

PRACTICAL PSYCHOPHARMACOLOGY

Treating Autism-Related Behavioral Problems

Surveys have shown that half of young patients with autism spectrum disorders are prescribed psychotropics, but drug treatment for autism's core social and communication impairments remains "more a goal and a hope than a reality," said Dr. Bryan King, director of child and adolescent psychiatry at the University of Washington, Seattle.

Still, pharmacotherapy research has become active in this area, and the first Food and Drug Administration approval for an autism-related indication was hailed as a milestone ("FDA Approves First Agent for Treating Autism Symptoms," November 2006, p. 1).

As exemplified by the approval of risperidone (Risperdal) for "irritability associated with autism" in children and adolescents, "most of the focus has been on the presence of maladaptive behaviors that occur frequently and arguably cause more difficulty than core symptoms," Dr. King said.

The severe disturbances for which risperidone is indicated, including aggression and self-injurious behavior, are the most urgent motives for pharmacotherapy. Other frequently medicated symptom clusters are hyperactivity and impulsivity, repetitive behavior and associated anxiety, and mood instability, he said.

Medications are probably most common with school-age children and adolescents. "At around 4 or 5 years, we start seeing the emergence of target symptoms for which they may be helpful," said Dr. Christopher J. McDougle, the Albert E. Sterne Professor and Chairman of Psychiatry at Indiana University, Indianapolis. "In many cases, medications can be reduced or discontinued as patients move into adulthood, as hyperactivity and ag-

gression can lessen over time," he said.

An argument can be made for starting medication earlier rather than later, said Dr. David Posey, chief of the Christian Sarkine Autism Treatment Center at Indiana University. "You want to consider if symptoms are not only disruptive to the caregiver but starting to interfere with the child's ability to be in the classroom and to benefit from available [behavioral] treatments," he said.

Clinical experience and limited research suggest that guanfacine may help control hyperactivity.

DR. McDOUGLE



In general, greater intellectual impairment is associated with more behavioral disturbances and so with pharmacotherapy, Dr. King said. Mood disorders appear to be more frequent in Asperger's syndrome, however, perhaps because these patients are more aware of their social deficits or have higher expectations, he suggested.

Drug choice is usually driven by the chief complaint, although "things like irritability and aggressiveness tend to trump the others," Dr. Posey said. Here, an atypical antipsychotic is usual, and its approval makes risperidone a logical first choice. Among other atypicals, aripiprazole (Abilify) has gained favor, particularly when weight is an issue. Doses are generally low, he said: 1-2 mg of risperidone for children and 2-3 mg for adults.

Irritability and disruptive behaviors that wax and wane suggest mood dysregulation, for which Dr. King would consider a mood stabilizer: "I'd look at lithium or anticonvulsants like valproate or carbamazepine."

Hyperactivity, impulsivity, and inattention are extremely common. "There are a lot of similarities to attention-deficit/hyperactivity disorder," but the response to psychostimulants is more problematic, Dr. King said. A large multicenter study sponsored by the National Institute of Mental

Health found methylphenidate to be more effective for hyperactivity than was placebo, but the response rate was lower than that in ADHD—closer to 50% than 70%—and tolerability was poorer. "A not insignificant percentage, about 18% of kids in the study, got worse or couldn't tolerate methylphenidate," he said.

Dr. Posey said some children are sensitive to adverse effects, even at low doses of methylphenidate. "It's frequent to hear about children who develop severe irritability—after a single tablet of a stimulant—that lasts 10-16 hours," he said.

Start with a low dose (around 2.5 mg), and make sure that parents are alert to the risk of worsening, he advised.

Atomoxetine (Strattera) appears to be reasonably effective for inattention and hyperactivity, and might be better tolerated than psychostimulants, Dr. Posey said. Here, too, he would start with a low dose and perhaps increase the dose at a somewhat slower rate than that recommended on the package insert.

The alpha-2 adrenergic receptor agonist guanfacine (Tenex) also seems, on the basis of clinical experience and limited research, to have some value for hyperactivity, Dr. McDougle said. "With guanfacine, they may get better or stay the same, but there's little risk of worsening." Its utility is clear within days. He would start at 0.5 mg one to two times daily, and go up by 0.5 mg each week to a maximum of 2 mg t.i.d. Most patients require less, he said.

Selective serotonin reuptake inhibitors are the usual first choice for repetitive behavior, anxiety, and low frustration tolerance, but as with psychostimulants, their efficacy is limited (for younger patients in particular) and activation is common. "When we use SSRIs for anxiety, we see response rates of 25%-35%," Dr. Posey said. Activation occurs in some 25%, even with conservative dosing, but "it tends to be mild and goes away when the drug is dis-

continued," he said. A low starting dose and slow titration can minimize problems," he said.

Atypical antipsychotics are frequently prescribed for patients who respond poorly to SSRIs, but they are not necessarily the best next step for anxiety, Dr. King said. "Some prefer to look at a mood stabilizer or, depending on the SSRI response, to consider buspirone [BuSpar]. For an individual who becomes activated at low doses of an SSRI, a partial agonist [could make] unique sense."

Most clinicians avoid benzodiazepines because of the disinhibition risk, "but the area deserves more study," Dr. King said. "If you compare its relative risks with antipsychotics, a case could be made."

Although no medication has yet been shown effective for the core symptom domains of autism, there are "glimmers of hope with respect to social relatedness," Dr. King said. Glutamatergic drugs like memantine (Namenda), amantadine (Symmetrel), and D-cycloserine have been promising in small trials, he said.

Positive experiences with drugs in general should be understood against the background of a substantial placebo response among autistic individuals, Dr. King said, and if adverse effects are an issue, a trial of dosage reduction or discontinuation may be indicated.

"With antipsychotics and antidepressants, it's important to assess each year whether the dosage can be reduced," Dr. Posey said. "If there's no noticeable difference with a 10%-25% reduction, see if the drug is still needed."

Dr. McDougle said he would factor life events into the timing. If a child is transitioning to a new school, or an older patient is moving into a group home or starting a job, "these life stressors may lead symptoms to persist for a time," he said.

By Carl Sherman, contributing writer

Gene Mutation Tied to 5% of Frontotemporal Dementia

BY JAMES BUTCHER
Contributing Writer

SALZBURG, AUSTRIA — Mutations in the progranulin gene are found in about 5% of patients with frontotemporal dementia, according to research presented at the 8th International Conference on Alzheimer's and Parkinson's Diseases.

Frontotemporal dementia (FTD) is the second most common cause of dementia, after Alzheimer's disease, in patients aged 65 years or younger. About 35%-50% of patients with FTD have a family history of dementia, which suggests the existence of a strong genetic component to the disease.

In 1998, researchers reported that mutations in the gene encoding the microtubule-associated protein tau (MAPT) caused familial FTD with parkinsonism linked to chromosome 17 (FTDP-17). However, not all families who showed linkage to the same region on chromosome 17 had mutations in MAPT, suggesting that mutations in at least one other gene were responsible for the disease in these patients. In addition, these patients had ubiquitin-

immunoreactive neuronal cytoplasmic inclusions (FTDU-17) but not tau-immunoreactive inclusion pathology.

In July 2006, two studies found that FTDU-17 is caused by mutations in progranulin, a polypeptide with growth-modulatory activity, leading to a loss of protein function (Nature 2006;442:916-9; Nature 2006;442:920-4). Since then, researchers have been screening their patient populations for the mutations to determine their prevalence in the FTD community.

Stuart Pickering-Brown, Ph.D., who works at the University of Manchester (England), presented data from the Manchester Cohort that currently includes 272 patients with FTD, with some being followed for over 20 years.

"We recently finished sequencing for progranulin mutations and found 14 cases," said Dr. Pickering-Brown, who noted that this frequency (5%) is about the same as for tau gene mutations (6%) in his cohort.

Clinically, the 14 patients had been diagnosed with frontotemporal dementias, primary progressive aphasia, and corticobasal degeneration, said Dr. Pickering-Brown. "All the cases had a family history of disease," he added.

The researchers also genotyped several single nu-

cleotide polymorphisms (SNPs) spanning the progranulin gene to determine whether a common variation at the locus increases the risk of sporadic disease, but they found no evidence of allelic association of any of the SNPs.

Dr. Brendan Kelley presented the latest data from the Mayo Clinic cohort of patients. He reported on the clinical characterization of eight kindreds, which included 31 individuals with progranulin mutations, of whom 16 were men. The patients were aged 49-83 years at disease onset (mean age 63 years) and had a disease duration of 1-12 years (mean 6.5 years). "Two individuals who died within 1 year both had accidents that may have been related to disinhibited behaviors," Dr. Kelley said.

Like the Manchester cohort, the clinical diagnosis varied widely and included FTD with and without parkinsonism, mild cognitive impairment, and Alzheimer's.

The discovery of this gene will not change clinical practice at this point, said Dr. Zbigniew Wszolek, a professor of neurology at the Mayo Clinic College of Medicine, Jacksonville, Fla., who chaired the session. In addition, Dr. Wszolek said he did not think clinical genetic testing was available yet, but patents have been filed.