

Antipsychotics in Patients with Dementia and Behavioral Disturbances

Background

Atypical antipsychotics are FDA approved for the treatment of schizophrenia and for mania in patients with bipolar disorder, but have also been found effective in the treatment of a variety of related conditions, including psychotic disturbances associated with dementia. Although this off-label use is widespread and may result in clinical improvement for many elderly patients with dementia, accumulating safety data for more than two years may have significant impact on this practice. Specifically, an increased risk of cardiovascular, cerebrovascular, and other adverse events has been reported in dementia patients treated with atypical antipsychotics.¹

On April 11, 2005, the FDA issued a public health advisory concerning all atypical antipsychotic medications. This alert advised health care providers, patients, and caregivers of safety concerns when using these medications for unapproved or “off-label” indications and applied to all atypical antipsychotics, including Abilify (aripiprazole), Clozaril (clozapine), Geodon (ziprasidone), Risperdal (risperidone), Seroquel (quetiapine), and Zyprexa (olanzapine). Symbyax (olanzapine and fluoxetine), a combination antipsychotic and antidepressant approved for the treatment of depressive episodes associated with bipolar disorder, was also included.¹

Prior to this warning, evidence for the use of these medications in the elderly population has been supported by several trials and while findings in these studies have maintained that non-pharmacologic treatments should be tried first for behavioral disturbances, it is recognized that atypical antipsychotics provide another rational therapeutic modality to improve patient care. Furthermore, past recommendations have endorsed the use of risperidone and olanzapine in the treatment of psychosis in patients with Alzheimer’s dementia, while clozapine and quetiapine are more effective for psychosis in Parkinson’s patients.

Summary of Atypical Antipsychotic Drugs^{2,3}

| Drug | Usual Dosage in Elderly | Common Side Effects | Cost per Month* |
|----------------------------|--------------------------------|---|-------------------------|
| Abilify (aripiprazole) | 2.5 to 15 mg qd | Headache, anxiety, insomnia | \$77 to \$309 |
| Clozaril (clozapine) | 6.5 to 75mg qd | Hypotension, sedation, weight gain, hyperglycemia, sialorrhea | \$11 to \$132 (generic) |
| Geodon (ziprasidone) | 20 to 120 mg qd | Sedation, GI upset | \$257 to \$514 |
| Risperdal (risperidone) | 0.25 to 3mg qd | Hypotension, EPS, weight gain, hyperprolactinemia | \$172 to \$374 |
| Seroquel (quetiapine) | 12.5 to 200mg qd | Hypotension, weight gain, sedation | \$96 to \$329 |
| Zyprexa (olanzapine) | 1.25 to 5mg qd | Hypotension, weight gain, hyperglycemia | \$78 to \$184 |

*Based on AWP

FDA Safety Information - Trials

In their advisory, the FDA cited 17 placebo-controlled trials in which 5,106 elderly patients with dementia were enrolled. These safety trials included aripiprazole, risperidone, quetiapine, and olanzapine. Several analyses showed an increased mortality rate (relative risk of 1.6 – 1.7) in elderly patients with dementia who were users of atypical antipsychotics vs. placebo. The main causes of death were identified as either heart-related (heart failure or sudden death) or infectious disease (pneumonia).¹

FDA Advisory

Based on the increased risk of mortality in multiple agents, representing three different chemical structure groups, the FDA has concluded that this is a class effect related to the common pharmacologic properties exhibited by antipsychotic medications. As such, the FDA has requested that manufacturers of the atypical agents add a boxed warning to their drug labeling describing these risks and to remind prescribers that these drugs are not approved for the treatment of behavioral symptoms in elderly patients with dementia.¹

The FDA is also considering a boxed warning be added to older antipsychotic medication labeling due to limited data suggesting a similar increase in mortality in these agents.¹ Although several reports indicate that there is not an increased risk when comparing older antipsychotics to newer agents, safety data comparing these agents to placebo in this population is lacking.^{4,5,6}

Recommendations

Psychotic symptoms and behavioral disturbances in patients with dementia represent a significant source of emotional distress on the part of caregivers, are a leading cause of institutionalization, and are often very difficult to manage medically. While atypical antipsychotics have benefit in the treatment of these symptoms with an acceptable safety profile for many patients, recent cautionary information suggests that this treatment option may need to be reevaluated.

Specifically, cardiovascular and cerebrovascular risks should be carefully considered and documented before initiating treatment with an atypical antipsychotic in a patient with a previous history of stroke, transient ischemic attack, or myocardial infarction. Consideration should also be given to other risk factors including hypertension, diabetes, current smoking, and atrial fibrillation.

As with most medications in this at-risk population, treatment should be commenced at the lowest possible dose and monitored and titrated carefully with regular reviews. In the case of atypical antipsychotics in dementia patients with psychosis, there are a variety of factors to be considered with benefit to patients and caregivers weighed carefully against the risk of adverse events and increased mortality.

References

1. Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances. FDA Public Health Advisory. Available at: <http://www.fda.gov/cder/drug/advisory/antipsychotics.htm> (accessed 4/05)
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