

ADVERSE ANTIEPILEPTIC DRUG EFFECTS

Adverse Antiepileptic Drug Effects: Toward a Clinically and Neurobiologically Relevant Taxonomy. Perucca P, Carter J, Vahle V, Gilliam FG. *Neurology* 2009;72(14):1223–1229. **BACKGROUND:** Adverse effects (AEs) of antiepileptic drugs (AEDs) are a major impediment to optimal dosing for seizure control. Better understanding of clinical properties of AEs is a prerequisite for systematic research of their neurobiological underpinnings. This study aimed to define specific patterns of AE occurrence and determine their clinical relevance based on their association with subjective health status. **METHODS:** Two hundred subjects with epilepsy completed validated self-report health assessments, including the Adverse Event Profile (AEP) and Quality of Life in Epilepsy Inventory (QOLIE)-89. Factor analysis was performed on the 19 AEP items to identify distinct classes of AEs. Correlations between AE class scores and QOLIE-89 scores were evaluated. Multivariate analysis was used to assess contributions of AE class scores to QOLIE-89 scores after controlling for depression and seizure frequency. Relationships between changes in AE class scores and changes in QOLIE-89 scores were also investigated in a subgroup of 62 subjects enrolled in a randomized trial. **RESULTS:** The mean number of AEs per subject was 6.5. AEs were segregated into five classes: Cognition/Coordination, Mood/Emotion, Sleep, Weight/Cephalgia, and Tegument/Mucosa. Higher scores in each AE class were associated with lower QOLIE-89 scores. Cognition/Coordination scores were the strongest predictor of QOLIE-89 scores. Improvements in Cognition/Coordination, Mood/Emotion, and Tegument/Mucosa scores were associated with improvements in QOLIE-89 scores. Improved Cognition/Coordination was the only predictor of improved QOLIE-89. **CONCLUSION:** Adverse effects (AEs) of antiepileptic drugs can be classified in five biologically plausible factors. When specific classes of AEs are identified and attempts are made to reduce them, quality of life is significantly improved.

COMMENTARY

The investigation by Perucca et al. disclosed a surprisingly high percentage (88%) of seemingly well-managed adult patients with epilepsy who indicated by questionnaire that they experienced adverse effects, which presumably were antiepileptic drug (AED) related. The investigators' cohort resembles epilepsy patients found in a typical neurology practice: 71% had focal epilepsy, which is equivalent to the 66% of epilepsy patients in an epidemiological study (1), and about 80% took only one or two AEDs. Nonetheless, per patient, a mean of 6.5 adverse events was listed.

Several publications have indicated the importance of dose-related issues in generating or preventing adverse events (2,3). The current work, incorporating a previous study (4), found that physician awareness of adverse events resulted in their subsequent reduction, likely from concurrent AED dose reduction. Quality of Life in Epilepsy-89 Inventory (QOLIE-89) scores also improved among those with an adverse event reduction. Factor analysis of the adverse event profile enabled the segregation of the events into the five classes that encompassed mental, emotional, and physical aspects. Curiously, only changes in the "Cognition/Coordination" class correlated with improved QOLIE-89 scores. However, a follow-up interval longer than the 4 months that occurred in this study could potentially reveal correlations in the other adverse event classes, as each of these components relate to aspects of life possessing an inertia for improvement.

Knowledge of the close relationship between adverse events and the AED dose has the potential to correct some management misconceptions that are commonly encountered in clinical practice. Misconceptions include: 1) assuming it is best to stop a new AED when it is associated with an adverse event; 2) thinking that there is no impact upon cognition when two or more AEDs are taken together, if each is within its therapeutic range; and 3) using a treatment plan that includes a full evaluation of an AED with stepwise increments to the maximum tolerated dose, then prescribing a maintenance dose that is one dose less than the maximum tolerated. While devoid of objective toxic signs, cognition is impaired with most AEDs taken under this system. When the clinicians help the patient to understand the adverse event/dose relationship, drugs reputed to significantly impair cognition, such as primidone, phenytoin, topiramate, can still be used by slowly introducing the agent with a purposefully low maximum dose.

Several factors may underlie the variety of adverse events reported by the patients in the study by Perucca et al. As the authors state, each adverse event class may represent dysfunction of a specific system, such as memory, motor, or mood. The mechanism of action of the AED may have an effect on which class of adverse events emerges. However, a patient's intelligence, occupation, and life goals also are likely to influence the threshold and degree of adverse events report as well as its class; for instance, a law student may report cognition problems, while a salesperson may focus more on mood-related events. The type and degree of encephalopathy that the epilepsy represents also would affect the areas of cognition prone to AED-related impairment; for example, verbal memory would tend to be

more impaired by left mesial temporal sclerosis associated with epilepsy.

As certain chronic disorders occur more commonly among persons with epilepsy, along with their therapies, they may influence incidence and class of adverse event in the future (5,6). *Diagnostic and Statistical Manual of Mental Disorders* Axis I psychiatric disorders have been found in 44 to 71 percent of patients with chronic epilepsy. Mood disorders, particularly depression, are the most prominent of these conditions and may even antedate the onset of epilepsy (7). Other disorders occurring commonly among patients with epilepsy include stroke, diabetes, and obesity. Increased sedentary behavior, to which AEDs likely contribute, and a greater tendency to smoke may underlie and aggravate such disorders (6), while their therapies may interact with AEDs and contribute to adverse events.

Nocturnal seizures, AEDs, comorbidities, and any encephalopathy that epilepsy represents can impair sleep. Sleep deprivation lowers seizure thresholds, leading to possible AED dose increases, daytime fatigue, and additional adverse events. Although effects on sleep appear to vary considerably among AEDs, the majority of these drugs either delay rapid eye movement sleep onset or decrease its percentage within the total sleep time (8). In addition, obstructive sleep apnea, a major disruptor of sleep, occurs in 10% of adult epilepsy patients as compared to 3% of the general population (6). Its management could improve sleep efficiency and reduce adverse events. In contrast, AEDs may improve sleep patterns, if they diminish or abolish seizures during sleep (9,10). Experimental enhancement of rapid eye movement sleep reduces amygdala-kindled seizure susceptibility (11).

Despite these variable and interactive components, the data from this study, confirmed by empirical clinical observation, indicate that prudent attention to potentially inimical effects of AEDs will likely improve quality of life. Surprisingly, decreased seizure incidence rates failed to influence quality of life; while, to the contrary, the importance of becoming seizure free after epilepsy surgery is significant, as measured on the QOLIE-89 (12,13). Such discrepancies reflect the marked differences among the many epilepsy syndromes with respect to seizure control, intelligence, as well as to neurological and other comorbidities. Therefore, the model developed in this study might be

individually applied to several epilepsies to clarify and enhance its usefulness.

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