Adverse antiepileptic drug effects

Toward a clinically and neurobiologically relevant taxonomy

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ABSTRACT

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. *Neurology*® 2009;72:1223-1229

GLOSSARY

AE = adverse effect; **AED** = antiepileptic drug; **AEP** = Adverse Event Profile; **BDI** = Beck Depression Inventory; **GABA** = γ -aminobutyric acid; **HRQOL** = Health-Related Quality of Life; **QOLIE** = Quality of Life in Epilepsy Inventory.

Adverse effects (AEs) of antiepileptic drugs (AEDs) are the most common impediment to achieving fully effective dosages.^{1,2} Hence, the efficacy profile of an AED cannot be uncoupled from its potential for causing toxicity and the concept of drug-resistant epilepsy cannot disregard the limitations imposed by AEs.³ AEs negatively impact quality of life,⁴ and reducing the burden of medication-related toxicity leads to significant improvements in subjective health status.⁵

A European survey of more than 5,000 patients receiving AEDs found that 88% experienced at least one AE.⁶ Furthermore, everyday practice and clinical trials indicate that patients often report simultaneously more than one AE.⁷⁻⁹ Although clinical experience suggests that certain types of AEs often cluster together, no study has investigated systematically the patterns

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Medications: Carbamazepine (Tegretol®; Novartis Pharmaceutical Corporation, East Hanover, NJ); lamotrigine (Lamictal®; GlaxoSmithKline, Research Triangle Park, NC); phenytoin (Dilantin®; Parke-Davis, New York, NY); valproate (Depakene®; Abbott Laboratories, North Chicago, IL); levetiracetam (Keppra®; UCB, Smyrna, GA).

of association of specific AEs. Defining these patterns is a necessary component of the process of understanding clinically relevant profiles of adverse AED effects, and a prerequisite for elucidating underlying neurobiological mechanisms to potentially guide development of less toxic AEDs.

Given the importance of disentangling complex interrelationships¹⁰ and uncovering latent constructs in a larger set of apparently independent variables,^{11,12} we used factor analysis to identify distinct patterns of association of AEs detected by a validated instrument¹³ in a large epilepsy sample. We also evaluated the clinical relevance of these patterns based on their relationships with subjective health status at baseline and over a prospective 4-month follow-up.

METHODS Patients and study design. The study included 200 consecutive adults with epilepsy receiving AED treatment and attending the epilepsy outpatient clinics at Washington University from February 1, 2001, to April 1, 2001. At enrollment, all subjects completed reliable and validated self-report health assessments, including the Adverse Event Profile (AEP),¹³ the Quality of Life in Epilepsy Inventory (QOLIE)-89,¹⁴ and the Beck Depression Inventory (BDI).¹⁵ A subgroup of these subjects ($n = 62$) met criteria (AEP score ≥ 45 and BDI score ≤ 12) for a prospective randomized trial on the value of using the AEP in clinical management.⁵ In this trial, subjects were randomly assigned to a group in which treating physicians had access to AEP results at each visit, or to another group in which AEP results were not made available to physicians. The two groups were followed up for 4 months. Physicians were asked to attempt to decrease AEs if this was considered feasible without causing seizure deterioration.

This study was approved by the institutional review board at Washington University. All subjects signed a written informed consent form.

Instruments. The analysis included the individual AEs of AEDs identified by the 19 items of the AEP instrument,¹³ whose reliability, validity, and sensitivity have been demonstrated in prior studies.^{5,6,16,17} In this instrument, the frequency of occurrence of a given AE during the previous 4 weeks is quantified on a 4-point Likert scale, with 1 indicating that there was never a problem; 2, rarely a problem; 3, sometimes a problem; and 4, always or often a problem. Items can be evaluated individually, or individual ratings can be summed to produce a total score. Total scores range from 19 to 76, with higher scores being indicative of a greater burden of AEs. In this analysis, an AE was considered present if its rating was 3 or 4, e.g., if it occurred “sometimes” or “always or often.”

The clinical relevance of the AE analysis was determined by association with QOLIE-89 scores ascertained at the time of the AEP assessment in each subject.¹⁶ The QOLIE-89 is a self-report measure of Health-Related Quality of Life (HRQOL),¹⁴ which contains the RAND Short Form 36¹⁸ as a generic core and 53 epilepsy-targeted items. Ratings are summarized in 17 subscales,

four domains, and a global score (QOLIE-89 score). Global scores range from 0 to 100, with higher scores indicating better HRQOL. Validity, reliability, and responsiveness to change of the QOLIE-89 have been demonstrated in a large epilepsy sample,¹⁴ and this instrument has been widely used in epilepsy studies.^{19,20}

Analysis strategy. The primary aim was to apply factor analysis theory to identify unrecognized components that underlie AEs of AEDs, using all AEP items assessed in the entire cohort ($n = 200$). This analysis was preceded by assessment of rates of occurrence of individual AEs and by explorative evaluation of bivariate correlations among AEs.

We also investigated relationships between QOLIE-89 scores and classes of AEs identified by factor analysis in the entire cohort, as well as relationships between changes in QOLIE-89 scores and change in classes of AEs in the subgroup enrolled in the randomized trial ($n = 62$). The contribution of depressive symptoms (BDI scores) and seizure frequency to these relationships was also assessed.

Statistical methods. We used the Spearman ρ to explore correlations between AEP items. A partial correlation method was used to evaluate the association of two AEP items (weight gain and headache) while controlling for use of the most commonly prescribed AEDs.

Factor analysis with orthogonal rotation, a linear transformation used to facilitate interpretation of results, was used to test whether individual AEP items segregate into separate classes of AEs. Only classes with eigenvalues ≥ 1.0 were retained in the analysis.¹²

Spearman correlation analysis was used to assess the association between QOLIE-89 scores and AEP scores for each class of AEs identified by factor analysis (AE class scores) in the entire cohort. The same analysis was used to investigate relationships between percent change in QOLIE-89 scores and percent change in each AE class scores in the subgroup followed up prospectively.

Multivariate linear regression was used to assess the contribution of each AE class score, BDI score, and seizure frequency (independent variables) to the QOLIE-89 score (dependent variable) in the entire cohort, and the contribution of percent change in each AE class score and seizure frequency to percent change in the QOLIE-89 score in the subjects followed up prospectively. Changes in BDI scores were not included in the latter analysis because the instrument was used only as an inclusion criterion at subject screening. Independent variables without significant predictive value at a level of 0.05 were removed before final analysis.

To calculate AE class scores, the digital scores of individual AEP items segregating into each class were normalized on a scale of 0 to 100 ($1 = 0$, $2 = 33.3$, $3 = 66.7$, and $4 = 100$) and added up, and the resulting sum was divided by the number of items in each class to yield a final class score of 0 to 100. Percent change in each AE class score was calculated as $(\text{baseline AE class score} - \text{final AE class score}) / \text{baseline AE class score} \times 100$. Similar computations were performed to calculate percent change in QOLIE-89 scores, BDI scores and seizure frequency.

Because the correlation analysis between individual AEP items was exploratory, no adjustments for multiple comparisons were made. Significance was set at a level of 0.05. When testing correlations between QOLIE-89 scores and AE class scores, the Bonferroni correction was used to adjust for multiple comparisons, setting significance at a level of 0.01.

Figure 1 Distribution of frequency of occurrence of each of the 19 adverse effects listed in the Adverse Event Profile questionnaire

RESULTS Characteristics of the study cohorts. Characteristics of the entire cohort ($n = 200$) are summarized in table e-1 on the *Neurology*[®] Web site at www.neurology.org. The mean age was 39.2 years, with equal proportions of men and women. Most subjects (71%) had localization-related epilepsy, followed by idiopathic generalized epilepsy (17%) and other syndromes (12%). The mean duration of epilepsy was 18.1 years. One half of the subjects were on AED monotherapy, 24% were on two AEDs, 17.5% were on three AEDs, and 3% were on four AEDs. The most common monotherapies were carbamazepine (Tegretol[®]; Novartis Pharmaceutical Corporation, East Hanover, NJ; 22 subjects), lamotrigine (Lamictal[®]; GlaxoSmithKline, Research Triangle Park, NC; 21 subjects), phenytoin (Dilantin[®]; Parke-Davis, New York, NY; 19 subjects), and valproate (Depakene[®]; Abbott Laboratories, North Chicago, IL; 13 subjects). The most common AED combinations were carbamazepine and lamotrigine (11 subjects), carbamazepine and levetiracetam (Keppra[®]; UCB, Smyrna, GA; 11 subjects), and lamotrigine and levetiracetam (10 subjects). Fifty-eight subjects (29.0%) were seizure-free in the past 6 months, 39 (19.5%) had less than a seizure per month, and the remaining 103 (51.5%) had one or more seizures per month. Mean instrument scores were 38.8 (SD 11.8) for the AEP, 9.6 (SD 9.3) for the BDI, and 64.6 (SD 19.4) for the QOLIE-89.

Details of the 62 subjects enrolled in the prospective trial have been described elsewhere.⁵ This subgroup had

similar age, proportion of men and women, and epilepsy syndromes distribution to the initial cohort, but it had a smaller proportion of seizure-free subjects (21%), a mean AEP score of 52.7 (SD 6.0) and a mean QOLIE-89 score of 45.7 (SD 15.8).

Rates of occurrence of individual AEs. Of the 200 subjects in the entire cohort, 24 (12%) did not report AEs, 176 (88%) reported at least one AE, and 164 (82%) reported at least two AEs. The mean number of AEs per subject was 6.5 (SD 4.6). The most common AEs were tiredness (63.3%), memory problems (58.3%), difficulty concentrating (44.4%), unsteadiness (43.8%), nervousness or agitation (43.2%), headache (42.7%), and sleepiness (41.1%) (figure 1).

Correlations between individual AEP items. The exploratory correlation analysis identified significant correlations for 167 of the 171 (97.7%) possible pairs of individual AEs (figure 2). The highest correlations were between depression and nervousness or agitation ($r = 0.63, p < 0.001$), difficulty in concentrating and nervousness or agitation ($r = 0.61, p < 0.001$), difficulty in concentrating and memory problems ($r = 0.60, p < 0.001$), tiredness and sleepiness ($r = 0.60, p < 0.001$), and dizziness and unsteadiness ($r = 0.60, p < 0.001$).

Identification of AE classes. Factor analysis of the 19 AEP items identified five classes into which AEs were found to segregate. These included 1) Cognition/Coor-

Figure 2 Correlations among the 19 Adverse Event Profile items in the entire cohort

The strength of correlation is indicated with a scale of gray (right bar), from white ($r = 0.05$) to black ($r = 0.63$, highest correlation). The diagonal running from the upper left to the lower right is intentionally left blank. All correlations are significant, except for those between weight gain and hair loss ($p = 0.09$), weight gain and trouble with mouth or gums ($p = 0.27$), and memory problems and problems with skin ($p = 0.09$).

dination (unsteadiness, double or blurred vision, difficulty in concentrating, shaky hands, dizziness, and memory problems); 2) Mood/Emotion (feelings of aggression, nervousness or agitation, and depression); 3) Sleep (tiredness, restlessness, upset stomach, sleepiness, and disturbed sleep); 4) Weight/Cephalgia (weight gain and headache); and 5) Tegument/Mucosa (hair loss, problems with skin, and trouble with mouth or gums). Figure 3 illustrates the degree of statistical association of each AE within each class and the unequivocal separation of each class from the others.

Relationships between HRQOL and classes of AEs. Higher scores in each of the five AE classes were associated with lower QOLIE-89 scores (figure e-1). The strongest correlation with QOLIE-89 scores was found for Cognition/Coordination ($r = -0.73$, $p < 0.001$), followed by Mood/Emotion ($r = -0.61$, $p < 0.001$), Sleep ($r = -0.61$, $p < 0.001$), Weight/Cephalgia ($r = -0.47$, $p < 0.001$), and Tegument/Mucosa ($r = -0.36$, $p < 0.001$).

In the multivariate analysis, Cognition/Coordination scores were the strongest predictor of QOLIE-89 scores ($\beta = -0.45$, $p < 0.001$), followed by BDI scores ($\beta = -0.43$, $p < 0.001$) and Weight/Cephalgia scores ($\beta = -0.11$, $p = 0.02$). These variables explained 71% of the variance in QOLIE-89 scores.

In the 62 subjects enrolled in the prospective trial, improvements in three of the five AE class scores were significantly associated with improvements in QOLIE-89 scores (figure e-2). The AE class for which changes in scores showed the strongest correlation with changes in QOLIE-89 scores was Cognition/Coordination ($r = 0.58$, $p < 0.001$), followed by Mood/Emotion ($r = 0.47$, $p = 0.003$) and Tegument/Mucosa ($r = 0.42$, $p = 0.01$). Correlations between changes in QOLIE-89 scores and changes in Sleep ($r = 0.32$, $p = 0.04$) and Weight/Cephalgia ($r = 0.31$, $p = 0.05$) showed similar trends without reaching significance.

In the multivariate analysis, improvements in Cognition/Coordination scores were the only predic-

tor of improved QOLIE-89 scores ($\beta = 0.45$, $p = 0.003$) and explained 18% of the variance.

DISCUSSION Considerable attention has recently been applied to mechanisms of drug resistance in epilepsy,^{21,22} including a commission statement from the International League Against Epilepsy.¹⁶ However, few studies have investigated clinical phenotypes or specific neurobiological mechanisms of AEs. In particular, no study has evaluated patterns of AE occurrence. Considering that many patients experience dose-limiting side effects, and that neuronal mechanisms of AEs could serve as the basis for new compound development, identification of consistent patterns of AE occurrence could support novel advances in the neuropharmacology of epilepsy.

In agreement with clinical practice⁶ and evidence from randomized controlled trials,^{2,8,9,23} our findings confirm that patients taking AEDs commonly report more than one AE. In the entire cohort, in which approximately 50% of subjects were treated with polytherapy, 83% reported two or more AEs, with an overall mean of 6.5. These results are consistent with those obtained using different methodologies for assessing AEs^{7,8} and underscore the prominent burden of toxicity associated with AEDs, particularly in patients with difficult-to-treat epilepsy.²⁴⁻²⁶

Our exploratory analysis demonstrated considerable variability in the strength of correlation between different AEs. This observation justified a formal investigation of the pattern of association of individual AEs using factor analysis. This statistical approach reduces variables to their core components and is therefore particularly suitable to determine whether specific AEs segregate into separate classes.

Factor analysis identified five classes of AEs, with AEs within each class having a higher probability to co-occur in the same patient. Three of these classes (Cognition/Coordination, Mood/Emotion, and Tegument/Mucosa) included AEs which, within each class, may be interpreted as having a plausible neurobiological basis. The cosegregation patterns of the two remaining classes, however, require further consideration. In the class referred to as Sleep, AEs such as disturbed sleep, sleepiness, tiredness, and restlessness may have a common mechanistic denominator in altered sleep or alertness, but a conceptual link between upset stomach and the other AEs in this class is not obvious. Interestingly, upset stomach showed the highest loading in this class (figure 3) and, in the exploratory correlation analysis, the highest correlation displayed by upset stomach was with disturbed sleep ($r = 0.54$, $p < 0.001$). A possible explanation for upset stomach cosegregating in the Sleep class is that this symptom may commonly re-

sult in disrupted sleep, thereby having an indirect mechanistic link with other AEs listed in the same class. The cosegregation of weight gain and headache into a separate class (Weight/Cephalgia) is also unexpected because of the different nature of these symptoms, but may be explained by a confounding by indication effect of valproic acid, a commonly used AED. In addition to causing weight gain,^{6,27} valproic acid has U.S. Food and Drug Administration approval for migraine prophylaxis,²⁸ and it might be preferentially prescribed in epilepsy patients with comorbid headache. This explanation is supported by the finding that a significant correlation between weight gain and headache was retained after controlling for the three most common monotherapies, carbamazepine ($r = 0.26$, $p < 0.001$), lamotrigine ($r = 0.27$, $p < 0.001$), and phenytoin ($r = 0.27$, $p < 0.001$), but was lost after controlling for use of valproic acid ($r = 0.00$, $p = 0.99$).

An additional aim of our study was to investigate the relationship between specific classes of AEs and subjective health status. In the entire cohort, higher scores in each class were associated with lower QOLIE-89 scores. This suggests that all aspects of medication toxicity impact on subjective health status, even though effects within the Cognition/Coordination class seem to be the most deleterious. Multivariate analysis, which controlled for depression (BDI scores) and seizure frequency, also identified Cognition/Coordination scores as the strongest predictor of QOLIE-89 scores. Depressive symptoms were also associated with poor subjective health status, whereas seizure frequency did not have a significant influence. These findings are reinforced by those obtained in the subjects followed prospectively for 4 months. In this subgroup, improvements in QOLIE-89 scores were associated with improvements in scores for three AE classes (Cognition/Coordination, Mood/Emotion, and Tegument/Mucosa), and again the highest association was with improved Cognition/Coordination scores. In the multivariate analysis, improved scores for Cognition/Coordination were the only predictor of improved QOLIE-89 scores. Overall, these results support existing evidence that, in patients with refractory epilepsy, AEs and mood disorders may be more important than seizure frequency in determining subjective health status.^{4,5}

Our results may have important implications for clinical care and neuropharmacologic research. First, recognition of specific patterns of AEs that predict subjective health status may overcome the inherent limitation of evaluating symptoms in isolation or as total aggregate, both in clinical practice and in AED trials. By focusing on specific AE classes and by taking appropriate action to reduce them, patient qual-

Figure 3 Radial plot illustrating the strength of segregation of individual adverse effects within each class as identified by factor analysis in the entire cohort

In this plot, the 19 spokes that radiate from a central point represent the 19 items of the Adverse Event Profile (AEP) questionnaire. Each item loadings for the five classes identified by factor analysis are plotted on a single spoke, with higher loadings indicating a higher level of segregation. The 19 items loadings on a given class are connected with a line to form a polygon. The highest loading on each spoke (and therefore the most distant intersection between each spoke and the five lines) illustrates to which class the corresponding AEP item is segregated.

ity of life can be significantly improved. Second, the finding that AEs segregate into separate classes creates the potential to investigate their specific underlying neurobiological mechanisms. Each class of AEs may result from dysfunction of specific components of complex neural networks that underlie physiologic functions. An example is provided by the neurobiology of sleep and related disorders. Sleep is a physiologic state whose underlying biologic circuit includes specific brain regions in the hypothalamus, basal forebrain, and brainstem and uses a variety of neurotransmitters, such as serotonin, galanin, and orexin.²⁹ A deficiency of orexin leads to narcolepsy.³⁰ Recent studies indicate that basal forebrain GABAergic neurons inhibit orexin neurons in the hypothalamus.^{31,32} Therefore, it is plausible that AEDs enhancing GABAergic transmission cause sleepiness by modulating the basal forebrain–hypothalamus network. Similar considerations can be made for mood and emotion. The role of specific cerebral structures, such as the hippocampus, the mammillary bodies, and the cingulate gyrus, in the control of emotion

has been recognized for decades.³³ Hippocampal dysfunction has been associated to occurrence of depression in temporal lobe epilepsy,³⁴ and interestingly some AEDs show a particular propensity to cause depressive symptoms in people with hippocampal injury.³⁵ The specific classes derived from our factor analysis allow insight into the structure of AEs that may bridge the gap between recent advances in neuroscience and neuropharmacology to support more effective development of new AEDs.

Studies aimed at assessing patterns of co-occurrence of AEs must ensure that reliable data are acquired through systematic screening in representative samples. Several aspects of the current investigation fulfilled these requirements: 1) a large cohort of consecutive epilepsy clinic subjects were enrolled; 2) AEs were assessed with a standardized instrument whose reliability, validity, and responsiveness had been previously demonstrated^{5,6,17}; and 3) the AE information obtained in the same study was found to improve outcome within the framework of a randomized trial.⁵

This study also has limitations. Although none of available methods for assessing AEs are perfect, use of questionnaires may lead to overestimation of AE rates.¹⁶ Not all symptoms reported by our subjects were necessarily caused by AEDs. For example, headache, memory loss, sleep disorders, and mood symptoms may be related to epileptic brain dysfunction per se rather than to its treatment. Moreover, physicians participating in the prospective trial may have been more vigilant about AEs, possibly biasing subjects' expectations and reactions to treatment changes. Our data were obtained at a tertiary care center, and therefore may not be generalizable to a community-based setting. Finally, new AEDs not represented in our sample may have unique AE profiles, which would require replication of our findings in future studies.

AUTHOR CONTRIBUTIONS

P. Perucca and F.G. Gilliam conducted the statistical analysis.

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