

## Use of Antipsychotic Drugs in Dementia: What's All the Agitation About?

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Neuropsychiatric symptoms (e.g., agitation, hallucinations, wandering) are highly prevalent problems that greatly reduce the quality of life for patients with advanced dementia as well as their caregivers.<sup>1,2</sup> Treatment of neuropsychiatric symptoms in dementia, also referred to as dementia-related psychosis, is challenging for at least two reasons: (1) the medications commonly prescribed to treat cognitive impairment in patients with dementia (e.g., donepezil [Aricept®]) may not be efficacious for treating dementia-related psychosis, or at least for agitation,<sup>3</sup> and (2) the evidence suggests that the efficacy of antipsychotic drugs for treating dementia-related psychosis is limited and serious adverse events (e.g., falls, stroke, and death) occur more commonly with these drugs than with placebo in patients with dementia.<sup>4-10</sup> Despite the limited evidence and safety concerns, antipsychotic drugs are the most commonly prescribed medications for the treatment of dementia-related psychosis. However, the use of antipsychotic drugs for treating dementia-related psychosis is being called into question because of recent U.S. Food and Drug Administration (FDA) warnings. This article discusses the FDA warnings associated with the use of antipsychotic drugs in patients with dementia and provides guidance to healthcare practitioners for making decisions about treating dementia-related psychosis in light of these safety warnings.

### What are antipsychotic drugs?

Antipsychotic or neuroleptic drugs commonly are categorized into two classes, the **conventional** (first generation) antipsychotic drugs (e.g., chlorpromazine [Thorazine®], haloperidol [Haldol®]) and the **atypical** (second generation) antipsychotic drugs (e.g., aripiprazole [Abilify®], olanzapine [Zyprexa®], quetiapine [Seroquel®], risperidone [Risperdal®]). Antipsychotic drugs are FDA-indicated for treating schizophrenia and, in some cases, mixed or manic episodes of bipolar disorder.<sup>11</sup> However, they are frequently used off label to treat dementia-related psychosis.

### What are the FDA warnings associated with antipsychotic drugs?

In April 2005, the FDA issued a Public Health Advisory to warn healthcare practitioners and the public about an increased risk of death associated with the use of **atypical** antipsychotic drugs to treat elderly patients with dementia-related psychosis.<sup>12</sup> In June 2008, after the FDA received data indicating an increased risk of death in elderly patients treated with **conventional** antipsychotic drugs for dementia-related psychosis, the FDA issued an update to the 2005 advisory to include this category of drugs as well.<sup>13</sup> The FDA requires that the manufacturers of antipsychotic drugs include information about the risk of death in elderly patients treated for dementia-related psychosis and state that these drugs are not approved for this indication in a Boxed Warning and the Warnings section of the drugs' prescribing information.

### Why are there FDA warnings about the use of antipsychotic drugs?

In 2005, two meta-analyses found that the odds of death among patients who received **atypical** antipsychotic drugs were approximately 1.6 times greater than among those who did not receive these drugs.<sup>9,12</sup> Most deaths were either due to

cardiovascular-related events (e.g., heart failure, sudden cardiac death) or infections (mostly pneumonia).<sup>12</sup>

Recently, three large observational studies found that the risk for death with **conventional** antipsychotic drugs was similar to the risk associated with atypical antipsychotic drugs.<sup>14-16</sup> In general, the greatest increase in death occurred among patients taking higher (above median, but unspecified) doses of conventional antipsychotic drugs and within 30 days of initiating antipsychotic therapy.<sup>15, 16</sup>

### Are there additional regulations pertaining to the use of antipsychotic drugs?

In addition to the FDA Boxed Warning, there are federal regulations regarding the use of antipsychotic drugs in nursing homes. In this setting, federal guidelines require documentation of a specific indication, a clearly stated plan for monitoring effectiveness and side effects, and a specific reason for continuing, adjusting, or discontinuing all drugs prescribed for the resident.<sup>13</sup> In addition, antipsychotic drugs require a gradual dose reduction, which emphasizes the importance of documenting the need and seeking the appropriate dose and duration for these drugs, as well as the importance of minimizing the risks associated with this class of drugs.

While not specific to the use of antipsychotic drugs, the updated Hospice Conditions of Participation<sup>17</sup> require hospices to perform a comprehensive assessment of the patient's drug profile to identify unnecessary drugs, detect both actual and potential drug interactions, and identify side effects of drugs. As part of the quality assessment and performance improvement activities, hospices must track adverse drug events and recommend appropriate corrective actions. In addition to identifying and rectifying drug-related problems, hospices are required to document the effectiveness of the drug therapy in the patient's medical record. Similar to the guidelines in nursing homes, the Conditions of Participation emphasize the importance of judicious drug use in hospice, which is particularly important for antipsychotic drugs because of the aforementioned reasons.

### How should I manage neuropsychiatric symptoms in a patient with dementia?

Before initiating and when deciding whether to continue treatment with an antipsychotic drug, consider the following principles:

- Begin by assessing the patient for medical (e.g., pain, delirium, infection) and environmental (e.g., excessive noise, temperature extremes) causes of the neuropsychiatric symptoms.<sup>18</sup> Treat the underlying cause if feasible.
- Remove medications that might be causing or contributing to the symptoms. While some medications are common culprits (e.g., antihistamines, anticholinergics), others (e.g., antibiotics) are more likely to cause or contribute to neuropsychiatric symptoms in the presence of certain medical conditions (i.e., kidney or liver failure).
- First-line therapy for neuropsychiatric symptoms in dementia is nonpharmacologic.<sup>18, 19</sup> Consider employing behavioral, environmental, or psychosocial interventions.<sup>20</sup> Consult good-practice guidelines on nonpharmacologic interventions from several professional organizations, such as the American Academy of Neurology, the Canadian Consensus Conference on Dementia, and the International Psychogeriatric Association.
- Determine whether the benefit of treatment with an antipsychotic drug outweighs the risks. For example, a patient with hallucinations and/or delusions may not warrant treatment with an antipsychotic drug if these symptoms are not distressing to the patient or placing him/her or others at harm.
- If an antipsychotic drug is deemed appropriate, consider the efficacy and side effects of each drug in the context of the individual patient. Use the lowest effective dose of the drug for the shortest period necessary. If necessary, titrate the antipsychotic drug slowly, every 2-5 days, to minimize or avoid side effects. In addition, continue nonpharmacologic interventions in conjunction with antipsychotic therapy.
- For a patient who is prescribed an antipsychotic drug, document the indication for the drug and the patient's goals

of care and carefully monitor the patient for effectiveness and side effects. Because the risk of mortality is highest in the first 30 days after initiating therapy, if clinical improvement is not seen within 2 to 4 weeks then the drug should be discontinued; a different antipsychotic drug or alternative therapy should be considered if necessary.<sup>5</sup> If clinical improvement is seen, periodically reevaluate the patient to determine the continued need for the drug. In the nursing home setting, trials of dose reduction are required; but consider adopting this practice for all patients regardless of setting of care. In many cases, the patient can eventually be weaned off the antipsychotic drug or kept at a very low dose.

### What is the take-away message?

Although they have not been approved for this indication, antipsychotic drugs are frequently used to treat dementia-related psychosis. Elderly patients with dementia-related psychosis treated with atypical and conventional antipsychotic drugs are at an increased risk of death. Notwithstanding the risk, when used appropriately, antipsychotic drugs can improve the quality of life of patients with advanced dementia. The decision to use antipsychotic drugs off-label for the treatment of dementia-related psychosis is left to the discretion of the prescriber and in hospice patients, for whom life expectancy is relatively short and the focus is on palliation of symptoms, goals of care and risk versus benefit should be carefully considered. Prescribers who prescribe antipsychotic drugs to elderly patients with dementia-related psychosis should discuss this risk of increased death with their patients and patients' caregivers<sup>13</sup> and document this discussion as well as the goals of care in the medical record.

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