

Therapeutic Class Overview

Alzheimer's Disease Agents

INTRODUCTION

- Alzheimer's disease (AD) is a progressive, degenerative neurological disease often presenting in later stages of life. In 2007, it was estimated that 5.1 million Americans are afflicted with AD, of which 4.9 million are aged ≥ 65 years. Before the age of 80 years, AD is more common in men and after the age of 80 years, the disease becomes more common in women (*Alzheimer's Association 2007, Letenneur et al 1999*).
- Patient presentation is diverse and includes a wide range of symptoms that manifest with cognitive and neuropsychiatric effects as a result of brain cell destruction. AD often begins with memory impairment that is followed, after several years, by a variety of other symptoms that affect motor function, planning and reasoning skills, and the ability to recognize objects and people (*American Psychiatric Association [APA] 2007, Bond et al 2012, Jones et al 2004, Wilcock et al 2003*).
- Patients often present with memory loss, aphasia, apraxia, agnosia, and loss of abstract planning skills.
 - Mild disease: Decline in ability to function at work or other usual activities, cognitive impairment, and poor judgment.
 - Moderate disease: Forgetfulness and poor understanding of safety risks that can lead to aimless wandering, mismanagement of finances, and household accidents like kitchen fires for which the individual may not understand how to manage.
 - Severe disease: Rely on others to carry out daily tasks involving grooming, feeding, and general self-care. (*APA 2007, Bond et al 2012, McKann et al 2011*).
- Various criteria have been developed in order to consistently and accurately diagnose AD, the most commonly used tools being the Mini Mental State Examination (MMSE), Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-V), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), and the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.
- These clinical diagnostic tools often correlate with pathological diagnosis, which is the only absolute method of diagnosis and can only be completed with an autopsy after death. During this autopsy, the examiner looks for amyloid-beta (A β) plaques and neurofibrillary tangles in the cerebral cortex, which confirm the diagnosis of AD (*APA 2007, Bond et al 2012, McKann et al 2011*).
- Typical management of AD includes an acetylcholinesterase (AChE) inhibitor with or without a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist depending on the severity stage diagnosis. These therapies, along with psychosocial treatment methods, have been shown to be effective in managing patient symptoms with some evidence to support their effect on the behavioral symptoms of AD (*APA 2007, Bond et al 2012, Jones et al 2004*).
- The AChE inhibitors include donepezil, rivastigmine, and galantamine. Memantine is a NMDA receptor antagonist.
- AChE inhibitors increase cholinergic function by inhibiting hydrolysis of acetylcholine. NMDA receptor antagonists prevent excess stimulation by blocking glutamate from binding (*Micromedex 2018, Wilcock et al 2003*).
- In the past, Vitamin E, NSAIDs, and estrogen supplements have been recommended for treatment of AD. This is no longer recommended due to a lack of supportive evidence regarding their efficacy as well as potential safety concerns associated with vitamin E (*APA 2007*).
- Tacrine will not be discussed in this overview since it has been withdrawn from the market. Several drug characteristics, the major ones being reversible hepatic toxicity and four times daily administration, made tacrine undesirable compared to the newer AChE inhibitors (*Drugs@FDA 2018*).
- Medispan class: Cholinomimetics – ACHE Inhibitors; Antidementia Agent Combinations; N-Methyl-D-Aspartate (NMDA) Receptor Antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aricept (donepezil)	✓
Exelon (rivastigmine)	✓
Namenda (memantine)	✓
Namenda XR (memantine)	✓
Namzaric (donepezil/memantine)	-
Razadyne (galantamine)	✓
Razadyne ER (galantamine)	✓

(Drugs@FDA 2018, Clinical Pharmacology 2018)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aricept (donepezil)	Exelon (rivastigmine)	Namenda, Namenda XR (memantine)	Namzaric* (donepezil/memantine)	Razadyne, Razadyne ER (galantamine)
Mild dementia of AD	✓	✓			✓
Moderate dementia of AD	✓	✓	✓	✓	✓
Severe dementia of AD	✓		✓	✓	
Mild to moderate dementia of PD		✓			

Abbreviations: XR = extended release; ER = extended release; AD = Alzheimer's disease, PD = Parkinson's disease

*Namzaric is indicated in patients with moderate to severe dementia of AD who are stabilized on certain doses of memantine and donepezil

(Prescribing information: Aricept 2015, Exelon 2016, Namenda 2013, Namenda XR 2014, Namzaric 2014, Razadyne 2016, Razadyne ER 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The following section highlights key studies associated with the treatment of AD, but does not represent the comprehensive body of evidence available.

Aricept

- A double-blind (DB), randomized controlled trial (RCT) (N = 290) in patients with moderate to severe AD evaluated the use of donepezil 5 to 10 mg/day compared with placebo for 24 weeks and was measured using the Clinician's Interview-Based Impression of Change with caregiver input (CIBIC+) as the primary outcome measure. The CIBIC+ least square scores for donepezil were above baseline severity until week 24, while it declined for placebo. A total of 63% of patients in the donepezil group and 42% of patients in the placebo group improved or had no change ($p < 0.0001$). Donepezil was favored over placebo for secondary outcome measures of the standardized Mini-Mental State Examination (sMME), the Severe Impairment Battery (SIB), Disability Assessment for Dementia (DAD), modified Instrumental Activities of Daily Living (IADL+), and the modified Physical Self-Maintenance Scale (PSMS+). Donepezil demonstrated consistent benefit in cognition, global function, behavior, and activities of daily living (ADL) in both primary and secondary outcome measures. Patients who withdrew from treatment due to adverse events represented 8% in the donepezil group and 6% in the placebo group (Feldman et al 2001).

Exelon

- An international RCT (N = 725) in patients with mild to moderately severe AD in Europe and North America evaluated the efficacy and safety of higher dose rivastigmine (6 to 12 mg/day) and lower dose rivastigmine (1 to 4 mg/day) vs placebo for an ITT population over 26 weeks. The outcome measures were the ADAS-cog, CIBIC+, and the progressive deterioration scale. On the ADAS-cog, more patients in the higher dose rivastigmine group improved clinically compared with placebo (24 vs 16%, respectively; $p < 0.1$). On the CIBIC+, more patients in both rivastigmine groups received ratings of marked, moderate, or minimal improvement than placebo (37% in higher dose group [$p < 0.001$] and 30% in lower dose group [$p < 0.05$] vs 20% placebo). On the progressive deterioration scale, more patients in the higher dose rivastigmine group significantly improved compared to placebo (29 vs 19%, respectively; $p < 0.01$). Rivastigmine improved cognition, global functioning, and ADL compared with placebo. More patients in the higher dose rivastigmine group (23%) withdrew from treatment due to adverse events compared to the lower dose rivastigmine group (7%) and the placebo group (7%) (*Rosler et al 1999*).
- One DB, RCT (N = 1195) of patients with mild to moderate AD evaluated the safety and efficacy of oral rivastigmine 12 mg daily or 2 doses of transdermal rivastigmine (10 and 20 cm²) vs placebo for 6 months. The primary efficacy measures were the ADAS-cog and the AD Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC). At week 24, 27.4% of patients in the 10 cm² group, 32.8% in the 20 cm² group, and 28.5% in the oral rivastigmine group had clinical improvement (4 point improvement in ADAS-Cog) compared with 19.9% in the placebo group ($p < 0.05$). The 20 cm² patch had a higher mean improvement on the ADAS-cog vs the 10 cm² patch. Both doses of the transdermal rivastigmine were superior to placebo (better cognition, attention, ADL, motor processing speed, and visual tracking) and were non-inferior to oral rivastigmine. The incidence of adverse events was not statistically significantly different between the 10 cm² patch (51%) and placebo (46%), but was higher in the 20 cm² patch group (66%) and oral capsules (63%) compared to placebo ($p \leq 0.001$ for both) (*Winblad et al 2007*).
- A systematic review of 13 RCTs evaluated the use in patients with mild to moderate AD treated for ≥ 12 weeks. Results demonstrated rivastigmine was beneficial for ADL (standardized mean difference [SMD], 0.20; 95% confidence interval [CI], 0.13 to 0.27; N = 3230; 6 studies); cognitive function on the ADAS-cog (mean difference [MD], -1.79; 95% CI, -2.21 to -1.37, N = 3232, 6 studies) and on the MMSE (MD, 0.74; 95% CI, 0.52 to 0.97; N = 3205; 6 studies), and the clinician's global assessment compared with placebo. No differences were found in behavioral changes and impact on caregivers. In addition, oral rivastigmine was associated with a higher risk of adverse events compared to rivastigmine transdermal patch (odds ratio [OR], 0.68; 95% CI, 0.58 to 0.80) (*Birks et al 2015*).

Namenda

- A pooled analysis of 2 RCTs (Phase 2 dose-finding study [N = 315] and Phase 3 study [N = 432]) in patients with moderate to severe dementia in Japan over 24 weeks found that memantine (10 to 20 mg/day) was superior to placebo based on the Clinician's Interview-based Impression of Change plus Japanese (CIBIC plus-J) assessment. The outcome measures were CIBIC plus-J, Severe Impairment Battery-Japanese version (SIB-J), and the Behavioral Pathology in AD Rating Scale (BEHAVE-AD). At weeks 4, 12, and 24, memantine had statistically significantly better outcomes than placebo on the SIB-J ($p < 0.0001$ for all timepoints). At week 24, memantine had statistically significantly less worsening than placebo on the CIBIC plus-J ($p = 0.047$). At week 24, memantine had statistically significant improvements than placebo on the BEHAVE-AD ($p = 0.0040$). Memantine was associated with less worsening of behavioral symptoms, language ability, language function, attention, visuospatial, and praxis compared with placebo (*Nakamura et al 2014*).
- One meta-analysis of 9 RCTs (N = 2433) in patients with AD for ≥ 24 weeks demonstrated that memantine monotherapy (10 to 20 mg/day) was effective in improving cognitive function, ADL, behavioral disturbances, global function assessment, and stage of dementia compared with placebo. Memantine significantly improved the primary outcome measures of cognitive function (SMD, -0.27; 95% CI, -0.39 to -0.14; $p = 0.0001$) and behavioral disturbances (SMD, -0.12; 95% CI, -0.22 to -0.01; $p = 0.03$). Memantine did not worsen symptoms of AD and potentially reduced agitation vs placebo (RR, 0.68; 95% CI, 0.49 to 0.94; $p = 0.02$) (*Matsunaga et al 2015*).
- One DB, RCT (N = 404) evaluated memantine 20 mg daily and placebo in patients with moderate to severe AD for 24 weeks who were established on stable treatment with donepezil. The primary outcome measures were the SIB and the modified 19-item Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL₁₉). Memantine demonstrated a statistically significant benefit over placebo for the SIB ($p < 0.001$) and ADCS-ADL₁₉ ($p = 0.03$) scales. Memantine had better outcomes in clinical global status, cognition, ADL, and behavior compared with placebo. A total of 12.4% of patients in the placebo group and 7.4% of patients in the memantine group withdrew treatment due to adverse events (*Tariot et al 2004*).

- In another RCT (N = 252) conducted over 28 weeks, patients with moderate to severe AD demonstrated superior outcomes for memantine 20 mg/day vs placebo in CIBIC+, SIB, and the Alzheimer's Disease Cooperative Study Activities of Daily Living modified for more severe dementia (ADCS-ADLsev). There was a high withdrawal rate (28.2%) noted within the trial; therefore, caution should be exercised with applying results. The primary outcome measures were CIBIC+ (MD, 0.3; p = 0.06) and ADCD-ADLsev (MD, 2.1; p = 0.02). The secondary outcome measures were SIB and other measures of cognition, function, and behavior. Patients treated with memantine had less deterioration and less time spent with caregivers. The proportion of patients who discontinued treatment due to adverse events were 17% within the placebo group and 10% within the memantine group (*Reisberg et al 2003*).

Namzaric

- One DB, RCT (N = 677) of patients with moderate to severe AD evaluated the use of memantine extended-release (ER) 28 mg vs placebo over 24 weeks. Patients were concomitantly administered cholinesterase inhibitors with 69% of patients co-administered donepezil. Of note, the donepezil plus memantine is the only combination treatment FDA-approved. For the primary outcome measures, combination treatment with memantine ER plus cholinesterase inhibitor was significantly better in CIBIC+ (p = 0.008), SIB (least square MD, 2.6; 95% CI, 1.0 to 4.2; p = 0.001), Neuropsychiatric Inventory (NPI, p = 0.005), and the Verbal Fluency Test (VFT, p = 0.004) vs placebo plus a cholinesterase inhibitor. No significant differences were found on the ADCS-ADL₁₉ (p = 0.177). Approximately, 6% of patients in the placebo group and 10% of patients in the memantine ER group discontinued treatment because of adverse events. The populations that included memantine plus galantamine or rivastigmine were too small to draw any firm conclusions for treatment (*Grossberg et al 2013*). Evidence was consistent with other studies (*Boinpally et al 2015*).
- The DOMINO-AD study was a DB, placebo-controlled (PC), RCT (N = 295) in patients with moderate to severe AD treated with donepezil for at least 3 months. Patients were divided into 4 treatment groups: continuation of donepezil, discontinuation of donepezil, discontinuation of donepezil and initiation of memantine, or continuation of donepezil and initiation of memantine (using the sMMSE and the Bristol Activities of Daily Living Scale [BADLS]). The primary outcome measures were the sMMSE (with higher scores translating to better cognitive function) and BADLS (with higher scores translating to greater impairment). The continuation of donepezil group scored higher on the sMMSE by 1.9 points (95% CI, 1.3 to 2.5; p < 0.001) and lower on the BADLS by 3.0 points (95% CI, 1.8 to 4.3, p < 0.001) compared with the discontinuation of donepezil group. The continuation of memantine group scored higher on the sMMSE by 1.2 points (95% CI, 0.6 to 1.8, p < 0.001) and lower on the BADLS by 1.5 points (95% CI, 0.3 to 2.8, p = 0.02) compared with the discontinuation of memantine group. The combination of donepezil and memantine showed no significant benefit vs donepezil alone (*Howard et al 2012*).

Razadyne

- One DB, RCT (N = 653) evaluated use in patients with mild to moderate AD over the period of 6 months. Results demonstrated that galantamine had improvements in ADL, cognition, global function, and daily function compared to placebo. The primary outcome measures were the CIBIC+ and the ADAS-cog. Galantamine (at lower [24 mg] and higher [32 mg] doses) demonstrated better outcomes for CIBIC+ compared to placebo (p < 0.05). On the ADAS-cog, patients on galantamine had significantly better cognition than patients on placebo at 6 months (lower dose, 3.1; 95% CI, 1.7 to 4.5; p < 0.001 and higher dose, 4.1; 95% CI, 2.7 to 5.6; p < 0.001). Galantamine patients reported more (incidence ≥ 5% vs placebo) nausea, vomiting, diarrhea, dizziness, headache, anorexia, and weight loss. There were a total of 18% of patients on galantamine and 9% of patients on placebo who discontinued treatment due to adverse events (*Wilcock et al 2000*).
- One open label (OL) extension trial of 2 DB and OL studies (N = 491) evaluated the safety and efficacy of galantamine 24 mg in patients with mild to moderate AD for a total treatment period of 24 months (with exposures up to 36 months). Cognitive deterioration occurred slowly in patients treated with galantamine according to the Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-cog), which was a co-primary outcome measure. On the ADAS-cog, 48.8% of patients on galantamine had ≤ 10 point increase, 15.3% maintained cognitive function at or above baseline, and majority of patients on galantamine had ≤ 20 point increase. For the additional co-primary endpoint, total DAD scores decreased significantly throughout the study (p < 0.002 at initial visit and p < 0.001 from baseline). The most common treatment emergent adverse events were agitation (16.1%), insomnia (12.4%), fall (11.2%), and urinary tract infection (10.2%) (*Pirttila et al 2004*).
- The SERAD study was a DB, PC, RCT (N = 407) in patients with severe AD treated with galantamine 24 mg vs placebo for 6 months. The primary outcome measures were the SIB and the minimum data set-activities of daily living (MDS-ADL). Patients who were treated with galantamine improved in the SIB score by week 26 (increased by 1.9 points),

while patients who were treated with placebo declined in the SIB score (decreased by 3.0 points) (least squares mean difference, 4.36; 95% CI, 1.3 to 7.5; $p = 0.006$). Both treatment groups declined in the MDS-ADL self-performance score at week 26 from baseline with 1.2 points in the galantamine group and 1.6 points in the placebo group; however, differences were not statistically significant (least squares mean difference, -0.41; 95% CI, -1.3 to 0.5; $p = 0.38$). Galantamine improved SIB domains of memory ($p = 0.006$), praxis ($p = 0.01$), and visuospatial ability ($p = 0.002$) compared with placebo. A total of 88% of patients in the galantamine group and 89% in the placebo group experienced at least 1 adverse event (*Burns et al 2009*).

- One PC, RCT (for 4 months) and OL extension (for an additional 4 months) in patients ($N = 130$) with mild to moderate AD evaluated galantamine 16 to 24 mg compared to placebo. Galantamine significantly improved the primary outcome measure of the Goal Attainment Scaling (GAS) on the clinician-rated GAS score vs placebo after 4 months (absolute difference, 4.0; $p = 0.02$; standardized response mean [SRM] = 0.41), but not on the patient-caregiver-rated GAS score (absolute difference between groups, 1.9; $p = 0.27$; SRM = 0.20). There were significant differences on the ADAS-cog scores and the CIBIC+ that favored galantamine. The most frequently reported adverse events (incidence > 10% vs placebo) were nausea and vomiting (*Rockwood et al 2009*).

Comparative Effectiveness Reviews

- One meta-analysis of 16 RCTs (5169 received AChE inhibitors [donepezil, galantamine, and rivastigmine] and 2795 received a placebo) in patients with mild to moderate AD found that AChE inhibitors were effective compared with placebo in AD. AChE inhibitors demonstrated significantly better global improvement response than placebo for minimal improvement or better, marked improvement, and stabilization or better. However, AChE inhibitors also had significantly more adverse events compared with placebo (8%; 95% CI, 5 to 11%). The proportion of patients administered AChE inhibitors who dropped out due to adverse events were 7% (95% CI, 3 to 10%) (*Lanctot et al 2003*).
- One head-to-head RCT ($N = 994$) evaluated the efficacy, safety, and tolerability of donepezil 5 to 10 mg vs rivastigmine 3 to 12 mg in patients with moderate to moderately severe AD over a 2 year period. For the primary outcome of SIB, results were similar. A total of 34.8% of patients administered donepezil and 36.5% of patients administered rivastigmine had SIB scores equal or better than baseline at 26 months. However, it was not statistically significant. At 104 weeks, rivastigmine demonstrated better efficacy in ADL than donepezil on the ADCS-ADL (24.7 vs 19.4%, $p = 0.047$) as well as better efficacy in global deterioration than donepezil on the global deterioration scale (GDS; 53.1% vs 45.3%, $p = 0.016$). Only 57.9% of patients completed the study, mainly due to adverse events (gastrointestinal-related) with more patients in the rivastigmine group experiencing adverse events during the titration Phase. (*Bullock et al 2005*).
- One systemic review evaluated the cognitive decline and the benefits of interventions for clinical Alzheimer's type dementia across 10 studies. Based on results, AChE inhibitors may not reduce the incidence of clinical Alzheimer's type dementia or provide a significant effect on cognitive performance in patients with mild cognitive impairment; however, evidence was of lower quality. A study of patients with normal cognition ($N = 28$) demonstrated insufficient evidence and no cognitive benefits compared with placebo over 26 weeks. The study of patients with mild cognitive impairment ($N = 769$) demonstrated low-strength evidence in delaying progression of dementia over 18 months to 2 years and demonstrated no benefit at 3 years compared with placebo (*Kane et al 2017*).

CLINICAL GUIDELINES

Overall

- Several guidelines outline the goals for AD therapy are to delay the progression of symptoms and to preserve functional ability. In general, guidelines do not prefer one agent over another. The choice of treatment is based on tolerability, adverse events and ease of use (*APA 2007, Bond et al 2012, Bullock et al 2005, Hogan et al 2004, Hort et al 2010, Jones et al 2004, Rabins et al 2014, Wilcock et al 2003, Wilkinson et al 2002*).
- All AChE inhibitors are FDA-approved for mild and moderate disease. Donepezil is the only AChE inhibitor that is also approved for severe disease. Memantine is the only NMDA antagonist approved for use in AD and is only indicated for patient with moderate or severe disease. These treatments all show evidence of slowing cognitive decline and improving global outcome, behavior, and activities of daily living (ADL). There is no sufficient evidence to support the use of any medications for the primary prevention of AD (*APA 2007, Bond et al 2012, Hort et al 2010*).
- Medication(s) should be chosen based on the severity of the disease since FDA approval is dependent on disease severity. Guidelines recommend starting patients on one of the approved AChE inhibitors (donepezil, rivastigmine, and galantamine). If symptoms have not improved and the patient has moderate or severe disease, it is recommended to add memantine as adjunct therapy (*APA 2007*). This is due to multiple studies showing that use of an AChE inhibitor in

combination with memantine yields better outcomes than an AChE inhibitor alone (*Bond et al 2012, Bullock et al 2005, Hogan et al 2004, Jones et al 2004, Wilcock et al 2003, Wilkinson et al 2002*).

- AChE inhibitors all show similar efficacy rates with differing tolerability, but none have been shown to be superior (*Bond et al 2012, Bullock et al 2005, Hogan et al 2004, Jones et al 2004, Wilcock et al 2003, Wilkinson et al 2002*).

American Psychiatric Association (APA)

- The American Psychiatric Association (APA) guidelines for AD recommend initiating non-pharmacological management (i.e., occupational therapy, physiotherapy, mental stimulation, social services, speech and language therapy, aromatherapy, education) approaches before prescribing medication due to the modest benefit and varying levels of support for these pharmaceutical treatments. Upon failure of non-pharmacologic treatments, medication should be initiated, but it is recommended that doctors discuss the medication risks and benefits before initiating treatment (*APA 2007, Hort et al 2010*).
 - There is evidence of modest improvement in some patients treated with AChE inhibitors and therapy is appropriate in patients with mild or moderate AD for whom the medication is not contraindicated. Evidence suggests similar efficacy among agents; however, they may differ in tolerability.
 - Memantine should be considered in patients with moderate to severe AD. There is modest evidence that the combination of memantine and donepezil is better than donepezil alone, but there is no evidence that this combination is better than memantine monotherapy.
 - Due to reduced clearance in elderly individuals, medication should be started at low doses and slowly titrated until a reduction in symptoms is seen. This is done to minimize the occurrence of adverse reactions which tend to be mild and predominantly affect the gastrointestinal system but also include confusion, orthostatic hypotension, sedation, and more (*APA 2007*).
 - The APA guidelines discourage the use of NSAIDs, Vitamin E, *Ginkgo biloba*, and estrogen supplements for the management of AD. No evidence has demonstrated an effect on cognitive decline and some have been shown to be detrimental to cognition and can cause extraneous adverse effects (*APA 2007, Hort et al 2010, Rabins et al 2014*).
- An 2014 update to the APA guidelines stipulate that AD evidence remains modest for certain medications (eg, cholinesterase inhibitors and memantine):
 - No clinically meaningful advantages have been observed with higher doses of donepezil; however, higher doses of the rivastigmine patch may produce efficacy advantages. There is no evidence to support the use for cognitive symptomatic treatment or prevention (*Rabins et al 2014*).
 - New trials for memantine in mild to moderate AD demonstrated no benefit.
 - Caution should be exercised when considering mood stabilizing medications for comorbid conditions due to lack of evidence except for atypical antipsychotics. Upon implementation, these mood stabilizers should be reduced when symptoms have been controlled for 4 to 6 months to assess the need for continued use (*APA 2007, Rabins et al 2014*).

European Federation of Neurological Societies (EFNS)

- The EFNS guidelines are in agreement with the 2007 APA guidelines. Other recommendations include:
 - Recommend AChE inhibitors (donepezil, galantamine, or rivastigmine) be considered at the time of diagnosis for mild to severe disease. Memantine should be considered in patients with moderate to severe AD.
 - Where possible, initial treatment should be non-pharmacological.
 - Evidence does not support the use for any medications for the primary prevention of dementia. Cholinesterase inhibitors, vitamin E, ginkgo and estrogens should not be used as treatments for those with mild cognitive impairment.
 - Memantine may provide benefits for some non-cognitive symptoms (ie, agitation and delusions) (*Hort et al 2010*).

SAFETY SUMMARY

- **Contraindications**
 - Patients who have a history of application site reaction with rivastigmine transdermal patch is suggestive of allergic contact dermatitis.

- **Warnings/Precautions**
 - Namenda, Namenda XR, Namzaric: Increased plasma levels of memantine and decreased urinary elimination of memantine may result if patients have conditions that raise urine pH
 - Razadyne, Razadyne ER: Serious skin reactions (i.e., Stevens-Johnson syndrome) have been reported; patient should discontinue at the first appearance of a skin rash
 - Exelon: May worsen driving or use of machinery in addition to the patient's dementia
 - Cholinesterase inhibitors (donepezil, rivastigmine, galantamine):
 - May exaggerate the neuromuscular blocking effects of succinylcholine-type muscle relaxation during anesthesia
 - May have vagotonic effects on the sinoatrial and atrioventricular nodes, causing heart block or bradycardia in patients with or without underlying cardiac conduction abnormalities
 - May increase gastric acid secretion due to increased cholinergic activity, causing gastrointestinal bleeding or peptic ulcer disease in patients with underlying conditions or on nonsteroidal anti-inflammatory drugs (NSAIDs)
 - May have the potential to cause generalized convulsions, but it may also be a manifestation of Alzheimer's disease
 - Should be prescribed with care to patients with a history of asthma or chronic obstructive pulmonary disease

- **The most common adverse events associated with each agent are:**
 - Aricept: Nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia
 - Exelon: Nausea, vomiting, anorexia, dyspepsia, asthenia
 - Exelon patch: Nausea, vomiting, diarrhea
 - Namenda: Dizziness, headache, confusion, constipation
 - Namenda XR: Headache, diarrhea, dizziness
 - Razadyne, Razadyne ER: Nausea, vomiting, diarrhea, dizziness, headache, decreased appetite

- **Key Drug Interactions**
 - Cholinesterase inhibitors can interfere with the activity of anticholinergic medications
 - Cholinesterase inhibitors have a synergistic effect when given with succinylcholine, cholinergic agonists (ie, bethanechol), other neuromuscular blocking agents, or other cholinesterase inhibitors
 - Exelon and metoclopramide: Increased risk of extrapyramidal adverse effects
 - Exelon and beta blockers: May cause additive bradycardic effects leading to syncope
 - Namenda/Namenda XR and other NMDA antagonists: Approach with caution since it has not been systemically evaluated

- **Other safety comments**
 - Aricept, Razadyne, Razadyne ER: Pregnancy category C
 - Exelon, Namenda, Namenda XR: Pregnancy category B

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aricept (donepezil)	Tablet, oral disintegrating tablet	Oral	Once daily in the evening	May be taken with or without food.
Exelon (rivastigmine)	Capsule, TD patch	Oral, TD	Capsule: Twice daily TD patch: Once in a 24 hour period	Capsule: Patients with moderate and severe renal impairment as well as mild and moderate hepatic impairment may only tolerate lower doses. TD patch: Consider dose adjustments in patients with mild to moderate hepatic impairment.
Namenda, Namenda XR (memantine)	Tablet, solution, capsule ER, titration pack	Oral	Once daily	May be taken with or without food. Capsule ER: May be taken whole, or sprinkled on applesauce. Lower doses are recommended in patients with severe renal impairment (CrCL 5 to 29 mL/min). Use with caution in patients with severe hepatic impairment.
Namzaric (donepezil/memantine)	Capsule ER, therapy pack	Oral	Once daily in the evening	May be taken with or without food, whole, or sprinkled on applesauce.
Razadyne, Razadyne ER (galantamine)	Tablet, capsule ER	Oral	Tablet: Twice daily, Capsule ER: Once daily	Should not exceed 16 mg/day for moderate hepatic impairment (Child Pugh score of 7 to 9) or in patients with CrCL of 9 to 59 mL/min. Do not use for severe hepatic impairment (Child Pugh score of 10 to 15) or in patients with CrCL of < 9 mL/min.

Abbreviations: CrCL = creatinine clearance, ER = extended release, TD = transdermal

See the current prescribing information for full details

CONCLUSION

- AD is a progressive, degenerative neurological disease often presenting in later stages of life. Patients often present with memory loss, aphasia, apraxia, agnosia, and loss of abstract planning skills.
- Non-pharmacological approaches should be initiated before prescribing medication due to the modest benefit and varying levels of support for these pharmaceutical treatments. Upon failure of non-pharmacologic treatments, medication should be initiated, but it is recommended that doctors discuss the medication risks and benefits before initiating treatment.
- Management of AD includes an AChE inhibitor with or without a noncompetitive NMDA receptor antagonist depending on the severity stage diagnosis (mild, moderate, or severe), along with psychosocial treatment methods, have been

shown to be effective in managing patient symptoms with some evidence to support their effect on the behavioral symptoms of AD.

- Common adverse effects for the class include nausea, vomiting, and diarrhea.
- All AChE inhibitors are FDA-approved for mild and moderate disease. Donepezil is the only AChE inhibitor that is also approved for severe disease. Memantine is the only NMDA antagonist approved for use in AD and is only indicated for patient with moderate or severe disease. Evidence has demonstrated that memantine may be combined with a cholinesterase inhibitor. AChE inhibitors all show similar efficacy rates with differing tolerability, but none have been shown to be superior.
- Clinical trials evaluating the efficacy and safety of AD agents include over 40 measurement tools, which measure outcomes related to global function, cognition, behavior, and quality of life. Indirect comparisons between treatments are difficult as there are methodologic limitations including inconsistent results, different tools of measure, inadequately described follow up, and sometimes high dropout rates. None-the-less, current clinical trials, systematic reviews, and meta-analyses support the efficacy of these medications for their FDA-approved indications and have shown to be superior to placebo. There is limited evidence available head-to-head.
- Rivastigmine is available as a transdermal patch and may have less side effects than oral rivastigmine. There may be efficacy advantages with administering higher doses of the rivastigmine patch. Rivastigmine is the only agent in class which has an indication for the symptoms of dementia in PD (*Birks et al 2015, Rabins et al 2014*).
- Several guidelines outline the goals for AD therapy are to delay the progression of symptoms and to preserve functional ability. In general, guidelines do not prefer one agent over another. The choice of treatment is based on tolerability, adverse events and ease of use (*APA 2007, Bond et al 2012, Bullock et al 2005, Hogan et al 2004, Hort et al 2010, Jones et al 2004, Rabins et al 2014, Wilcock et al 2003, Wilkinson et al 2002*).
- AD treatments demonstrate evidence of slowing cognitive decline and improving global outcome, behavior, and ADL; however, improvements are modest. Other limitations include inconsistent evidence from large, well-designed trials and in many cases well-designed trials are generally conducted under a duration of 1 year. There is no sufficient evidence to support the use of any medications for the primary prevention of AD.

REFERENCES

- Alzheimer's Association. Alzheimer's Disease Facts and Figures 2007. Alzheimer's Association. Website. https://www.alz.org/national/documents/Report_2007FactsAndFigures.pdf Accessed April 23, 2018.
- American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias, second edition. *Am J Psychiatry*. 2007;164(12):4-56.
- Aricept [package insert], Woodcliff Lake, NJ: Eisai, Inc.; July 2015.
- Birks JS, Chong LY, Grimley EJ. Rivastigmine for Alzheimer's disease (review). *Cochrane Database of Systematic Reviews*. 2015;9:CD001191.
- Boinpally R, Chen L, Zukin SR, et al. A novel once-daily fixed-dose combination of memantine extended release and donepezil for the treatment of moderate to severe Alzheimer's disease: two phase I studies in healthy volunteers. *Clin Drug Investig*. 2015;35(7):427-35.
- Bond M, Rogers G, Peters J, et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): a systematic review and economic model. *Health Technol Assess*. 2012;16(21):1-470.
- Bullock R, Touchon J, Bergman H, et al. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. *Curr Med Res Opin*. 2005;21(8):1317-1327.
- Burns A, Bernabei Roberto, Bullock R, et al. Safety and efficacy of galantamine (Reminyl) in severe Alzheimer's disease (the SERAD study): a randomised, placebo-controlled, double-blind trial. *Lancet Neuro*. 2009;8:39-47.
- Clinical Pharmacology Web site. <http://www.clinicalpharmacology-ip.com/default.aspx>. Accessed March 16, 2018.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. <https://www.accessdata.fda.gov/scripts/cder/daf/>. Accessed March 16, 2018.
- Exelon [package insert], East Hanover, NJ: Novartis Pharmaceuticals, Corp.; November 2016.
- Feldman H, Gauthier S, Hecker J, et al. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology*. 2001;57:613-620.
- Grossberg GT, Manes F, Allegri RF, et al. The Safety, Tolerability, and Efficacy of Once-Daily Memantine (28 mg): A Multinational, Randomized, Double-Blind, Placebo- Controlled Trial in Patients with Moderate-to-Severe Alzheimer's Disease Taking Cholinesterase Inhibitors. *CNS Drugs*. 2013;27:469-478.
- Hogan DB, Goldlist B, Naglie G, et al. Comparison studies of cholinesterase inhibitors for Alzheimer's disease. *Lancet Neuro*. 2004;3(10):622-626.
- Hort J, O'Brien JT, Gainotti G, et al. EFNS guidelines for the diagnosis and management of Alzheimer's disease. *European Journal of Neurology*. 2010;17:1236-1248.
- Howard R, McShane Rupert, Lindsay J, et al. Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease. *N Engl J Med*. 2012;366:893-903.

- Jones RW, Soininen H, Hager K, et al. A multinational, randomized, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease. *Int J Geriatr Psychiatry*. 2004;19(1):58-67.
- Kane RL, Butler M, Fink HA, et al; for the Agency for Healthcare Research and Quality (AHRQ). Interventions to Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer's-Type Dementia. *AHRQ Comparative Effectiveness Reviews*. 2017 Mar. Report No: 17-EHC008-EF;188:172-176.
- Lanctot KL, Herrmann N, Yau KK, et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. *CMAJ*. 2003;169(6):557-564.
- Letenneur L, Gilleron V, Commenges D, et al. Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. *J Neurol Neurosurg Psychiatry*. 1999 Feb; 66(2): 177-183.
- Matsunaga S, Kishi T, Iwata N. Memantine Monotherapy for Alzheimer's disease: A Systematic Review and Meta-Analysis. *PLOS ONE*. 2015;10(4):1-16.
- McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the national institute on aging and the Alzheimer's association workgroup. *Alzheimers Dement*. 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005.
- Micromedex Solutions Web site. <http://www.micromedexsolutions.com/home/dispatch>. Accessed March 16, 2018.
- Nakamura Y, Kitamura S, Homma A, Shiosakai K, Matsui D. Efficacy and safety of memantine in patients with moderate-to-severe Alzheimer's disease: results of a pooled analysis of two randomized, double-blind, placebo-controlled trials in Japan. *Expert Opin Pharmacother*. 2014;15(7):913-925.
- Namenda [package insert], St. Louis, MO: Forest Laboratories Ireland, Ltd.; October 2013.
- Namenda XR [package insert], St. Louis, MO: Forest Laboratories Ireland, Ltd.; September 2014.
- Namzaric [package insert], Cincinnati, OH: Forest Pharmaceuticals, Inc.; July 2016.
- Pirttila T, Wilcock G, Truyen L, et al. Long-term efficacy and safety of galantamine in patients with mild-to-moderate Alzheimer's disease: multicenter trial. *European Journal of Neurology*. 2004;11:734-741.
- Rabins PV, Rovner BW, Rummans T, Schneider LS, Tariot PN. Practice Guideline for the Treatment of Patients with Alzheimer's disease and other dementias. *APA Guideline Watch*. 2014;1-26.
- Razadyne [package insert], Titusville, NJ: Janssen Pharmaceuticals, Inc.; September 2016.
- Razadyne ER [package insert], Titusville, NJ: Janssen Pharmaceuticals, Inc.; September 2016.
- Reisberg B, Doody R, Stoffer A, Schmitt F, Ferris S, Mobius HJ. Memantine in Moderate-to-Severe Alzheimer's Disease. *N Engl J Med* 2003;348:1333-41.
- Rockwood K, Fay S, Song X, MacKnight C, Gorman M. Attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomized controlled trial. *CMAJ*. 2006;174(8):1099-1105.
- Rosler M, Anand Ravi, Cicin-Sain A, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *BMJ*. 1999;318:633-40.
- Tariot PN, Farlow MR, Grossberg GT, et al. Memantine Treatment in Patients with Moderate to Severe Alzheimer Disease Already Receiving Donepezil A Randomized Controlled Trial. *JAMA*. 2004;291(3):317-324.
- Wilcock G, Howe I, Coles H, et al. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. *Drugs Aging*. 2003;20(10):777-789.
- Wilcock GK, Lilienfeld S, Gaens Els. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. *BMJ*. 2000;321:1-7.
- Wilkinson DG, Passmore AP, Bullock R, et al. A multinational, randomized, 12-week, comparative study of donepezil and rivastigmine in patients with mild to moderate Alzheimer's disease. *Int J Clin Pract*. 2002;56(6):441-446.
- Winblad B, Cummings J, Andreasen N, et al. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease – rivastigmine patch versus capsule. *Int J Geriatr Psychiatry*. 2007;22:456-467.

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