Increased Risk of Death with Antipsychotic Drug Treatment for Dementia

On June 16, 2008, the FDA issued an Alert notifying health care professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis. Examples of medications noted in the advisory include: typical antipsychotics (e.g., haloperidol (HALDOL), thioridazane (MELLARIL), and atypical antipsychotic drugs (e.g., aripiprazole (ABILIFY), olanzapine (ZYPREXA), quetiapine (SEROQUEL), and risperidone (RISPERDAL)). SYMBYAX (olanzapine/fluoxetine), which is approved for treatment of depressive episodes associated with bipolar disorder, is also included in the agency’s advisory.

Previously, in April 2005, the FDA informed health care professionals and the public about the increased risk of mortality in elderly patients receiving atypical antipsychotic drugs to treat dementia-related psychosis. At that time, the analyses of 17 placebo-controlled trials that enrolled 5377 elderly patients with dementia-related behavioral disorders revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Atypical antipsychotics are categorized into three drug classes based on their chemical structure. Because the increase in mortality was observed with atypical antipsychotic medications in all three chemical classes, the FDA concluded that the effect was probably related to the common pharmacologic effects of all atypical antipsychotic medications, including those that have not been systematically studied in the dementia population. Therefore, clozapine and ziprasidone, which were not included in the trials, were also included in the warning. Based on this analysis, FDA requested that the manufacturers of atypical antipsychotic drugs include information about this risk in a Boxed Warning and the Warnings section of the drugs’ prescribing information.

Recently, two observational epidemiological studies\(^1\)\(^2\) were published that examined the risk of death in patients who were treated with conventional antipsychotic drugs. Both retrospective cohort studies were performed in Canada on very large patient populations (27,259 and 37,241 adults 65 years of age or older). In the first study the researchers found that atypical antipsychotics were associated with increased mortality as compared to no antipsychotic use as early as 30 days and persisting until study end at 180 days. In addition, investigators also found that conventional antipsychotic use showed a marginally higher risk compared to atypical antipsychotic use. In the second study, the investigators compared the 180-day all cause mortality with use of a conventional antipsychotic versus an atypical antipsychotic. They found that the risk of death in the group of patients treated with conventional antipsychotic medications was comparable to, or possibly greater than, the risk of death in the group of patients treated with atypical antipsychotic medications. The causes of death with the highest relative risk were cancer and cardiac disease.

Considerations for Healthcare Professionals

- Elderly patients with dementia-related psychosis treated with conventional or atypical antipsychotic drugs are at an increased risk of death.
- Antipsychotic drugs are not approved for the treatment of dementia-related psychosis. Furthermore, there is no approved drug for the treatment of dementia-related psychosis. Health care professionals should consider other management options.
- Physicians who prescribe antipsychotics to elderly patients with dementia-related psychosis should discuss this risk of increased mortality with their patients, patients’ families, and caregivers.
- To report any unexpected adverse or serious events associated with the use of these drugs, please contact the FDA MedWatch program and complete a form on line at http://www.fda.gov/medwatch/report/hcp.htm or report by fax to 1-800-FDA-0178, by mail using the postage-paid address form provided on line, or by telephone to 1-800-FDA-1088.
For further information or questions pertaining to this newsletter, e-mail Richard Reynolds at richard_g_reynolds@bcbsnm.com.

References:

