Choose Atypicals for Early Onset Schizophrenia

Two drawbacks are the need for slow titration with younger patients and the high cost of newer agents.

BY NANCY WALSH
New York Bureau

NEW YORK — A second-generation antipsychotic should be the first-line choice in early onset schizophrenia, Harvey N. Kranzler, M.D., said at the psychopharmacology update institute of the American Academy of Child and Adolescent Psychiatry.

The atypical antipsychotic agents cause significantly fewer extrapyramidal symptoms and less tardive dyskinesia than the older neuroleptics.

While little in the way of controlled data are available for any of these drugs in pediatric patients, the Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth collaborative group has been formulating guidelines, particularly on dosing and titration.

"We're learning from clinical experience, and our mantra is start low and go slow," said Dr. Kranzler of the collaborative group.

The second-generation agents risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), and ziprasidone (Geodon) all are serotonin-dopamine antagonists, but they differ in specific receptor activity with the result that they vary to some degree in side effect profiles. Because of those differences in receptor blockade, if one does not work another can be tried, which was generally not so with the older neuroleptics, said Dr. Kranzler, director of the division of child and adolescent psychiatry and professor of psychiatry at Albert Einstein College of Medicine, New York.

One drawback to those drugs is that because of the need for slow titration, it may take some time to achieve effect. "This sometimes presents problems when you have a very agitated or out-of-control youngster," he said. In such a situation, treatment initiation can combine an atypical with an older antipsychotic such as haloperidol (Haldol) or chlorpromazine (Thorazine) to get a handle on the severe symptoms, he said. The traditional antipsychotic can then be titrated down.

The importance of improving pharmacotherapy for young patients with schizophrenia has been demonstrated by studies showing the poor prognosis when onset occurs before age 12, increased negative symptoms in adulthood when symptoms begin before age 15, and worse psychosocial impairment in patients whose illness begins before age 21.

Regarding the individual drugs, Dr. Kranzler offered advice based on clinical experience at his center:

► **Risperidone.** "At present, risperidone is often our first-line atypical, because it was the first one we had and we have more of a comfort level with it." This agent also has the quickest onset of action of the second-generation drugs, similar to that of the traditional neuroleptics.

Risperidone should be used in the lowest dose possible, generally in the 0.25- to 2- mg/day range, according to Dr. Kranzler. Initially, this drug was typically given in doses of 3-6 mg/day in children, "but I don't go above 3 mg any more. If you're at 3 mg or above you might as well use Haldol—it's quicker, less expensive, and no different in side effect profile or receptor activity," he said.

A common mistake is to give risperidone on a twice-daily or thrice-daily dosing schedule. "Once you've gotten through the titration period go to once a day dosing except for younger children," he said. The main reasons are cost and compliance. "The economics of atypical antipsychotics are breaking the bank of the Medicaid and managed care systems, and it really is a great concern and we must be cognizant of this," he said.

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► **Olanzapine.** This agent showed efficacy in childhood onset schizophrenia in an open-label study, and, like risperidone, is now undergoing controlled studies.

And as with risperidone, clinicians should attempt to use as low a dose as possible and on a once-daily schedule. Higher dosages in the range of 15-30 mg/day might be required for optimal efficacy, however.

The cost of this agent is again a concern. In fact, some systems throughout the country are considering removing this drug from their formularies, Dr. Kranzler said.

► **Quetiapine.** Preliminary studies have also shown effectiveness for quetiapine in adolescents with psychosis, aggression, and affective symptoms. With this agent, t.i.d. or b.i.d. dosing is needed, with titration up to 800 mg/day if needed, he said.

"Quetiapine is the most frequently prescribed antipsychotic in the country today, because it is used by clinicians other than psychiatrists as a sleep medication at 25 mg. It is a low dose and it does work, but it is an antipsychotic medication with all its receptor activity," he cautioned. It also is expensive, he said.

► **Ziprasidone.** This, too, is a very useful medication, but must be titrated very slowly because of its potential for activation, he said. It has some norepinephrine and serotonin uptake blocking activity, and may have beneficial antidepressant and antianxiety properties.

Prolongation of the QTc interval has been a concern with this drug, but "has not been a problem in our hands," he said. ► **Aripiprazole (Abilify).** The atypical class of antipsychotics now includes a third-generation agent, aripiprazole. This drug is a dopamine-serotonin system stabilizer that has partial D2 agonist activity and modulates central serotonergic pathways. It improves executive functioning and negative symptoms, and may also affect depression and anxiety.

► **Clozapine (Clozaril).** Among the atypicals, clozapine exhibits the most complex receptor blockade activity, and because of its side effect profile is not considered a first-line antipsychotic. But it is very effective in treatment-resistant patients, Dr. Kranzler said. "You want to be comfortable using it, because it can save these kids' lives," he said. In his center, 43 of 57 severely ill hospitalized patients were able to be discharged on clozapine. "They are not paragons of mental health but they are able to function in residences," he said. ■

Study Shows High Rates of Psychiatric Polypharmacy

BY ROBERT FINN
San Francisco Bureau

PHOENIX, ARIZ. — Four out of five children and adolescents under psychiatric treatment were receiving pharmacotherapy in a recent study, and slightly more than half of these received more than one psychiatric medication, Joyce C. West, Ph.D., said at a meeting of the New Clinical Drug Evaluation Unit sponsored by the National Institute of Mental Health.

The use of concomitant pharmacotherapy was significantly higher among patients with co-occurring Axis I, II, or III disorders than among those without. But among children and adolescents with only a single identified disorder, about 40% were receiving two or more medications, Dr. West of the American Psychiatric Institute for Research and Education in Arlington, Va., told this newspaper.

"Given that we don't know about the efficacy or the potential safety and risks of concomitant pharmacotherapy in this population, the overall pattern highlights the need for more research," she said.

Data for the study came from the American Psychiatric Association's Practice Research Network 1997 and 1999 studies of psychiatric patients and treatment.

These studies surveyed 754 psychiatrists who provided detailed data on a systematically selected national sample of 3,088 patients, 392 of whom were younger than 18 years.

Overall, 84% of these patients were receiving psychiatric medications, and 52% were receiving two or more psychiatric medications. Among all the child and adolescent patients, 10.2% were receiving three psychiatric medications, and 2.9% were receiving four or more psychiatric medications.

Antidepressants, used by 52% of the patients, were the most common of these medications, followed by stimulants (41%), antipsychotics (23%), antimanic agents (23%), and antianxiety medications (8%).

Patients who had been diagnosed with bipolar disorder, schizophrenia, and disruptive behavioral disorders were the most likely to be taking two or more psychiatric medications.

Rates of polypharmacy in patients with those diagnoses were 87%, 70%, and 61%, respectively. Polypharmacy was least common in patients with anxiety disorders, 44% of whom were receiving multiple medications.

Among the patients taking two or more psychiatric medications, an antidepressant together with a stimulant was the most common combination, seen in 21% of the patients.

About 11% of polypharmacy patients were receiving an antidepressant and an antipsychotic, and 7% were receiving an antidepressant and an antimanic agent, Dr. West said. ■

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"This one is a little hyper, but he's easy to put in time-out"