TREATING ALZHEIMER’S DISEASE
Frequently Asked Questions

1. What is Alzheimer’s disease?
Alzheimer’s disease (AD) is a progressive, neurodegenerative disease characterized by the accumulation of beta-amyloid plaques (protein deposits) between brain cells (neurons) and neurofibrillary tangles (misplaced, twisted tau protein fibers) within cells that lead to neuronal death, causing severe impairments in cognition, behavior, and functioning (Alzheimer’s Association, 2005). Course of the disease can extend from 5 to 20 years.

Symptoms of mild AD (Mini-Mental State Examination (MMSE) score ≥ 20) can be subtle and include short-term memory loss, depression, and difficulties with instrumental activities of daily living (ADL) such as driving, managing finances, and shopping. In moderate AD (MMSE score of 10-19), memory loss worsens and the impairment spreads to include abilities such as language and abstract thought. Individuals may also experience a variety of behavioral changes, such as wandering, insomnia, and delusions, and require significant assistance with basic (e.g., dressing, using the toilet) as well as instrumental ADLs. In addition to loss of complex language and basic ADLs, individuals with severe AD (MMSE score < 10) become totally dependent and increasingly passive over time, and may exhibit agitation, depression, anxiety, apathy, and irritability. (Geldmacher, 2007; Forchetti, 2005)

2. How can current Alzheimer’s disease medications help?
While there is currently no way to reverse the pathological processes of AD, four Acetylcholinesterase (AChE) Inhibitors and one N-methyl D-aspartate (NMDA) Receptor Antagonist, have been approved by the FDA to treat symptoms of AD, offering global improvements in cognition, behavior, and functioning (Geldmacher, 2007; Alzheimer’s Association, 2007).

**AChE Inhibitors:**
Donepezil (Aricept®)
Rivastigmine (Exelon®)
Galantamine (Razadyne®)

**Note:** Tacrine (Cognex®), the first AChE inhibitor approved in 1993, is rarely prescribed due to significant hepatotoxicity (Geldmacher, 2007).

**NMDA Receptor Antagonists:**
Memantine (Namenda®)

Although improvements with AChE inhibitors are generally modest, the Quality Standards Subcommittee of the American Academy of Neurology that develops scientifically sound and clinically relevant practice parameters in neurology has concluded that the effects are clinically significant and recommends these medications as a standard of care for individuals with AD (Doody et al., 2001).

Acetylcholine is a chemical neurotransmitter used by neurons to function and send signals. The loss of acetylcholine-producing neurons in the basal forebrain and the cerebral cortex, particularly in the hippocampus, has been shown to lead to cognitive decline (Geldmacher, 2007). To combat this process, AChE inhibitors reduce the breakdown of acetylcholine, helping to compensate for the loss of functioning neurons (Alzheimer’s Association, 2007).

NMDA receptor antagonists work by regulating glutamate, another essential neurotransmitter involved with cognitive functions like memory and learning that, when produced in excessive amounts, may lead to brain cell death (Alzheimer’s Association, 2007).
Since AChE inhibitors work differently than NMDA receptor antagonists, they may be combined with memantine (Namenda®) to treat moderate-to-severe AD (Geldmacher, 2007; Forchetti, 2005).

<table>
<thead>
<tr>
<th>CLASS</th>
<th>DRUG</th>
<th>INDICATION</th>
<th>SUPPLIED</th>
<th>DOSAGE</th>
<th>SIDE EFFECTS</th>
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<tbody>
<tr>
<td><strong>AChE Inhibitors</strong></td>
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<tr>
<td>ARICEPT®</td>
<td>Donepezil HCl</td>
<td>Mild</td>
<td>Tab: 5mg, 10mg, 23mg</td>
<td>Mild to Moderate: 5mg QHS titrated to 10mg after 4 – 6 wks</td>
<td>Nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia, dizziness, depression</td>
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<tr>
<td>EXELON®</td>
<td>Rivastigmine Tartrate</td>
<td>Mild</td>
<td>Patch: 5 cm² (4.6mg/24hr)</td>
<td>Cap: 1.5mg, 3mg, 4.5mg, 6mg</td>
<td>Nausea, vomiting, abdominal pain, dyspepsia, constipation, somnolence, anorexia, asthenia, headache, dizziness, fatigue, diarrhea, tremor</td>
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<tr>
<td>RAZADYNE®</td>
<td>Galantamine Hydrobromide</td>
<td>Mild</td>
<td>Tab: 4mg, 8mg, 12mg</td>
<td>Razadyne: 4mg BID titrated to 16 – 24mg/day</td>
<td>Dizziness, confusion, headache, constipation, coughing, HTN, pain, vomiting, somnolence, hallucinations</td>
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<td><strong>NMDA Receptor Antagonist</strong></td>
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<tr>
<td>NAMENDA®</td>
<td>Memantine HCl</td>
<td>Moderate</td>
<td>Solution: 2mg/mL</td>
<td>5mg QD titrated to 10mg BID</td>
<td>Dizziness, confusion, headache, constipation, coughing, HTN, pain, vomiting, somnolence, hallucinations</td>
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**NMDA Receptor Antagonist**
* Combined therapy with an AChE Inhibitor appears to be most effective

**AChE Inhibitors**
* Adverse events are dose-related but generally mild and only temporary
* Extending the titration period can reduce the side effects

3. **How does the physician decide which AD medicine or combination of medications should be prescribed?**

AChE inhibitors work in similar ways, so the choice of drug within this class is based on the level of disease, tolerance to side effects, and administration regimen (Forchetti, 2005; Cummings et al., 2002).

For moderate to severe AD, an AChE inhibitor may be prescribed in combination with a NMDA-receptor antagonist due to their different mechanisms of action (Alzheimer’s Association, 2007). Long-term donepezil (Aricept®) as an adjunct to memantine (Namenda®) has been clinically...
proven to improve cognition, ADLs, global function, behavior, and care dependence versus cognitive and functional benefits from memantine alone in a prospective, double-blind, placebo-controlled, Phase III trial published in the January 2004 *Journal of the American Medical Association* (Geldmacher, 2007; Forchetti, 2005).

4. **When should one begin taking AD medications?**

   Optimal treatment entails early, accurate clinical diagnosis and early, long-term institution of therapy (Geldmacher, 2007; Desai & Grossberg, 2005; Forchetti, 2005).

5. **Should patients diagnosed with Mild Cognitive Impairment be treated with AD medications?**

   Studies have concluded that AChE inhibitors do not delay the onset of AD or dementia in patients with mild cognitive impairment (MCI) (Raschetti, Albanese, Vanacore & Maggin, 2007; Desai & Grossberg, 2005).

   Many patients with MCI, however, notice a small but significant improvement in cognitive deficits when taking AChE inhibitors (Doody, 2009). Thus, in MCI, AChE inhibitors may be used, as long as reasonable expectations are maintained.

6. **Is it worthwhile to switch medications if they do not appear to be helping?**

   To date, there have been no studies directly comparing AChE inhibitors with one another (Geldmacher, 2007, Doody et al, 2001); however, all AChE inhibitors raise acetylcholine levels in the brain by inhibiting acetylcholinesterase, delaying the deterioration in AD symptoms (Alzheimer's Association, 2007; Cummings et al, 2002).

   As a result, switching from one AChE inhibitor to another may not produce significantly different results, but side effects and administration regimens vary greatly and can make one more favorable over another for certain individuals (Geldmacher, 2007; Desai & Grossberg, 2005).

   For moderate-to-severe AD, evidence suggests that individuals may benefit from combining long-term use of donepezil (Aricept®) with memantine (Namenda®) (Geldmacher; Forchetti, 2005).

7. **When should AD medications be discontinued?**

   Since neuropathologic changes associated with AD are progressive, symptom improvement with medications eventually declines (Alzheimer's Association, 2007). If side effects develop and do not resolve, compliance is poor, or deterioration continues at the pretreatment rate after 6 – 12 months of treatment, one may consider discontinuation of medications with physician supervision (Cummings et al, 2002).

   Current neurology practice guidelines, however, did not, at the time they were developed, have the benefit of published long-term studies with AChE inhibitors. Recent long-term studies indicate that continued use of AChE inhibitors may help AD patients live longer in non-institutionalized settings with associated personal, social, and economic benefits (Geldmacher, 2007). Similar data on memantine (Namenda®) are not yet available (Geldmacher).

8. **Where can I get information on clinical trials for AD?**

   - Alzheimer's Disease Clinical Trials Database
     Alzheimer's Disease Education and Referral Center, National Institute on Aging  
     (800) 438-4380
   - U.S. National Institutes of Health, Clinical Trials  
     [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)
   - Alzheimer's Association  
     [www.alz.org/TrialMatch](http://www.alz.org/TrialMatch)
References


