

## Current Literature

In Clinical Science



## Baseline Psychiatric Evaluations Are Needed to Treat Seizures

### Depressive and Anxiety Disorders in Epilepsy: Do They Differ in Their Potential to Worsen Common Antiepileptic Drug-Related Adverse Events?

Kanner AM, Barry JJ, Gilliam F, Hermann B, Meador KJ. *Epilepsia* 2012;53:1104–1108.

**PURPOSE:** To compare the effect of anxiety disorders, major depressive episodes (MDEs), and subsyndromic depressive episodes (SSDEs) on antiepileptic drug (AED)-related adverse events (AEs) in persons with epilepsy (PWE). **METHODS:** The study included 188 consecutive PWE from five U.S. outpatient epilepsy clinics, all of whom underwent structured interviews (SCID) to identify current and past mood disorders and other current Axis I psychiatric diagnoses, according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria. A diagnosis of SSDE was made in patients with total Beck Depression Inventory-II (BDI-II) scores > 12 or the Centers of Epidemiologic Studies-Depression (CES-D) > 16 (in the absence of any DSM diagnosis of mood disorder). The presence and severity of AEs was measured with the Adverse Event Profile (AEP). **KEY FINDINGS:** Compared to asymptomatic patients (n = 103), the AEP scores of patients with SSDE (n = 26), MDE only (n = 10), anxiety disorders only (n = 21), or mixed MDE/anxiety disorders (n = 28) were significantly higher, suggesting more severe AED-related AEs. Univariate analyses revealed that having persistent seizures in the last 6 months and taking antidepressants was associated with more severe AEs. Post hoc analyses, however, showed that these differences were accounted for by the presence of a depressive and/or anxiety disorders. **SIGNIFICANCE:** Depressive and anxiety disorders worsen AED-related AEs even when presenting as a subsyndromic type. These data suggest that the presence of psychiatric comorbidities must be considered in their interpretation, both in clinical practice and AED drug trials.

### Commentary

In adults with new onset seizures, baseline neuropsychiatric symptoms (memory, depression, anxiety) either on the A-B Neuropsychological Assessment Scale (ABNAS) or on prior or current psychiatric medical chart records predict antiepileptic drug (AED) treatment response of seizure control or lack thereof at the 12-month (1) and 20-year follow-up (2), respectively. Self-report depression symptoms are related to adverse AED effects in both nontertiary epilepsy patients (3) and in tertiary clinic patients on AED polytherapy (4). Furthermore, mood/emotion is one of the AED adverse event profile scores related to quality of life in new onset seizure patients on low-dose AED above and beyond effects of depression and seizure frequency (5). The findings of these studies demonstrate that depression and anxiety are related to both treatment response and development of adverse effects in epilepsy patients treated with AEDs.

Kanner and colleagues have provided additional important clinical information regarding seizure management and the associated role of the psychiatric comorbidity. They have dem-

onstrated that epilepsy patients with depression and anxiety diagnoses—combined depression and more than one anxiety diagnosis—as well as those with self-reported depression and anxiety symptoms that do not meet diagnostic criteria for a mood or anxiety disorder are at risk for AED side effects. This finding underscores the need for baseline psychiatric evaluation of epilepsy patients for optimal seizure management that might include, as suggested by Ettinger (3), slower titration of AEDs. Could ruling out depression and anxiety diagnoses as well as symptoms when patients are first diagnosed with epilepsy and treating the psychiatric comorbidity also decrease suicidal risk and its FDA reported association with AEDs, improving the depression-related poor quality of life of these patients (6)?

From a research perspective, Kanner et al. caution against misinterpretation of a worse toxic profile in AED drug studies that might occur for two reasons: First, these studies include treatment-resistant epilepsy patients who are at risk for both an increased adverse event profile (AEP) and psychopathology. Second, AED drug studies exclude subjects with a psychiatric diagnosis but not those with self-report depression and anxiety symptoms that do not meet diagnostic criteria.

The carefully planned design of this study included examining if the relationship between AED-related adverse events is consistent when controlling for adverse event profile (AEP)

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symptoms that might mimic depression and anxiety symptoms. In addition, the comparison of AED adverse events in the patients on antidepressant treatment to non-treated patients, those with and without seizure control, and subjects treated with AED monotherapy vs. those on polytherapy ruled out the possible role of these confounding variables. However, despite a disproportionately higher number of 131 females versus 62 males in the sample, the authors did not examine gender effects. This is particularly important because women without epilepsy have higher rates of depression and anxiety diagnoses, atypical depression, and depression with anxiety symptoms, as well as different treatment responses and adverse events from antidepressant drugs than men (see review in (7)). Women with epilepsy also have more prevalent depression (3–5), poor quality of life related to AED adverse events (5), and more AED side effects (5, 8) than do men with this illness.

Additional study limitations include lack of information on ethnicity and socioeconomic status, especially given ethnic-related differences in the presentation of psychiatric diagnoses and symptoms and an increased prevalence of depression and anxiety diagnoses in lower socioeconomic groups (9). The authors acknowledged that the small sample size of the group with major depression might underlie the lack of significant AED adverse event differences across psychiatric comorbidities, including the subsyndromic group. Similarly, the findings on the subgroups with more than one anxiety diagnosis need to be replicated on larger samples.

Regarding the association of the AEP scores with seizure control, the authors concluded that the psychiatric comorbidity contributed to the AEP finding because there were no significant differences in these scores by seizure control in both the psychiatric comorbidity symptomatic and asymptomatic groups. In terms of antidepressant treatment, however, the lack of a significant difference in the AEP scores of the asymptomatic patients on and off antidepressants might be reflected in the small sample size of 12 and 90, respectively, in these subgroups. The authors noted that suboptimal antidepressant doses in 84% of the patients might contribute to their being symptomatic and that the AEP profile might also reflect side effects to antidepressant treatment.

In conclusion, this study adds to the cumulative evidence demonstrating that both seizures and the psychiatric comorbidity are integral components of this neuropsychiatric disorder. It also provides background for prospective studies to determine if there is a two-way relationship of depression and anxiety diagnoses and symptoms with AED-induced adverse effects in patients with epilepsy.

by Rochelle Caplan, MD

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## *Epilepsy Currents Journal*

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