

PHARMACY FACTS – September 2009

Black Box Warnings Associated with Antipsychotics¹⁻⁷

In April 2005, the Food & Drug Administration (FDA) notified healthcare professionals that elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death. Subsequently, the FDA reviewed additional information that indicates the similar risk is also associated with conventional antipsychotics. As a result, there is currently a Boxed Warning in product labelings describing this risk and noting that these drugs are not approved for the treatment of dementia-related psychosis.

The studies and several analyses have demonstrated an approximately 1.6-1.7 fold increase in mortality in such patients. The specific causes of mortality were either due to heart related events (e.g., heart failure, sudden death) or infections (e.g., pneumonia).

Antipsychotics as a group are associated with numerous severe adverse events, including increased mortality rates, cerebrovascular accidents, tardive dyskinesia, neuroleptic malignant syndrome, hyperlipidemia, weight gain, diabetes mellitus, sedation, parkinsonism and worsening of cognition. Given the side effects and potential toxicity of antipsychotic agents, the risks and benefits of these medications must be reassessed on an ongoing basis.

Psychosis, aggression, and agitation are common in patients with dementia. According to the American Psychiatric Association, a careful evaluation for general medical, psychiatric, environmental or psychosocial problems that may underlie the disturbance should be undertaken. For example, agitation is more likely to occur later in the course of dementia and can result from an occult general medical problem, medication side effects, untreated or undertreated pain, constipation, depression, psychotic symptoms or delirium. Agitation often resolves with treatment of an underlying condition.

The following are some recommendations regarding the use of antipsychotics in patients with dementia:

- Low starting dosages and gradual dose titration are recommended.
- Periodic attempts (e.g., every several months) to reduce or withdraw the medication should be considered for all patients.
- Agents with significant anticholinergic properties should be avoided in patients with dementia.
- A more sedating medication could be given at bedtime for a patient who has difficulty falling asleep in addition to psychosis, but antipsychotics are not used primarily for sleep disorders or anxiety.

- 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.

Use of Antipsychotics for Sleep Disturbances¹

Sleep disturbances are common in patients with dementia. Interventions include maintaining daytime activities and giving careful attention to sleep hygiene. Pharmacologic intervention is generally considered when other approaches have failed. When primarily treating the sleep disturbance, medications with possible effectiveness should be considered (e.g., zolpidem, zaleplon). Certain antipsychotics that are more sedating than others (e.g., Seroquel) might have been used to manage sleep disturbances in patients who are not diagnosed with psychosis or behavioral disturbances. However these medications should not be used solely for this purpose especially when considering their adverse effects.

Pharmacologic Treatment Options for Alzheimer's Dementia^{1,2,3,8-13}

Approximately 5.2 million Americans are diagnosed with Alzheimer's dementia (AD) including an estimated 200,000 patients under the age of 65. With the aging of the baby boomers, the prevalence of this medical condition is expected to double by 2020.

The use of certain classes of medications should be avoided in patients with Alzheimer's dementia. Agents that cause increased confusion (e.g., sedative-hypnotics, barbiturates) and anticholinergics especially in those prescribed an acetylcholinesterase inhibitor are a few examples.

Currently, there are several medications approved for the treatment of Alzheimer's dementia: Aricept, Exelon, Razadyne, Namenda. The most common side effects associated with acetylcholinesterase inhibitors are gastrointestinal (GI) events (e.g., nausea, vomiting, diarrhea, decreased appetite) with bradycardia and heart block reported as well. Therefore, caution should be exercised in patients with cardiac conduction conditions or those with a history of falls or syncope or at increased risk for developing GI ulcers. Common side effects of Namenda include dizziness, headache, constipation, and confusion. These medications are started at low doses with gradual dosage titration recommended if tolerated. Certain patients may benefit from higher doses, but the higher the dose, the more likely are side effects. Common side effects of Namenda include dizziness, headache, constipation, and confusion.

It is recommended that global assessment be performed periodically (e.g., at least 6 months) to evaluate patients' cognitive status, identify sudden changes in daily functioning, comorbid medical conditions, behavioral and psychotic symptoms and to monitor the effects of pharmacologic and non-pharmacologic treatment. The mini-mental status exam (MMSE) has become the most commonly utilized tool for cognition assessment. However, MMSE scores may not be appropriate for

patients who have learning or other disabilities (e.g., sensory impairments) or linguistic difficulties. In such cases, other appropriate methods of assessment should be used. There are alternative tools that have been validated of which some are available in languages other than English.²

Medication Facts⁸⁻¹³

Drug	FDA-Approved Indications	Dosage & Administration	Clinical Considerations
Acetylcholinesterase inhibitors (AChEIs)			
<p>Aricept (donepezil) - tablets</p> <p>Aricept ODT - orally disintegrating tablets</p>	<p>Dementia of Alzheimer's type</p>	<p>Mild to moderate: 5 mg, 10mg</p> <p>Severe: 10mg QD</p> <p>Administer in the evening, just prior to retiring without regard to meals</p>	<p>10 mg did not provide statistically significant clinical benefit than 5mg, in clinical studies, but it might provide additional benefit for some patients.</p> <p>Available evidence suggests adverse effects may be influenced by the rate of dose titration. Increase the initial dose of 5mg to 10 mg after 4-6 weeks of treatment.</p> <p>No dosage adjustment required in renal or hepatic impairment.</p>
<p>Exelon (rivastigmine)-capsules**, oral solution</p> <p>Exelon Patch - Transdermal system</p>	<p>Mild to moderate AD</p> <p>Mild to moderate dementia associated with Parkinson's disease</p>	<p><u>Oral</u></p> <p>Initial: 1.5 mg BID</p> <p>Dose escalation: 3 mg BID → 4.5 mg BID → 6 mg BID at a minimum of 2 week intervals if tolerated</p> <p><u>Patch</u></p> <p>Initial: 1 patch 4.6 mg/24 hrs QD</p> <p>Dose escalation: 4.6 mg → 9.5mg after a minimum of 4 weeks if well tolerated</p> <p>Maintenance: 1 patch 9.5 mg/ 24 hrs QD</p> <p>When switching oral to transdermal patch</p>	<p>Therapeutic dose</p> <ul style="list-style-type: none"> - AD: 3 to 6 mg BID - Dementia of Parkinson's disease: 1.5 to 6 mg BID <p>No dosage adjustment required in renal or hepatic impairment.</p> <p>Exelon capsule and oral solution may cause more nausea and vomiting and less muscle cramping vs. other AChEIs.</p> <p>Patch: Similar rates of nausea and vomiting shown at 4.6 mg vs. placebo. Higher incidences of GI side</p>

		< 6mg oral → 4.6 mg/24 hrs 6-12 mg oral → 9.5 mg/24 hrs	effects expected at higher doses. If treatment is interrupted for longer than several days, treatment should be reinitiated at the lowest daily dose.
Galantamine** (Razadyne)- tablets, oral solution Razadyne ER**	Mild to moderate AD	<u>Razadyne</u> Initial: 4 mg BID Dose escalation: 4 mg BID → to 8 mg BID → 12 mg BID at 4 week intervals Maintenance: 16-32 mg/day given in 2 divided doses Administer with morning and evening meals <u>Razadyne ER</u> Initial: 8 mg QD Dose escalation: 8 mg QD → 16 mg QD → 24 mg QD at 4 week intervals Administer in the morning with food	32 mg did not provide increased efficacy in clinical studies and is less well tolerated than lower doses Max dose in patients with moderate to severe hepatic impairment or moderate renal impairment: 16 mg/day Not recommended for severe hepatic [Child-Pugh score of 10-15] or severe renal impairment [CrCl < 9 mL/min]
NMDA receptor antagonist			
Namenda (memantine)-tablets, oral solution	Moderate to severe Alzheimer's dementia	Initial: 5 mg QD Dose escalation: Increase the dose in 5 mg increments at 1 week intervals (e.g., 5 mg BID → 5 mg & 10 mg → 10 mg BID) Target dose: 20 mg/day Can be taken with or without food	Patients with severe renal impairment (CrCl 5-29 ml/min): 5 mg BID

** generic equivalents available

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