Drugs Remain Secondary in Autism Treatment

Psychopharmacologic agents are frequently used but still do not correct the core deficits of the disorder.

BY JEFF EVANS
Senior Writer

BALTIMORE — Psychopharmacologic medications now are often used to alleviate or modify behavior symptoms or comorbid disorders in children with autism, but they do not appear to correct the disorder's core deficits, Scott M. Myers, M.D., said at a meeting on developmental disabilities sponsored by Johns Hopkins University.

The goals of treatment for children with autistic spectrum disorders include maximizing their functional independence and quality of life; promoting their learning, development, and socialization; and alleviating family distress. The reduction of maladaptive behaviors may help to achieve these goals, stressed Dr. Myers, a neurodevelopmental pediatrician at the Geisinger Medical Center in Danville, Pa.

"I think it's important to focus on treating the specific impairments rather than [on] the diagnostic categorization," he said.

Dr. Myers said he considers using psychopharmacologic medications when behaviors and symptoms interfere with learning and academic performance, socialization, health and safety, and quality of life. Examples of target behaviors include hyperactivity, aggression, self-injury, inattention, mood lability, sleep disturbance, anxiety, and interfering repetitive behaviors.

The Food and Drug Administration has not approved any drug for the treatment of autism in children or adults.

Studies involving more than 2,000 families with an autistic child in North Carolina and Ohio found that about 45%-50% of children with autism were taking psychotropic medication. In these studies, 22% of the children received antidepressants, 15%-17% took antipsychotics, and 11%-14% took stimulants. About 12% of children with autism were taking anticonvulsants (J. Child Adolesc. Psychopharmacol. 2002;12:311-21; J. Autism Dev. Disord. 2003;33:527-34).

But despite their frequent use, medications take a secondary role to educational and behavioral interventions in the treatment of autistic spectrum disorders, he said.

Sometimes medical or environmental factors may cause or exacerbate a behavior or set of behaviors. Pain or discomfort may be the result of an infection, a dental problem, constipation, occult fracture, headache, esophagitis, gastritis, or allergies. Obstructive apnea can interfere with sleep and contribute to daytime behavior problems. Seizures may require treatment, and the medications used to treat them can affect behavior. Iron or zinc deficiency may be a treatable cause of pica.

Awareness of these potential factors will help to direct appropriate therapy, Dr. Myers said. He advises beginning with low doses that are carefully titrated because autistic patients may require very low or very high doses of psychopharmacologic medications, especially the serotonergic agents. Changes in medications or doses should not be made hastily, and only one change in medication should be made at a time.

Fluoxetine is the best studied of the SSRIs in children with autistic spectrum disorders, but no double-blind controlled trials have been conducted.

► **Selective serotonin reuptake inhibitors (SSRIs).** Fluoxetine (Prozac) is the best studied of the SSRIs in children with autistic spectrum disorders, although no double-blind controlled trials have been conducted. In a study of 129 children with autism aged 2-8 years, 17% had an excellent response and 52% had a good response to treatment with fluoxetine at 0.15-0.5 mg/kg for a mean of about 3 years. The highest-functioning children benefited most from fluoxetine, as did those with hyperlexia, a family history of major affective disorder, or a family history of unusual intellectual achievement (Dev. Med. Child Neurol. 2002; 44:652-9).

Limited evidence exists for choosing any one specific SSRI over another. Instead, it may be best to consider the drug's half-life and capacity to inhibit cytochrome P450 enzymes. Fluoxetine, sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), and escitalopram (Lexapro) are available in liquid form, he added.

Most of the benefits that may occur with SSRI therapy in children with autism are reflected in improved ratings of affect, general behavior, social interaction, rituals, perseveration, stereotypy, and depressive symptoms. SSRIs have been noted to cause adverse reactions in these patients.

► **Atypical antipsychotics.** Two double-blind, placebo-controlled trials have demonstrated positive responses to the atypical antipsychotic risperidone (Risperdal). In these two trials totaling 132 patients, 57%-69% of patients responded positively to risperidone, compared with 6%-12% of placebo patients (Arch. Gen. Psychiatry 1998;55:633-41; N. Engl. J. Med. 2002;347:314-21).

Reports of the use of other atypical antipsychotics—such as olanzapine (Zyprexa), quetiapine (Seroquel), and ziprasidone (Geodon)—have come from small case series or open-label studies with some success in about half of patients.

► **α-2 Adrenergic agonists.** Very little empirical evidence exists for the use of these agents, which include clonidine (Catapres) and guanfacine (Tenex), in children with autism. Two small (eight and nine patients), double-blind, controlled trials of clonidine each demonstrated modest, short-term improvement in inattention, hyperactivity, impulsivity, and hyperarousal behaviors (J. Clin. Psychopharmacol. 1992;12:322-7; J. Clin. Psychiatry 1992;53:77-82). A retrospective study of guanfacine showed that 24% of 80 patients aged 3-18 years had clinically improved hyperactivity, inattention, and tics (J. Child Adolesc. Psychopharmacol. 2004;14:233-41). Additional research is warranted.

► **CNS stimulants.** Methylphenidate has proved to be effective in improving hyperactivity, impulsivity, and inattention in some patients without worsening behavior or increasing symptoms, such as stereotypies or irritability, but such is not the case for all patients, Dr. Myers said.

► **Anticonvulsants.** In an open-label study of valproic acid, 10 of 14 patients had a sustained clinical response with decreases in affective instability, impulsivity, aggression, and core symptoms. All of the patients who had any electroencephalograph abnormalities or seizures responded to valproic acid (J. Clin. Psychiatry 2001;62:530-4). Lamotrigine (Lamictal) did not have any noticeable effects separate from placebo in a double-blind trial of 28 autistic patients, despite some encouraging results in a previous open-label trial (J. Autism Dev. Disord. 2001;31:175-81; Neuropediatrics 1994;25:284-9). ■

Link Found Between Maternal Asthma/Allergy and Autism

BY KERRI WACHTER
Senior Writer

WASHINGTON — Maternal asthma and allergic disorders may somehow be linked with autism spectrum disorders, according to preliminary research presented at a meeting of the Centers for Disease Control and Prevention's National Center for Birth Defects and Developmental Disabilities.

Mothers of autistic children were more likely to have asthma or allergic disorders than the mothers of healthy control children in a study of 2,500 children, said Lisa Croen, Ph.D., a researcher at Kaiser Permanente Northern California, Oakland.

Immune function abnormalities have been widely reported in association with autism, though the evidence has been largely anecdotal.

For the study, the researchers identified 407 children in an outpatient database (for Northern California) who were born between January 1995 and June 1999 and were diagnosed with an autism spectrum disorder. As controls, healthy children (2,095) were randomly sampled and frequency-matched on birth year, gender, and birth hospital.

Maternal disease status was determined based on diagnoses in the period 2 years prior to and 2 years after giving birth. The researchers specifically looked at diagnoses of 44 autoimmune diseases, such as psoriasis and type 1 diabetes; asthma; and allergic disorders, such as allergic rhinitis, conjunctivitis, atopic eczema, angioedema, anaphylaxis, and urticaria.

The group of autistic children was predominantly male (82%). Children in the autism group were more likely to be twins. Mothers of autistic children were slightly older than the mothers of control children. There was a strong association between increasing maternal education and autism.

The researchers found that 16% of the mothers of autistic children were diagnosed with asthma during the 5-year period surrounding their pregnancies, compared with 11% of the mothers of healthy children. Likewise, one-quarter of the mothers with autistic children had an allergic disease, compared with 18% of the control mothers. "Allergic rhinitis was the particular finding that drove the allergy finding," Dr. Croen said.

Whether the mother was diagnosed with asthma or allergy made no difference in terms of the child's risk of autism. Mothers diagnosed with asthma at any time prior to, during, and after pregnancy, always had a greater risk of having a child with autism than healthy mothers. Although the same was true for mothers with allergic disorders, the associations were not as strong.

The researchers also looked for associations between medications that mothers were taking and the frequency of autism in the children, to see if this could account in part for the association between maternal asthma/allergy and autism. They found no correlation between asthma or allergy medication use and an increased frequency of autism. The researchers also noted that the association between maternal asthma or allergy and autism was greater for autistic children who had one or more autistic siblings than for those with healthy siblings.

Maternal autoimmune diseases did not appear to be associated with a greater risk of autism. Mothers of children in the control group were just about as likely as mothers of autistic children to have any of the 44 autoimmune diseases—10% vs. 8%, respectively.

The researchers have postulated several biologic mechanisms for the association. First, it could be because of maternal immune response during pregnancy. In particular, they hypothesize that maternal antibodies may cross the placenta and disrupt fetal neurodevelopment by crossreacting with fetal brain antigens, through a process called molecular mimicry. The second hypothesis is that asthma and allergy share environmental risk factors with autism spectrum disorders. Another possibility is that asthma and allergy share genetic susceptibility with autism spectrum disorders—in other words, the diseases share common genes. ■