Donepezil May Improve Some Autism Symptoms

BY BETSY BATES
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STANFORD, CALIF. — A preliminary analysis of a randomized, double-blind, placebo-controlled study of donepezil suggests that the Alzheimer's drug may slightly improve some neuropsychologic functions in children with autism, Dr. Antonio Hardan said at a pediatric update sponsored by Stanford University.

At the halfway point in a 20-week trial, improvements were seen in scores on the some, but not all, neurocognitive tests among 10 autistic children aged 7-17 years receiving the drug, compared with 10 receiving placebo.

Specifically, children somewhat improved their performance on tests aimed at measuring spatial executive functioning (the Design Fluency Test), selective attention (the Color-Word Interference Test) and the California Verbal Learning Test.

"We didn't see magic improvement or large improvements," said Dr. Hardan, director of the autism and developmental disabilities clinic at Lucile Packard Children's Hospital of Stanford (Calif.) University.

No improvement was seen on the Expressive One-Word Vocabulary Test, which measures language skills.

The trial is small and incomplete, and the results should be interpreted with caution, Dr. Hardan said, but "it opens up a whole group of medications to study."

The use of donepezil (Aricept) in autism was first studied by Dr. Hardan at the University of Pittsburgh in an open-label study of eight children, half of whom demonstrated improvement on the Aberrant Behavior Checklist and Clinical Global Impression Scale. Improvements were suggested in irritability and hyperactivity, but not in inappropriate speech, lethargy, or stereotypies, he reported (J. Child Adolesc. Psychopharmacol. 2002;12:237-41).

Another novel study of an existing drug in autism is ongoing at Indiana University, Indianapolis, where a broad-spectrum antibiotic once used to treat tuberculosis led to apparent improvement in social withdrawal in a pilot study. A randomized, double-blind study is currently underway, pitting d-cycloserine, a partial agonist of the *N*-methyl-D-Aspartate (NMDA) glutamate receptor subtype, against placebo, Dr. Hardan said. Although these are small studies, it is encouraging to see research into existing drugs to determine whether they might be effective in treating children with autism spectrum disorders, he said.

It took 15 years for risperidone (Risperdal) to be approved for the treatment of autism-related irritability, noted Dr. Hardan, who published an early case study suggesting the drug's efficacy in 1996. Parents who must wait so long for drug approval feel they are "losing a lot of time," he said. "That's why they jump at any opportunity [to use a treatment, even one] that could be potentially hazardous for their child."

Dr. Hardan stressed that research must be driven by theories that make scientific sense, followed by proof-of-concept studies to see whether evidence exists that an agent may be helpful.

He pointed to "the [high] price of shortcuts," such as secretin, hailed as a possible treatment based on one uncontrolled observational study that hinted it may have improved behavior in three children undergoing gastrointestinal procedures. No verification was made to determine whether the children actually met diagnostic criteria for autism, he noted. "Based on this, secretin was unfortunately the most studied medication in autism."

Fifteen randomized, double-blind studies eventually produced uniformly negative results. "You can't find anything consistent like that in medicine," he said.

The scientific community needs to "get realistic" when it comes to funding potentially beneficial treatments, he urged. ■

Is Autism on the Rise or Is the Diagnosis Expanding?

An apparent increase in the prevalence of autism and autistic spectrum disorders (ASDs) may be largely explained by differences in diagnosis, rather than true differences in the number of children with these conditions, Dr. Hardan suggested.

"Is there an increase in incidence versus an increase in recognition?" asked Dr. Hardan. Several observations point to the latter, he said.

Much of the increase in prevalence is among children with mild symptoms: children with high-functioning autism, those with Asperger's syndrome, and children with pervasive developmental disorder, not otherwise specified.

"Fifteen or 20 years ago when somebody was verbal, it was very unlikely people were going to consider this an autism spectrum disorder," he said.

On the other end of the spectrum, children with moderate to severe mental retardation were given that diagnosis decades ago, whereas today many children receive the autism diagnosis.

Traditionally, autism spectrum disorders were exclusively made in school-age children. "Now people in their 20s and 30s who are struggling in daily living activities come to us and ask: 'Do I have an autism spectrum disorder?' Sometimes, some people do," said Dr. Hardan, but a diagnosis in adulthood would have been unthinkable years ago.

Another important contributor to the apparently increasingly prevalence of autism is simple misdiagnosis, he maintained.

Children with ADHD often have social deficits, difficulties in developing peer relationships, and what Dr. Hardan described as "poor coherence between visual and verbal behaviors." But what may resemble autism or an autistic spectrum disorder, often is not.

Children frequently referred to the clinic at Stanford who are misdiagnosed as autistic include those with severe anxiety symptoms, early onset personality disorders, and reactive attachment disorders. Children in the latter category, often adopted from overseas, have many features that could lead a clinician to mistakenly diagnose autism, including severe social deficits and stereotypical behaviors.

Methodological factors may also have contributed to apparent increases in autism prevalence, as depicted in a recent article, "The autism epidemic: fact or artifact?" (J. Am. Acad. Child Adolesc. Psychiatry 2007;46:721-30).

MRI Imaging Is Key

Autism *from page 1*

autistic children is significantly larger than their age-matched peers. In adulthood, the brain size of individuals with autism appears to normalize or even atrophy slightly, but the head circumference in about 20%-30% of individuals with autism will remain larger than normal.

"The brain can shrink, but the cranial box cannot," Dr. Hardan noted.

A study conducted at the University of Pittsburgh found that despite differences in early childhood, by age 12, brain volumes among children with autism were no different than in normally developing children, when controlling for height (Neurology 2002;59:175-83).

Research from the University of California, San Diego, found that patterns of brain growth were irregular in very young children with autism, with 2- and 3-year-olds possessing 39% more cerebellar white matter, 18% more cerebral white matter, and 12% more cerebral cortical gray matter than their peers, but with differences dissipating as the children grew older (Neurology 2001;57:245-54). Abnormally accelerated growth of some regions of the brain gave way over time to abnormally slowed brain growth.

New work from Dr. Hardan's group has found that among children aged 8-12 with autism, compared with healthy controls, increases in gray matter volume and total brain size may be explained by marked increases in total sulcal and gyral thicknesses in the cerebrum and temporal and parietal lobes, but not in the frontal and occipital lobes.

Cortical thickness, striking in young children, also decreases over time, he reported.

Importantly, cortical thickness abnormalities in autism can be distinguished from those in children with attention-deficit/hyperactivity disorder, which are thinner at baseline than in normal children and continue to decrease over time. The specific patterns of cortical thickness abnormalities may offer important new clues as to the underlying defects in neural circuitry that may explain behavioral and social deficits in children with autism, he explained.

Dr. Hardan also underscored the importance of functional MRI imaging for children with autism.

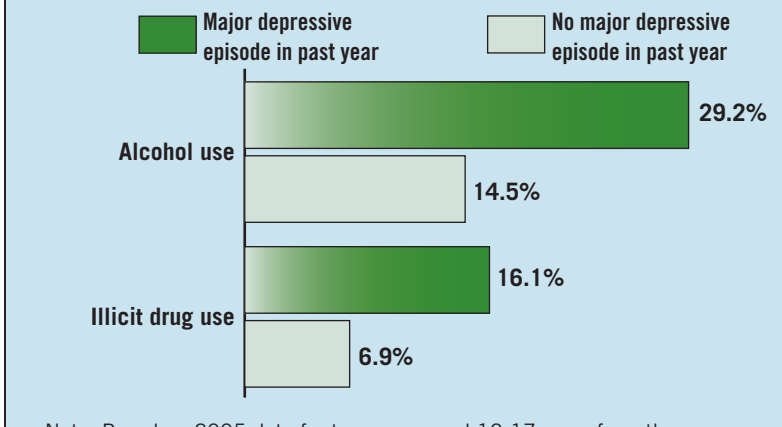
Rather than looking at the brain itself, this approach studies cortical activation within the brain as children with autism are shown images of faces or objects. Unlike in normal children, the fusiform gyrus is activated when children with autism look at objects, not faces.

Related research has been able to track the visual focus of very young children and has demonstrated that those with autism focus on the chin or cheek of a human face, rather than the eyes, as is the case for normal subjects shown still images or movies. The same pattern has now been seen in how toddlers at high risk of developing autism focus on their mothers' faces, he said.

The technique might be used to intervene early with children at risk for autism, and also can be used to objectively measure improvement when medications or behavioral interventions are employed in an attempt to improve the condition. "It's a very exciting area of research," Dr. Hardan said. ■

DATA WATCH

Initiating Substance Use Linked With Major Depressive Episodes in Teenagers



Note: Based on 2005 data for teenagers aged 12-17 years from the National Survey on Drug Use and Health.
Source: Substance Abuse and Mental Health Services Administration