Atomoxetine Found Safe for ADHD Long Term

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CHICAGO — Atomoxetine for the treatment of attention-deficit/hyperactivity disorder is generally safe and well tolerated in children and adolescents for up to more than 4 years of treatment, results of two open-label extension studies show.

Dr. Craig L. Donnelly reported the findings, which were based on 714 children and adolescents who had been treated for more than 3 years and 508 who had been treated for more than 4 years.

No new or unexpected safety or tolerability concerns emerged during more than 4 years of treatment, said Dr. Donnelly, director of child and adolescent psychiatry at Dartmouth-Hitchcock Medical Center, Lebanon, N.H.

The study will be published in the February issue of the Journal of the American Academy of Child and Adolescent Psychiatry.

Previous studies have found treatment of ADHD with atomoxetine to be safe and well tolerated by children and adolescents for 2 years (J. Am. Acad. Child Adolesc. Psychiatry 2006;45:919-27; J. Pediatr. 2006; 149:112-9). The new studies were conducted to determine the safety and tolerability of atomoxetine (Strattera) in children and adolescents who had received treatment for more than 3 or 4 years.

As with previous safety and tolerability reports, "patients experienced significant changes in vitals and growth compared with their baseline; however, changes were within the range of normal development," Dr. Donnelly wrote in a poster at the annual meeting of the American Academy of Child and Adolescent Psychiatry. No clinically significant abnormalities were found in height, weight, blood pressure, mean laboratory values, or electrocardiograms.

Headache was the most common adverse event, reported by just over half of the patients, and fewer than 2% had significant changes in hepatic function.

The participants (aged 6-17 years; mean age at baseline 10.5 years) came from 13 double-blind, placebo-controlled trials and 3 open-label extension studies. They met DSM-IV diagnostic criteria for ADHD at entry into their initial studies. Researchers measured vital signs, electrocardiogram, weight, growth, hepatic function, treatment-emergent adverse advents, and reasons for discontinuation, and compared changes from baseline to end point.

The most common treatment-emergent adverse event was headache, reported by 53.9% of patients who had been taking the medication for more than 3 years and 53.7% of patients who had been taking the medication for more than 4 years. Other common treatment-emergent adverse events included nasopharyngitis (37.8%, 37.6%), vomiting (37.4%, 37.8%), cough (33.6%, 37.0%), upper abdominal pain (32.8%, 33.9%), pharyngolaryngeal pain (32.1%, 34.8%), pyrexia (31.8%, 33.3%), and upper respiratory tract infection (30.8, 32.1).

Fewer than 2% of patients had potentially clinically significant changes in hepatic function test results; two patients discontinued treatment for this reason.

Suicidal ideation and behavior occurred in 1.5% and 0.4% of patients, respectively; no suicides occurred during these studies. Transient aggressive/hostile behavior occurred in less than 6% of patients.

Of the 1,553 patients in the long-term, open-label study, 839 (54%) discontinued treatment before 3 years, citing adverse event (8.5%), perceived lack of efficacy (26.2%), patient decision (49.3%), physician decision (4.5%), satisfactory response (1.9%), and other (9.5%).

The study was sponsored by Eli Lilly & Co. Dr. Donnelly is as a consultant and a member of the speakers bureau for Eli Lilly. He has conducted other research funded by the company. ■

3.4 Events per 1,000 Patients

Antiepileptics *from page 1*

"Pfizer will work closely with the FDA to update the labeling of our antiepileptic medications Lyrica [pregabalin] and Neurontin [gabapentin], in a timely manner," he said.

"We have not heard directly from the FDA, but we will work to address any of the agency's concerns," said Tricia Geoghegan, a spokesperson for Ortho-McNeil Neurologics, makers of topiramate.

Ms. Geoghegan noted that the label for Topamax (topiramate) has always included "content about this topic," but added that revisions will be made should the FDA request them.

The agency's decision drew on data from placebo-controlled clinical trials that enrolled a total of 43,892 patients aged 5 and older taking the medications for epilepsy, psychiatric disorders, and other conditions.

The FDA meta-analytic review of 199 trials determined that patients receiving antiepileptic drugs were at a twofold risk of suicidal behavior or thoughts (0.43%), compared with patients receiving placebo (0.24%). The difference translates to 1 additional case of suicidality per 530 patients treated with antiepileptic drugs.

The relative risk for suicidality was highest among patients receiving drugs for epilepsy (3.5), compared to psychiatric (1.5) and other indications (1.9).

However, the absolute rate of events was highest in psychiatric patients (8.5 suicidality reports per 1,000 patients receiving antiepileptic medications, compared with 5.7 per 1,000 for psychiatric patients taking placebo).

Among epilepsy patients, 3.4 events per 1,000 were reported for those receiving antiepileptic medications, compared with 1.0 for those assigned to receive placebo.

Not enough evidence could be gleaned from the reviewed investigations to determine whether patients taking antiepileptic drugs are also at risk for completed suicides, the FDA concluded.

Four patients who were randomly assigned to receive antiepileptic drugs committed suicide during the trials that were examined by the FDA, while no patient assigned to placebo took his or her own life.

Those numbers, however, were not high enough to justify a warning of suicide on drug labeling, the press release stated.

"The biological reasons for the increase in the risk for suicidal thoughts and behavior observed in patients being treated with antiepileptic drugs are unknown," according to the FDA.

A review article about suicidality and antiepileptic medications noted that the baseline suicide rate among patients with epilepsy is 5 times higher than that seen in the general population, and higher still (25-fold) in patients with temporal lobe epilepsy and complex partial seizures (Drug Saf. 2007;30:123-42).

Although that article commented on antiepileptic medications' disparate mechanisms of action and varying effects on serotonin metabolism (a hypothesized link to suicidality), the FDA report found that the risk for suicidal thought or behavior was "generally consistent" among the 11 drugs studied.

As the name implies, antiepileptic drugs were introduced and approved for the treatment of seizures. However, they are prescribed for many psychiatric conditions, including bipolar disorder, depression, and anxiety; neuropathic and chronic pain; and migraine headaches, among other conditions.

"Patients being treated with antiepileptic drugs for any indication should be monitored for the emergence of worsening of depression, suicidal thoughts, or behavior, or any unusual changes in mood or behavior," said Dr. Russell Katz, director of the division of neurology products in the FDA's Center for Drug Evaluation and Research, in a press release.

"Symptoms such as anxiety, agitation, aggression, hostility, mania, and insomnia may be precursors to emerging suicidality," the alert stated.

Physicians were asked to:

► Balance the risk for suicidal thoughts or behavior with the clinical need for the drug and the risk associated with untreated illness.

► Be aware of the possibility of, and monitor for, the emergence or worsening of depression, the emergence of suicidal thoughts or behavior, and any other unusual changes in mood or behavior.

► Understand that morbidity, mortality, and increased risk of suicidal thoughts and behaviors are associated with epilepsy and other illnesses for which antiepileptic drugs are prescribed, independent of treatment with antiepileptic drugs.

In addition, physicians were urged to review with patients and families common signs of depression and warning signs of suicidal behavior, including talking or thinking about taking one's life, becoming preoccupied with death and dying, withdrawing from friends and family, and giving away possessions.

Although physicians were encouraged to discuss the risks and benefits of continuing treatment, they were also urged to warn patients and families against stopping medications abruptly. ■

The FDA's health care alert is available at www.fda.gov/cder/drug/InfoSheets/HCP/antiepileptics200812.htm.

Agents to Receive Suicidality Warnings

The Food and Drug Administration called for new labeling for the following medications, some of which also are available as generic formulations:

Carbamazepine (marketed as Cabatrol, Equetro, Tegretol, Tegretol XR)
Clonazepam (Klonopin)
Clorazepate (Tranxene)
Divalproex sodium (Depakote, Depakote ER, Depakene)
Ethosuximide (Zarontin)
Ethotoin (Peganone)
Felbamate (Felbatol)
Gabapentin (Neurontin)
Lamotrigine (Lamictal)
Lacosamide (Vimpat)
Levetiracetam (Keppra)
Mephenytoin (as Mesantoin)
Methosuximide (Celontin)
Oxcarbazepine (Trileptal)
Phenytoin (Dilantin Suspension)
Pregabalin (Lyrica)
Primidone (Mysoline)
Tiagabine (Gabitril)
Topiramate (Topamax)
Trimethadione (Tridione)
Zonisamide (Zonegran)