

TO COMPLY WITH AED THERAPY . . . WHAT PATIENTS ARE NOT TOLD!

Nonadherence to Antiepileptic Drugs and Increased Mortality: Findings from the RANSOM Study. Faught E, Duh MS, Weiner JR, Guérin A, Cunnington MC. *Neurology* 2008;71(20):1572–1578. OBJECTIVES: The primary objective was to investigate whether nonadherence to antiepileptic drugs (AEDs) is associated with increased mortality and the secondary objective to examine whether nonadherence increases the risk of serious clinical events, including emergency department (ED) visits, hospitalizations, motor vehicle accident (MVA) injuries, fractures, and head injuries. METHODS: A retrospective open-cohort design was employed using Medicaid claims data from Florida, Iowa, and New Jersey from January 1997 through June 2006. Patients aged 18 years with 1 diagnosis of epilepsy by a neurologist and 2 AED pharmacy dispensings were selected. Medication possession ratio (MPR) was used to evaluate AED adherence on a quarterly basis with MPR 0.80 considered adherent and <0.80 nonadherent. The association of nonadherence with mortality was assessed using a time-varying Cox regression model adjusting for demographic and clinical confounders. Incidence rates for serious clinical events were compared between adherent and nonadherent quarters using incidence rate ratios (IRRs) with 95% CIs calculated based on the Poisson distribution. RESULTS: The 33,658 study patients contributed 388,564 AED-treated quarters (26% nonadherent). Nonadherence was associated with an over threefold increased risk of mortality compared to adherence (hazard ratio = 3.32, 95% CI = 3.11–3.54) after multivariate adjustments. Time periods of nonadherence were also associated with a significantly higher incidence of ED visits (IRR = 1.50, 95% CI = 1.49–1.52), hospital admissions (IRR = 1.86, 95% CI = 1.84–1.88), MVA injuries (IRR = 2.08, 95% CI = 1.81–2.39), and fractures (IRR = 1.21, 95% CI = 1.18–1.23) than periods of adherence. CONCLUSION: These findings suggest that nonadherence to antiepileptic drugs can have serious or fatal consequences for patients with epilepsy.

COMMENTARY

Patients with epilepsy have a three-fold higher risk of dying than the general population (1). Some of the causes cannot be foreseen or prevented, while others, such as suicide or complications of status epilepticus that is triggered by poor antiepileptic drugs (AEDs) compliance, are causes of death that can be averted. As shown in the study by Faught and colleagues,

poor AED adherence is associated with a three-fold higher risk of dying, while an average of 12% of all deaths in people with epilepsy are caused by suicide (2).

There are several reasons, inconspicuous or not, for poor AED compliance, some with obvious solutions and others for which solutions may seem to be more elusive. For example, forgetting a treatment dose is common among people regularly taking any type of medication. The solution is obvious: use of a pillbox. High costs of medication have become a more frequent cause for poor compliance. Patients lower the dose of the AED or intentionally miss a dose to delay running out of medication.

An open discussion with patients regarding their ability to afford the prescribed AED is necessary during this period of economic crisis. Indeed, solely for financial reasons, some patients are requesting that their neurologist change the prescribed AED to generic formulations or even to first generation AEDs.

Toxicity to AEDs is one of the strongest predictors of poor quality of life among people with epilepsy (3) and ultimately becomes a cause of poor AED compliance. This problem can be easily averted by educating patients on potential adverse events at the time of prescribing a new AED and in case of their occurrence, by adjusting the AED dose or considering its replacement with another medication. Furthermore, to facilitate the identification of AED-related common adverse events, patients can be asked at each visit to complete the Adverse Event Profile, a 17-item self-report screening instrument developed specifically for patients taking this class of medications (4).

Similarly, the presence of comorbid mood disorders can contribute to poor compliance, by making patients feel hopeless/helpless about their life, seizure disorder, and futile about treatment efficacy. Mood disorders can worsen cognitive functions, including memory, which obviously will enhance the propensity to forget to take prescribed AEDs (5). Clearly, their early identification and aggressive treatment is an obvious solution to the poor compliance associated with these comorbid disorders. Given that major depressive disorders occur in the lifetime of 30% of patients with epilepsy, clinicians must screen for this condition in every patient (6). The Neurological Disorders Depressive Inventory for Epilepsy (NDDI-E), a six-item self-report screening instrument, was developed specifically to identify major depressive episodes in patients with epilepsy. It takes 3 minutes to complete. A score of greater than 15 is strongly suggestive of a positive diagnosis (7).

Among the more inconspicuous causes of poor AED compliance is the patient's difficulty accepting a diagnosis of epilepsy, particularly when denial is used as a coping mechanism to deal with the explicit obstacles and unspoken fears associated with seizures in one's life. Unspoken fears include the fear of dying as a consequence of a seizure, but more generally, may relate to the patient's loss of predictability regarding physical safety. The latter issue is frequently the first serious mental health-related consequence of an epilepsy diagnosis and may be unrecognized by patients and family members alike. Failure to come to terms with the loss of predictability can have long-term consequences. For patients, it may be expressed as avoidant behavior or present with the development of episodes of anxiety and depression, contributing to poor AED compliance. Among family members, loss of predictability can result in overprotection of the patient or rejection of the diagnosis (patients may perceive this attitude as rejection of themselves). Unfortunately, clinicians treating epilepsy seldom discuss such feelings of loss with patients, although these emotions can effec-

tively be addressed with awareness of them and encouragement to mourn the loss, just as one mourns the loss of a loved one.

Dying from a seizure is a fear that patients and family members often dare not ask about it or do not think is a potential complication of epilepsy. Furthermore, sudden unexpected death in epilepsy (SUDEP), which accounts for approximately 2% of deaths in population-based cohorts of epilepsy and up to 25% of deaths in cohorts of more severe epilepsy, is associated with poor AED compliance (8). The risk of SUDEP is seldom discussed with patients, and currently much controversy surrounds the issue of when and whether to bring it to the attention of patients. The dilemma focuses on the pros and cons of an early discussion of SUDEP with patients with epilepsy (9). Given the data from Faught's study, the risk of death associated with poor AED compliance—of which SUDEP is one potential consequence—would favor an early discussion. Furthermore, information on SUDEP is easily found on various web pages dedicated to epilepsy. Failure to prepare patients to deal with these facts carries the potential of having a devastating effect on their mental well-being. In summary, death from poor AED compliance can and should be prevented: discussions with patients must encompass the obvious and less obvious causes, which the clinician is responsible for bringing up during office visits.

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References

1. Lhatoo SD, Sander JW. Cause specific mortality in epilepsy. *Epilepsia* 2005;46:36–39.
2. Jones JE, Hermann BP, Barry JJ, Gilliam FG, Kanner AM, Meador KJ. Rates and risk factors for suicide, suicidal ideation, and suicide attempts in chronic epilepsy. *Epilepsy Behav* 2003;4:S31–S38.
3. Gilliam F, Kuzniecky R, Faught E, Black L, Carpenter G, Schrodt R. Patient-validated content of epilepsy-specific quality-of-life measurement. *Epilepsia* 1997;38:233–236.
4. Gilliam FG, Fessler AJ, Baker G, Vahle V, Carter J, Attarian H. Systematic screening allows reduction of adverse antiepileptic drug effects: a randomized trial. *Neurology* 2004;62:23–27.
5. Kanner AM. Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms and treatment. *Biol Psychiatry* 2003;54:388–398.
6. Gilliam FG, Barry JJ, Hermann BP, Meador KJ, Vahle V, Kanner AM. Rapid detection of major depression in epilepsy: a multicentre study. *Lancet Neurol* 2006;5:399–405.
7. Tellez-Zenteno JF, Patten SB, Jetté N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. *Epilepsia* 2007;48:2336–2344.
8. Tomson T, Walczak T, Sillanpaa M, Sander JW. Sudden unexpected death in epilepsy: a review of incidence and risk factors. *Epilepsia* 2005;46(suppl 11):54–61.
9. Brodie MJ, Holmes GL. Should all patients be told about sudden unexpected death in epilepsy (SUDEP)? *Pros Cons Epilepsia* 2008;49(suppl 9):99–101.