

THE WAITING ROOM

THIS WAY IN

Are the Proposed Criteria for Diagnosing Autism Spectrum Disorders Too Restrictive?

BY OLGA RUKOVETS



A proposed change in the way autism spectrum disorders (ASDs) are diagnosed has some doctors, patients, and parents concerned that specialized services in schools and institutions may be compromised.

The American Psychiatric Association has proposed in its fifth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM)—the reference manual for mental health disorders in the United States—that the subcategories of ASD be eliminated. As a result, the new manual would subsume Asperger's syndrome and pervasive developmental disorder-not otherwise specified (PDD-NOS) under the single category of autism spectrum disorder (ASD).

Ginny Kelly, who serves on the board of the Autism Society of Acadiana in Louisiana, worries that her 18-year-old son, Johnathan, who has Asperger's, would not be considered on the autism spectrum under the new criteria—which could affect his eligibility for services. “Why would we want to dismiss a tangible diagnosis when we’re finally beginning to make strides in treatment?” Kelly asks. (The American Psychiatric Association will be inviting public comment during the spring of this year—go to dsm5.org for more information.)

WHY CHANGE THE CRITERIA?

Autism is a developmental disorder that appears in the first three years of life, affecting the brain's normal development of social and communication skills. Asperger's syndrome is often considered a high-functioning form of autism. PDD-NOS is an ASD that does not fully meet the criteria for autism or Asperger's syndrome.

The changes to the DSM are largely a response to concerns that the current criteria are

too broad, resulting in overdiagnosis and misdiagnosis of children who either do not have ASD or have other disorders with similar symptoms, such as ADHD, obsessive-compulsive disorder, and social anxiety disorder. Misdiagnosis can be especially harmful when children are put on inappropriate medications.

But some experts believe the proposed criteria are too restrictive and would lead to the loss of services for higher-functioning individuals who have ASD, such as those with Asperger's syndrome. The new criteria do provide fewer ways to diagnose someone in terms of combinations of symptoms. (Visit <http://bit.ly/zPRYyq> to see a full comparison of the criteria, and go to <http://bit.ly/yhitgq> for the American Academy of Neurology's guidelines on screening and diagnosing of autism.)

Fred R. Volkmar, M.D., Irving B. Harris Professor in the Child Study Center and Professor of Pediatrics, Psychiatry, and Psychology and chief of child psychiatry at Yale-New Haven Children's Hospital, says that changing the criteria could make it more difficult to interpret study results. “If you start changing the diagnostic criteria too much, understanding the results of clinical trials becomes more complicated because you're looking at different populations,” says Dr. Volkmar, who resigned from the DSM-5 Committee because he disagreed with the process.

FOR THE SAKE OF CLARITY

According to Rebecca Landa, Ph.D., director of the Center for Autism & Related Disorders at Kennedy Krieger Institute in Baltimore, MD, the new criteria are mostly a reorganization of the current ones. “They provide more information about symptoms

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and enable health care professionals to rate ASD from mild to very severe. Importantly, the new criteria eliminate some of the confusion that results when, for example, one doctor diagnoses a child with PDD-NOS, and another diagnoses the same child with autism,” Dr. Landa says.

Max Wiznitzer, M.D., an associate professor of pediatric neurology at Case Western Reserve University in Cleveland, OH, and a Fellow of the American Academy of Neurology, agrees. He states that the DSM-5 eliminates subgroups solely for the sake of clarity, not to exclude anyone from diagnosis. “Although we know differences exist in ASD, where we draw the lines between these subgroups causes confusion,” Dr. Wiznitzer says. Because ASD is a disorder that often passes through many different hands—neurologists, psychiatrists, psychologists, school counselors—it is very important to have a detailed and uniform system of diagnosis, he says. Ultimately, though, the diagnostic criteria are only as good as the specialist using them, stresses Dr. Wiznitzer.

MORE ACCURATE DIAGNOSIS?

An analysis published online in the *Journal of the American Academy of Child & Adolescent Psychiatry* in November 2011 suggests that the proposed criteria are better at ensuring that young people without an ASD are not mistakenly diagnosed with one.

Using a large Internet-based registry, researchers compared caregiver-reported symptoms of 14,744 siblings (8,911 with ASD and 5,863 without ASD) from two questionnaires in order to test different statistical models for diagnosing ASD. The

best model had two categories—people with autism and people without autism. “Furthermore, the ‘autism’ category had only two symptom dimensions: one was social communication and interaction, and the other was repetitive behavior. This is in keeping with the general structure of the proposed [DSM-5] diagnostic criteria,” says lead study author Thomas W. Frazier, Ph.D., of the Cleveland Clinic Children’s Hospital Center for Autism and Center for Pediatric Behavioral Health in Cleveland, OH. (In contrast, the current criteria have three symptom dimensions: social communication, social interaction, and restriction/repetitive behavior.)

However, when Dr. Frazier and colleagues analyzed caregiver-reported symptoms associated specifically with high-functioning ASD, they found that the proposed criteria could exclude anywhere from 20 percent to 40 percent of people with very high-functioning ASD, he says. “If you have folks who no longer meet the diagnostic criteria for ASD, then the question becomes: Would they meet the criteria for something else? And would that something else be sufficient for them to get the services that they need?” Dr. Frazier asks.

According to Dr. Wiznitzer, the database that Dr. Frazier used cannot accurately measure potential exclusion because it contains caregiver-reported data without the validation of an ASD expert—and because the symptoms for high-functioning ASD used in the analysis were imprecise. Dr. Wiznitzer says the take-away message of the study is that the new criteria will lead to more accurate diagnosis.

For an extended conversation on the proposed revision, listen to a podcast with Dr. Thomas W. Frazier at bit.ly/wfzqrG.

AAN EVENT

Second Annual Brain Health Fair

On Saturday, April 21, the American Brain Foundation—formerly the American Academy of Neurology (AAN)

Foundation—hosted its second annual Brain Health Fair, a free, day-long event connecting patients, families, and caregivers affected by a neurologic disorder with important resources to battle brain disease (BrainHealthFair.com).

The event was held on the opening day of the 64th Annual Meeting of the AAN, which brought thousands of neurologists to New Orleans. The Brain Health Fair also coincided with the start of “Brain Health



Awareness Week,” as declared by Louisiana Governor Bobby Jindal.

As part of the keynote address, the Foundation presented Steve Gleason with a National Achievement Award for his extraordinary efforts to increase awareness about amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig’s disease). A former professional football player, Gleason made history for the New Orleans Saints when he blocked a punt against the Atlanta

Falcons in 2006 that led to the Saints’ first touchdown at home since Hurricane Katrina devastated the city. In 2011, Gleason revealed that he had been diagnosed with ALS. (Go to neurologynow.com to watch the keynote speech video.)

Attendees of the Brain Health Fair had the opportunity to attend free classes taught by leading neurologists about the latest research advances in Alzheimer’s disease, autism, brain injuries, epilepsy, headaches, multiple sclerosis, Parkinson’s disease, sleep disorders, stroke, and other types of neurologic disease. *Neurology Now* was one of the many sponsors of the event, where Editor-in-Chief Dr. Robin Brey was on hand to answer questions and chat with readers of the magazine. (Go to neurologynow.com to watch a video interview with Dr. Brey.)

New Migraine Guidelines from the American Academy of Neurology

If you are one of the roughly 30 million Americans who has migraines—recurrent headaches lasting from 4 to 72 hours and usually characterized by throbbing pain, nausea, vomiting, and extreme sensitivity to light or sound—you might benefit from preventive therapy, which involves taking a medication regularly instead of only when a headache strikes.

In fact, nearly 38 percent of people with migraines could benefit from preventive treatment, according to one study—but less than a third of patients take advantage of preventive treatment.

Now, two new guidelines from the American Academy of Neurology (AAN) and the American Headache Society provide an informed review of the evidence for a variety of pharmaceutical and complementary treatments for migraine prevention. Many experts suggest that if you have migraine attacks very frequently and find that acute medication (taken at the onset of pain) is not working or is causing side effects, preventive therapy may be appropriate.

Lead author Stephen D. Silberstein, M.D., professor of neurology and director of the Jefferson Headache Center at Thomas Jefferson University in Philadelphia, PA, and a Fellow of the AAN, says the pharmaceutical drugs shown to be effective by a high level of evidence (at least two consistent Class I studies) include the antiepileptic drugs topiramate (Topamax), sodium valproate (Epilem), and divalproex sodium (Depakote); and some beta blockers, including metoprolol (Lopressor, Toprol), propranolol (Inderal), and timolol (Istalol). For the short-term prevention of migraines associated with a woman's menstrual cycle, the use of frovatriptan (Frova) was shown to be effective.

A Class I study is a randomized, controlled clinical trial, which means people are chosen in adherence to rigorous criteria and then assigned at random to either a specific medical treatment or a placebo (sometimes known as a sugar pill). This type of study is also called placebo-controlled. (For more on levels of evidence and the classification of trials, see our articles: <http://bit.ly/gT-Ap6> and <http://bit.ly/NNProof>.)

“These drugs have been shown through well-designed, placebo-controlled trials to prevent migraine,” Dr. Silberstein says. “As a doctor, it's always important to know as much as possible about the medications you are prescribing. Particularly, have they been shown to work?”

The absence of such evidence doesn't mean a drug won't

work, Dr. Silberstein adds. “But it is and always has been good practice to know the evidence in order to make your own informed decisions,” he stresses.

The second guideline looks at complementary treatments and nonsteroidal anti-inflammatory drugs (NSAIDs) for migraine prevention. Butterbur, an herbal preparation, was shown to be effective by a high level of evidence, the authors wrote. Therapies that were shown *probably* to be effective (at least one Class I study or two Class II studies, which are considered less reliable than Class I studies) include the NSAIDs fenoprofen (Nalfon), ibuprofen (Advil, Motrin), ketoprofen (Orudis, Oruvail), naproxen (Aleve, Naprosyn), and naproxen sodium (Naprelan); the supplement magnesium; vitamin B2 (riboflavin); and the herbal preparation feverfew (MIG-99). These treatments are often used in people who prefer not to use prescription pharmaceutical drugs or in combination with those drugs in order to enhance their benefit, Dr. Silberstein says.

However, complementary treatments—including vitamins, supplements, and herbal preparations—are drugs, stresses Gary Gronseth, M.D., professor and vice chairman of the neurology department at the University of Kansas in Kansas City, Fellow of the AAN, and member of the *Neurology Now* Editorial Advisory

Board. “There is nothing intrinsically safe about them just because they don't require a prescription. Like all drugs, they have side effects and interact with other medications. Feverfew, for example, can interact with other drugs that are metabolized by the liver. Some of these interactions can be very serious.”

Migraine management still requires some trial and error on the part of doctor and patient—using available evidence from guidelines and knowledge of side effects, according to Dr. Silberstein.

“There's no way of knowing in advance who is going to respond to which medica-

tion,” he says. For example, “topiramate is frequently associated with weight loss, so we might pick that as the drug of choice for someone who is overweight. We might prescribe tricyclic antidepressants, which have been associated with weight gain, in a patient who needs to gain weight,” he says.

Dr. Silberstein also cautions that not enough clinical evidence has been gathered to support the use of any one migraine treatment over another—that's an important research question that still needs to be addressed.

Most important, though, the guidelines show that many effective treatments are available for migraine, according to Dr. Silberstein. “Not all of them will work for everyone, but we do have options,” he says.

To access the full AAN guidelines for the prevention of migraine, visit www.aan.com/guidelines.

Go to neurologynow.com to watch a video interview with Dr. Gronseth about the new AAN migraine guidelines. —*Olga Rukovets*



IN THE PIPELINE

Skin-Cancer Drug Tested in Mice with Model of Alzheimer's Disease



A study released this February in the online version of the journal *Science* suggests that the drug bexarotene, which is approved by the U.S. Food and Drug Administration (FDA) for treating skin cancer, may also be beneficial in treating Alzheimer's disease (AD). Researchers at Case Western Reserve University in Cleveland, OH, found that bexarotene helped increase levels of apolipoprotein E (APOE) in mice whose brains had been genetically engineered to model aspects of AD damage. APOE helps carry cholesterol and other fats through the bloodstream.

That boost in APOE led to the clearing of a protein called amyloid beta and to improved behavior in the mice. One of the hallmarks of AD is the accumulation of amyloid beta between nerve cells (neurons) in the brain. In a healthy brain, amyloid beta is broken down and eliminated; in AD, it accumulates to form hard plaques.

"We were able to reverse all the cognitive problems in these mice with AD," says principal investigator Gary E. Landreth, Ph.D., director of the Alzheimer Center at Case Western. "What this suggests is that, in mice, the AD process is fully reversible in the early stages of the disease. Bexarotene is the best drug anyone has ever seen in a mouse."

News of the study spread fast. Neurologists and patient advocacy groups around the country were overwhelmed with calls from patients and caregivers asking to receive the drug. However, experts warn that just because a medication works in the lab doesn't mean it will be safe and effective in humans.

"We've seen other treatments that work in animal models of AD but don't work in people," says Rachelle S. Doody, M.D., Ph.D., Fellow of the American Academy of Neurology and director of the Alzheimer's Disease and Memory Disorders Center at Baylor College of Medicine in Houston, TX.

"This was a mouse study, and mice are not a great model of the disease," adds Dr. Landreth. The reason? Mice only live to be two years old and don't lose neurons, which is a hallmark of the disease in people.

Before bexarotene could become available to humans as an AD treatment, its safety and effectiveness would have to be proven in human trials. That process could take five to seven years and cost hundreds of millions of dollars, Dr. Landreth says.

"If the drug doesn't get into the human brain, we pack up and go home. If it doesn't affect signs of the disease, such as the amount of amyloid beta in the brain, then we also pack up and go home. If we fail, we want to go on to the next thing." —*Todd Farley*

Help the American Brain Foundation Cure Brain Disease

The American Brain Foundation—formerly the American Academy of Neurology (AAN) Foundation—recently announced its goal of becoming



the world's leader in raising money for research to cure brain diseases, such as Alzheimer's disease, stroke, Parkinson's disease, autism, and epilepsy. Since 1993, the Foundation has raised more than \$16 million dollars for research. The name change and new look are part of its intensified effort to lead the fight for cures.

"This is an exciting chapter in our organization's history as we aim to become the leader in funding research to cure brain disease, which affects more than 50 million Americans," says John Mazziotta, M.D., Ph.D., Chair of the American Brain Foundation's Board of Trustees and Professor and Chair of UCLA's Department of Neurology and Brain Mapping Center in Los Angeles. "Brain disease is in the news every day, yet research funding is flat. Thankfully, we have tremendous treatments on the horizon and a more knowledgeable and concerned public to help us in this fight to cure brain disease once and for all."

"Whether you are a patient, caregiver, neurologist, researcher, or someone who cares deeply about our cause, we are counting on you to join us in this fight by making a donation today at www.CureBrainDisease.org," says Dr. Mazziotta.