

Atypical Antipsychotics Still Used After Warning

Pattern probably reflects perceptions that clinical benefits outweigh risks for older dementia patients.

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

MADRID — Prescriptions for atypical antipsychotics have not decreased significantly among elderly patients with dementia, despite the black box warning of an increased risk of death associated with the drugs, Henry Riordan, Ph.D., said at the 10th International Conference for Alzheimer's Disease and Related Disorders.

Overall, prescribing has declined only 2.4%, even though the number of new prescriptions issued has decreased by 37%, Dr. Riordan said at the meeting presented by the Alzheimer's Association. This pattern probably reflects physicians' perceptions that the clinical benefits of the drugs outweigh their well-documented risks for older dementia patients with serious behavioral issues.

More than 80% of Alzheimer's patients will eventually develop psychotic symptoms, said Dr. Riordan, vice president and global head of medical and scientific affairs for I3 Research in Basking Ridge, N.J.

"These are the issues that typically result

in institutionalization and take a big chunk out of these patients' quality of life," he said in an interview.

The problem lands patients, families, and physicians on the horns of a very sharp dilemma. "Withholding the drugs is dangerous, especially when you are dealing with behavior that can be either self-injurious or harmful to caregivers," Dr. Riordan said, but the risks of atypical antipsychotics were well documented years before the Food and Drug Administration's warning.

Fifteen of the 17 randomized atypical antipsychotic trials the FDA reviewed found a significantly increased risk of death—usually cardiovascular or infectious—among elderly, demented patients taking the drugs, compared with placebo. The resultant black box warning highlighted the danger and reiterated that the drugs are not approved for the treatment of patients with dementia-related psychosis.

Among the six drugs included in the study, only two showed significant pre- and postwarning prescribing changes: quetiapine and olanzapine.

To estimate the impact of the black box warning on prescribing patterns, Dr. Riordan examined claims data from a large U.S. health plan, for 10 months before and 10 months after the 2005 warning was issued. The database included 900,000 people older than 65 years of age; 20,515 had a diagnosis of dementia. Of those, 5,000 were taking at least one atypical antipsychotic before the black box warning. Ten months after the warning, 4,883 people were still taking the drugs. New prescriptions had decreased significantly, however, declining from 3,423 to 2,148. "This probably tells us that if you were on the drug, you stayed on it, but that physicians might have been looking at something else for patients with

new symptoms."

A supporting pattern emerged when Dr. Riordan broke down the data by age: Prescriptions decreased more among patients younger than 81 (5%) than they did among older patients (0.73%). "Here we're probably seeing a risk-benefit ratio that's perceived as different for older people," Dr. Riordan said. "If someone has been on it with good efficacy, it would probably just

be continued. But the physician's thought process might be very different for someone younger, in the earlier stages of the disease."

Six drugs were used in the study: aripiprazole (Abilify), clozapine (Clozaril), ziprasidone (Geodon), risperidone (Risperdal), quetiapine (Seroquel), and olanzapine (Zyprexa). Among the six drugs, only two showed significant pre- and postwarning prescribing changes.

Prescriptions for quetiapine increased significantly, while those for olanzapine decreased significantly. "It could be that quetiapine is being used more now for its sedative effect in sleep difficulty, and clozapine less due to its issues with increasing cardiovascular risk factors."

Dr. Riordan now is investigating whether the decrease in new prescriptions caused any similar increases in prescriptions for alternative treatments, like mood stabilizers or antianxiolytics.

Unfortunately, he said, there is no evidence to suggest that anything other than the atypical antipsychotic agents is effective in treating the psychotic symptoms of dementia.

"We really need something new that is both safe and effective, and until we get that, people will continue to wrestle with these very difficult decisions," Dr. Riordan said. ■

Study Questions Value of Second-Generation Drugs in AD

BY CHRISTINE KILGORE
Contributing Writer

Findings from a study of olanzapine, quetiapine, and risperidone in patients with Alzheimer's disease call into question the clinical value of these second-generation antipsychotic drugs and suggest that physicians should use them judiciously.

The double-blind, placebo-controlled trial of more than 400 patients demonstrated no clear benefit from treatment with the atypical antipsychotic medications in patients with psychosis, aggression, and agitation associated with Alzheimer's disease (N. Engl. J. Med. 2006;355:1525-38).

Overall, drug-related adverse events offset any advantages, said Dr. Lon S. Schneider, of the Keck School of Medicine at the University of Southern California, Los Angeles, and the other investigators of the National Institute of Mental Health's "Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease" (CATIE-AD) study group.

The 42-site trial assessed the effectiveness of olanzapine (Zyprexa), quetiapine (Seroquel), and risperidone (Risperdal) in 421 patients with a broad spectrum of

disease severity and behavioral problems that were severe enough to disrupt their functioning.

The patients, who were ambulatory and living at home or in an assisted-living facility, were randomized to receive one of the drugs or placebo and were followed for 36 weeks.

In a trial designed to reflect real-world clinical practice, physicians participating in the study determined their patients' starting doses and adjusted the doses or discontinued treatment as they saw necessary.

Medications were dispensed as identically-appearing small and large capsules containing lower and higher doses of the drugs.

During the study period, the physicians increased initial doses to a mean daily dose of 5.5 mg of olanzapine, 1 mg of risperidone, and 57 mg of quetiapine.

There was no significant difference between the groups in terms of the primary outcome, the length of time patients remained on the drugs before physicians decided to discontinue for any reason. The median time to discontinuation ranged from approximately 5 weeks with quetiapine to 8 weeks for olanzapine and placebo. Overall, 63% of patients were no longer receiving their medications at 12 weeks.

Nor were there significant differences between groups in terms of the number of patients with at least minimal improvement on the Clinical Global Impression of Change scale at 12 weeks.

Improvement was seen in 32% of patients on olanzapine, 29% of patients taking risperidone, 26% of patients on quetiapine, and 21% of patients assigned to placebo.

Olanzapine and risperidone fared best in terms of the time to discontinuation of treatment because of "lack of efficacy," (a median time of 22 weeks and 27 weeks, respectively).

This finding was offset, however, by increased rates of discontinuation because of "intolerability" or "adverse events" such as sedation or extrapyramidal symptoms. Treatment was stopped for these reasons in 24% of patients who received olanzapine, 18% of those on risperidone, 16% who received quetiapine, and 5% of those receiving placebo.

In an accompanying editorial,

Dr. Jason Karlawish, who is with the Alzheimer's Disease Center in the University of Pennsylvania's Institute on Aging in Philadelphia, said that despite the Food and Drug Administration's warnings against the use of atyp-

ical antipsychotics in elderly patients with dementia-related psychosis, "clinicians, including me, continue to prescribe these drugs."

Physicians "have done this without clear evidence of the nature and extent of the clinical value of antipsychotic medications—until now," he wrote (N. Engl. J. Med. 2006;355:1604).

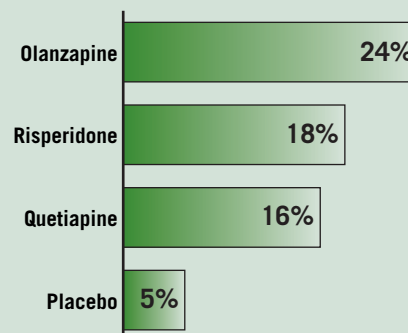
Such study designs do not reflect clinical practice and "hence, will not likely lead to appropriate changes in clinical practice," he said.

These new findings suggest that atypical antipsychotics may be "best prescribed in systems of care that can provide the skills and expertise needed to ensure that the risks associated with the drugs are justified by their potential benefits," Dr. Karlawish concluded.

The recent NEJM report covers phase I of the CATIE-AD study.

In a second phase of CATIE-AD, to be reported in the future, patients whose treatment was discontinued during the 36-week period of phase I could be randomly assigned to receive another one of the three atypical antipsychotic drugs. Or they might be assigned to receive the antidepressant medication citalopram (Celexa). ■

Treatment Discontinuation Due to Intolerability Or Adverse Events



Note: Based on a study of 421 patients.
Source: New England Journal of Medicine