Newer AEDs Raise Risk of Self-Harm, Suicidality

BY MICHELE G. SULLIVAN

FROM NEUROLOGY

Newer antiepileptic drugs that are associated with a high risk of depression may be the only agents in this class of medications that increase the risk of suicidal and self-harming behavior, according to a large, case-control study.

Epilepsy patients who took newer antiepileptic drugs (AEDs) with depressive side effects (levetiracetam, topiramate, tiagabine, and vigabatrin) had threefold greater odds of suicidal or self-harming behavior, compared with similar patients who did not use AEDs.

But a subanalysis of the cohort that looked at 15 different AEDs, including barbiturates and conventional drugs, found that only levetiracetam significantly increased the odds of suicidal behavior or self-harm (odds ratio, 6.4). The relationship between suicidal or self-harming behavior and the drugs topiramate and vigabatrin became nonsignificant in the subanalysis, according to the report published in Neurology.

The investigators, led by Dr. Frank Andersohn of Charité University Medical Center in Berlin, found that patients with preexisting psychiatric disorders may bear the brunt of these increased risks. "In our study the risk of self-harm or suicidal behavior observed for new AEDs with a high risk of depression was only evident in patients with, but not in those without, psychiatric comorbidity. This apparently differential AED effect with respect to psychiatric comorbidity was, however, not significant and may thus have been observed by chance alone."

Controls were far more likely to have psychiatric comorbidity, including a history of self-harm, antidepressant use, depression without treatment, and psychotic disorder.

However, the investigators noted that the low number of cases reduced the study's power to detect significant interactions between psychiatric comorbidity and suicidal and self-harming behavior.

The study included up to 5 years of follow-up data on 44,300 patients with epilepsy who were treated with at least one AED during 1990-2005. All patients were included in the U.K. General Practice Research Database. The 453 cases of self-harming or suicidal behavior were matched by age and sex with 8,962 controls who had no such experience (Neurology 2010;75:335-40).

The entire cohort was approximately 52% male; the mean age was 36 years. Most (68%) had an undefined epilepsy type. Controls were significantly more likely to have psychiatric comorbidity, including a history of self-harm, antidepressant use, depression without treatment, psychotic disorder, mania, anxiety disorder, borderline personality disorder, alcohol dependence, and other substance abuse.

Of the 453 cases, 294 had attempted suicide and 159 had self-harmed. There were 78 patients who died initially or within 4 weeks of the onset of self-harm or suicidal behavior.

Of the entire group, 382 cases (84%) and 7,903 controls (88%) had been exposed to at least one AED in the year before the index date. For cases, the index date was the date of harm, but for controls it was the date that resulted in the same time of follow-up as the case to which that patient was matched. Within that time period, 62% of the cases and 72% of the controls were currently using the drugs.

Among the four new AEDs with a confirmed increased risk of depression, only current use was significantly associated with greater odds for suicidal or self-harming behavior. No significant relationship was seen with recent or past AED use.

In further analyses, Dr. Andersohn and his associates found that the relationship between self-harm and depression-inducing AEDs existed only in patients with a psychiatric disorder (OR, 8.48).

They also examined the risk associated with each individual AED. Self-harming or suicidal behaviors were not significantly associated with barbiturate AEDs (phenobarbital, primidone, and methylphenobarbital), conventional AEDs (carbamazepine, valproate, phenytoin, ethosuximide, and acetazolamide), or newer AEDs that do not carry an increased risk of depression (oxcarbazepine, lamotrigine, gabapentin, or pregabalin).

Among AEDs associated with depression, levetiracetam was the only agent associated with increased odds for self-harming or suicidal behavior. But this drug was taken by just two cases (0.4%) and eight controls (0.1%).

Dr. Andersohn and his colleagues noted that potential explanations of the biological relationship between AEDs and self-harm have been controversial.

"Drug-induced folate deficiency and enhanced GABA [gamma-aminobutyric acid] neurotransmission, especially in patients with hippocampal sclerosis, have been discussed as potential pharmacologic mechanisms of AED-induced depression and suicidality. However, contradictory data indicate that GABA-active agents can be effective in treating depression."

In an editorial, Dr. Marco Mula and Dr. Josemir W. Sander suggested that other factors may be responsible for this apparent association. For much of the study period, the high-risk AEDs implicated were available only as add-on therapy in the United Kingdom, "suggesting that the exposed patients were receiving these drugs as part of polytherapy regimens. Therefore, these patients possibly had drug-refractory epilepsy, a group that is at the upper end of the suicide risk spectrum" (Neurology 2010;75:300-1).

Additionally, the study could not specifically identify the type of epilepsy for each patient. "In fact, the issue of suicidality in epilepsy needs to take into account all epilepsy variables, but mostly a careful examination of the mental state of the patients," wrote Dr. Mula of the University Hospital Maggiore della Carità in Novara, Italy, and Dr. Sander of the University College London Institute of Neurology.

They noted that recent research suggests that a subgroup of epilepsy patients tends to develop psychiatric side effects whenever a new medication is introduced. "These people are usually drug-refractory, with a previous history, and often a family history, of psychotic disorders and may possibly have a functional abnormality in the limbic system" that predisposes them to self-harming behaviors. ■

VITALS

Major Finding: Newer antiepileptic drugs that pose an increased risk of depression were associated with a significant increase in the odds of suicidal and self-harming behavior (odds ratio, 3.08).

Data Source: A nested, case-control study of 44,300 patients who took at least one AED in 1990-2005.

Disclosures: The study was sponsored by Bayer Schering Pharma, for which one investigator has served as a consultant. Two other investigators reported financial relationships with companies that manufacture AEDs.

Drug-Related Side Effects Still Problem for Epilepsy Patients

BY HEIDI SPLETE

FROM THE ANNUAL MEETING OF THE AMERICAN ACADEMY OF NEUROLOGY

TORONTO – About 40% of epilepsy patients are bothered by side effects of their antiepileptic drugs, based on data from a survey of adults with epilepsy.

Information on the tolerability of antiepileptic drugs (AEDs) and the reasons for discontinuing treatment are limited, said George J. Wan, Ph.D., in a poster presentation.

To examine drug tolerability and treatment satisfaction, Dr. Wan, of Ortho-McNeil Janssen Scientific Affairs LLC, and his colleagues reviewed data from the National Survey of Epilepsy, Comorbidities, and Health Outcomes (EPIC), a large survey conducted in the United States in 2009 that included 7,500 epilepsy patients and 2,500 controls.

The researchers evaluated responses from 5,117 self-reporting epilepsy patients. A total of 2,395 respondents reported being formally diagnosed with epilepsy or a seizure disorder; of those, 1,415 (59%) were taking antiepilepsy drugs at the time of the survey. About 60% of the respondents reported taking one AED, 35% reported taking two or three, and 5% reported taking four or more. The respondents had been taking AEDs for an average of 115 months.

A total of 772 respondents said that they were "not at all" bothered by side effects from AEDs during the 4 weeks leading up to the survey. But 519 respondents reported some degree of bother: 22% were mildly bothered; 12%, moderately bothered; 5%, markedly bothered; and 1%, extremely bothered.

The researchers did not identify specific side effects.

Overall, 72% of the respondents said they were either "somewhat satisfied" or "very satisfied" with their current AED regimens. But a total of 304 respondents said that they had discontinued their medications. Of those, 50% discontinued on their doctor's advice; 45% discontinued because of side effects; 30%, because of improvement in seizures or the disappearance of seizures; and 21%, because of inadequate seizure control. Some respondents indicated more than one reason for discontinuing their AEDs, the researchers noted.

In addition, after controlling for baseline characteristics and lifetime seizures, patients who were taking two or more AEDs were significantly less likely to be satisfied with the side effects compared with those who were taking one AED, the researchers reported.

The study was limited by the use of self-reports, but the results confirm that drug-related side effects remain a significant problem for epilepsy patients and highlight the need to develop more tolerable treatments, the researchers said, adding that "further research is needed to quantify the impact of AED treatment on other patient-reported outcomes, including health status." ■

VITALS

Major Finding: Of patients who stopped taking AEDs, 45% cited side effects as a reason; those taking two or more AEDs were less likely to be satisfied with the side effects than were those taking one AED.

Data Source: National Survey of Epilepsy, Comorbidities, and Health of 7,500 epilepsy patients and 2,500 controls.

Disclosures: The presenter is an employee of Ortho-McNeil Janssen Scientific Affairs LLC, which supported the study.