Studies Backing Drug Use For Autism Are Limited

BY JEFF EVANS
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NEW YORK — The body of data for using newer pharmacotherapeutic agents to treat autistic symptoms is struggling to keep up with the use of such drugs in practice, Lawrence Scahill, Ph.D., said at a psychopharmacology update sponsored by the American Academy of Child and Adolescent Psychiatry.

"An evidence-based discussion of autism is relatively brief, because we don't have a lot of evidence, unfortunately," said Dr. Scahill, director of the research unit on pediatric psychopharmacology at the Yale Child Study Center, New Haven, Conn.

Some medications have proven to be useful in treating target symptoms of autism, such as hyperactivity, tantrums, aggression, self-injury, and anxiety, he said.

In a survey of medication patterns in patients with autism or pervasive developmental disorder (PDD) in North Carolina, the use of any medication to treat the conditions rose from 31% in 1992-1993 to 45% in 2001, Dr. Scahill noted (J. Child Adolesc. Psychopharmacol. 2005;15:116-26).

The use of several classes of drugs rose during that period, including antipsychotics (from 12% to 17%), antidepressants (from 6% to 21%), and stimulants (from 7% to 14%). For antipsychotics and antidepressants, these changes reflect switches to atypicals and SSRIs, said Dr. Scahill, who disclosed that he serves as a consultant for Janssen Pharmaceutica N.V., which manufactures risperidone (Risperdal), and Pfizer Inc., which manufactures fluoxetine.

SSRIs for Repetitive Behavior, Anxiety

SSRIs such as fluoxetine have been used in PDD to treat repetitive behavior, anxiety, and aggression, as well as to improve socialization, Dr. Scahill said.

Liquid fluoxetine proved to be more effective in treating repetitive behaviors than placebo in a randomized, double-blind, crossover study of 39 children and adolescents with autistic spectrum disorders. In the first phase of the trial, patients who received fluoxetine improved their scores on a clinician-rated instrument focused on repetitive behavior (the Children's Yale-Brown Obsessive Compulsive Scale–PDD) by 10%, compared with placebo patients who improved by 4%. The second phase of the study, in which the patients switched treatments, yielded similar results.

Adverse events occurred at a rate similar to that of placebo. The average dose of fluoxetine was 10 mg/day, beginning with 2.5 mg/day for the first week. "In terms of benefit, if you're aiming [SSRIs] at repetitive behavior, I don't say 'Don't do it,' but don't expect big effects," he said.

Aggression, Tantrums, Self-Injury

Risperidone is the atypical antipsychotic that has been studied most extensively in PDD, with open and controlled trials involving a total of 223 patients.

The FDA previously declared risperidone as nonapprovable for the treatment of autism in children, but it is now being submitted for approval for the treatment of tantrums, aggression, and self-injury, Dr. Scahill said.

In an 8-week, randomized, double-blind trial, risperidone significantly reduced aggressive behavior, tantrums, and self-injurious behavior by 57% in 49 children, compared with 14% in 52 children on placebo, according to the parent-rated irritability subscale of the Aberrant Behavior Checklist. Clinician ratings yielded similar results. The patients averaged 1.8 mg/day (N. Engl. J. Med. 2002;347:314-21).

During a 4-month open-label extension of the study for 63 responders to risperidone, irritability scores did not worsen, and patients did not require more risperidone to maintain their response (Am. J. Psychiatry 2005;162:1361-9). These responders gained an average of 5.6 kg during a total of 6 months of treatment with risperidone (Am. J. Psychiatry 2004;161:1125-7).

In a 2-month, randomized, double-blind discontinuation of risperidone, patients who continued to receive risperidone had a significantly lower rate of relapse (2 of 16) than those who gradually replaced risperidone with placebo (10 of 16).

ADHD Symptoms

Even though hyperactivity is a common problem in children and adolescents with PDD, "the evidence to support the use of methylphenidate in this population is frightfully little," Dr. Scahill said.

Until recently, methylphenidate had been studied in only two investigations of 10 children with PDD and ADHD. On the Conners Hyperactivity Index, teachers reported an 11% improvement at a dose of 10-20 mg twice daily (J. Autism Dev. Disord. 1995;25:283-94), 32% improvement at 0.3 mg/kg per dose, and 47% improvement at 0.6 mg/kg per dose (J. Am. Acad. Child Adolesc. Psychiatry 1999;38:805-12).

In a more rigorous study of 66 children with PDD and hyperactivity conducted by Dr. Scahill and his colleagues, methylphenidate improved hyperactivity significantly but less than it would in typically developing children with ADHD, according to teacher and parent ratings (Arch. Gen. Psychiatry 2005;62:1266-74). Children in the randomized, double-blind, crossover trial tolerated three dose levels of the drug in a 7-day test dose period and then received placebo for 1 week, followed by 3 weeks of the three methylphenidate doses in random order.

Thirty-four patients who responded to treatment based on a less conservative definition of response later received 8 weeks of open-label methylphenidate at an individually determined best dose.

Adverse events such as decreased appetite and increased repetitive behavior and stereotypies occurred mainly with the highest dose, even though it was "not really that high" (0.5-0.6 mg/kg per dose), Dr. Scahill said. Few adverse events occurred in the 38% (25 of 66) of patients who responded to either the low dose (0.125-0.18 mg/kg per dose) or the medium dose (0.25-0.35 mg/kg per dose). ■