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No Link Between Antiepileptics and Suicidality in Patients With Bipolar Disorder

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December 11, 2009 — Antiepileptic drugs (AEDs) are not associated with increased risk for suicide attempts in patients with bipolar disorder and may even have a protective effect, new research suggests.

These findings run contrary to an [alert](#) issued last year by the US Food and Drug Administration (FDA) that warned that AEDs may increase the risk for suicidal thoughts and actions based on its meta-analysis of a wider population group.

"The FDA has an obligation to warn people about potential problems with drugs, but, at the same time, there can be unintended consequences, such as patients not receiving the treatments they really need," lead author Robert D. Gibbons, PhD, statistics professor, Center for Health Statistics at the University of Illinois at Chicago, told *Medscape Psychiatry*.

"Overall, we found that there didn't seem to be any difference in suicide attempt rates between those people who were treated with one of these antiepileptic drugs and people who did not receive them," he added.

The study is published in the December issue of *Archives of General Psychiatry*.

Dr. Gibbons and colleagues found that, as a class, AEDs were also associated with a reduction in suicide attempt rates relative to pretreatment levels in patients who are ultimately prescribed these drugs and relative to patients not receiving any psychotropic medication at all.

"I think it's important that clinicians add this piece of information to the risk-benefit equation that they use in determining whether or not a patient should be treated with one of these [AEDs]," said Dr. Gibbons.

Beyond The FDA Warning

"Anticonvulsant medications are life-saving in the treatment of seizure disorders and are also extensively used for other indications, such as mood disorder and trigeminal neuralgia," write the study authors.

However, in 2005, the FDA requested suicidality data on randomized clinical trials from the sponsors of 11 AEDs: gabapentin, divalproex, felbamate, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide, and carbamazepine. They then conducted a meta-analysis of 199 placebo-controlled trials that included a total of 43,892 patients.

The results of the analysis showed that patients treated with these drugs reported more suicidal behavior or ideation than those treated with placebo (0.43% vs 0.22%; 2.1 per 1000 more treated patients), which led to the issuing of the alert to healthcare providers.

"The FDA warning implicated all 11 AEDs, which is surprising given their often quite different modes of action," the investigators write.

They also note that these treatment questions are especially important for patients with bipolar disorder, where both attempted and completed suicides are major concerns.

"Without treatment, approximately 10 per 1000 individuals with bipolar disorder complete suicide annually, and about 40 per 1000 attempt suicide," write the study authors. These risks are "approximately 100-fold and 10-fold higher, respectively, than for the general population.

"Of all the people who get treated with an antiepileptic drug, these are the people who have the highest risk for suicide," said Dr. Gibbons. "Therefore, this was the group we wanted to focus on while examining the association between the 11 implicated AEDs and risk of suicide attempts."

Using the PharMetrics medical claims database from 2000 to 2006, the investigators evaluated a cohort of 47,918 patients with bipolar disorder (1226 with at least 1 suicide attempt), including 25,432 nonmedicated patients who were receiving no AEDs, lithium, or central nervous system medication.

The investigators used *International Classification of Diseases, Ninth Revision (ICD-9)* codes to identify suicide attempts, including deliberate self-harm.

No Difference Between Groups

The study results showed no overall difference in suicide attempt rates for the patients treated with AEDs compared with those not treated with an AED or lithium (13 per 1000 person-years [PY] for both groups; event rate ratio [ERR], 0.88; 95% confidence interval, 0.72 – 1.08; *P* = .22).

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Similar results were seen for the individual AEDs, with the exception of significantly greater posttreatment risk found for topiramate (27 per 1000 PY, $P = .004$) and carbamazepine (29 per 1000 PY, $P = .01$) compared with those receiving no treatment.

Overall, the rate of suicide attempts was significantly higher before treatment with the AEDs than after (72 vs 13 per 1000 PY; ERR, 0.19; $P < .001$). These rates were also significantly greater for all individual drugs and lithium except for topiramate and carbamazepine.

"Even for these 2 AEDs, there was no evidence that they increased suicide rates," write the study authors.

In addition, patients treated only with 1 AED (and not an antidepressant, other AED, or antipsychotic concurrently) had a significantly lower suicide rate compared with the untreated group (3 vs 15 per 1000 PY, $P < .001$).

"This suggests that in this very pure group, there was some evidence of a protective effect from the AED," said Dr. Gibbons.

Compelling Results

"Despite [FDA] reports regarding increased risk of suicidality associated with AED treatment, the current study reveals that, as a class, AEDs do not increase risk of suicide attempts in patients with bipolar disorder," write the study authors.

However, they caution that drawing causal interference from observational data is complicated, especially for the study of suicide.

"Suicide and [suicide attempts] are rare events, and their determinants are difficult to estimate precisely in all but the largest samples," they explain. In addition, "patients who receive treatment often have increased severity of illness and may therefore be at increased suicide risk to begin with."

They add that there are several possible reasons for the difference between the results of this study and the findings by the FDA. This includes the FDA evaluating adverse event reports of suicidal thoughts and behavior, whereas this analysis focused solely on suicide attempts.

"Most of the suicidality events in the FDA analyses were observed for only 2 of the 11 AEDs — lamotrigine and topiramate," write the study authors. "By contrast, the other 9 drugs showed no significant association with suicidality either individually or combined," they add.

No Comment Yet From the FDA

"The FDA also did not show an increased risk of suicidal thoughts or behavior for psychiatric indication and, of course, bipolar is a major psychiatric indication," noted Dr. Gibbons. "On the other hand, ours is a very specific study about 1 group of patients. While they're at the highest risk for suicide attempts and completions and thoughts, they may not be necessarily representative of patients with other indications.

"The strength of our analysis is that we're looking at real people who are out in the real world. The strength of their analysis is that they looked at studies that were randomized. However, many of those trials were not representative of the general population who ultimately get treated with [AEDs].

"No one study is ever going to answer all these questions definitively, but I think the data we have shown [are] quite compelling, and I think it makes it pretty clear that there is no increased risk of suicide risk in treating these patients with these drugs," concluded Dr. Gibbons.

Medscape Neurology contacted the FDA for comment, but it declined to comment at this time. The agency said it is currently reviewing Dr. Gibbons' study and will respond at a later date.

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