

Do antiepileptic drugs cause suicidal behavior?

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Neurology® 2013;81:1889–1890

In this issue of *Neurology*®, Pugh et al.¹ present data to support the hypothesis that antiepileptic drugs (AEDs) are used in response to suicide-related behaviors (SRBs) associated with pain and psychiatric illness, rather than being a cause of SRBs. Further, they point out that these conditions are inherently associated with increased suicidal behaviors and therefore confound assessment of the causal relationship of AEDs and SRB.²

Using the Veterans Administration (VA) database of patients ≥ 65 years old, Pugh et al. examined the temporal relationship between the report of SRB, as documented by *ICD-9-CM* codes, and initial prescription of AED monotherapy. They found that AEDs, mainly gabapentin, which accounted for 76% of the AED use, and valproate (7%), are often prescribed immediately after these patients report SRBs. The majority of the patients, 62%, had a prior diagnosis of chronic pain. Overall, pain and psychiatric illness occurred “commonly” prior to AED use, including diagnoses of depression, anxiety, bipolar disorder, posttraumatic stress disorder, schizophrenia, substance abuse/dependence, conditions associated with chronic pain, and dementia. Rates of these conditions were higher than in veterans without AED exposure, as were psychiatric hospitalization and prescriptions for antidepressant or antipsychotic medications in the previous year. Epilepsy was a previous diagnosis in only 3.6% of the study population, and only 6 of the 3,225 patients with epilepsy had SRB after AED. There was no difference in epilepsy prevalence between those with or without SRBs.

The authors published a previous article in which they reported an association between AED use and SRBs in this mature VA population.³ They showed that psychiatric illness was the strongest predictor of SRBs and therefore is a confounder in assessing causal relationships between AEDs and SRBs. They returned to the dataset and carefully examined the temporal relationship of AED use to SRB occurrence and found that the highest rates of SRBs are in the month before AED prescriptions. SRBs gradually decrease over 12 months after AED prescriptions,

although the total number of SRBs is slightly greater in the year after AED use than the prior year. Thus, AEDs appear to be given in response to SRBs or other psychiatric symptoms, suggesting that SRBs occur in this population regardless of AED use.

After AED prescription, additional patients reported SRBs; however, nearly a quarter of the patients had SRBs both before and after AED use. If we begin with a bird’s-eye view, 90,230 patients were prescribed an AED as per inclusion criteria in the 2-year study period, and 150 patients (1.7%) had SRBs, either before or after AED use, or both before and after AED use. As our view sharpens, we see details revealing that the cohort consists mainly of VA chronic pain patients who have SRBs, are treated predominately with gabapentin, and then some of them continue to have SRBs.

Neurologists and other providers who care for epilepsy patients have struggled with the US Food and Drug Administration (FDA) warning from 2008 associating completed suicides and suicide attempts with AED use in placebo-controlled clinical trials.⁴ The main problems are lack of knowledge on the causal relationship of AEDs and SRBs, possible differential AED risks, appropriate techniques for surveillance to detect the high-risk patients, and the best way to discuss this rare but serious adverse effect with patients. The powerful psychoactive effects of AEDs are well-appreciated; these effects can be negative in patients for whom an AED is otherwise effective and well tolerated, or can be positive with beneficial psychotropic effects. A recent report using the Columbia Suicide Severity Rating Scale documented that epilepsy patients, who have similar characteristics to those eligible for clinical trials (i.e., frequent monthly seizures), exhibited recent high-risk suicidal ideation rates of 1.6%–3.9%.⁵ Therefore, we now have available an expected rate of suicidality and a technique to assess its presence and severity. Further, neurologists are starting to appreciate that depression is not always the only predictor of suicidality, but rather impulsivity is a key contributor to the patient becoming suicidal.⁶

The bird’s-eye view of the FDA warning (from the executive summary) shows an analysis from 199

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

placebo-controlled trials consisting of 27,863 patients in AED arms and 16,029 patients in placebo arms across 11 different AEDs.⁶ There were 4 completed suicides in the AED patients and none among placebo patients. The risk of events for the AED-treated patients was observed within 1 week. By AED mechanistic category, no specific AED group showed an increased risk (sodium channel blocking, GABAergic and GABA-mimetic, and carbonic anhydrase inhibitor). The estimated overall odds ratio (OR) of an AED-treated patient experiencing an SRB vs a placebo patient was 1.80 (95% confidence interval [CI] 1.24, 2.66). The epilepsy indication subgroup had the largest estimated OR (3.53 [95% CI 1.28, 12.10]) compared to the psychiatric indication subgroup (1.51 [95% CI 0.95, 2.45]). However, the psychiatric indication subgroup had the largest placebo risk, consistent with the findings of Pugh et al.

Pugh et al. suggest a hypothesis that unlinks the causal relationship between AED use and suicidal behaviors, which is supported by their findings in this elderly population composed primarily of patients with chronic pain who were prescribed gabapentin. Therefore, this study raises ideas about the association of suicidality and AEDs in epilepsy patients; perhaps the patients who had suicidality after AED use in the FDA analysis were those who had suicidality before treatment, given that at least 1.6% of intractable epilepsy patients report suicidality,³ which is similar to the rate reported by Pugh et al. in this VA population. If this interesting and well-performed analysis could be extrapolated to epilepsy patients, then we could also explore a possible disconnect from a causal relationship to the statistical relationship of AEDs and suicidality.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

C. Harden reports receiving research support from the Epilepsy Therapy Project and the NIH; speakers' bureau for GlaxoSmithKline, UCB Pharma, and Lundbeck; consultant for Eisai and Upsher Smith; and editorial board for *Epilepsy Research*. K. Meador reports receiving research support from the GlaxoSmithKline, Eisai Medical Research, Myriad Pharmaceuticals, Marinus Pharmaceuticals, NeuroPace, Pfizer, SAM Technology, Schwartz Biosciences, and UCB Pharma, the Epilepsy Foundation, and the NIH; received salary support to Emory University from the Epilepsy Consortium for research consultant work related to NeuroPace, Novartis, Upsher-Smith, and Vivus; served as a consultant for Eisai, GlaxoSmithKline, Johnson and Johnson (Ortho McNeil), Medtronic Spherics, and UCB Pharma, but the monies went to a charity of the company's choice; received travel support from Sanofi Aventis; and also serves on the Professional Advisory Board for the Epilepsy Foundation and the editorial boards for *Cognitive and Behavioral Neurology*, *Epilepsy and Behavior*, *Neurology*[®], and *Journal of Clinical Neurophysiology*. Go to Neurology.org for full disclosures.

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