Increased Risk of Cerebrovascular Adverse Events and Death in Elderly Demented Patients Treated With Atypical Antipsychotics: What's a Clinician to Do?

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Recent U.S. Food and Drug Administration (FDA) warnings of increased risk of cerebrovascular adverse events (CVAEs) and increased mortality with atypical antipsychotics in older patients with dementia have received considerable attention and resulted in black box warnings for this drug class. Clinicians who treat these patients have a challenging clinical dilemma. Behavioral problems in this patient group can be severe and can result in nursing home placement. While atypical agents can be helpful in managing these symptoms, they are associated with serious safety issues, and none are approved by the FDA for use in this condition.

An increased risk of CVAEs was first noted in an Australian study of risperidone in older patients with dementia.[1] Subsequently, increased risks of CVAEs were noted for olanzapine[2] and aripiprazole.[3] The increased risk for these 3 agents varied among the samples and with the definition of CVAE and method of calculation, but overall, there was a 2-fold increase in risk. The CVAEs included strokes, transient ischemic events, and undetermined events thought to be vascular in origin. In 6 of the risperidone trials conducted by Janssen, 15 of the 33 CVAEs were considered serious, and 18 were not.[2] Actual rates of CVAEs varied from 1.3% to 4.0% and appeared to increase with advanced age or presence of vascular dementia. Because these studies also suggested an increased mortality rate among patients treated with atypical drugs, the FDA reviewed all placebo-controlled studies of atypical antipsychotics conducted in older demented patients with behavioral disturbances. Seventeen studies with 20 active treatment arms (risperidone, 7 trials; olanzapine, 5; aripiprazole, 3; quetiapine, 2; haloperidol, 2; and ziprasidone, 1) were reviewed.[4] These studies included 5377 patients with a mean age of 81 years. Treatment significantly increased mortality about 1.6 to 1.7 times. Actual rates of death were 4.5% for drug and 2.6% for placebo, and risk was related to increasing dose. No difference in mortality risk between drugs was noted.

Whether the mortality risk and CVAE risk have a similar underlying mechanism is yet unclear. The FDA notes that the cause of death varied in their review, and cerebrovascular events did not appear to be overrepresented; however, the documented cause of death may not reflect the events leading up to the patients' decline. Whether the FDA had data that would allow for an analysis of other risk factors or mediating factors is also unclear. Orthostatic hypotension seems a likely mediating variable in some patients; falls are another possibility, and oversedation can lead to aspiration. CVAE risk is higher in patients with vascular dementia, vascular disease, or risk factors for stroke. CVAE and mortality risks are higher in patients aged > 80 years.

Clinicians are thus faced with a difficult decision in older demented patients presenting with behavioral problems. If nonpharmacologic interventions fail, medication may be needed. While the use of antipsychotics to control behavior is often criticized, psychotic symptoms can be frightening to the patient, and medication may relieve that distress.

A full review of the efficacy of the atypical antipsychotics in dementia is beyond the scope of this column. In brief, a few studies using primary outcome measures and several studies using secondary outcome measures have demonstrated efficacy of the atypical agents. Few of the 17 studies mentioned have been published. While efficacy data are limited, the recent Expert Consensus Guideline for Treatment of Dementia and Behavioral Disturbances[5] recommends risperidone, quetiapine, olanzapine, and aripiprazole for treatment of psychosis associated with dementia.

Would use of the conventional antipsychotics reduce the safety risks? A population-based study in Canada found the risk of CVAEs was not different for risperidone, olanzapine, and the conventional antipsychotics.[6] Another large population-based study of over 18,000 patients with a stroke-related hospital admission found similar rates for risperidone, olanzapine, and quetiapine, but rates for haloperidol and benzodiazepines were *higher* than that for risperidone.[7] The FDA analysis of mortality risk also found no advantage for haloperidol versus the atypicals, but only 2 studies included haloperidol as a comparator.

In patients with agitation or aggression without psychosis, clinicians may wish to consider alternative agents. Carbamazepine, divalproex, and citalopram each have some supporting evidence; however, mortality risk has not been established for any of these agents. While divalproex has the largest placebo-controlled database of these agents, that number—about 500 patients—may be too small to detect an increased risk. A sample of about 2200 patients would be needed to have an 80% chance of finding a difference if the actual rates were 4% and 2% for drug and placebo.

Because the patient with dementia may have limited capacity for medical decisions, informing the responsible family member or conservator becomes crucial. In addition to considering the risks and benefits, the family will need to consider the consequences of not managing disturbed behavior in terms of the safety of the patient and others and the setting in which the patient can be managed. Documentation of informed consent (at least a progress note) will be essential. Written informed consent is sometimes obtained, but this practice varies considerably from one community to another. Certainly written consent does not ensure adequate education of caregivers.

Use of the lowest effective dose and careful monitoring to avoid or reduce hypotension, gait disturbance, and oversedation may seem reasonable precautions to reduce the risk of CVAEs and other fatal adverse events; however, until we have a better understanding of the mechanisms involved, these risks are unlikely to be eliminated. Our understanding of adverse events such as these would benefit greatly from an improved postmarketing drug surveillance system.

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