure of six AEDs, as a significant minority of patients (16.6%) is rendered seizure-free by addition of newly administered AEDs even after failure of two to five past antiepileptic drugs.

COMMENTARY

Drug-resistant (i.e., pharmacoresistant, refractory, or medically intractable) epilepsy is defined as failure to achieve seizure control despite adequate trials of antiepileptic drug (AED) therapy. While approximately 30% of all patients with epilepsy are estimated to have drug-resistant epilepsy, studies have not utilized a consistent definition of drug resistance, limiting comparison across studies (1). The new International League Against Epilepsy (ILAE) consensus definition of drug-resistant epilepsy requires “failure of two tolerated, appropriately chosen and used antiepileptic drug schedules to achieve

sustained seizure freedom” (i.e., either 12 months or three times the longest interseizure interval) (2).

Several recent studies have examined prognosis for remission in adults with intractable epilepsy. Luciano and Shorvon found that 43 of 155 (28%) patients had ≥ 12 -month seizure remission after introduction of a new AED (3). They included patients with seizure frequency that was greater than one seizure per month and epilepsy duration ≥ 5 years but did not specify a minimum number of prior AED trials. Idiopathic epilepsy, shorter duration of epilepsy, and fewer than five failed AED trials were associated with remission. Callaghan et al., in a retrospective study of 246 adult patients with intractable epilepsy (i.e., greater than one seizure per month and failed at least two prior AED trials), reported an approximately 5% per year rate of 6-month terminal remission (4). Among their patients,

a history of status epilepticus, long duration of intractability, greater than six prior AED trials, and mental retardation were associated with a lower likelihood of seizure remission.

The two complementary studies, reviewed here, provide new information about long-term prognosis in patients with drug-resistant epilepsy. Choi et al. retrospectively studied 187 patients with intractable epilepsy over a mean of 3.8 years. Included patients were older than 18 years, had failed at least 2 adequate trials of AEDs, and had at least 1 seizure per month for 3 consecutive months. A total of 20 of 187 subjects (10.7%) achieved ≥ 12 months of complete seizure remission. The Kaplan–Meier estimate of the cumulative probability of ≥ 12 -month seizure remission was 18% at 5 years. Seizure remission was temporary in some subjects; of the 20 subjects who achieved remission, 5 (25%) had a subsequent seizure relapse, with estimated cumulative probability 33% at year 2, and 44% at year 3 following remission. No clinical factors, including history of epilepsy surgery, status epilepticus, age of onset, epilepsy syndrome classification, mental retardation, febrile seizure, symptomatic etiology, mesial temporal sclerosis, duration of epilepsy, or number of failed AEDs (≥ 5) predicted either a 12-month seizure remission or a subsequent relapse.

Schiller and Najjar prospectively studied a cohort of 429 patients receiving new AEDs. Intractable epilepsy (defined as failure of 2 or more AEDs) accounted for 212 (49.4%) of the cohort. Similar to the findings of Choi et al., a significant fraction of intractable patients entered a 12-month remission. The major factor determining treatment response (i.e., seizure free > 12 months) was the number of prior failed AED trials. Rates of seizure remission declined gradually, with 61.8% becoming seizure-free after the first AED, 41.7% after the second AED, 16.6% after two to five AEDs, and 0% after six to seven AEDs. Response rates showed a gradual decline with each new AED trial: for every 1.5 ineffective AEDs, the likelihood of seizure freedom decreased by 50% and eventually reached 0%. A similar decline in response rates was seen for improvement in seizure control (defined as $\geq 50\%$ reduction in seizure frequency), although 25 to 30 percent of patients continued to show improvement even after more than seven failed AED trials. These findings suggest that intractability may not be an all-or-none phenomenon, but may gradually develop over time.

Several important questions about prognosis remain unanswered. The Choi et al. and Schiller and Najjar studies included patients with multiple different epilepsy syndromes, limiting the ability to counsel an individual patient regarding prognosis. Many studies include only intractable patients with high baseline seizure rates. What happens to other patients with intractable epilepsy, those whose seizure frequency does not meet the stringent inclusion criteria of at least one seizure per month? In Choi's study, 71% of 1,308 subjects did not meet seizure-frequency inclusion criteria; it is not clear what proportion of these subjects were seizure free at the index date versus exper-

encing rarer seizures. Schiller and Najjar found that baseline seizure frequency independently predicted outcome; remission rates in patients experiencing > 10 seizures in a 3-month baseline were lower than in those with less frequent seizures. While some patients have more seizures when AEDs are changed, neither study addresses the issue of deterioration in seizure control. Over the long term, does the chance for a modest reduction in seizure frequency outweigh the risk of seizure worsening or adverse effects of a new AED? A 50% decrease in seizure frequency may not represent significant improvement from the patient's point of view. While seizure freedom was associated with improvement in quality-of-life measures in a short-term AED study, a $\geq 50\%$ decrease in seizure frequency did not have a measurable impact on quality of life (5).

Several recent studies have concluded that the prognosis of intractable epilepsy may not be as "dismal" as previously thought, since each year a small proportion of patients achieves seizure freedom (3,4). The two current studies cited here suggest that patients rarely achieve seizure freedom once multiple AEDs have failed and that seizure control may not be permanent even for the small proportion who do enter remission. A central tenet of epilepsy treatment has been "no seizures and no side effects." For many intractable patients, seizure freedom is an elusive and perhaps unattainable goal, given current treatment options. With nearly 20 major AEDs now available for the treatment of epilepsy, there are literally hundreds of potential AED regimens. Many patients become caught up in an interminable cycle of near-futile AED additions and substitutions.

How can the findings from these studies be translated into clinical practice? First, for patients who have failed two to five AEDs, there is a small but definite benefit from additional AED trials. In the Choi et al. study, almost all (17/20) of the individuals achieving remission had undergone a medication change (usually addition of a new AED) within the 3 months prior to the start of their remission. Similarly, Schiller and Najjar found that most patients achieved remission within 4 months of initiation of a new AED. Spontaneous remission, without a change in therapy, is unlikely to occur. Second, as mentioned, substantial improvement in seizure control (i.e., $\geq 50\%$ reduction) may be achieved even after multiple failed AEDs. Thus, while AEDs are often discarded because they did not make the patient completely seizure free, careful attention to which drugs provided the most benefit may warrant reintroduction of these failed therapies. Finally, patients with intractable epilepsy should be aggressively evaluated to determine if they are candidates for epilepsy surgery. Even for the most difficult surgical populations, such as nonlesional extratemporal epilepsy (6), the reported rates of 12-month seizure freedom (30–40%) exceed the 5-year estimate of 12-month seizure freedom seen in Choi's study.

More importantly, the findings of these studies mandate a new approach to the study of drug-resistant epilepsy.

Well-designed, prospective, long-term observational studies of intractable epilepsy are sorely needed to improve knowledge of the natural history and pathophysiologic mechanisms of intractable epilepsy. Some patients may take years to become refractory to therapy or may have variable periods of remission (7,8). The recent ILAE definition of drug-resistant epilepsy (2) will help to standardize studies and allow comparisons across different populations at different time points. The new armamentarium of AEDs does not seem to have significantly altered the prognosis of intractable epilepsy. Mere suppression of clinical seizures is not the answer; therapies that can modify the course of disease must be developed. In the meantime, clinical research studies that address ways to improve quality of life in the face of continuing seizures are needed—focusing on reduction of seizure severity, minimization of AED side effects, and aggressive management of comorbidities.

by Susan Herman, MD

References

1. Berg AT. Identification of pharmaco-resistant epilepsy. *Neurol Clin* 2009;27:1003–1013.
2. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, Moshe SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010;51:1069–1077.
3. Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. *Ann Neurol* 2007;62:375–381.
4. Callaghan BC, Anand K, Hesdorffer D, Hauser WA, French JA. Likelihood of seizure remission in an adult population with refractory epilepsy. *Ann Neurol* 2007;62:382–389.
5. Birbeck GL, Hays RD, Cui X, Vickrey BG. Seizure reduction and quality of life improvements in people with epilepsy. *Epilepsia* 2002;43:535–538.
6. Tellez-Zenteno JF, Hernandez Ronquillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: A systematic review and meta-analysis. *Epilepsy Res* 2010;89:310–318.
7. Berg AT, Langfitt J, Shinnar S, Vickrey BG, Sperling MR, Walczak T, Bazil C, Pacia SV, Spencer SS. How long does it take for partial epilepsy to become intractable? *Neurology* 2003;60:186–190.
8. Sillanpaa M, Schmidt D. Natural history of treated childhood-onset epilepsy: Prospective, long-term population-based study. *Brain* 2006;129:617–624.