Balance SSRI Benefits With Risks for Children

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WASHINGTON — It is important to balance risks with benefits when considering a selective serotonin reuptake inhibitor to treat a child or adolescent, several experts said at the annual meeting of the American Academy of Child and Adolescent Psychiatry.

Among other things, session participants discussed the Food and Drug Administration's requirement of a black box warning alerting prescribers and patients to the risk of suicidal behavior with antidepressants in children and adolescents.

"I think this is very important. This is not a contraindication. This [warning] box is not telling clinicians that they can't use these drugs. What it's saying is that if a clinician is considering using an antidepressant in a child or adolescent, they need to consider the risk and balance that against the clinical need," said Thomas Laughren, M.D., of the FDA's division of neuropharmacological drug products, Rockville, Md.

Selective serotonin reuptake inhibitors (SSRIs) do appear to work better than placebo in the short-term therapy of depression in children and adolescents, said Neal Ryan, M.D., of the Western Psychiatric Institute and Clinic in Pittsburgh. This is probably true in general, though fluoxetine is the only one with an indication for children.

Combining an SSRI with cognitive-behavioral therapy (CBT) might even be more effective, according to recent findings. In the Treatment for Adolescents with Depression Study (TADS), SSRIs combined with CBT showed the best results for treating depression. The results also suggested that pharmacotherapy is more effective than psychotherapy alone, but this finding needs to be duplicated in other studies, Dr. Ryan said.

For clinicians, the real problem is how

Depression Does Not Predict Mortality

Depressive symptoms are not independent predictors of mortality, according to data from a national sample of 3,617 adults.

The findings of previous studies of associations between depressive symptoms and mortality have been inconsistent, and few of these studies have used population-based samples, said Susan A. Everson-Rose, Ph.D., of Rush University Medical Center, Chicago, and her colleagues (Psychosom. Med. 2004;66:823-30).

The study included noninstitutionalized adults aged 25 years and older who were participating in an ongoing, longitudinal study called Americans' Changing Lives.

A total of 542 deaths occurred during 7.5 years of follow-up. Each increase of 1 standard unit on the Center for Epidemiological Studies Depression scale (CES-D) predicted a 21% increase in death from any cause after age, race, and gender were adjusted for. However, no excess risk of mortality was associated with CES-D scores in a fully adjusted model that included demographics, education, income, behavioral risk factors, and three indicators of health status (hypertension, functional impairment, and life-threatening conditions).

The physical complaints of patients with depression often resemble symptoms of other health problems, and distinguishing between clinical depression and poor physical health can be difficult.

Patients with scores in the highest quintile on the CES-D had an 85% greater risk of death from any cause, compared with participants with the lowest CES-D scores, but no other quintiles showed an increased mortality risk, the investigators said.

Depressive symptoms were not significantly associated with mortality risk in a healthy subgroup of 2,833 adults (with 306 deaths) who reported good or excellent health at baseline. In addition, depressive symptoms were not associated with increased mortality risk in patients without functional impairments at baseline.

Although depressive symptoms were associated with greater physical impairment over time, the CES-D does not measure clinical depression, which has been studied as a possible link to mortality and cardiovascular health, the investigators noted.

—Heidi Splete

to balance the increased short-term risk—an extra 2 per 100 patients who will either attempt suicide or exhibit suicidality because of the use of an SSRI—and the potentially decreased long-term risk of suicidal thoughts and behavior attributable to depression, Dr. Ryan said.

Clinicians are left with the dilemma of what to do about the next depressed child to come into the office: Pick an SSRI alone, choose psychotherapy alone, or combine an SSRI with psychotherapy. "I think we're going to have a rich debate on that," he said.

When considering an SSRI in a pediatric patient, it's important to inform the family of potential risks and benefits and follow the FDA's monitoring suggestions. "I think also that we need to advocate for more studies. I think we're all scared that we won't get any more data on this question," he said.

Mark Olfson, M.D., of Columbia University, New York, is not optimistic about the prospects for this type of research: "For the foreseeable future, I believe the pharmaceutical industry is going to view this whole area as radioactive and stay away from it."

Future research should focus on which subgroups of patients are at higher risk and when in the course of treatment. One strategy would be to monitor depressed children closely for short periods of SSRI therapy, looking for somatic subjective dysphoria, changes in attention, changes in impulsivity, or other indicators of suicidality, Dr. Olfson said.

Dr. Ryan said that he sees a need for longer-term studies.

The long-term effects of the treatment of depression have not been studied. It may be that effective drug therapy for depression may decrease the long-term risk of suicide, but there is no clear evidence yet, he said.

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It's also important to look at the bigger public health picture, Dr. Olfson said. "We need to be clear about the distinctions between suicidal ideation and the suicide attempts that were the subject of the randomized controlled trials analyses and actual suicide or serial suicide attempts that we encounter in practice."

The rates of suicidal ideation and suicide attempts in a normal adolescent population also need to be considered. According to the Centers for Disease Control and Prevention's 2003 National Youth Risk Behavior Survey, 16.9% of normal adolescents in grades 9-12 had seriously considered attempting suicide in the previous 12 months and 8.5% had attempted suicide at least once in that time period, he noted.

"Those numbers stand in very sharp contrast to the comparatively small number of kids who show up in our emergency rooms and hospitals following actual suicide attempts," Dr. Olfson said. "It's my own belief—that, in fact, the recent increase in the use of these medications in kids has actually saved lives." ■

Genetic Defect May Raise Risk of Depression

A recently discovered genetic mutation that causes dysfunction in the synthesizing of serotonin might explain why some depressed patients are resistant to drug treatment, researchers say.

Xiaodong Zhang, M.D., and colleagues at Duke University, Durham, N.C., screened 87 adults with unipolar major depression, 60 adults with bipolar disorder, and 219 controls for a mutant allele known as 1463A in an enzyme that helps direct synthesis of serotonin known as human tryptophan hydroxylase 2 (hTPH2).

The gene mutation occurred in 10% of patients with major depression, compared with 1% of the controls. None of the individuals with bipolar disorder had the mutation (Neuron 2005;45:11-6).

Seven of the nine depression patients with the hTPH2 mutation had a family history of mental illness or drug and alcohol abuse, six had either attempted suicide or shown suicidal behavior, and four demonstrated generalized anxiety symptoms. In addition, seven of the patients with the mutation showed a lack of responsiveness to an SSRI, and the other two responded only to high doses.

Communication among neurons may stall if serotonin levels are low, as they often are in people with depression, anxiety, posttraumatic stress disorder, and even attention-deficit hyperactivity disorder. Additional larger studies are needed to confirm these findings and explore links between genetics and depression.

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