Suicide Attempts in Patients With Bipolar Disorder Tend to Precede, Not Follow, Initiation of Antiepileptic Drugs

To the Editor: In 2008, the US Food and Drug Administration (FDA) issued an alert stating that antiepileptic drugs (AEDs) can increase suicidal thoughts and behaviors.[1] However, subsequent studies found conflicting evidence regarding the relationship between antiepileptic drugs and suicidal behavior.[2–4] Furthermore, the American Epilepsy Society and others have cautioned against the unintended consequences of putting warnings on safe drugs.[2,3,5] We examined the timing of suicide attempts in relation to initiation of antiepileptic drugs among patients with bipolar disorder.

Method. We reanalyzed data from Gibbons and colleagues' study[5] of the relationship between AEDs and suicide attempts in

patients with bipolar disorder. This observational study used the PharMetrics medical claims database (commercially available from PharMetrics, Inc, under restricted license) to examine a cohort of 47,918 bipolar disorder patients with a minimum 1-year window of data before and after the index date of bipolar disorder diagnosis. Here, we examine suicide attempts for the n = 13,385 bipolar disorder patients who received AED monotherapy, defined for a 1-year period following the index episode as taking 1 AED but not lithium. Treatment with other medications was permitted. Since all participants were retained during the study time period, we compared suicide attempt rates 1 month before and after the initiation of AEDs by using a 2-sided McNemar test. Within the paired design, the odds ratio (also known as Mantel-Haenszel odds ratio) was calculated among the discordant pairs.

Results. Figure 1 gives both the number and the rate (per 1,000 person-years) of suicide attempts by time before and after AED initiation. The trend line is fairly flat with the exception of a large peak observed during the month before the start of AEDs. The suicide attempt rate during the month before AED initiation was significantly higher than the rate during the month after AED initiation (OR = 3.83, 95% CI, 2.55–5.94; $P < .0001$).

These data do not support the hypothesis that institution of AED pharmacotherapy is associated with an increase in the rate of suicide attempts in patients with bipolar disorder. Rather, they suggest that AED treatment is initiated in response to presence of episodes associated with increased risk for suicidal behavior. These findings comport with those of Simon and colleagues,[6] who found suicide attempts to be more frequent in the month prior to antidepressant prescription compared to afterward. Together, these 2 analyses underscore the importance of examining data before as well as after treatment initiation in studies using naturalistic data to understand drug effects on suicidal acts.

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Sue M. Marcus, PhD
smarcus@nyspi.columbia.edu
Bo Lu, PhD
Sungwoo Lim, MS
Robert D. Gibbons, PhD
Maria A. Oquendo, MD

Author affiliations: Departments of Psychiatry (Drs Marcus and Oquendo) and Biostatistics (Dr Marcus), Columbia University, New York, New York; Department of Biostatistics, College of Public Health, The Ohio State University, Columbus (Dr Lu); New York City Department of Health and Mental Hygiene, New York, New York (Mr Lim); and Department of Medicine and Health Studies, University of Chicago, Chicago, Illinois (Dr Gibbons).

Author contributions: Dr Marcus had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Marcus and Lu were responsible for study concept and design. Dr Gibbons was responsible for the acquisition of data. All authors were involved in drafting the manuscript. Drs Marcus, Lu, Gibbons, and Oquendo conducted critical revision of the manuscript for important intellectual content. Drs Marcus, Lu, and Gibbons and Mr Lim performed the statistical analysis.

Potential conflicts of interest: **Dr Gibbons** reports having served or currently serving as an expert witness for the US Department of Justice and Wyeth and Pfizer Pharmaceuticals, the latter involving gabapentin, one of the drugs considered in this research letter. **Dr Oquendo** receives royalties for the use of the Columbia Suicide Severity Rating Scale and received financial compensation from Pfizer for the safety evaluation of a clinical facility, unrelated to the current manuscript. She was the recipient of a grant from Eli Lilly to support a year's salary for the Lilly Suicide Scholar, Enrique Baca-Garcia, MD, PhD. She received unrestricted educational grants and/or lecture fees from Astra-Zeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, Otsuka, Pfizer, Sanofi-Aventis, and Shire. Her family owns stock in Bristol-Myers Squibb. **Drs Marcus** and **Lu** and **Mr Lim** have no conflict of interest to disclose.

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