Alzheimer’s Agents
Therapeutic Class Review (TCR)

February 4, 2019

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FDA-APPROVED INDICATIONS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Dementia Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AD – Mild to Moderate</td>
</tr>
<tr>
<td>Acetylcholinesterase Inhibitors (AChEIs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>donepezil (Aricept®)¹</td>
<td>generic, Eisai</td>
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<tr>
<td>galantamine (Razadyne®, Razadyne ER®)²</td>
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<td>rivastigmine³</td>
<td>generic</td>
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<tr>
<td>rivastigmine (Exelon® Patch)⁴</td>
<td>generic, Novartis</td>
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<tr>
<td>(N-methyl-D-aspartate) NMDA Receptor Antagonist</td>
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<td></td>
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<tr>
<td>memantine (Namenda®)⁵</td>
<td>generic, Forest/Allergan</td>
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<tr>
<td>memantine extended-release (Namenda XR®)⁶</td>
<td>generic, Forest/Allergan</td>
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<tr>
<td>AChEi and NMDA Receptor Antagonist Combination Products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>donepezil and memantine ER (Namzaric®)⁷</td>
<td>Allergan</td>
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</tr>
</tbody>
</table>

AD – Alzheimer’s disease; PD – Parkinson’s disease

*Indicated for patients stabilized on 10 mg/day of donepezil prior to initiation (with or without memantine).

OVERVIEW

Dementia is characterized by irreversible loss of or decline in memory and other cognitive abilities. Approximately 5.7 million Americans suffer from Alzheimer's disease (AD), 5.5 million of which are aged 65 and older.⁸ AD is the most common type of dementia, accounting for 60% to 80% of dementia disorders in the elderly and is the sixth leading cause of death in the United States (U.S.).⁹ Other types of dementia include vascular dementia, dementia with Lewy bodies, mixed dementia, and frontotemporal dementia.¹⁰ Dementia may also be associated with human immunodeficiency virus (HIV), normal pressure hydrocephalus, Huntington’s disease, Korsakoff’s syndrome, multiple sclerosis (MS), Parkinson’s disease (PD), and Creutzfeldt-Jakob disease. Many other conditions can cause dementia or delirium symptoms, such as thyroid disorder and vitamin deficiencies, but are reversible once the underlying condition is addressed.

AD is characterized by progressive cognitive decline associated with impairment of activities of daily living (ADL) and behavioral disturbances. Patients with AD eventually lose all cognitive, analytical, and physical functioning.¹¹,¹² Ten warning signs of AD include memory loss that disrupts daily life,
challenges in planning or solving problems, difficulty completing familiar tasks, confusion with time or place, trouble understanding visual images and spatial relationships, difficulties with speaking or writing, misplacement of items or losing the ability to retrace steps, decreased or poor judgment, withdrawal from work or social activities, and mood or personality changes. In addition, there are 7 stages of AD over the course of the disease and individuals will not experience the same symptoms or rate of disease progression.\(^\text{13}\)

Beginning in 2011, the National Institute for Aging (NIA) and the Alzheimer’s Association published consensus guidelines by revising the definition of Alzheimer’s to include 3 phases of the disease: preclinical, mild cognitive impairment, and dementia.\(^\text{14,15,16}\) This reflects current thinking that Alzheimer’s begins creating distinct and measurable changes in the brains of affected people years, perhaps decades, before memory loss and cognitive symptoms become noticeable.\(^\text{17}\)

General agreement among AD researchers includes identified risk factors for being diagnosed with AD.\(^\text{18,19}\) One risk factor is age over 65 years, with the doubling every 5 years after the age of 65 until the age of 85 when the risk reaches nearly one-third. Family history also plays a part when the patient has a parent, sibling, or child with Alzheimer’s and will be more likely to develop the disease. As a result, genetics play a role with AD in both risk genes and deterministic genes. Studies have estimated that 56% to 65% of patients with AD have the gene apolipoprotein E-e4 (APOE-e4). Individuals with deterministic genes (amyloid precursor protein [APP] or presenilin 1) are guaranteed to develop the disease, while those with presenilin 2 gene have 95% chance of developing AD.\(^\text{20}\) Genetic testing is available for these biomarkers, but health professionals do not recommend routine genetic testing for screening or diagnosis; instead, diagnosis is based on a complete medical assessment including mental status testing, physical, neurological, and blood tests to rule out other causes.

Although the causes of AD have not been completely identified, the etiology of the disease is thought to be multifactorial. Plaques and tangles are also hallmark indicators of Alzheimer’s disease (AD).\(^\text{21}\) Cognitive impairment is more highly correlated with neurofibrillary pathology than amyloid pathology. The aspect of AD pathology that is most closely tied to cognitive impairment is neurodegeneration, particularly synapse loss.\(^\text{22}\) The discovery of extensive cholinergic cell loss as AD progresses led to the cholinergic hypothesis and the development of drugs that target the cholinergic system. The cholinergic hypothesis suggests that a dysfunction of acetylcholine (ACh)-containing neurons in the brain plays a part in the decline of cognitive function seen in patients with AD.\(^\text{23}\)

Abnormalities also exist in the glutamate pathways of patients with AD. Glutamate is the main excitatory neurotransmitter in the cerebral cortex and hippocampus. The glutamate-gated N-methyl-D-aspartate (NMDA) receptor is activated during memory formation. Persistent activation of NMDA receptors due to chronic, excessive glutamate release is toxic to neurons, and the over-activation leads to deficits in cognitive function and neuronal death.\(^\text{24}\) Loss of these glutamatergic fibers correlates with the clinical signs of dementia.\(^\text{25,26}\)

Some evidence indicates that a compromise of the serotonergic system contributes significantly to the onset and progression of AD. Specifically, data suggest that serotonin receptors modulate ACh, as well as other neurotransmitters, including glutamate, dopamine, and norepinephrine.\(^\text{27,28}\) Regardless of the specific cause, the characteristic features of neurofibrillary tangle pathology and neuronal death are noted in all cases.
Tacrine (Cognex®) was the first cholinesterase inhibitor approved; however, this agent is no longer available in the United States; it has been replaced by newer acetylcholinesterase agents with less adverse effects. Three acetylcholinesterase inhibitors (AChEIs) commonly utilized for the treatment of AD are galantamine (Razadyne, Razadyne ER), rivastigmine (capsules, Exelon Patch), and donepezil (Aricept). Each of these drugs has shown cognitive benefit over placebo; however, it remains unclear if their use slows disease progression and cognitive decline, delays nursing home placement, or alters mortality. A risk-benefit assessment of dementia medications, which included 257 randomized or observational trials showed that cholinesterase inhibitors produce small improvements in cognitive, functional, and global benefits in patients with mild to moderate disease, but the clinical significance of these effects is unclear. The efficacy appears to wane over time, with minimal benefit seen after 1 year. There is no evidence for benefit for those with advanced disease or those aged over 85 years.

Memantine (Namenda, Namenda XR), an NMDA receptor antagonist, has been shown to improve cognition in moderate to severe dementia and is approved by the Food and Drug Administration (FDA) for treatment of moderate to severe AD. There are data showing that use of memantine in combination with AChEIs is beneficial in moderate to severe AD patients. Dementia patients should be evaluated every 6 months using the Mini-Mental Status Examination (MMSE) score and global, functional, and behavioral assessment if the patient is being treated with any of these medications. Caregiver’s input on the patient’s condition at follow-up should be obtained. Medication should only be continued if it is determined that it is producing a beneficial effect. There are limited data showing evidence for a prolonged duration of effect.

Management objectives for treatment of AD and PD-related dementia include improving cognition and delaying disease progression, as well as promoting quality of life and social functioning, maintaining patient’s dignity, educating and supporting caregivers, and assisting with decision-making and competency determinations. In 2008, the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) developed guidelines for the pharmacological treatment of dementia. While these guidelines were reaffirmed in 2013, ACP no longer considers them as current/active. At the time of the guideline, AAFP-ACP guideline panel reviewed the medical literature and found limited evidence regarding the effectiveness of the approved drugs in regard to the following: cognition, global function, behavior/mood, and quality of life/activities of daily living. The guidelines recommend that the decision to initiate a trial of therapy with an AChEI or memantine should be based on individual assessment by a clinician. Tolerability, adverse effect profile, ease of use, and cost should be considered when selecting treatment. AAFP completed their own review of the treatment of Alzheimer’s dementia in 2017. Based on their literature review and evidence rating, they state that cholinesterase inhibitors should be considered for treatment of cognitive and functional decline in patients with mild to moderate AD. Dose ranges recommended include donepezil 5 mg to 10 mg per day, at least 16 mg per day of galantamine, and 6 mg to 12 mg per day orally or 9.5 mg per day transdermally of rivastigmine. Memantine, at a target dose of 20 mg per day, should be considered for treatment of cognitive and functional decline in patients with moderate to severe AD. In patients with moderate to severe AD or mixed dementia who are already receiving a cholinesterase inhibitor, memantine should be considered to treat cognitive and functional symptoms. Notably, they state these medications have demonstrated statistically significant, but clinically small, delays in cognitive and function decline. They further recommend the use of vitamin E, a structured physical exercise program, and cognitive stimulation in select populations.
The American Psychiatric Association (APA) has also addressed the treatment of AD and other dementias in their 2007 guidelines and 2014 Guideline Watch. They state that the available efficacy evidence remains modest for AChEIs in mild to moderate AD and memantine in moderate to severe AD. Based on evidence available at publication, no increased benefit is seen with higher doses of donepezil, but higher doses of rivastigmine may increase benefit. Combination therapy (memantine with an AChEI) may result in a slight benefit, but overall clinical significance of this is unclear. Likewise, sustained benefit with either memantine or an AChEI is unclear. Efficacy data on the use of AChEIs remain weak for the treatment of PD dementia, with most evidence associated with rivastigmine.

The 2011 from the World Federation of Societies of Biological Psychiatry (WFSBP) on the treatment of AD state that donepezil, galantamine, rivastigmine, and memantine show a modest effect on the symptomatic treatment of AD over a limited time period. They further state that the AChEIs have reasonable adverse effects and that memantine is associated with fewer side effects; however, WFSBP recommends all agents discussed in this review for the treatment of AD. Based on their research, these agents provide modest symptom improvement (a median of 2.3 points on the Alzheimer’s’ Disease Assessment Scale – cognitive subscale [ADAS-cog] over 6 months). Ultimately, drug selection should be individualized as it is dependent on disease stage and adverse effect profile. Patient assessment should occur every 3 to 6 months to assess efficacy, dosage, and tolerability.

The American Academy of Neurology (AAN) published a practice parameter on the management of dementia in 2001 (reaffirmed in 2003). They state that an AChEI should be considered in patients with mild to moderate AD (standard recommendation). Only limited data on memantine were available at the time of the literature review; thus, the role of memantine is not addressed in these guidelines. An update is in progress. The AAN Mild Cognitive Impairment (MCI) guideline was updated in 2017 and states that data is insufficient to support pharmacological therapy for MCI; however, prescribers may elect treatment with AChEIs (Level B) after communicating with the patient the drug’s lack of proven efficacy (Level A).

Parkinson’s disease (PD) is a fairly common neurological disorder that affects approximately 2% of adults older than 65 years. Approximately 50% to 80% of those with PD will eventually experience PD dementia and the average time from onset of PD to developing dementia is about 10 years. For dementia related to PD, the dementia symptoms progress similarly to dementia with Lewy body or AD in that, in most cases, amyloid plaques and neurofibrillary tangles are present. Early onset PD primarily targets movement but, as the disease progresses, mental functions including memory and task completion are impacted. Brain changes include deposits of alpha-synuclein clumps (Lewy bodies) in the substantia nigra which is thought to cause degeneration of the dopamine-producing nerve cells. In dementia associated with PD, cholinergic deficits are the most consistent findings associated with cognitive and neuropsychiatric symptoms. Rivastigmine (capsules, Exelon Patch) is FDA-approved for mild to moderate dementia associated with Parkinson’s disease.

PHARMACOLOGY

AChEIs exert their therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of ACh through reversible inhibition of its hydrolysis by acetylcholinesterase (AChE). Centrally, the resulting increase in ACh improves cognition. Peripheral enhancement of ACh causes the gastrointestinal adverse effects noted with AChEIs. As the disease
progresses, the therapeutic effect of the AChEIs may lessen as fewer cholinergic neurons remain functionally intact. Rivastigmine is also a selective inhibitor of butyrylcholinesterase (BuChE).

Memantine (Namenda, Namenda XR) is an uncompetitive NMDA glutamate-type receptor antagonist with low to moderate affinity that binds preferentially to NMDA receptor-operated cation channels. Memantine allows the NMDA receptor to be activated during physiological memory formation, but blocks the receptor during pathological (excitotoxic) activation.\(^5^9,6^0\) Memantine also demonstrates antagonistic effects at the serotonin and nicotinic receptors.

**PHARMACOKINETICS**\(^6^1,6^2,6^3,6^4,6^5,6^6,6^7\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-Life (hr)</th>
<th>Metabolism</th>
<th>Protein Binding (%)</th>
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<tbody>
<tr>
<td><strong>AChEIs</strong></td>
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</tr>
<tr>
<td>donepezil (Aricept)</td>
<td>70</td>
<td>CYP2D6, 3A4</td>
<td>96</td>
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<tr>
<td>galantamine (Razadyne, Razadyne ER)</td>
<td>7</td>
<td>CYP2D6, 3A4</td>
<td>18</td>
</tr>
<tr>
<td>rivastigmine (capsules, Exelon Patch)</td>
<td>1.5 (oral) 3 (patch)</td>
<td>hydrolysis by esterases</td>
<td>40</td>
</tr>
<tr>
<td><strong>NMDA Receptor Antagonist</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>memantine (Namenda, Namenda XR)</td>
<td>60–80</td>
<td>renal tubular secretion and partial hepatic metabolism</td>
<td>45</td>
</tr>
<tr>
<td><strong>AChEI and NMDA Receptor Antagonist Combination Products</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>donepezil and memantine ER (Namzaric)</td>
<td>donepezil 70  memantine 60–80</td>
<td>CYP2D6, 3A4 renal tubular secretion and partial hepatic metabolism</td>
<td>96 45</td>
</tr>
</tbody>
</table>

The effectiveness of the fixed-dose donepezil/memantine ER (Namzaric) was established by demonstrating the bioequivalence of Namzaric with memantine ER co-administered with donepezil.

**CONTRAINDICATIONS/WARNINGS**\(^6^8,6^9,7^0,7^1,7^2,7^3,7^4\)

Cholinesterase inhibitors (donepezil [Aricept, Namzaric], galantamine [Razadyne, Razadyne ER], rivastigmine [capsules, Exelon Patch] and the NMDA receptor antagonist memantine (Namenda, Namenda XR, Namzaric) are contraindicated for patients with known hypersensitivity to any ingredient of the product. Donepezil (Aricept) and the fixed-dose combination donepezil/memantine ER (Namzaric) are also contraindicated in patients with known hypersensitivity to piperidine derivatives. Rivastigmine is also contraindicated in patients with hypersensitivity to other carbamate derivatives. Rivastigmine patch is contraindicated in patients with previous history of application site reactions with rivastigmine transdermal patch, suggestive of allergic contact dermatitis.

Cholinesterase inhibitors are likely to exaggerate succinylcholine-type and other similar neuromuscular agents during anesthesia, potentially resulting in prolonged neuromuscular blockade and extended respiratory depression. These agents may increase gastric acid secretion due to increased cholinergic
activity and should be monitored closely for symptoms of active or occult gastrointestinal bleeding. Cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or chronic obstructive pulmonary disease due to their cholinomimetic effects.

In addition, cholinesterase inhibitors may have vagotonic effects that may manifest as bradycardia or heart block in patients with or without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported with the use of donepezil and rivastigmine. In randomized controlled trials, bradycardia was reported more often with galantamine than with placebo; however, the bradycardia was rarely severe and rarely required treatment discontinuation.

Cholinesterase inhibitors are believed to have some potential to cause generalized convulsions; however, seizure activity may also be a manifestation of AD. In clinical trials, seizures occurred in 0.3% of patients treated with memantine and 0.6% of patients treated with placebo.

Drugs that increase cholinergic activity (rivastigmine, donepezil, and galantamine) may cause urinary obstruction. Conditions that raise urine pH may decrease urinary elimination of memantine resulting in increased plasma concentrations.

Cholinesterase inhibitors may increase gastric acid secretion due to increased cholinergic activity. Although clinical studies of donepezil in doses of 5 mg to 10 mg per day have shown no increase in the incidence of either peptic ulcer disease or gastrointestinal bleeding, patients treated should be monitored closely for symptoms of active or occult gastrointestinal bleeding, particularly if they are at increased risk for developing ulcers (e.g., a history of ulcer disease, concurrent use of nonsteroidal anti-inflammatory drugs [NSAIDs]).

Rivastigmine and galantamine/galantamine ER may cause CNS depression, which may impair physical or mental abilities.

Some donepezil products may contain aspartame, which is metabolized to phenylalanine, and should be avoided/used with caution in patients with phenylketonuria.

Rivastigmine may exacerbate or induce extrapyramidal symptoms; worsening PD symptoms has been reported.

Patients prescribed oral or transdermal rivastigmine at higher than the recommended dose have experienced significant gastrointestinal adverse effects, including nausea, anorexia/decreased appetite, and weight loss. When initiating therapy, the patient should be started at the lowest dose and then titrated to the maintenance dose. If treatment is interrupted for longer than 7 days, treatment should be restarted with the lowest dose.

Medication errors have been known to occur with rivastigmine transdermal (Exelon patch) and have resulted in serious adverse events; some cases have required hospitalization and, rarely, led to death. The majority of medication errors have involved not removing the old patch when putting on a new one and the use of multiple patches at one time. Patients and caregivers must be given proper instruction on the dosage and administration of rivastigmine patches and including removal of patches after 24 hours.

Disseminated hypersensitivity reactions of the skin, such as allergic dermatitis, have been reported with the use of rivastigmine with both the oral and transdermal routes of administration. Treatment should be discontinued if disseminated hypersensitivity reaction of the skin occurs. Application site
reactions may occur with rivastigmine patch. Treatment should be discontinued if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g., increasing erythema, edema, papules, vesicles), and if symptoms do not significantly improve within 48 hours after removal of patch. Patients who continue to require rivastigmine therapy should be switched to oral therapy only after negative allergy testing.

Serious skin reactions (Stevens-Johnson syndrome and acute generalized exanthematous pustulosis) have been reported with the use of galantamine/galantamine ER. Patients should stop the drug immediately at the first sign of skin rash, unless the rash is clearly not drug-related.

Worsening of corneal condition has been observed in memantine clinical trials; periodic ophthalmic exams during use are recommended.

**DRUG INTERACTIONS**

Antimuscarinics are functional antagonists of the AChEIs and reduce the effectiveness of AChEIs when co-administered.\(^{82,83}\) Drugs with anticholinergic effects have been shown to interfere with the activity of the AChEIs. Common anticholinergics include amantadine, cyclobenzaprine, orphenadrine, disopyramide, and sedating antihistamines.

Parasympathomimetic drugs can produce additive pharmacologic effects when used with AChEIs. Concurrent use is unlikely to be tolerated and should be avoided. Additionally, a synergistic effect would be expected when cholinesterase inhibitor is given concurrently with succinylcholine or similar neuromuscular blocking agents.

Donepezil and galantamine should be cautiously used with QTc prolonging agents; close monitoring for evidence of QTc prolongation or other alterations of cardiac rhythm is recommended. AChEIs may enhance the bradycardic effect of bradycardia-causing agents.

Donepezil (Aricept, Namzaric) is metabolized by CYP2D6 and CYP3A4; therefore, there is potential for an interaction with drugs that are inhibited or metabolized by these isoenzymes. Although clinically significant interactions have not been documented, patients taking drugs that are metabolized by the same isoenzymes should be monitored. Induction of CYP3A4 could also increase the elimination of donepezil. Donepezil is highly protein bound (96%), but interactions where donepezil displaces or is displaced by other protein bound drugs have not been reported.

Rivastigmine (capsules, Exelon Patch) is hydrolyzed by esterases, but no significant drug interactions have been reported.

Galantamine (Razadyne, Razadyne ER) is a primary substrate for CYP3A4 and is metabolized to a lesser extent by CYP2D6. Co-administration of galantamine with a strong inhibitor of CYP3A4, such as ketoconazole, increased the area under the curve (AUC) of galantamine by 30%. When administered with the strong inhibitor of CYP2D6, paroxetine 20 mg per day, the oral bioavailability of galantamine increased by about 40%. Galantamine has not been shown to have a significant effect on other drugs metabolized by the CYP450 enzyme system.\(^{84}\)

The use of memantine (Namenda, Namenda XR, Namzaric) in combination with other NMDA antagonists, such as amantadine, ketamine, and dextromethorphan, has not been evaluated and use should be approached with caution. Memantine is partially excreted by renal tubular secretion.\(^{85}\)
administration of memantine with other drugs that are excreted in this manner, such as hydrochlorothiazide, nicotine, and ranitidine, may result in increased serum concentrations of 1 or both drugs. When given with metformin, competition between the 2 drugs for renal elimination may increase the risk of lactic acidosis due to accumulation of metformin. Conditions that raise urine pH may decrease urinary elimination of memantine resulting in increased plasma levels.

**ADVERSE EFFECTS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Anorexia</th>
<th>Diarrhea</th>
<th>Dizziness</th>
<th>Headache</th>
<th>Withdrawal Due to Adverse Event</th>
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</thead>
<tbody>
<tr>
<td>AChEIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>donepezil (Aricept) mild-mod AD</td>
<td>11 (6)</td>
<td>5 (3)</td>
<td>4 (2)</td>
<td>10 (5)</td>
<td>8 (6)</td>
<td>10 (9)</td>
<td>5-13 (5)</td>
</tr>
<tr>
<td>donepezil (Aricept) severe AD</td>
<td>6 (2)</td>
<td>8 (4)</td>
<td>8 (4)</td>
<td>10 (4)</td>
<td>2 (1)</td>
<td>4 (3)</td>
<td>12 (7)</td>
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<td>galantamine (Razadyne)</td>
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<td>13 (4)</td>
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<td>9 (7)</td>
<td>9 (6)</td>
<td>8 (5)</td>
<td>7-10 (7)</td>
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<tr>
<td>rivastigmine mild-mod AD</td>
<td>17-47 (12)</td>
<td>13-31 (6)</td>
<td>≤17 (3)</td>
<td>5-19 (11)</td>
<td>6-21 (11)</td>
<td>4-17 (12)</td>
<td>6-15 (4-5)</td>
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<tr>
<td>rivastigmine (Exelon Patch) mild-mod AD</td>
<td>7-21 (5)</td>
<td>5-19 (3)</td>
<td>3-9 (2)</td>
<td>5-10 (3)</td>
<td>1-7 (1)</td>
<td>3-4 (2)</td>
<td>9.6-12.7 (5)</td>
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<td>6 (3)</td>
<td>7 (3)</td>
<td>7 (3)</td>
<td>7 (5)</td>
<td>nr**</td>
<td>nr**</td>
<td>20.5 (14.2)</td>
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<td>3 (2)</td>
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<td>7 (5)</td>
<td>6 (3)</td>
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<td>6 (5)</td>
<td>10 (6.3)</td>
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<tr>
<td>donepezil and memantine ER (Namzaric) reported</td>
<td>1 (1)</td>
<td>reported</td>
<td>5 (4)</td>
<td>3 (1)</td>
<td>6 (5)</td>
<td>10/12 (6/7)</td>
<td></td>
</tr>
</tbody>
</table>

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Rates of adverse effects for donepezil and memantine ER (Namzaric) are not determinable

*In clinical trials, once daily treatment with Razadyne ER was well tolerated and adverse events were similar to those seen with Razadyne.

**Dizziness and headache are adverse events of rivastigmine patch, although not specifically reported in severe AD study
In general, a dose-response relationship exists for the incidence of adverse events for the agents in this class.

In patients with severe AD, incidence of adverse effects for rivastigmine patch 13.3 mg/24 hours patch versus 4.6 mg/24 hours is as follows: agitation (12% versus 14%), urinary tract infections (8% versus 10%), fall (8% versus 6%), and insomnia (7% versus 4%) have been reported. Application site reactions have been reported for rivastigmine patch.

In donepezil postmarketing experience, rhabdomyolysis, QTc prolongation, torsade de pointes, Stevens Johnson syndrome, and toxic epidermal necrolysis have been reported.

Key postmarketing adverse effects reported with galantamine include atrioventricular block and other cardiac abnormalities, paresthesias, hyperhidrosis and dehydration, dysgeusia, and muscular weakness.

Some postmarketing adverse effects reported with memantine include blood dyscrasias, congestive cardiac failure, pancreatitis, hepatitis, renal failure, Stevens-Johnson syndrome, and suicidal ideation.

Notably, postmarketing experience with rivastigmine reported aggression and nightmares, tachycardia, seizure, Stevens-Johnson syndrome, urticaria, allergic dermatitis, and abnormal liver function tests and hepatitis.

SPECIAL POPULATIONS\(^{93,94,95,96,97,98,99}\)

**Pediatrics**

There are no adequate and well-controlled trials documenting the safety and efficacy of the AChEIs in any illness occurring in children; therefore, the AChEIs are not recommended for use in children. Also, there are no well-controlled trials demonstrating safety and efficacy for the NMDA receptor agonist, memantine, in children.

**Pregnancy**

Galantamine (Razadyne, Razadyne ER) is classified as Pregnancy Category C. Donepezil (Aricept), memantine (Namenda, Namenda XR), rivastigmine (generic, Exelon), and the combination of donepezil and memantine ER (Namzaric) do not have adequate data on the developmental risk associated with the use in pregnant women.

**Renal Impairment**

The dose of galantamine should be titrated cautiously in patients with moderate renal impairment, and galantamine and the total daily dose generally should not exceed 16 mg. The use of galantamine is not recommended in patients with severe renal impairment (creatinine clearance \([\text{CrCl}] < 9 \text{ mL/min}\)). Pharmacokinetic studies have shown that clearance of oral rivastigmine is reduced in patients with moderate to severe renal impairment \((\text{CrCl} \leq 50 \text{ mL/min})\); therefore, total daily doses of oral rivastigmine may need to be reduced. In patients with severe renal impairment \((\text{CrCl} 5 \text{ to } 29 \text{ mL/min})\), the target dose of memantine immediate-release tablets is 5 mg twice a day and for memantine extended-release capsules is 14 mg daily.
Hepatic Impairment

The total daily dose of galantamine in patients with moderate hepatic impairment (Child-Pugh B) should not exceed 16 mg, and galantamine use is not recommended in patients with severe hepatic impairment (Child-Pugh C).

Memantine should be used with caution in patients with severe hepatic impairment; no dosage adjustment is required in patients with mild to moderate hepatic impairment (Child-Pugh A and B).

Patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment may be able to only tolerate lower oral doses of rivastigmine; use of the 4.6 mg/24 hours patch should be considered as an initial and maintenance therapy in patients with mild or moderate impairment. No data are available on the use of rivastigmine in patients with severe hepatic impairment.
### DOSAGES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dosage</th>
<th>Minimum Therapeutic Dosage* (Minimum Time to Reach)</th>
<th>Target Dosage** (Minimum Time to Reach)</th>
<th>Special Considerations</th>
<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AChEIs</strong></td>
<td></td>
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<tr>
<td>donepezil (Aricept)</td>
<td>5 mg daily</td>
<td>5 mg daily (0 weeks)</td>
<td>10 mg daily (4 to 6 weeks)</td>
<td>--</td>
<td>Tablets: 5 mg, 10 mg, 23 mg</td>
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<td></td>
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<td></td>
<td></td>
<td>Tablets, orally disintegrating: 5 mg, 10 mg (generic only)</td>
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<tr>
<td>galantamine (Razadyne)</td>
<td>4 mg twice daily</td>
<td>8 mg twice daily (4 weeks)</td>
<td>12 mg twice daily (8 weeks)</td>
<td>Moderate hepatic and/or renal impairment – reduce target dosage; do not exceed 16 mg/day</td>
<td>Tablets: 4 mg, 8 mg, 12 mg</td>
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<tr>
<td></td>
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<td></td>
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<td></td>
<td>Oral solution: 4 mg/mL (generic only)</td>
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<tr>
<td>galantamine ER (Razadyne ER)</td>
<td>8 mg daily</td>
<td>16 mg daily (4 weeks)</td>
<td>24 mg daily (8 weeks)</td>
<td>Moderate hepatic and/or renal impairment – reduce target dosage; do not exceed 16 mg/day</td>
<td>Capsules: 8 mg, 16 mg, 24 mg</td>
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<tr>
<td>rivastigmine</td>
<td>1.5 mg twice daily</td>
<td>3 mg twice daily (2 weeks)</td>
<td>6 mg twice daily (6 weeks)</td>
<td>Moderate to severe renal and/or mild to moderate hepatic impairment or low (&lt; 50 kg) body weight – reduce target dose</td>
<td>Capsules: 1.5 mg, 3 mg, 4.5 mg, 6 mg (generic only)</td>
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<tr>
<td>rivastigmine (Exelon Patch)</td>
<td>4.6 mg/24 hours</td>
<td>9.5 mg/24 hours (4 weeks)</td>
<td>9.5 mg/24 hours (4 weeks); for severe AD after a minimum additional 4 weeks, may increase to 13.3 mg/24 hours (max dose)</td>
<td>Mild to moderate hepatic impairment or low (&lt; 50 kg) body weight – reduce target dose</td>
<td>Transdermal system:</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>• 4.6 mg/24 hours (5 cm² size contains 9 mg drug)</td>
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<td></td>
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<td></td>
<td>• 9.5 mg/24 hours (10 cm² size contains 18 mg drug)</td>
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<td></td>
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<td></td>
<td></td>
<td>• 13.3 mg/24 hours (15 cm² contains 27 mg drug)</td>
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</tbody>
</table>
## Dosages (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dosage</th>
<th>Minimum Therapeutic Dosage* (Minimum Time to Reach)</th>
<th>Target Dosage** (Minimum Time to Reach)</th>
<th>Special Considerations</th>
<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NMDA Receptor Antagonist</strong></td>
<td></td>
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</tr>
<tr>
<td>memantine (Namenda)</td>
<td>5 mg daily</td>
<td>nd</td>
<td>10 mg twice daily (3 weeks)</td>
<td>Severe renal impairment – 5 mg twice daily</td>
<td>Tablets: 5 mg, 10 mg Dose Pack: a titration pack containing twenty-eight 5 mg tablets and twenty-one 10 mg tablets (total of 49 tablets) Oral solution: 2 mg/mL (generic only)</td>
</tr>
<tr>
<td>memantine ER (Namenda XR)†</td>
<td>7 mg daily</td>
<td>nd</td>
<td>28 mg once daily (4 weeks)</td>
<td>Severe renal impairment – 14 mg once daily</td>
<td>Extended-release capsules: 7 mg, 14 mg, 21 mg, 28 mg Titratin Pack: contains 7 of each extended-release tablet strengths (7 mg, 14 mg, 21 mg, 28 mg) for a total of 28 tablets per pack (brand only)</td>
</tr>
<tr>
<td><strong>AChEI and NMDA Receptor Antagonist Combination Products</strong></td>
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<tr>
<td>donepezil and memantine ER (Namzaric)</td>
<td>10 mg/28 mg daily in the evening for those stabilized on both donepezil 10 mg/day and memantine; 10 mg/7 mg daily in the evening for those stabilized on donepezil 10 mg/day but not on memantine</td>
<td>nd</td>
<td>10 mg/28 mg once daily; if not initiated on 28 mg of memantine, memantine dose may be increased in 7 mg increments weekly to target dose as tolerated</td>
<td>Severe renal impairment – 10 mg/14 mg once daily (those stabilized on both donepezil and memantine); 10 mg/7 mg initially (those stabilized on donepezil but not on memantine) and may be titrated to a target dose of 10 mg/14 mg</td>
<td>Extended-release capsules (can sprinkle on food): 10 mg/7 mg 10 mg/14 mg 10 mg/21 mg 10 mg/28 mg Dose Pack: a titration pack of 28 extended-release capsules: seven 10 mg/7 mg, seven 10 mg/14 mg, seven 10 mg/21 mg, and seven 10/28 mg</td>
</tr>
</tbody>
</table>

* Minimum Therapeutic Dosage – The lowest dosage at which a statistically significant improvement in cognition over placebo has been observed.

** Target Dosage – Recommended dosage in the prescribing information.

† Patients on Namenda 10 mg or lower may be switched to Namenda XR 28 mg following the final tablet dose.
CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant of clinical trials; however, there are no randomized, double-blind, directly comparative studies of the drugs in this class. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance and use data analysis techniques consistent with the study question. Due to the paucity of high-quality, active-control, randomized, controlled trials, placebo-controlled studies of these drugs in dementia associated with AD and PD were included in the review. Studies were included if they were of 6 months (24 weeks) duration or greater and had recognized cognitive and/or functional primary outcome measures. Due to high rates of loss to follow-up in many studies of the drugs in this class, clinical trials with less than 50% loss to follow-up were considered in this review. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Efficacy trials conducted did not use the fixed-dose combination donepezil/memantine ER (Namzaric), but bioequivalence of Namzaric to co-administered extended-release memantine and donepezil has been demonstrated.107

Efficacy Scales

Various validated assessment scales are used to evaluate patient response and efficacy in clinical trials for drugs used in the treatment of dementia associated with AD and PD.

Cognition

Alzheimer’s Disease Assessment Scale (ADAS) – This scale is the gold standard for measuring change in cognitive function in drug trials.108 A trained observer evaluates memory, language, and praxis. The FDA has proposed that therapeutic response to drugs used for AD be defined as an improvement of 4 or more points on the ADAS.109

Behavioral Rating Scale for Geriatric Patients (BGP) – This measures observable aspects of cognition, function, and behavior. The total BGP score has a significant association with the level of dependency.110

Mini-Mental Status Examination (MMSE) – This is the most widely used measure of cognitive function. It assesses orientation, registration, attention, recall, and language.111 The MMSE has been shown to successfully differentiate between dementia, depression, or a combination of both.112
Severe Impairment Battery (SIB) – This is a cognitive assessment tool that examines elements of attention, orientation, language, memory, visual-spatial ability, construction, praxis, and social interaction.\textsuperscript{113}

**Global / Functional**

Alzheimer’s Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL) – The ADCS-ADL consists of questions directed at the patient’s caregiver and is used to measure the functional capacity of the patient.\textsuperscript{114} A subset of 19 items rates the patient’s ability to eat, dress, bathe, telephone, travel, shop, and perform other household chores.\textsuperscript{115} A modification of this assessment, ADCS-ADL-sev, is used for patients with severe dementia.

Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) – The ADCS-CGIC is a 7-point categorical scale that provides a single global rating of change from baseline ranging from marked improvement to no change to marked worsening. The ADCS-CGIC is a valid and reliable instrument for use in clinical trials.\textsuperscript{116}

Bristol Activities of Daily Living Scale (BrADL) – This scale, which assesses 20 daily living abilities, was designed specifically for use in patients with dementia. The validity of this scale was measured by verifying that the items in the scale were important to caregivers and that there is good test-retest reliability.\textsuperscript{117}

Clinician’s Interview-Based Impression of Change Plus Caregiver Input (CIBIC-plus) – There are a variety of CIBIC formats, each different in depth and structure. The CIBIC-plus requires use of caregiver information. Generally, CIBIC results are not comparable across trials.\textsuperscript{118}

Disability Assessment for Dementia Scale (DAD) – This is a newer functional scale, rated by a trained observer, specifically developed for patients with AD. This scale assesses basic and instrumental ADLs.\textsuperscript{119}

Neuropsychiatric Inventory (NPI) – This is a validated instrument that measures disturbed behavior through assessment of 10 domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, and aberrant motor behavior.\textsuperscript{120} In the NPI, each item is rated according to its frequency and severity based on a caregiver interview.

Progressive Deterioration Scale (PDS) – This measures function in both instrumental and basic ADLs by asking the caregiver to assess function using 27 items and to rate the patient’s performance on a visual analogue scale that employs a fulcrum line with bipolar descriptions of ADLs at either end. This scale has been shown to be reliable and valid.\textsuperscript{121}

**Mild to Moderate Dementia of the Alzheimer’s Type**

**donepezil (Aricept) 10 mg daily versus donepezil (Aricept) 23 mg daily**

A 24-week, randomized, double-blind trial evaluated continuation of 10 mg daily of donepezil versus increasing to 23 mg daily.\textsuperscript{122} This study randomized 1,467 patients, aged 45 through 90 years, who were taking donepezil 10 mg daily for at least 12 weeks. The effectiveness analyses included 1,371 patients (mean age 73.8 years). A total of 296 (30.2\%) patients withdrew from the donepezil 23 mg group, and 87 (17.9\%) patients withdrew from the donepezil 10 mg group. After 24 weeks, the change in least squares mean (LSM) changes from baseline score on the SIB was significantly greater with
donepezil 23 mg (LSM, +2.6; standard error [SE], 0.58) than with donepezil 10 mg (LSM, 0.4; SE, 0.66), p<0.001). Also at week 24, the between-treatment difference in CIBIC-plus score was not significant. In post hoc analysis, LSM changes from baseline in SIB score and CIBIC-plus treatment effect at endpoint were greater with donepezil 23 mg than 10 mg in patients with more advanced AD compared with less impaired patients (SIB, +1.6 [SE, 0.78] versus -1.5 [SE, 0.88], respectively [p<0.001]; CIBIC-plus, 4.31 [SE, 1.09] versus 4.42 [SE, 1.1]; p=0.028). Treatment-emergent adverse events were reported in 73.3% of patients on donepezil 23 mg and 63.7% of patients on donepezil 10 mg. The most common adverse effects related to the 23 mg dose included nausea (0.9% versus 0.2% with the 10 mg dose), dizziness (0.7% versus 0.2%), and vomiting (0.6% versus 0%). Post hoc analysis of the results of this study was used to gain FDA approval for the marketing of the 23 mg daily donepezil dose.

donepezil (Aricept) versus galantamine (Razadyne)

In a multicenter, rater-blinded study, 182 patients with AD were randomized to 52 weeks of treatment with galantamine (8 mg/day for 4 weeks, then 16 mg/day for 4 weeks with optional titration to 24 mg/day) or donepezil (5 mg/day for 4 weeks with optional titration to 10 mg/day). The study was completed by 78% to 80% of patients in each group. At the end of the study, approximately 70% of patients in each group were receiving the maximum dose. In each group, the BrADL scores were constant through month 9, then worsened thereafter. At week 52, there was a similar functional responder rate (defined as no increase in BrADL score), 39%, in each group. In terms of cognition, galantamine patients’ scores on the MMSE at week 52 did not differ significantly from baseline (-0.52 ± 0.39, p<0.5 versus baseline), whereas donepezil patients’ scores deteriorated significantly from baseline (-1.58 ± 0.42, p<0.0005 versus baseline). The between-group difference in MMSE change did not reach statistical significance (p≤0.1). The ADAS-cog responder rates were not statistically different in the galantamine (45%) and donepezil (32%; p<0.1) groups at the conclusion of the study. Patients treated with galantamine who had MMSE scores of 12 to 18 demonstrated an increase (worsening) in the ADAS-cog/11 score of 1.61 ± 0.8 versus baseline, compared with an increase of 4.08 ± 0.84 for patients treated with donepezil. Additionally, caregivers of patients receiving galantamine were more likely to report reductions in burden compared with caregivers of patients receiving donepezil. Changes from baseline in NPI were similar for both treatment groups. Both galantamine and donepezil were well tolerated, with most adverse events being transient, of mild to moderate intensity, and consistent with the findings of previous clinical trials.

galantamine (Razadyne) versus galantamine ER (Razadyne ER)

In a double-blind, parallel-group trial, 971 patients with mild to moderate AD were randomized to treatment for 6 months with galantamine 8 or 12 mg twice daily, galantamine ER 16 or 24 mg once daily, or placebo. The mean change from baseline in ADAS-cog was similar in the galantamine (-1.6 ± 0.4) and galantamine ER (-1.3 ± 0.3) groups, and both treatments were superior to placebo (+1.3 ± 0.3). Compared to placebo, both galantamine regimens were associated with a significant improvement in ADCS-ADL but not in CIBIC-plus or NPI. Galantamine ER had similar tolerability and safety profiles compared with twice-daily galantamine.
rivastigmine versus placebo

In a double-blind study, 725 patients with mild to moderately severe AD were randomized to receive either placebo or rivastigmine 1 to 4 mg/day (low dose) or 6 to 12 mg/day (high dose). Doses were titrated up within the assigned dosage range over the first 12 weeks then continued at that dose for an additional 14 weeks. Patients in the high-dose rivastigmine group demonstrated improvement in the ADAS (p<0.05) and CIBIC-plus (p<0.001) compared to patients in the placebo group. The CIBIC-plus improved more frequently in the high-dose rivastigmine group (37%) than in the low-dose (30%) or placebo (20%) groups.

rivastigmine patch (Exelon Patch) versus rivastigmine capsule versus placebo

The efficacy, safety, and tolerability of rivastigmine transdermal patches were compared to rivastigmine capsules and placebo in the 24-week, double-blind, double-dummy, placebo- and active-controlled IDEAL (Investigation of transdermal Exelon in Alzheimer’s disease) study with 1,195 participants with AD. Patients were randomized to placebo or 1 of 3 active treatment target groups: 9.5 mg/24 hours rivastigmine patch (low dose group); 17.4 mg/24 hours rivastigmine patch (high dose group); or 6 mg rivastigmine capsule administered twice daily. Primary efficacy measures were ADAS-cog and Alzheimer’s Disease Cooperative Study-Clinical Global and Impression of Change. Secondary outcome measures assessed a range of domains, including behavior, cognitive performance, attention, executive functions, and activities of daily living. All rivastigmine treatment groups showed significant improvement relative to placebo. The low dose patch group showed similar efficacy to capsules with approximately two-thirds fewer reports of nausea and vomiting; incidences were not statistically significantly different from placebo. The high dose patch group showed earlier improvement and numerically superior cognitive scores versus the low dose patch group with similar tolerability to capsules. Local skin tolerability was good.

A prospective outcome of the IDEAL study was to evaluate caregiver preference for rivastigmine patches compared to capsules. Caregivers rated patch adhesion throughout. The AD Caregiver Preference Questionnaire (ADCPQ) assessed patch versus capsule from caregivers’ perspective based on expectations, preferences, and satisfaction with treatment. A total of 1,059 caregivers completed the ADCPQ while their respective patients were on study drug. More than 70% of caregivers preferred the patch to capsules. It was preferred with respect to ease of use (p<0.0001) and ease of following treatment regimen (p<0.0001). Caregivers indicated greater satisfaction overall (p<0.0001) and less interference with daily life (p<0.01) with the patch versus capsule.

Moderate to Severe Dementia of the Alzheimer’s Type

donepezil (Aricept) versus rivastigmine

Patients with moderate to moderately severe AD were randomly assigned to rivastigmine 3 to 12 mg/day or donepezil 5 to 10 mg/day over a 2-year period. In the double-blind study, 994 patients received treatment, and 58% of these patients completed their assigned treatment regimen. The average decline in SIB, the primary efficacy measure, was similar between the 2 groups. Approximately 36% of patients in each group retained SIB scores that were equal or better than baseline. The 2 groups were also similar in the secondary measure of cognition, change in MMSE score from baseline, as well as in the change in NPI. At the conclusion of the study, 19% of patients receiving donepezil and 25% of those receiving rivastigmine retained ADCS-ADL scores that were equal or better than baseline (p=0.047). Fewer patients receiving donepezil (16%) than rivastigmine (26%) discontinued their
assigned treatment due to adverse events. The most frequent reason for premature discontinuation in both treatment groups was adverse events, primarily gastrointestinal. Adverse events were more frequent in the rivastigmine group during the titration phase but similar in the maintenance phase.

**memantine (Namenda) versus placebo**

A total of 252 patients with moderate to severe AD were randomized to receive placebo or memantine titrated to 20 mg daily in double-blind fashion for 28 weeks. Seventy-two percent of patients completed treatment. At endpoint (completion or early withdrawal from the study), patients receiving memantine had less deterioration on ADCS-ADL-sev (p=0.02), a primary efficacy variable, SIB (p<0.001) and FAST (p=0.02). There were no differences between active treatment and placebo in CIBIC-plus (p=0.06), MMSE (p=0.18), or NPI (p=0.03). Treatment with memantine did significantly reduce caregiver burden, as measured by BGP, in comparison to placebo (p=0.01). In an open-label, 24-week extension to the trial, 175 patients received memantine 20 mg daily. In the study extension, subjects who had originally received placebo experienced a significantly slower rate of decline in ADCS-ADL-sev in the open-label phase compared to the randomized phase of the trial (p=0.21). Conversely, subjects who received memantine during all 52 weeks experienced a faster rate of decline in ADCS-ADL-sev in the open-label phase (p=0.035). The rate of decline in the CIBIC-plus slowed during the open-label phase in both original randomization groups compared to the randomized phase (p<0.001 for both groups). While participants who received memantine during the entire 52-week treatment period experienced a similar rate of decline in the SIB during the randomized and open-label study phases (p=0.086), the outcome improved during the open-label phase for those who had received placebo during the randomized phase (p=0.049).

In a 24-week, double-blind, placebo-controlled trial, patients not receiving a cholinesterase inhibitor (n=350) were randomized to receive memantine 20 mg/day or placebo. Prospectively defined analyses failed to demonstrate a statistically significant benefit of memantine treatment compared with placebo on the SIB at the endpoint of 24 weeks although a significant advantage was observed at weeks 12 and 18. The 19-item ADCS-ADL did not differ significantly between groups in any analysis. CIBIC-plus did not significantly favor memantine at week 24 despite a significant advantage for memantine at weeks 12 and 18. Other secondary outcomes showed no significant treatment differences. Post-hoc analyses of potentially confounding covariates and alternative methods of imputing missing data did not substantially alter the results. Due to violations of normality assumptions for the SIB and ADCS-ADL19, nonparametric analyses were performed; statistically significant benefit of memantine over placebo was demonstrated at week 24 for the SIB but not the ADCS-ADL19. Type and incidence of adverse events were similar in both groups.

In a 24-week, double-blind study, 404 patients with moderate to severe AD and MMSE scores of 5 to 14 who were receiving stable doses of donepezil were randomized to memantine at a starting dose of 5 mg/day increased to 20 mg/day or placebo. The change in total mean scores favored memantine versus placebo for both primary outcome measures, SIB (p<0.001), and ADCS-ADL (p=0.03). Secondary outcomes, including BGP (p=0.001) and NPI (p=0.002), also showed significant benefits of memantine compared to placebo. Improvement in CIBIC-plus occurred in 55% of memantine patients and 45% of those receiving placebo (p=0.03). Treatment discontinuations because of adverse events for memantine versus placebo were 15 (7.4%) versus 25 (12.4%), respectively.
memantine ER (Namenda XR) versus placebo

Extended-release memantine was studied in a randomized, double-blind, placebo-controlled trial in 677 outpatients with moderate to severe Alzheimer’s disease. Patients were diagnosed with AD by DSM-IV criteria and NINCDS-ADRDA criteria with a Mini Mental State Examination (MMSE) score ≥ 3 and ≤ 14. All patients had been receiving AChEI therapy at a stable dose for 3 months prior to screening. The mean patient age was 76.5 years with a range of 49 to 97 years, and approximately 72% of patients were female and 94% were Caucasian. Patients were randomized to receive either extended-release memantine 28 mg/day or placebo while continuing to receive an AChEI (donepezil, galantamine, or rivastigmine). Co-primary efficacy parameters of Severe Impairment Battery (SIB) to assess cognitive performance and the Clinician’s Interview-Based Impression of Change (CIBIC-Plus) were used to assess efficacy every 4 weeks for 24 weeks. After 24 weeks, the mean difference in the SIB change scores for the memantine XR 28 mg/AChEI-treated (combination therapy) patients compared to the patients on placebo/AChEI (monotherapy) was 2.6 units (95% confidence interval [CI], 1 to 4.2; p=0.001), CIBIC-Plus (p=0.008), and verbal fluency test (p=0.004); memantine ER 28 mg/AChEI treatment was statistically significantly superior to placebo/AChEI based on an LOCF analysis. Memantine ER did not achieve significance on the secondary endpoint of Alzheimer’s Disease Cooperative Study-Activities of Daily Living (ADCS-ADL19) (p=0.177). Adverse events with a frequency of 5% or greater than placebo that were more prevalent in the memantine group were headache and diarrhea.

rivastigmine (Exelon Patch) 13.3 mg/24 hours versus rivastigmine (Exelon Patch) 4.6 mg/24 hours

ACTION: A randomized, double-blind, parallel-group, prospective, 24-week multicenter study in patients with severe Alzheimer’s disease, evaluated the efficacy and safety of rivastigmine 13.3 mg/24 hours patch versus 4.6 mg/24 hours patch. A total of 716 patients with a Mini-Mental Status Examination (MMSE) score of ≥ 3 to ≤ 12 were randomized into 1 of the following treatments: rivastigmine patch 13.3 mg/24 hours (n=356) or rivastigmine patch 4.6 mg/24 hours (n=360) in a 1:1 ratio. The study was divided into an 8-week titration phase followed by a 16-week maintenance phase. Participants with stable doses of memantine were allowed into the study. Primary outcomes were change from baseline at week 24 on the AD cooperative study-activities of Daily Living scale-severe impairment version (ADCS-ADL-SIV) and the Severe Impairment Battery (SIB) based on last observation carried forward (LOCF) approach. At the end of the study, the mean decline from baseline on assessments of cognition and overall function was significantly less with the 13.3 mg patch. Decline in the mean ADCS-ADL-SIV score from baseline for the MFAS-LOCF analysis was less at each time point in the 13.3 mg/24 hours (p=0.0247) rivastigmine patch treatment group than in the 4.6 mg/24 hours rivastigmine patch (p<0.001) treatment group. The 13.3 mg/24 hours dose was statistically significantly superior to the 4.6 mg/24 hours dose at weeks 16 and 24 (primary endpoint). The incidence of adverse events (AE) and serious adverse events (SAE) was comparable with the 13.3/24 hours and the 4.6/24 hours patch (AE, 74.6% and 73.3%; SAE, 14.9% and 13.6%). Discontinuation due to AE and SAE was higher with the 13.3 than the 4.5 patch (AE, 13.5% and 10.9%; SAE 8.2% and 4.5%).
Dementia Associated with Parkinson’s Disease

**rivastigmine versus placebo**

In a 24-week, double-blind study, 541 patients with mild to moderate PD-associated dementia were randomized to receive rivastigmine 1.5 mg twice daily, titrated up to 12 mg daily, or matching placebo. Patients in the rivastigmine group had a mean improvement of 2.1 points (8.8%) for the ADAS-cog (a primary efficacy variable) compared to a 0.7 point (2.9%) worsening in the placebo group (p<0.001). Patients in the rivastigmine group also had more favorable outcomes based on ADSC-CGIC, a primary efficacy measure, with moderate or marked improvement noted in 19.8% of patients compared to 14.5% of patients in the placebo group (p=0.02). Marked or moderate worsening of ADSC-CGIC scores occurred in 33.7 and 42.5% of patients in the rivastigmine and placebo groups, respectively. Rivastigmine also provided benefit compared to placebo in ADCS-ADL (p=0.02), NPI (p=0.02), and MMSE (p=0.03). The occurrence of adverse events rated as serious was similar in both groups (13% in the rivastigmine group and 14.5% in the placebo group, p=0.69). However, the predominant adverse events were cholinergic in nature with the most frequent being nausea (affecting 29% of patients in the rivastigmine group and 11.2% of those in the placebo group, p<0.001) and vomiting (affecting 16.6% and 1.7%, respectively; p<0.001). Approximately 17% of patients on active treatment prematurely discontinued due to adverse events (compared to 8% of patients in the placebo group).

**META-ANALYSES**

Researchers performed a meta-analysis of randomized, double-blind, placebo-controlled, parallel-group trials of donepezil, galantamine, and rivastigmine published through early 2002. They identified 16 trials of over 8,000 patients in which the drugs were used in therapeutic doses for at least 12 weeks and for which a cognitive outcome was reported. The pooled mean proportion of global responders (improvement in CGI-C or CIBIC-plus) to AChEI in excess of that for placebo was 10% (95% CI, 4 to 17; p<0.05). The number needed to treat (NNT) to yield 1 additional global responder was 12 (95% CI, 9 to 16). The NNT to yield 1 additional cognitive responder (4 points or greater improvement on ADAS-cog) was 10 (95% CI, 8 to 15). The NNT for 1 additional patient to experience an adverse event was 12. The rates of adverse events, dropout for any reason, and dropout because of adverse events were all 7% to 8% higher among patients receiving AChEI treatment than among those receiving placebo (p<0.05 for all comparisons). The difference among each of the 3 AChEIs and placebo in adverse events and dropout rates was similar, with the exception of the dropout rate for galantamine (14%; 95% CI, 8 to 21) differing from placebo more than that for donepezil (3%; 95% CI, 1 to 6).

A meta-analysis using both electronic and manual search strategies examined the effect of donepezil, galantamine, and rivastigmine on AD clinical outcomes and completion rates. Regression analyses compared the effect of dose on clinical outcomes and completion rates, using 10 donepezil, 6 galantamine, and 5 rivastigmine studies. All 3 drugs showed beneficial effects on cognitive tests compared to placebo. For donepezil and rivastigmine, larger doses were associated with a larger cognitive effect; this was not the case with galantamine. The odds of clinical global improvement demonstrated superiority over placebo for each drug with no dose effects noted. Dropout rates were greater with galantamine and rivastigmine. There was little difference in dropout rate for each drug at each dose level except with high-dose donepezil. This was accounted for by the high dropout rate in two 52-week studies using larger doses.
A meta-analysis that included 22 placebo-controlled clinical trials of donepezil, galantamine, and rivastigmine estimated an average 3.9 point reduction in ADAS-cog scores and a 0.26 to 0.54 point improvement in CIBIC-plus scores from treatment with these agents.\textsuperscript{140}

A meta-analysis was performed to compare the safety and efficacy of donepezil monotherapy versus donepezil plus memantine in patients with moderate to severe AD.\textsuperscript{141} The review included 11 studies from 2004 to 2015 that met the inclusion criteria. Hedges' g was used to determine the effect size. Compared with donepezil monotherapy, donepezil plus memantine combination treatment resulted in limited improvements in the following measures: cognitive functions (p<0.001); behavioral and psychological symptoms in dementia [BPSD] (p<0.001), and global functions (p=0.004). Gradual titration of memantine in combination with a fixed dose and gradual titration of donepezil as well as a fixed dose and gradual titration of memantine resulted in limited improvements in cognitive functions (p=0.005), BPSD (p=0.001), and global functions (p=0.001). This review concluded that combination use of donepezil and memantine led to greater improvement in cognitive functions, BPSD, and global functions than donepezil monotherapy in patients with moderate to severe AD.

**SUMMARY**

Alzheimer’s disease (AD) is an irreversible decline in memory and cognition outside the baseline of normal aging and the most common form of dementia. Medications may assist in delaying the cognitive declines for a period of time in mild to moderate Alzheimer’s symptoms. A common pattern of response to treatment with acetylcholinesterase inhibitors (AChEIs) is initial improvement in cognition, followed by maintenance of cognitive gains above baseline, but then a final cognitive decline to below baseline levels; however, the final level of cognition in patients receiving pharmacologic treatment remains above the level predicted for those not receiving pharmacologic treatment.

Pharmacologic interventions with the FDA-approved medications addressed in this review have demonstrated statistically significant improvement over placebo per various scales used to evaluate the changes in patients with dementia due to AD. Most of the scales used to assess outcomes in clinical trials are not practiced routinely in clinical settings, and the interpretation of their clinical significance is dependent on the expertise of the practitioner. In addition, many of the cognitive and functional improvements demonstrated in clinical trials were not clinically important even though they demonstrated statistical significance, so their clinical relevance is unknown. Although the evidence of improvement on global assessment tools was available for donepezil (Aricept), galantamine (Razadyne, Razadyne ER), rivastigmine (Exelon Patch), and memantine (Namenda, Namenda XR), the changes were generally modest and the evidence regarding their effect on quality of life was mixed. Likewise, data demonstrating efficacy of donepezil/memantine ER (Namzaric) or memantine with other AChEIs are limited.

Currently, there is no reliable method established to predict the patients that will have a clinically significant response, and a high percentage of patients diagnosed with AD are unlikely to respond to cholinesterase inhibitors. In patients that do respond, these agents provide only modest symptomatic relief, depending on the severity of the disease, for a limited duration of time, and data are lacking to demonstrate efficacy and safety with the long-term use of these agents in AD. Reliable evidence is also lacking that proves that the symptomatic treatment with these agents can alter the pathological course of dementia associated with AD or Parkinson’s disease (PD). It remains unclear if use of these drugs delays nursing home placement or alters mortality.
The AChEIs are similar per the global and cognitive rating scales, but demonstrate small therapeutic effects at 6 months. Despite the relatively small treatment effect, the AChEIs are recommended as first-line treatment in patients with mild to moderate AD, primarily due to a lack of effective alternatives. Clinical practice guidelines do not differentiate among any of the AChEIs or memantine (Namzaric) when initiating treatment.

Options for the AChEIs vary in terms of formulations and dosing. Galantamine (Razadyne) and oral rivastigmine are dosed twice daily; whereas, donepezil (Aricept), galantamine ER (Razadyne ER), and transdermal rivastigmine (Exelon Patch) are administered once daily. Galantamine is available in an oral solution and donepezil as an orally disintegrating tablet. Rivastigmine is also available as a transdermal patch (for application to the upper or lower back, upper arm, or chest), which may improve therapy compliance due to ease of administration for caregivers. The effectiveness of all the cholinergic products is limited by the maximum tolerated dose.

All of the cholinesterase inhibitors must be slowly titrated upward to minimize the gastrointestinal (GI) adverse effects of the products. Among galantamine, donepezil, and rivastigmine, the incidence of gastrointestinal complaints (nausea, vomiting, diarrhea, anorexia, and weight loss) is highest with rivastigmine and lowest with donepezil. Rivastigmine does not have CYP450-mediated drug interactions, which may offer an advantage for some patients on multiple pharmacologic treatments.

Cholinesterase inhibitors are indicated for the treatment of mild to moderate AD. All agents in this review, except galantamine/galantamine ER and oral formulations of rivastigmine, are approved to treat moderate to severe AD. Rivastigmine oral and transdermal formulations are also indicated to treat mild to moderate dementia related to PD. Namzaric, the fixed-dose combination of an AChEI, donepezil, and the NMDA receptor antagonist memantine ER is available for moderate to severe AD for those already stabilized on donepezil. All single-entity drugs are available as generics; donepezil/memantine ER (Namzaric) is only available as a branded product.

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