



It's the Seizures, S#%&*D! The Tragedy of Recurring Seizures in Adults

Response to First Antiepileptic Drug Trial Predicts Health Outcome in Epilepsy.

Perucca P, Hesdorffer DC, Gilliam FG. *Epilepsia* 2011;52(12):2209–2215.

PURPOSE: Failure to respond to the initial antiepileptic drug (AED) is a predictor of increased risk of pharmacoresistant epilepsy. Whether response to the first AED also predicts adverse health outcomes is unknown. **METHODS:** This longitudinal study compared rates of major adverse health outcomes (loss of driving privileges, unemployment, divorce/separation, injury, emergency room admission, hospitalization, and death) in 33 patients who failed the first AED (cases) and 30 patients who became seizure-free with the first AED (controls). Patient data were obtained by chart review and confirmed through a structured interview with each subject at 5-7 years after starting AED treatment. We also assessed between-group differences in quality of life, depression, and adverse AED effects by using standardized instruments completed by each subject at the end of follow-up. **KEY FINDINGS:** The number of major adverse health outcomes was similarly high during the first year of AED treatment [mean \pm standard deviation (SD) 2.64 ± 0.99 for cases and 2.50 ± 1.14 for controls], but thereafter decreased to a greater extent in controls than in cases ($p < 0.001$). Controls had a higher cumulative probability of experiencing ≥ 1 year free from major adverse health outcomes compared to cases ($p = 0.002$). Two cases died during the follow-up, both of sudden unexpected death. Cases had worse quality of life ratings than controls, whereas no significant between-group differences were found for measures of depression and adverse AED effects. In a post hoc analysis limited to cases, patients who became seizure-free with subsequent AED treatments showed for the first 4 years major adverse health outcome rates similar to those recorded in patients with persisting seizures. After 4 years, however, cases who achieved late seizure freedom tended to show a more favorable outcome. **SIGNIFICANCE:** Patients with epilepsy failing the initial AED trial are at increased risk of experiencing adverse health outcomes, at least for the first 4 years after diagnosis. Incorporating these findings into clinical decision making may aid in reducing delays in surgical referrals for pharmacoresistant epilepsy.

Commentary

The report from Perucca et al. confirms the reality of what we face in the office each day: any seizure occurrence is a major risk for our adult patients. The risk is not the inconvenience of losing 15 to 30 minutes of normal functioning, but is the subtle cumulative risk of a severe social setback such as loss of employment or divorce, and the immediate, impending physical risk of injury, hospitalization, and death. In this study, the authors reviewed the course of a group of carefully selected, high-functioning adults who initiated epilepsy treatment at the Columbia Presbyterian Comprehensive Epilepsy Center. The cohort was divided into two groups: the “controls” ($n = 30$), those who were seizure-free after the first appropriate antiepileptic drug (AED); and the “cases” ($n = 33$), those who were not seizure-free. The occurrence of major adverse health outcomes per year for 5 consecutive years after starting treatment was compared between the two groups. Patients were identified through chart review, and then

were contacted to participate in the study, which included completing a structured interview and questionnaires. The major adverse health outcomes were loss of driving privileges, unemployment, divorce or separation, injury, emergency room admission, hospitalization, and death. The source of how these events were determined to be major adverse health outcomes is not cited, and they appear to have been derived by the authors. They seem appropriate, however, and interestingly encompass several severe psychosocial stressors.

Notably, the groups were well matched, with 80 to 90 percent of subjects in each group driving and employed at the time of AED initiation; not so after 5 years, especially for the “case” group. (There was no assessment of how many seizures likely occurred before AED treatment in each group. However, if there were more seizures prior to treatment in the “case” group, it would probably not change the eventual implications of this paper, since, to quote Kwan and Brodie: “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” [1].)

The major epilepsy comorbidities put forth as having as much or more adverse impact on quality of life than seizure



occurrence, such as medication side effects and mood issues, are well accounted for in this study. The Adverse Event Profile (AEP) and the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) are validated assessments for persons with epilepsy, but these scale scores did not differ between groups. And yet, the “cases” were on a generally downhill course, which was reflected in their quality of life scales. Therefore, the increased rates of major adverse health outcomes cannot be attributed to AED adverse effects or depressed mood, but rather to seizures alone.

What therefore, accounts for the relentless occurrence of major adverse events in persons with ongoing seizures, including two deaths in the “cases” but none in the “controls”? Seizures carry physical risks, legal constraints, perceived stigma by the patient, and actual stigmatizing behavior by others. Employers may have a discriminatory attitude toward people who have seizures in the workplace and yet have the responsibility to impose safety-based limitations upon them. These two stances, one clearly morally bad, the other good, become intertwined to the point where one could clearly serve the other. Relationships are strained when illness becomes part of day-to-day concerns, often triggering constant and heightened worry and hyper-vigilance on the part of family members. Not least, the financial stress of chronic illness can be overwhelming. The injuries, emergency room visits, AED trials, anxiety, fear, loss of confidence and self-esteem for the patient, and frayed nerves among family members all contribute to the risks documented in this study. These factors are hard to measure, but the message is that they could be mitigated significantly if the seizures were stopped.

We clearly need to continue to work with our patients, aiming toward seizure-freedom. This study demonstrates that this is the most important thing we can do in order to maximize the quality of life for our epilepsy patients. How can epilepsy doctors and general neurologists improve epilepsy outcomes? We can listen to our patients more carefully, review their studies more vigilantly, think more creatively regarding treatment approaches, and not settle for less than seizure-freedom unless the refractory situation is hitting us over the head. The American Academy of Neurology has put forth eight practice improvement (PI) measures for epilepsy care (2), which include

documentation of seizure type, frequency, injuries, medication side effects, and EEG and MRI results and dates on which they were performed. Further, documentation of whether the patient is well-controlled or intractable is required at every visit and consideration for surgical referral is then prompted for refractory patients. For epilepsy doctors, these PI measures seem mundane, and we perform them all the time. However, widely incorporating them into neurology practices could re-focus and crystallize the decision pathway for patients who are otherwise continuing to have seizures and for whom, in their partnership with their doctors, there is no existing strategy toward seizure-freedom.

There are many obstacles on the path toward seizure freedom. One is the continuing erosion of reimbursement for sitting and talking with a patient, to discuss treatment options. Procedures are reimbursed, not relationships. However, for epileptologists, one cannot get to the “procedure” without the “relationship.” Another more insidious problem is the perception of a toxic and unethical involvement of physicians with drug and device industries. Fruitful collaborations that could improve the chances of discovering novel compounds to treat epilepsy are currently discouraged by academia, targeted by media, and obstructed by oversight bodies. Further, there is the perception that having seizures once in a while is OK. Healthcare providers may think it is OK, but our patients certainly know that it is not.

by Cynthia L. Harden, MD

References

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314–319.
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