Commentary
Pugh et al’s excellent study provides the temporal information confirming that suicide-related behavior in veterans aged 64 years and older who have depression and bipolar disorder is at its highest level in the month before initiation of monotherapy AED treatment. Their findings lend support for the role of the underlying psychopathology in suicide-related behavior found in patients with epilepsy (1), psychiatric disorders (2), and pain (3) treated with AEDs. As such, they add to the evidence for this relationship demonstrated in the well-designed large studies conducted since the U.S. Federal Drug Administration (FDA) warned that antiepileptic drugs (AEDs) increase suicidal behavior (4).

Together with the increase prevalence of psychiatric disorders—including depression, anxiety, and schizophrenia—before the onset of epilepsy and the higher incidence of suicide-related behavior in the 3 years before and 2 years following onset of epilepsy (5), these findings underscore the need to screen for psychiatric disorders and suicide-related behavior in every newly diagnosed patient with epilepsy before beginning treatment with an AED. Pugh et al’s findings emphasize the need for a similar approach in geriatric patients with pain given the high prevalence of undiagnosed depression and anxiety disorders (6) and posttraumatic stress disorder in these patients (7). Their findings also leave no doubt as to the importance of assessing newly diagnosed psychiatric geriatric patients for suicide-related behavior before prescribing an AED.

Extensive suicide research conducted over the past two decades has identified risk factors for suicide-related behavior across the ages (See review in [8]). These include past suicide-related behavior, access to firearms, family history of mood disorder and of suicide-related behavior, social isolation, poverty, unemployment, and substance abuse including alcohol. Most importantly, a recent study demonstrated the prognostic importance of suicidal ideation found in 12.1% of 6483 youth, ages 13 to 18 (9). One-third of these ideators developed suicidal plans within 1 year, of whom one-third made a suicide attempt. Thus, clinicians should recognize that patients who have suicidal ideation need the help of a mental health professional even if they do not have a suicidal plan.

We now have robust data confirming that patients in need of AED treatment—whether for epilepsy, psychiatric diagnoses, or pain—should undergo screening and, where necessary, comprehensive psychiatric diagnosis and treatment. Brief screening instruments for depression, anxiety disorders, and bipolar disorder are readily available and easily scored in adults and youth with epilepsy. They also include items

Temporal Trends in New Exposure to Antiepileptic Drug Monotherapy and Suicide-Related Behavior.

OBJECTIVE: Because some recent studies suggest increased risk for suicide-related behavior (SRB; ideation, attempts) among those receiving antiepileptic drugs (AEDs), we examined the temporal relationship between new AED exposure and SRB in a cohort of older veterans. METHODS: We used national Veterans Health Administration databases to identify veterans aged ≥65 years who received a new AED prescription in 2004–2006. All instances of SRB were identified using ICD-9-CM codes 1 year before and after the AED exposure (index) date. We also identified comorbid conditions and medication associated with SRB in prior research. We used generalized estimating equations with a logit link to examine the association between new AED exposure and SRB during 30-day intervals during the year before and after the index date, controlling for potential confounders. RESULTS: In this cohort of 90,263 older veterans, the likelihood of SRB the month prior to AED exposure was significantly higher than in other time periods even after adjusting for potential confounders. Although there were 87 SRB events (74 individuals) the year before and 106 SRB events (92 individuals) after, approximately 22% (n = 16) of those also had SRB before the index date. Moreover, the rate of SRB after AED start was gradually reduced over time. CONCLUSIONS: The temporal pattern of AED exposure and SRB suggests that, in clinical practice, the peak in SRB is prior to exposure. While speculative, the rate of gradual reduction in SRB thereafter suggests that symptoms may prompt AED prescription.
on suicidal thoughts. Since some of the instruments address behavior, thoughts, and symptoms that occur in the 2 weeks or 1 month prior to filling out these questionnaires, clinicians should also ask all epilepsy patients about the previously described red flags before starting treatment with an AED and when crossing over to another AED.

If clinicians routinely include screening for psychiatric disorders and suicide-related behavior as part of their practice for optimally treating seizures with AEDs, they will improve the quality of care for epilepsy patients. Documentation of the extent of the unmet mental health needs of these patients will provide the clinical data needed to get the necessary insurance coverage for psychiatric treatment of epilepsy patients. Ultimately, this could lead to recruiting more psychiatrists and other mental health-care professionals to work with epilepsy patients.

However, the studies conducted to date have not answered whether AEDs play a causal role in suicide-related behavior and, if so, which are the involved AEDs and what are the underlying mechanisms. To answer these questions, the field is in need of well-designed prospective long-term studies of epilepsy, psychiatric, and pain disorder patients treated with AED monotherapy and separate studies for individuals in these diagnostic groups who require AED polytherapy. Among epilepsy patients, those with difficulty to control seizures treated by AED polytherapy are usually at higher risk for behavioral AED adverse effects (10, 11), including depression and psychosis. They also are vulnerable for cognitive side effects (12), which, in turn can induce poor self-esteem, difficulty coping, and subsequent depression and anxiety. Since these behavioral and cognitive adverse effects can trigger suicide-related behavior, they need to be studied prospectively.

Pugh et al.’s study demonstrated a gradual decrease in suicide-related behavior over the 12 months following initiation of AED monotherapy treatment in geriatric veterans with pain, psychiatric disorders, and epilepsy. They suggested that this decline in suicide-related behavior implies a possible therapeutic effect. Studies are, therefore, warranted to investigate if AED treatment decreases suicide-related behavior in epilepsy patients and if this is associated with the type of psychiatric diagnosis. More specifically, is AED treatment more effective in patients with epilepsy who have bipolar disorder compared to those with major depression or anxiety disorder diagnoses? An additional unstudied important research question is whether psychopharmacological treatment for the specific psychiatric diagnosis or diagnoses, cognitive behavior training, and combined psychopharmacological and psychotherapeutic treatment reduce the prevalent suicide-related behavior in epilepsy patients? Antidepressant treatment decreased suicide-related behavior in the subjects participating in the National Institute of Mental Health Collaborative Depression Study who had a mood disorder, whereas AEDs (carbamazepine, lamotrigine, and valproate) had no protective effect on the patients with bipolar disorder (13). However, the previously described study on suicide 6,483 youth ages 13 to 18 found that treatment that started prior to the onset of suicidal behaviors failed to prevent these behaviors (9). Similar evidence is reported in adults (See reviews in [8]).

So, there appears to be light at the end of the tunnel, built in 2008 by the FDA report. Clinicians now have access to evidence for the role of underlying psychiatric disorders in the suicide-related behavior of individuals treated with AEDs, available screening instruments for psychiatric disorders and suicide, and knowledge about the risk factors for suicide-related behavior. Researchers can lead the way to the end of the tunnel by conducting prospective studies to determine if AEDs increase suicide-related behavior, who is vulnerable for this effect, and what are the involved mechanisms.

by Rochelle Caplan, MD

References

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. **Identifying information.**
Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

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This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

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Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

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American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Section #1 Identifying Information

1. Today’s Date: March 27, 2014

2. First Name  Rochelle     Last Name Caplan  Degree MD

3. Are you the Main Assigned Author?  ☒ Yes  ☐ No

   If no, enter your name as co-author:

4. Manuscript/Article Title:

5. Journal Issue you are submitting for:  Epilepsy Currents 14.3

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

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* This means money that your institution received for your efforts on this study.

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Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

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* This means money that your institution received for your efforts.
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