About
Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Publication History

Medications listed in the tables included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

1. Dosage [*]

Adults
Alzheimer’s disease is associated with significant losses in cholinergic neurons and decreased concentrations of acetylcholine, a neurotransmitter significantly involved in learning and memory processes. Acetylcholinesterase inhibitors (ACIs) exert pharmacologic effects by increasing availability of intrasynaptic acetylcholine in the presence of intact cholinergic neurons. All available ACIs are FDA-approved in adults for the management of mild to moderate Alzheimer’s dementia, while donepezil is also FDA-approved for management of severe Alzheimer’s disease. Additionally, rivastigmine (Exelon®) is FDA-approved for use in mild-to-moderate dementia associated with Parkinson’s disease.

Recently, a combination product containing donepezil and memantine extended-release (Namzaric®) has been FDA-approved for use in patients with moderate to severe Alzheimer’s dementia stabilized on donepezil and memantine. Memantine, a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist, exerts pharmacologic effects by blocking glutamate activity, the key excitatory neurotransmitter in the central nervous system. Glutamate is released into synapses when certain neurons die and activates NMDA receptors, causing overexcitation, an influx of calcium ions and, ultimately, death of downstream neurons. NMDA receptor activation is thought to be one of the main causes of neurodegeneration in various types of dementia, including Alzheimer’s-associated dementia.

Recommended adult dosages for ACIs and ACI combination therapy are summarized in Table 1.
### Table 1: Recommended Adult Dosages for ACIs

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosage Form/Strength</th>
<th>Maximum Recommended Dosage</th>
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<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
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</table>
| donepezil (Aricept®, generics) | • tablets (5 mg, 10 mg, 23 mg)  
• orally disintegrating tablets (5 mg, 10 mg) | mild to moderate Alzheimer’s:  
• 10 mg/day, as a single dose  
moderate to severe Alzheimer’s:  
• 23 mg/day, as a single dose |
| galantamine (Razadyne®, Razadyne® ER, generics) | • immediate-release:  
  o tablets (4 mg, 8 mg, 12 mg)  
  o oral solution (4 mg/ml)  
• extended-release:  
  o capsules, extended-release (8 mg, 16 mg, 24 mg) | mild to moderate Alzheimer’s:  
• immediate-release: 24 mg/day, in 2 divided doses  
• extended-release: 24 mg/day once daily |
| rivastigmine (Exelon®, generics) | • immediate-release:  
  o capsules (1.5 mg, 3 mg, 4.5 mg, 6 mg)  
• transdermal (extended-release):  
  o transdermal patch (4.6 mg/24 h, 9.5 mg/24 h, 13.3 mg/24 h) | mild/moderate Alzheimer’s, Parkinson’s disease dementia:  
• immediate-release: 12 mg/day, in 2 divided doses  
• transdermal/extended-release: 13.3 mg/24 h |
| **Combination Therapy** | | |
| memantine extended-release/donepezil (Namzaric®) | • capsules (7 mg/10 mg, 14 mg/10 mg, 21 mg/10 mg, 28 mg/10 mg) | moderate to severe Alzheimer’s dementia in patients stabilized on memantine and donepezil:  
• 28 mg/10 mg once daily |

Although not FDA-approved, ACIs have also been evaluated for use in vascular dementia, dementia with Lewy bodies, post stroke aphasia, and memory improvement in multiple sclerosis patients.

**Renal Impairment**

Patients prescribed galantamine with moderate renal impairment [creatinine clearance (CrCl) 9-59 ml/min] should have doses titrated cautiously; dosages should not exceed 16 mg daily. Galantamine is not recommended for use in patients with severe renal impairment (CrCl < 9 ml/min).

Patients with severe renal impairment (CrCl 5-29 ml/min) stabilized on memantine 5 mg twice daily immediate-release or 14 mg daily extended-release and donepezil 10 mg daily or donepezil 10 mg once daily without memantine may utilize memantine/donepezil combination therapy in doses not exceeding 14 mg/10 mg daily.

**Pediatrics**

ACIs and memantine/donepezil combination therapy are not recommended for use in children, as adequate, well-controlled clinical trials have not documented safety and efficacy of these agents for any disease state in the pediatric population.

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2. Duration of Therapy
ACIs do not alter the long-term progressive decline of Alzheimer’s disease, but have been shown to delay time to institutionalization, which may be cost-effective. ACIs may be prescribed to stabilize dementia in Alzheimer’s patients, as determined by periodic assessment of functional and cognitive ability. ACIs should be discontinued when dementia becomes unresponsive to therapy and progressively severe, as the efficacy of these agents diminishes due to loss of intact cholinergic neurons.

3. Duplicative Therapy [*]
Combined use of two or more ACIs does not provide enhanced therapeutic benefit and may result in additive adverse effects. Concurrent administration of two or more ACIs is not recommended and will be reviewed.

4. Drug-Drug Interactions [*]
Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for ACIs are summarized in Table 2. Only those drug-drug interactions classified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed.

<table>
<thead>
<tr>
<th>Target Drug</th>
<th>Interacting Drug</th>
<th>Interaction</th>
<th>Recommendations</th>
<th>Clinical Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACIs</td>
<td>anticholinergics</td>
<td>potential for reduced cholinergic activity with centrally acting anticholinergics, which may manifest as reduced activities of daily living but not cognitive function; peripherally acting anticholinergics less likely to attenuate ACI therapeutic effects</td>
<td>monitor for diminished cholinergic effects; choose agents with less centrally acting anticholinergic activity</td>
<td>moderate (DrugReax) 3- moderate (CP)</td>
</tr>
<tr>
<td>ACIs</td>
<td>cholinergic agents and other cholinesterase inhibitors</td>
<td>enhanced cholinergic/ adverse effects</td>
<td>avoid combination, if possible; if combination needed, monitor for enhanced cholinergic effects; may adjust doses to achieve tolerable clinical effects</td>
<td>moderate (DrugReax) 2-major (CP)</td>
</tr>
<tr>
<td>ACIs</td>
<td>drugs that lower seizure threshold (e.g., bupropion)</td>
<td>concurrent use may increase seizure risk as seizures observed with ACIs</td>
<td>use cautiously together; begin with low ACI doses and titrate slowly</td>
<td>major (DrugReax)</td>
</tr>
<tr>
<td>ACIs</td>
<td>NSAIDs</td>
<td>potential for additive gastrointestinal effects</td>
<td>monitor for gastrointestinal intolerance and/or bleeding</td>
<td>3-moderate (CP)</td>
</tr>
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<td>ACIs</td>
<td>beta blockers</td>
<td>increased risk of bradycardia when prescribed concurrently; ACIs may increase vagal tone, resulting in bradycardia, hypotension, and syncope</td>
<td>monitor blood pressure, heart rate during therapy</td>
<td>3-moderate (CP)</td>
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<tr>
<td>donepezil</td>
<td>QT interval-prolonging medications</td>
<td>adjunctive use may increase risk of QT interval prolongation and torsades de pointes as donepezil has increased risk of QT interval prolongation and torsades de pointes</td>
<td>avoid combined use; if used together, monitor patients for efficacy and cardiovascular adverse outcomes</td>
<td>contraindicated (DrugReax) 1-severe (CP)</td>
</tr>
<tr>
<td>donepezil, galantamine</td>
<td>CYP3A4 and CYP2D6 inducers</td>
<td>potential for reduced donepezil serum concentrations and decreased efficacy</td>
<td>monitor for reduced donepezil efficacy</td>
<td>3-moderate (CP)</td>
</tr>
<tr>
<td>donepezil, galantamine</td>
<td>CYP3A4 and CYP2D6 inhibitors</td>
<td>potential for increased donepezil and galantamine serum concentrations</td>
<td>monitor for increased cholinergic effects</td>
<td>major, moderate (DrugReax) galantamine: 2-moderate; donepezil, galantamine: 3-moderate (CP)</td>
</tr>
<tr>
<td>donepezil/ memantine</td>
<td>alkalinizing agents (e.g., select carbonic anhydrase inhibitors, sodium bicarbonate)</td>
<td>memantine clearance reduced by about 80% in alkaline conditions (pH ≥ 8); adjunctive administration with alkalinizing agents may decrease memantine elimination and increase memantine serum levels and potential for increased pharmacologic/adverse effects</td>
<td>administer drug combination cautiously together; monitor patients for increased pharmacologic/adverse effects</td>
<td>moderate (DrugReax) 3-moderate (CP)</td>
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</table>
Table 2. Drug-Drug Interactions for ACIs (continued)

<table>
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<td>donepezil/ memantine</td>
<td>other drugs excreted by renal tubular secretion (e.g., amiloride, cimetidine, dofetilide, nicotine, quinidine, ranitidine)</td>
<td>memantine eliminated by renal tubular cationic transport; combined administration may result in altered serum levels of both memantine and other drugs excreted by renal tubular secretion due to competition for transport system; elevated dofetilide levels may increase potential for arrhythmias, including torsades de pointes</td>
<td>monitor patient responses, observe for adverse effects or loss of efficacy, and adjust doses as necessary</td>
<td>moderate (DrugReax) dofetilide, procainamide, quinidine: 2-major; all other drugs: 3-moderate (CP)</td>
</tr>
<tr>
<td>rivastigmine</td>
<td>metoclopramide</td>
<td>combined use may increase risk of extrapyramidal effects as both agents associated with extrapyramidal signs/symptoms</td>
<td>avoid concurrent use; monitor closely for extrapyramidal effects if combined therapy necessary</td>
<td>contraindicated (DrugReax) 2-major (CP)</td>
</tr>
</tbody>
</table>

*CP = Clinical Pharmacology

ACI = acetylcholinesterase inhibitor; CYP = cytochrome P450 enzyme

References


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