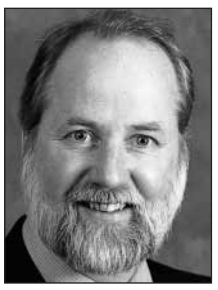
Data Limited on Pharmacotherapy for Autism

BY JEFF EVANS
Senior Writer

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.



"We don't have great medications for the core symptoms of autism," such as delay or disinterest in social interaction, repetitive behavior and restricted interests, and impaired communication. But some medications have proven to be useful in treating target symptoms, such as hyperactivity, tantrums, aggression, self-injury, and anxiety, he added.

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, even though data do not exist to support the use of many medications, Dr. Scahill noted (J. Child Adolesc. Psychopharmacol. 2005;15:116-26).

The use of several classes of drugs rose noticeably 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 is the manufacturer of 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% (12.8 to 11.6), compared with placebo patients who improved by 4% (from 13.4 to 12.9). 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 patients received an average dose of fluoxetine of 10 mg/day, beginning with 2.5 mg/day for the first week.

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DR. SCAHILL

By increasing the dose slowly, the investigators avoided SSRI-induced activation, which may include insomnia and increased motor activity, talkativeness, impulsive behavior, or aggression, Dr. Scahill said.

"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. Open and controlled trials with risperidone have involved 223 patients with PDD. The Food and Drug Administration 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 per 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 did patients who gradually replaced risperidone with placebo (10 of 16).

ADHD Symptoms

Even though "we know that hyperactivity is a very 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 trials of 10 children with PDD and ADHD. On the Conners Hyperactivity Index, teachers reported 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 (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 to a lesser degree 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 methylphenidate during 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 (0.125-0.18 mg/kg per dose) or the medium dose (0.25-0.35 mg/kg per dose). ■

Paternal Depression Relatively Common, Hurts Children

QUEBEC CITY — Paternal depression is relatively common and can negatively affect child behavior, Shreya Davé reported at the annual meeting of the North American Primary Care Research Group.

A clear link has been established between maternal depression and impaired social development of children. But little is know about paternal depression and its effects.

Ms. Davé presented a cross-sectional study in which questionnaires were sent to 2,352 biological fathers with children aged 4-6 years who were identified from 13 general practices in greater London and Hertfordshire, England.

Questionnaires included a diagnostic depression measure (Patient Health Questionnaire) and standardized inventories on child behavior (Strengths and Difficulties Questionnaire), parenting, couple relationship, alcohol use, and demographics.

Mothers were sent a similar but smaller packet. Their responses were used to assess child behavior and were thought to be a more objective way to assess the relationship of paternal depression and child behavior, said Ms. Davé, a research fellow in the department of primary care and population sciences at University College London.

The prevalence of paternal depression was 8% in the study, with 29 of the 365 fathers who responded scoring positively for depressive symptoms.

Of the 365 responders, 12 (3%) fathers had major depressive symptoms and 17 (5%) had mild or moderate depressive symptoms.

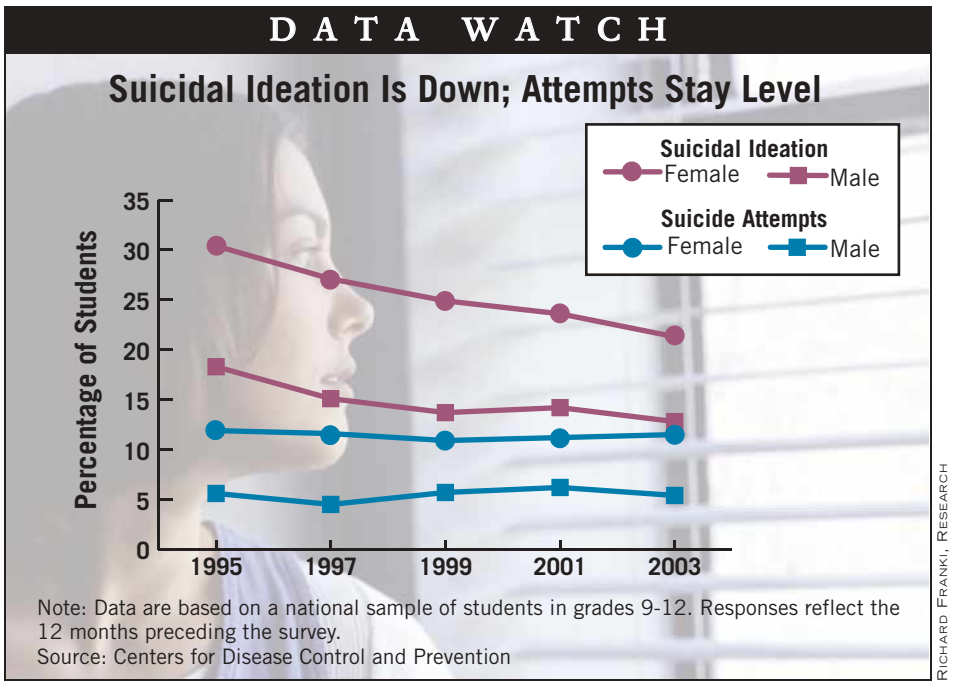
Fathers with major depression were almost 20 times more likely to have a child with signs of peer problems (odds ratio 19.17) and 13 times more likely to have a child with a low score on an assessment of prosocial behavior (OR 13.22), after controlling for maternal depression, couple relationship quality, paternal age, and number of children.

Limitations of the study were its cross-sectional design, low response rate, and wide confidence intervals resulting from the small number of participants, she said. But the findings clearly point to the need for further studies.

If it is addressed proactively, Ms. Davé said, paternal depression is a treatable condition.

—Patrice Wendling

DATA WATCH



RICHARD FRANKI, RESEARCH