Guidelines Reflect Usual Care

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fever—reduces the occurrence of recurrent febrile seizures, whereas daily carbamazepine and phenytoin do not. The adverse effects associated with the effective treatments, however, include behavioral and sleep disturbances and irritability (phenobarbital, primidone); lethargy, drowsiness, and ataxia (diazepam); and rare fatal hepatotoxicity, thrombocytopenia, weight change, gastrointestinal disturbances, and pancreatitis (valproic acid).

Considering the unfavorable benefit-to-harm ratio, "long-term therapy [with these agents] is not recommended," wrote Dr. Patricia K. Duffner and colleagues on the Febrile Seizures Subcommittee of the AAP's Steering Committee on Quality Improvement and Management (Pediatrics 2008;121:1281-6).

"With the exception of a high rate of recurrence, no long-term effects of simple febrile seizures have been identified," the authors stated, noting that studies that looked at whether potential adverse outcomes—such as neurocognitive inattention, behavioral abnormalities, or a decline in IQ and/or academic performance—could be a consequence of recurrent simple febrile seizures have produced no evidence of such.

Although the risk of developing epilepsy is slightly higher in a subpopulation of children who experience recurrent simple febrile seizures relative to the general population, it remains extremely low. The risk of developing epilepsy by the age of 7 years is 1% among children who experience simple febrile seizures, the same as in the general population.

Among children who have had multiple simple febrile seizures, are younger than 12 months at the time of their first febrile seizure, and have a family history of epilepsy, the risk of generalized afebrile seizures developing by 25 years of age is 2.4%, the investigators reported, noting that the increase is most likely the result of genetic predisposition rather than seizure-induced structural brain changes.

The recommendation against using prophylactic antiepileptic medication for simple febrile seizures is consistent with the current standard of care, said Dr. Sheryl Haut, of the Epilepsy Management Center at Montefiore Medical Center and assistant professor of neurology at the Albert Einstein College of Medicine in the Bronx, New York.

The risk of developing epilepsy by age 7 is 1% among both the subset of children with simple febrile seizures and the general population.

"Simple febrile seizures are, by definition self-limited, occurring in children without a known neurologic abnormality. While there are theoretical risks for experiencing any seizure, such as injury to the brain or body, these risks have not been reported in association with simple febrile seizures." The greater concern, Dr. Haut said in an interview, "is that simple febrile seizures will lead to the development of epilepsy, as many patients who develop epilepsy have previously had febrile seizures. However, the current evidence suggests that a shared susceptibility to febrile seizures and epilepsy leads to this association, and it is not the case that the febrile seizures resulted in the development of epilepsy."

With respect to anticonvulsant therapy, "the new guideline basically confirms that things mostly have not changed in terms of therapeutic interventions since the publication of the previous guideline."

"The only thing that has emerged in the interim, which comes up in the guideline, is the possible use of rectal diazepam. This is something that is used for generalized seizures that last more than 10 minutes to break the seizure, and is not recommended for simple seizures. However, for families living far from a medical facility who might be worried about not being able to get help in the case of a complex febrile seizure, some physicians are offering this as a way to provide some assurance." ■

FDA Panels Reject Boxed Warning on Suicidality Risk for Epilepsy Drugs

BY ELIZABETH MECHCATIE
Senior Writer

BELTSVILLE, MD. — A boxed warning about an increased suicidality risk with the use of antiepileptic drugs should not be added to the labels of drugs in this class, but patients prescribed these drugs should receive information about this risk with every prescription, according to the majority of two federal advisory panels.

At a joint meeting of two Food and Drug Administration advisory committees, panel members agreed with evidence indicating an increased suicidality risk, but voted 14-4 with 3 abstentions against a proposal to include it in a black box warning in the labels of all antiepileptic drugs (AEDs). However, most (17-4) voted that patients should receive a medication guide describing the finding with each AED prescription filled.

Among panelists' concerns was that a black box could reduce appropriate prescribing of AEDs and affect compliance. Dr. Daniel Pine, chief of child and adolescent research at the National Institute of Mental Health's mood and anxiety disorders program, Bethesda, Md., advised the FDA to come up with "creative ways, short of a black box" to communicate this information.

The panels reviewed the results of an FDA analysis of data on 11 AEDs that compared the rates of suicidality (episodes of suicidal ideation, suicidal behavior, or completed suicide) between patients in treatment and placebo groups. In a meta-analysis of 199 prospective, randomized, parallel-arm, placebo-controlled trials of 27,863 patients on treatment and 16,029 on placebo, the overall odds ratio for suicidality with treatment was a statistically significant 1.80. Odds ratios for individual AEDs ranged from 0.57 to 2.75. There were four completed suicides among people on treatment (0.1%), and none among those on placebo, and the rate of suicidal behavior or ideation was 0.37% among patients on an AED, and 0.24% among those on placebo.

The AEDs in the meta-analysis were carbamazepine (Carbatrol, Equetro), divalproex sodium (Depakote, Depakote ER), felbamate (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), pregabalin (Lyrica), tiagabine (Gabitril), topiramate (Topamax), and zonisamide (Zonegran). Of the 199 trials, 31% evaluated AED use in epilepsy, 28% were for AED use for 8 psychiatric indications, and 41% were for 11 other indications.

When analyzed separately, odds ratios exceeded 1 (indicating an increased risk) for all but 3 of the 11 AEDs. The odds ratio was under 1 for carbamazepine, which had the second fewest patients in studies; and for divalproex; an odds ratio for felbamate could not be calculated because there were not many patients in the trials and there were no suicidality events among patients on placebo or the drug.

"We're quite comfortable saying there's causality between suicidality and AEDs," Dr. Russell Katz, director of the FDA's division of neurology products, said. The signal was detected across different mechanisms of action, and appeared to be independent of the AED's mechanism.

The statisticians on the panel agreed that the analyses were solid. This is "a signal that is an important one for the field to be aware of," said Andrew Leon, Ph.D., professor of biostatistics in psychiatry, Weill Cornell Medical Center, New York. He and another statistician were among those in favor of the black box.

The panels agreed in a 20-0 vote with 1 abstention that an overall increase in suicidality was shown for the AEDs analyzed, and most agreed (15-5 with one abstention) that this finding should apply to all currently approved, chronically administered AEDs. Dr. Katz said the FDA had proposed applying the warning to all marketed AEDs because limiting the warning to the 11 in the meta-analysis could shift prescribing to others.

During an open public hearing, representatives of the American Epilepsy Society, the American Academy of Neurology, and the Epilepsy Society expressed concerns that a black box warning about suicidality in AED labels could affect patient compliance.

The FDA usually follows the recommendations of its advisory panels, which are not binding. ■

'Classic' EEG Pattern May Not Be So Common

BY AMY ROTHMAN SCHONFELD
Contributing Writer

CHICAGO — Analysis of EEG patterns in a group of drug-naive children diagnosed with absence seizures found that although 80% of individuals demonstrated consistent patterns, only 18% of this group demonstrated the classic pattern commonly described in textbooks, according to Dr. Yoshimi Sogawa.

"Textbooks will tell you that absence bursts are characterized by 3-Hz spike and wave discharges, are nonevolving, and start and end abruptly. What we are finding is that is not true," said Dr. Sogawa, a neurologist at the Children's Hospital at Montefiore, New York.

The study participants, part of the largest cohort gathered to date of children with absence seizures (n = 400), were enrolled in the National Institutes of Health Childhood Absence Epilepsy Trial. Dr. Sogawa analyzed the EEGs of 103 drug-naive children. Of this group, 80 children showed a consistent EEG pattern while 23 who showed intraindividual variability were excluded from further analysis. Making an analogy to a musical sonata, Dr. Sogawa subdivided the 3-Hz spike-wave discharges into multiple components.

Within a burst, she identified five components:

► Introduction (I): initial change from baseline, consisting of irregular slowing with or without spikes.

► Exposition (E): the characteristic 3-Hz spike-wave discharge.

► Development (D): variations on the 3-Hz pattern.

► Recapitulation (R): reemergence of the E-like pattern.

► Coda (C): combination of rhythmic slow activity.

With these elements, Dr. Sogawa found that three predominant patterns emerge. The most frequent combination was the I-E-D-C pattern (59%), followed by the semiclassic I-E-D-R pattern (23.8%), and then the "classic" I-E-C pattern (17%).

"These patterns bring up the question: What is childhood absence epilepsy? It is not a single entity. There are so many variations," according to Dr. Sogawa. This variability certainly brings into question the diagnostic value of the classic EEG pattern.

Dr. Sogawa suggested that the distribution of a particular EEG component may reflect genetic variability, perhaps related to calcium channel function, and may underlie the differences in sensitivity to antiepileptic medications that she often sees. Speaking at the annual meeting of the American Academy of Neurology, Dr. Sogawa said genetic analyses are underway to see how different EEG patterns correlate with drug response and comorbidity.

Dr. Sogawa said she had nothing to disclose. ■