AES Position on Risk of Suicidal Thoughts and Behavior with Antiepileptic Medications

The FDA issued an alert on January 31, 2008 to health care providers regarding the risk of suicidal thoughts and behavior with antiepileptic drugs (AEDs). Following a preliminary analysis of data from several AEDs that suggested an increased risk of suicidality, in March 2005 the FDA requested this type of data from manufacturers of marketed AEDs for which there were adequately designed controlled clinical trials. The FDA received and reviewed data from 199 placebo-controlled studies of 11 drugs. The drugs included carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide.

The combined analysis of these clinical trials included 43,892 patients; 4 suicides and 105 reports of suicidal symptoms were found among the 27,863 patients who were given the AEDs, compared to 0 suicides and 35 reports of suicidal symptoms among the 16,029 patients treated with placebos. Taken together, the risk of suicidal thoughts and behavior was 0.43 percent for those on drug therapy and 0.22 percent for those given placebos. This risk corresponds to an estimated 2.1 per 1,000 more patients in the drug treatment groups who experienced suicidality than in the placebo groups.

The increased risks began as early as the first week of therapy and did not decrease throughout the duration of the clinical trial. The results were generally consistent among all the different AEDs studied and were seen in all demographic subgroups with no clear pattern of risk across age groups. However, the relative risk for the AED-treated groups compared to placebo group was higher among patients with epilepsy than among those given the drugs for psychiatric or other problems.

All AEDs were associated with a similar risk so it appears to not be specific to a single drug or class of AEDS. The report cautioned patients currently taking antiepileptic medications not to make any changes without first talking to their health care provider.

Future action plans for the FDA include the following. The agency is now requiring that manufacturers in their studies track suicidal symptoms. The FDA will be working with manufacturers of marketed AEDs to include this new information in the labeling for these products. The agency anticipates that labeling changes will be applied broadly to the entire class of drugs. FDA is also planning to discuss these data at an upcoming advisory committee meeting. The following recommendations are for healthcare providers who prescribe AEDs:

- Balance the risk for suicidality with the clinical need for the drug
- Be aware of the possibility of the emergence or worsening of depression, suicidality, or any unusual changes in behavior;
- Inform patients, their families, and caregivers of the potential for an increase in the risk of suicidality so they are aware and able to notify their healthcare provider of any unusual behavioral changes. Symptoms such as anxiety, agitation, hostility, mania and hypomania may be precursors to emerging suicidality.
The epilepsy community has been increasingly aware that epilepsy is more than seizures and is associated with comorbidity. Note that the risk in the placebo arms was also substantial. Treating professionals are also aware of the many risks of taking AEDs including allergic reactions, effects on liver and bone marrow, effects on bone health and teratogenicity. In particular, AEDs are associated with a variety of cognitive and behavioral side effects. It is after all the same neurons whose function we are altering to control seizures that also control behavior. Thus the recent FDA finding is not a complete surprise, especially given the low level of risk reported. The American Epilepsy Society position is and remains that, in the vast majority of patients with epilepsy, the benefits of treatment outweigh the risks. This FDA report, while reemphasizing the need to balance risks of therapy versus benefits and to monitor our patients, does not alter the AES position. The FDA finding will hopefully lead to enhanced awareness among providers about psychiatric comorbidities in our patients, increase communication about emotional well-being between patients, their families, and their providers, and ultimately lead to future studies to better identify and effectively treat psychiatric comorbidities in our patients.

###

The American Epilepsy Society, is the leading organization of clinical and research professionals working to advance and improve the treatment of epilepsy through the promotion of research and education for healthcare professionals. Society membership includes epileptologists and other medical professionals, allied healthcare professionals, and scientists concerned with the care of people who have seizure disorders.

January 2008