The Future of Alzheimer's Disease Treatment: Implications for Managed Care Pharmacists

This educational activity is sponsored by Postgraduate Healthcare Education, LLC and supported by an educational grant from Biogen.

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Dr. Rainka is an investigator on phase I-IV clinical trials and has co-authored several papers in peer-reviewed journals. In 2009, she was nominated to become a board member of the Western NY Alzheimer's Association, where she also served as Secretary until 2014. Dr. Rainka also serves on the board of Dent's research affiliate, Dent Neurosciences Research Center.

Disclosure

Dr. Rainka disclosed that she has received grants/research support from Acadia and Alexa; served as a clinical investigator for Adamas, Alexa, Allergan, Avanir, Biogen, Eisai, Eli Lilly, Novartis, Pfizer, Roche, and Teva; and owns stock in the following companies: Abbvie, Acadia, Alkermes, Biogen, Eli Lilly, Novartis, and Roche.

The clinical reviewer, **Lisa Hutchison, PharmD, MPH, BCPS, BCGP,** has no actual or potential conflict of interest in relation to this program.

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UAN: 0430-0000-18-063-L01-P
Credits: 1.0 hour (0.10 CEU)
Type of Activity: Application

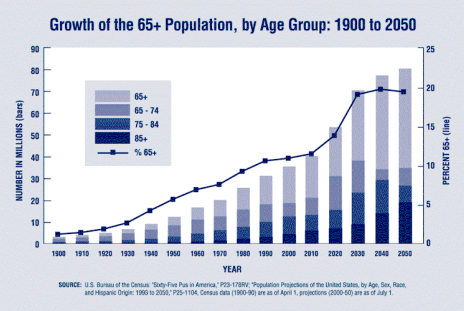
Learning Objectives

- **Discuss** the pathogenesis of Alzheimer's Disease (AD) and reasons behind its increasing prevalence
- **Compare and contrast** currently available treatments for AD
- **Appraise** investigational treatments for AD and potential implications for future formulary decision-making

Epidemiology of AD

- Risk factors:
  - Age *(greatest)*
    - 10% of population over age 65 years has AD
      - 65-74 years old: 3%
      - 75-84 years old : 17%
      - 85 years and older: 32%
  - Family history
  - APOE-e4 gene
- Expected explosion in AD:
  - Aging baby boomer population in the U.S.
  - Continuing extension of life expectancy
  - Overall growth of the global population

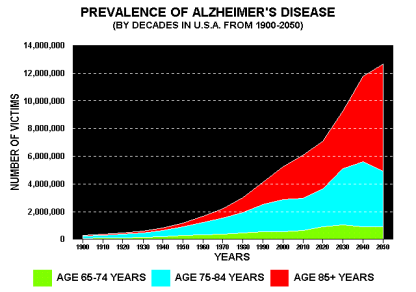
- *Baby boomer generation: people born between the mid-1940s and the mid-1960's*
- *By 2030-31: all baby boomers will be over the age of 65 years*
  - *Oldest group reaches 85 years and older*

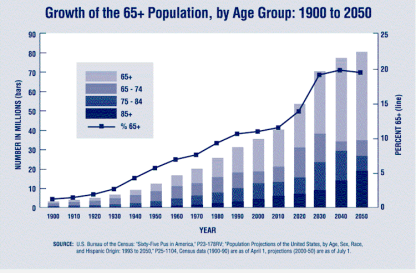


Alzheimer's Association. *Alzheimers Dement.* 2018;14(3):367-429.

Epidemiology of AD

- Prevalence of AD in the U.S. is estimated to triple from 2010 to 2050
- More than 5.7 million people currently living with AD in the U.S.
  - More than 95% are 65 years of age or older
  - Approximately 200,000 patients have a form of younger-onset AD
- Globally, AD is estimated to affect at least 47.5 million people
- By 2050, prevalence of AD is expected to reach nearly 14 million in the U.S. and 100 million globally





Alzheimer's Association. *Alzheimers Dement.* 2018;14(3):367-429.;
Cummings J, et al. *Alzheimers Dement (N Y).* 2017;3(3):367-84.;
Hebert L, et al. *Neurology*. 2013:80(19):1778-83.;
Qui C, et al. *Dialogues Clin Neurosci*. 2009;11(2):111-28.

What is Dementia?

Diagnosed when cognitive/behavioral (neuropsychiatric) symptoms:

1. Interfere with the ability to function (work/usual activities)
2. Represent a decline from previous levels of functioning/performing
3. Are not explained by delirium or major psychiatric disorder

McKhann GM, et al. *Alzheimers Dement.* 2011;7(3):263-9.

What is Dementia?

Cognitive impairment is detected and diagnosed through a combination of:

- History-taking from the patient and a knowledgeable informant
- An objective cognitive assessment
  - Either a "bedside" mental status examination or neuropsychological testing

Cognitive or behavioral impairment involves at least 2 of the following domains:

- Impaired ability to acquire/remember new information
  - *Repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route*
- Impaired reasoning/handling of complex tasks, poor judgment
  - *Poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities*
- Impaired visuospatial abilities
  - *Inability to recognize faces or common objects, to find objects in direct view despite good acuity, to operate simple implements, or to orient clothing to the body*
- Impaired language
  - *Difficulty thinking of common words when speaking, hesitations*
  - *Speech, spelling, writing errors*
- Changes in personality, behavior, or comportment
  - *Uncharacteristic mood fluctuations, agitation, impaired motivation or initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors*

McKhann GM, et al. *Alzheimers Dement.* 2011;7(3):263-9.

Types of Dementia

- Dementia of the Alzheimer's type
- Vascular dementia/multi-infarct dementia
- Mixed dementia
- Dementia with Lewy bodies
- Parkinson's dementia
- Frontotemporal lobar degeneration
- Creutzfeldt-Jakob disease

Alzheimer's Association. *Alzheimers Dement.* 2018;14(3):367-429.; McKhann GM, et al. *Alzheimers Dement.* 2011;7(3):263-9.

Other Sources of Cognitive Impairment

- Depression
- Delirium
  - Urinary tract infections
  - Adverse drug reactions
- Underlying conditions
  - Vitamin B12 deficiency
  - Normal pressure hydrocephalus
  - Hypothyroidism
  - Brain tumor
  - Infectious causes: HIV, neurosyphilis
  - Chronic drug intoxication
  - Alcoholism

What is AD?

Meets criteria for dementia PLUS:

1. Insidious onset
   - Symptoms have a gradual onset over months to years, not suddenly over hours or days
2. Clear-cut history of worsening of cognition by report or observation
3. Initial and most prominent cognitive deficits are evident on history and examination in 1 of the following categories:
   - Amnestic presentation *(most common)*
     - Impairment in learning and recall of recently learned information and cognitive dysfunction in at least 1 other cognitive domain
   - Nonamnestic presentations
     - Language presentation
     - Visuospatial presentation
     - Executive dysfunction

What is AD?

The diagnosis of probable AD dementia ***should not*** be applied if:

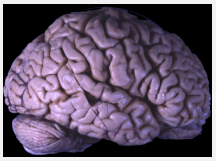
a) Substantial concomitant cerebrovascular disease
b) Core features of Dementia with Lewy bodies
c) Prominent features of frontotemporal dementia
d) Prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia
e) Evidence for another concurrent, active neurological disease or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition

McKhann GM, et al. *Alzheimers Dement.* 2011;7(3):263-9.

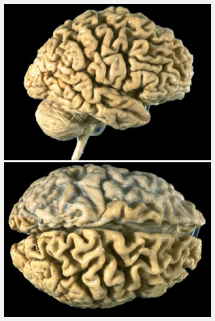
What is AD?

- Progressive, neurodegenerative disease of brain atrophy with ventricular enlargement
- Degeneration of cholinergic and other neurons
- Neuropathologic studies
  - Neuronal loss (cortex, limbic, amygdala, hippocampus)
  - Neurofibrillary tangles
  - Senile plaques
  - Accumulation of β-amyloid

Without atrophy

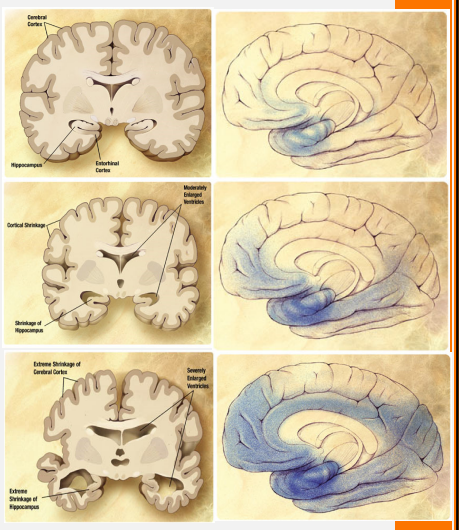


Cortical atrophy



What is AD?

- Pre-clinical AD
  - Signs first noticed in the entorhinal cortex, then proceed to the hippocampus.
  - Changes begin 10-20 years before symptoms
  - Memory loss is the first sign of AD
- Mild-moderate AD
  - Cerebral cortex shrinks
- Severe AD
  - Extreme shrinkage occurs in the brain
  - Patients dependent on others for ADLs
  - Death usually occurs from aspiration pneumonia or other infections

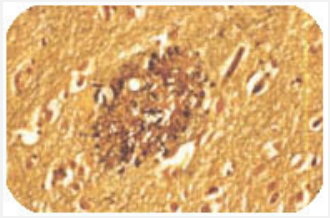


ADL, activities of daily living.

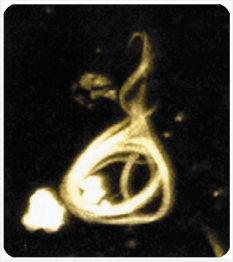
National Institute on Aging. https://adrccares.org/wp-content/uploads/2016/01/alzheimers_disease_unraveling_the_mystery_0.pdf. Published September 2008. Accessed November 26, 2018.

Pathogenesis Theories of AD

- Hallmark features:
  - β-amyloid plaques: dense deposits of protein and cellular material that accumulate outside and around nerve cells

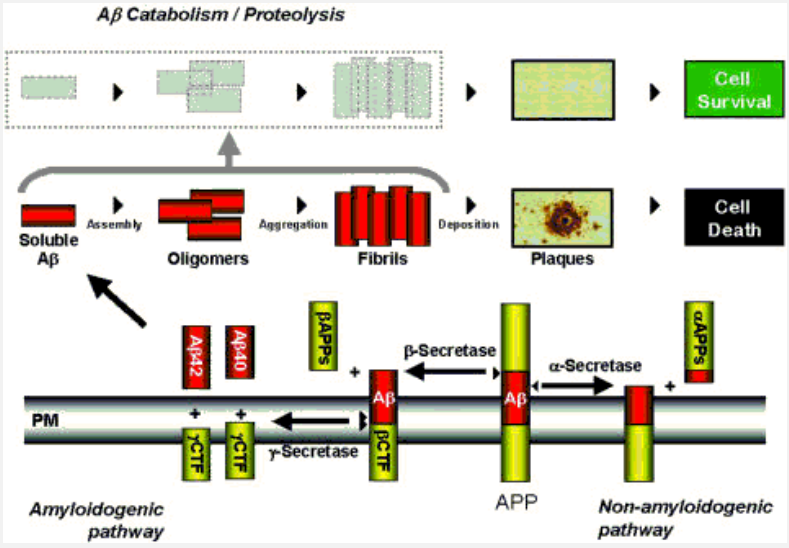


  - Neurofibrillary tangles: twisted fibers that build up inside the nerve cell



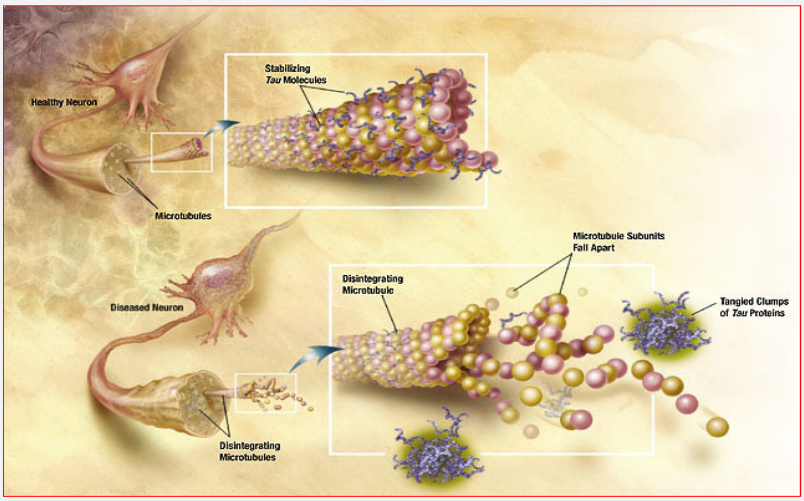
National Institute on Aging. https://adrccares.org/wp-content/uploads/2016/01/alzheimers_disease_unraveling_the_mystery_0.pdf. Published September 2008. Accessed November 26, 2018.

β-Amyloid Plaques



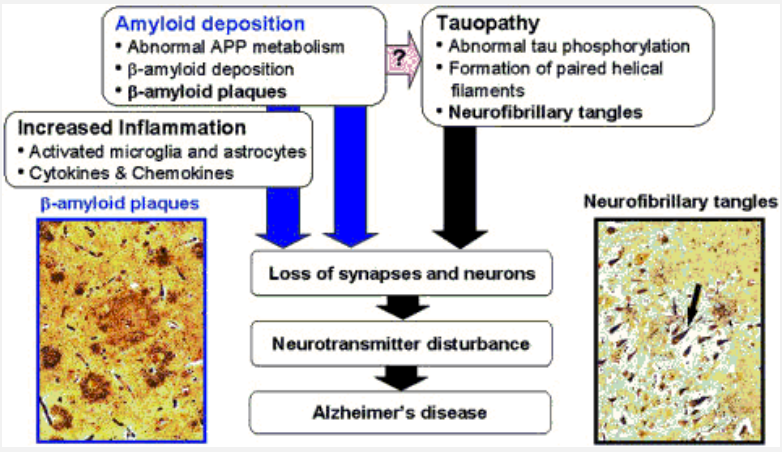
Jacobsen JS, et al. *NeuroRx*. 2005;2(4):612-26.

Neurofibrillary Tangles



National Institute on Aging. https://adrccares.org/wp-content/uploads/2016/01/alzheimers_disease_unraveling_the_mystery_0.pdf. Published September 2008. Accessed November 26, 2018.

β-Amyloid Plaques and Neurofibrillary Tangles



APP, β-amyloid precursor protein.

Jacobsen JS, et al. *NeuroRx*. 2005;2(4):612-26.

Clinical Evaluation and History

Should be obtained with an informant, if possible

- Social history, including drug and alcohol use
- Medical history
- Medications
- Description of neuropsychological complaints
  - Cognitive, memory, and behavior problems
  - Effect on daily life
    - Difficulty with driving, work, or family relationships
- Details on temporal course of illness
  - Chronic
  - Progressive (neurodegenerative disease)
  - Stepwise (multi-infarct)
  - Static (traumatic injury, episode of severe hypotension)

Cordell CB, et al. *Alzheimers Dementia*. 2013;9(2):141-50.

Clinical Assessment

- Structured cognitive assessment
  - Multiple cognitive domains:
    - Episodic memory
    - Executive memory
    - Attention
    - Language
    - Visuospatial skills
  - Examples: Mini-cog, MMSE, MOCA, SLUMS
    - Neuropsychological tests for difficult diagnosis
- Neurologic exam (gait, motor function, reflexes)
- ADL and IADL functioning
- Assessment for depression
- Review for medications that may adversely affect cognition
- Rule out other concurrent, active neurological disease, delirium, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition

IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; SLUMS, St. Louis University Mental Status Examination.

Cordell CB, et al. *Alzheimers Dementia*. 2013;9(2):141-50.

Laboratory Testing

- Complete blood count
- Chemistry panel (electrolytes, calcium, albumin, BUN, creatinine, transaminase)
- Thyroid-stimulating hormone
- If at risk, test for STDs (HIV, VDRL test for syphilis)
- Serum B_{12} and folate levels

BUN, blood urea nitrogen;
STDs, sexually transmitted diseases;
VDRL, venereal disease research laboratory test.

Cordell CB, et al. *Alzheimers Dementia*. 2013;9(2):141-50.

Imaging Evaluation

- Head CT or MRI is a supplemental aid in the diagnosis of dementia, especially if neurologic physical exam findings are noted appropriate in the presence of:
  1) History suggestive of a mass lesion
  2) Focal neurologic signs or symptoms
  3) Dementia of abrupt/recent onset, rapidly progressing
  4) History of seizures
  5) History of stroke
  6) History of head trauma
  7) Young onset (< 65 years)

CT, computed tomography;
MRI, magnetic resonance imaging.

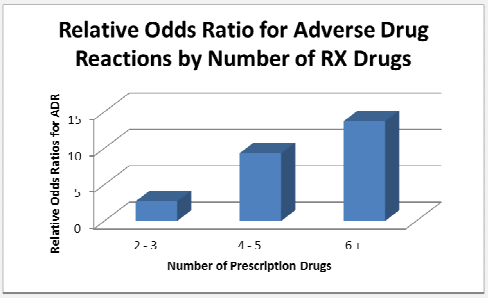
Cordell CB, et al. *Alzheimers Dementia*. 2013;9(2):141-50.

The "Cholinergic Hypothesis"

- Acetylcholine (ACh) is an important neurotransmitter in areas of the brain involved in memory formation (hippocampus, cerebral cortex, and amygdala)
- Concentrations of ACh are markedly decreased in AD
- Enhancement or restoration of cholinergic function may significantly reduce the severity of cognitive loss

Ferreira-Vieira TH, et al. *Curr Neuropharmacol.* 2016;14(1):101-15.

Adverse Drug Reactions and Global Cognitive Impairment



Larson EB, et al. *Ann Int Med.* 1987;107(2):169-73.

Severity of anticholinergic burden

Mild: drowsiness, fatigue, mild amnesia

Moderate: excitement, restlessness, confusion, memory impairment

Severe: agitation, delirium, ataxia, muscle twitching, cognitive impairment

Feinberg M. *Drugs Aging.* 1993;3(4):335-48.;
Mintzer J, Burns A. *J R Soc Med.* 2000;93(9):457-62.;
Scheife R, Takeda M. *Clin Ther.* 2005;27(2):144-53.

Anticholinergic Drug Level in Medications Frequently Used in the Elderly

Medication (with detectable anticholinergic activity, ranked high to low)	Anticholinergic drug level (ng/mL of atropine equivalent)	Anticholinergic level associated with impairment
Cimetidine	0.86	
Prednisolone	0.55	X
Theophylline	0.44	X
Digoxin	0.25	X
Nifedipine	0.22	X
Furosemide	0.22	
Ranitidine	0.22	X
Isosorbide dinitrate	0.15	X
Warfarin	0.12	X
Dipyridamole	0.11	X
Codeine	0.11	X
Triamterene/HCTZ	0.08	
Captopril	0.02	

Anticholinergic effects

- Mydriasis
  Blind as a bat
- Dry skin
  Dry as a bone
- Fever
  Hot as a hare
- Depressed/agitated mental status
  Mad as a hatter
- Flushed skin
  Red as a beet

Tune L, et al. *Am J Psychiatry*. 1992;149(10):1393-4.
Mintzer J, Burns A. *J R Soc Med.* 2000;93(9):457-62

Other Anticholinergic Medications

- Sleep medications (diphenhydramine)
- Antihistamines (diphenhydramine)
- Certain bladder medications (oxybutynin)
- Certain pain medications (codeine)
- Antiemetics/antivertigo (meclizine, scopolamine, promethazine, prochlorperazine)
- Medications for Parkinson's disease (benztropine, trihexphenidyl)
- Gastrointestinal (GI) antispasmotics (belladonna, clindinium, hyoscyamine, scopolamine)
- Tricyclic antidepressants (TCAs) (cyclobenzaprine, amitriptyline)
- Typical antipsychotics (chlorpromazine, thioridazine)
- Atypical antipsychotics (clozapine)

Mintzer J, Burns A. *J R Soc Med.* 2000;93(9):457-62.

Example: Bladder Medications

Drug	Muscarinic receptor specificity	Lipophilicity	Size	Polarity	Penetration into CNS
Darifenacin (Enablex)	M3 selective (highest)	+++	Large (507.5 g/mol)	Positive (9.20 pKa)	Low
Oxybutynin (Ditropan)	M1 and M3 selective	++++	Small (393.9 g/mol)	Neutral (6.44 pKa)	Highest
Solifenacin (Vesicare)	Primarily M3 selective	++++	Large (480.6 g/mol)	Positive (8.88 pKa)	Low
Tolterodine (Detrol)	Non-selective	++ (> 30x less than oxybutynin)	Large (475.6 g/mol)	Positive (9.87 pKa)	Low
Trospium (Sanctura)	Non-selective	+	Large (427.9 g/mol)	Positive (High) (11.05 pKa)	Low (less likely than tolterodine or oxybutynin)

CNS, central nervous system.

DrugBank. https://www.drugbank.ca/salts/DBSALT001639. Accessed November 24, 2018.; DrugBank. https://www.drugbank.ca/drugs/DB00209. Accessed November 24 2018.; Kay GG, Granville LJ. *Clin Ther*. 2005;27(1):127-38.; National Center for Biotechnology Information. https://pubchem.ncbi.nlm.nih.gov/compound/Solifenacin_succinate#section=Top.; O'Mara NB. *Pharmacist's Letter*. 2005;21(210209).; Scheife R, Takeda M. *Clin Ther*. 2005;27(2):144-53.; Yamada S, et al. *Int Neurourol J*. 2012;16(3):107-15.

Could Anticholinergic Drugs Also Be Associated With Dementia?

- Cumulative anticholinergic use is associated with an increased risk for dementia[1]
  - Most common anticholinergic classes used were TCAs, first-generation antihistamines, and bladder antimuscarinics
- Dementia associated with an increasing cholinergic activity score, particularly for antidepressant, urological, antiparkinson drugs (not GI drugs)[2]
  - This result was also observed for exposure 15-20 years before a diagnosis

1. Gray SL, et al. *JAMA Intern Med*. 2015;175(3):401-7.
2. Richardson K, et al. *BMJ*. 2018;361:k1315.

Management Strategies: Caregiving

- In 2017, 16.1 million families and other unpaid caregivers in the U.S. provided care to people with AD or other dementias
  - 18.4 billion hours of unpaid care, valued at $232.1 billion
- 59% of family caregivers rated the emotional stress of caregiving as "high" or "very high"
  - Caregivers of persons with AD have higher prevalence of depression, anxiety, and cognitive and health decline than other types of caregivers

Alzheimer's Association. *Alzheimers Dement.* 2018;14(3):367-429.;
Alzheimer's Association. Treatments. https://www.alz.org/alzheimers-dementia/treatments. Accessed November 19, 2018.;
Press D, Alexander M. Treatment of dementia. Up to Date. Updated January 16, 2018. Accessed November 18, 2018.

Management Strategies:

Non-Pharmacologic Approaches

- Compensatory techniques (e.g., memory book)
- Environmental adaptations (e.g., well-lit, quiet atmosphere)
- Case management
- Exercise programs, occupational therapy
- Psych educational/psychotherapeutic approaches, cognitive rehabilitation
- Caregiver support groups, counseling
- Alzheimer's Association
- The 36-hour day
- Respite/day care
- Advanced directives, power of attorney, living will, do not resuscitate orders, healthcare proxy

Alzheimer's Association. *Alzheimers Dement.* 2018;14(3):367-429.;
Alzheimer's Association. Treatments. https://www.alz.org/alzheimers-dementia/treatments. Accessed November 19, 2018.;
Press D, Alexander M. Treatment of dementia. Up to Date. Updated January 16, 2018. Accessed November 18, 2018.

Management Strategies: Pharmacologic Treatment of AD Symptoms

- Medications for memory
  - Acetylcholinesterase inhibitors (AChE-I's), memantine
- Treatments for behaviors
  - *Non-drug approaches*
  - Antidepressants, anxiolytics, antipsychotics **(black box)**, antiepileptic drugs
- Treatment for sleep changes
  - TCAs, benzodiazepines, sedative/hypnotics, antipsychotics **(black box)**
- Alternative treatments
  - Caprylic acid and coconut oil
  - Coenzyme Q10
  - Coral calcium
  - Ginkgo biloba
  - Huperzine A
  - Omega-3 fatty acids
  - Phosphatidylserine
  - Tramiprosate
  - Vitamin E
  - Light therapy
  - Melatonin
  - Vitamin B

Alzheimer's Association. *Alzheimers Dement.* 2018;14(3):367-429.;
Alzheimer's Association. Treatments. https://www.alz.org/alzheimers-dementia/treatments. Accessed November 19, 2018.;
Press D, Alexander M. Treatment of dementia. Up to Date. Updated January 16, 2018. Accessed November 18, 2018.;
Press D, Alexander M. Management of neuropsychiatric symptoms of dementia. Up to Date. Updated November 9, 2018. Accessed November 18, 2018.

Acetylcholinesterase Inhibitors

- Mechanism of action
  - Block acetylcholinesterase
  - Block metabolism of ACh
- Adverse effects
  - Cholinergic: SLUDGE
    - **S**ialorrhea
    - **L**acrimation
    - **U**rination
    - **D**efecation
    - **G**I (emesis, diarrhea)
    - **E**mesis
  - CNS: Headache, insomnia, vivid dreams
  - Cardiac: bradycardia, syncope, heart block, hypotension
    - Caution: drug interactions with drugs that induce bradycardia or alter AV nodal conductions
  - Other GI: anorexia, weight loss

- Contraindicated in patients with baseline bradycardia/known cardiac conduction system disease (e.g., sick sinus syndrome, incomplete heart block) due to risk of syncope, falls, and fractures

AV, atrioventricular.

Press D, Alexander M. Cholinesterase inhibitors in the treatment of dementia. Up to Date. Updated March 26, 2018. Accessed November 18, 2018.

Donepezil (Aricept)

Tablet and orally-disintegrating tablet

- Mechanism of action
  - CNS-selective AChE-I
- Indicated for mild to severe AD
- Dosing
  - 1 tablet daily at bedtime (or morning if sleep disturbance) with or without food
  - 5 mg daily for 4 to 6 weeks
  - If tolerated, increase to 10 mg daily
  - If tolerated, after 3 months, may increase to 23 mg daily
  - *5-mg, 10-mg, 23-mg daily doses are clinically effective, but some patients might derive additional benefit by dosage escalation*
  - *Evidence does not support a clinically important advantage of escalating to 23 mg and there are increased side effects and costs*
  - No dose adjustments are needed for renal or hepatic impairment
- Pharmacokinetics
  - Half-life: 72 hours
  - Metabolized by the hepatic cytochrome P450 (CYP) 2D6 and 3A4 isozymes
- Adverse effects
  - Symptomatic bradycardia can occur (related to cholinergic toxicity)
  - Rare cases of rhabdomyolysis and/or neuroleptic malignant syndrome have been reported in post-marketing surveillance

Aricept [package insert];2016.; Lexicomp, Inc. Donepezil. Updated October 31, 2018. Accessed November 19, 2018.;
Press D, Alexander M. Cholinesterase inhibitors in the treatment of dementia. Up to Date. Updated March 26, 2018. Accessed November 18, 2018.

Rivastigmine (Exelon)

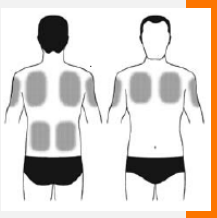
Capsule

- Mechanism of action
  - CNS-selective AChE-I
- Indicated for mild to severe AD and mild to moderate Parkinson's dementia
- Dosing
  - Usual dose: 6 to 12 mg/day given twice daily
    - Start 1.5 mg twice daily, increase by 3 mg daily every 2 weeks
- Adverse effects
  - GI disturbances (much more common than for donepezil or patch)
    - Occur mainly during dose adjustment
    - Slow titration is very important
    - One study found lower incidence of GI adverse effects when dosed off-label 3 times daily
    - *Taking with food increases AUC, decreases GI upset*
- Pharmacokinetics
  - Half-life: 2 hours
  - NOT metabolized by the CYP 2D6 and 3A4

*AUC, Area under the curve

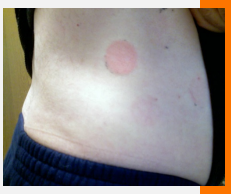
Exelon [package insert];2016.; Lexicomp, Inc. Rivastigmine. Updated November 16, 2018. Accessed November 19, 2018.;
Press D, Alexander M. Cholinesterase inhibitors in the treatment of dementia. Up to Date. Updated March 26, 2018. Accessed November 18, 2018.

Rivastigmine (Exelon)



Patch

- Mechanism of action
  - CNS-selective AChE-I
- Indicated for mild to severe AD
- Dosing/administration
  - Initial dose: 4.6 mg/24 hours
  - After a minimum of 4 weeks of treatment and if well tolerated, dose should be increased to 9.5 mg/24 hours
  - May be further increased to 13.3 mg/24 hours
  - *Use 4.6 mg/24 hours only in patients with mild to moderate hepatic impairment and in patients with low body weight (< 50 kg)*
  - *The patch has not been studied in patients with severe hepatic impairment*
  - *Poor absorption from torso and thigh than in areas indicated for use*



- Switching from capsules or oral solution:
  - < 6 mg of oral rivastigmine => Exelon patch 4.6 mg/24 hours
  - 6 to 12 mg of oral rivastigmine => Exelon patch 9.5 mg/24 hours
  - Apply the first patch on the day following the last oral dose
- Adverse effects
  - Site reactions
  - *Similar to other AChEi; Less GI upset w/ patch than rivastigmine capsules*

Exelon [package insert];2016.; Lexicomp, Inc. Rivastigmine. Updated November 16, 2018. Accessed November 19, 2018.;
Press D, Alexander M. Cholinesterase inhibitors in the treatment of dementia. Up to Date. Updated March 26, 2018. Accessed November 18, 2018.

Galantamine (Razadyne)

Tablet, extended-release capsule, solution

- Mechanism of action
  - CNS-selective AChE-I
- Indicated for mild to moderate AD
- Dosing
  - Immediate-release: 4 mg twice daily (8 mg/day) for at least 4 weeks, then 8 mg twice daily
    - May increase to 12 mg twice daily
  - Extended-release: 8 mg daily -> 16 mg daily -> 24 mg daily
  - *Should not be used in patients with end-stage renal disease or severe hepatic impairment*
    - *A maximum dose of 12 mg is advised in patients with moderate renal (CrCl 9 to 59 mL/minute) or hepatic impairment*
- Pharmacokinetics
  - Half-life: 7 hours
  - Metabolized by CYP 2D6 and 3A4

CrCl, creatinine clearance.

Lexicomp, Inc. Galantamine. Updated October 31, 2018. Accessed November 19, 2018.; Press D, Alexander M. Cholinesterase inhibitors in the treatment of dementia. Up to Date. Updated March 26, 2018. Accessed November 18, 2018.; Razadyne/Razadyne ER [package insert];2018.

Acetylcholinesterase Inhibitors: Tips

- Discontinue other agents with anticholinergic effects
- Selection is based on ease of use, individual tolerability, cost and clinician/patient preference
- In one trial, rates of discontinuation were similar for all 3 drugs in this class
  - Donepezil was most likely to be titrated to max dose and least likely to be discontinued due to cost
  - Other studies have found higher rates of discontinuation for rivastigmine
  - Donepezil seems less likely to cause GI adverse effects and more likely to cause sleep disturbances than other drugs in this class
- Initiate AChE-I and monitor for side effects
  - Reduce dosage or discontinue if side effects are intolerable
  - Consider switching agents if intolerant to one agent
  - If sleep disturbance, move dosing to morning
  - If nausea, take with food or at bedtime
- Monitor efficacy by caregiver report, quantified mental status examination, effects on ADLs, or effects on behavior

Press D, Alexander M. Cholinesterase inhibitors in the treatment of dementia. Up to Date. Updated March 26, 2018. Accessed November 18, 2018.

Memantine (Namenda)

Tablet, extended-release capsule, oral solution

- Mechanism of action
  - NMDA receptor antagonist
- Approved for moderate to severe stages of AD
- Abnormal glutamate activity is thought to lead to sustained low-level activation of NMDA receptors, resulting in neuronal damage and loss, and cholinergic deficit
  - Under normal physiologic conditions, the NMDA receptor ion channel is blocked by magnesium ions, which are displaced after agonist-induced depolarization
  - Pathologic or excessive receptor activation, as postulated to occur during AD, prevents magnesium from re-entering and blocking the channel pore, resulting in a chronically open state and excessive calcium influx
  - Memantine binds to the intra-pore magnesium site, but with longer dwell time, and functions as an effective receptor blocker only under conditions of excessive stimulation
    - Memantine does not affect normal neurotransmission and blocks the influx of calcium ions

Lexicomp, Inc. Memantine. Updated October 27, 2018. Accessed November 19, 2018.

NMDA, N-methyl-D-aspartate.

Memantine (Namenda)

- Pharmacokinetics
  - T_{max} = 3-7 hours
  - Food has no effect
  - Half-life: 60-80 hours
  - Metabolism is primarily independent of CYP isozymes
    - Clearance is significantly reduced by alkaline urine
      - *Use caution with medications, dietary changes, or patient conditions that may alter urine pH*
- Cautions
  - Use with caution in patients with a history of seizure disorder: may increase risk of seizures
  - Use with caution in patients with cardiovascular disease: although adverse cardiac events were infrequent in clinical trials, an increased incidence of cardiac failure, angina, bradycardia, and hypertension (compared with placebo) was observed

Lexicomp, Inc. Memantine. Updated October 27, 2018. Accessed November 19, 2018.

Memantine: Dosing

- Immediate release (IR)
  - Starting dose is 5 mg daily
  - Target dose is 20 mg daily
  - 5 mg/week dose titration
  - *Doses above 5 mg should be given twice daily*
- Extended release (ER)
  - Starting dose is 7 mg once daily
  - Increase dose by 7 mg daily to a target maximum dose of 28 mg once daily
  - *Wait at least 1 week between dosage changes (if previous dose well tolerated)*
- When switching from IR product to the ER product, begin the ER product the day after the last dose of the IR product
  - Patients on IR 10 mg twice daily should be switched to ER 28 mg once daily
- In patients with renal impairment (CrCl 5-29 mL/minute)
  - IR: start 5 mg once daily; after at least 1 week of therapy and if tolerated, may titrate up to a target dose of 5 mg twice daily
  - ER: target dose of 14 mg once daily

Lexicomp, Inc. Memantine. Updated October 27, 2018. Accessed November 19, 2018.

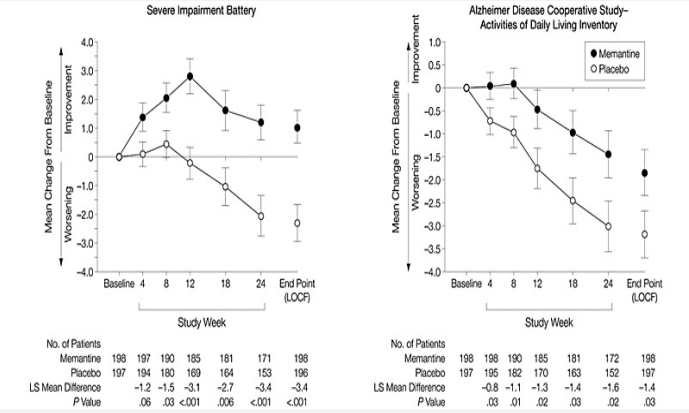
Memantine: Adverse Reactions

Body system	Adverse reaction*	Incidence	Placebo incidence
Cardiovascular	Hypertension	4%	2%
	Hypotension	2%	1%
CNS	Aggressive behavior	2%	1%
	Anxiety	4%	3%
	Confusion	6%	5%
	Depression	3%	1%
	Dizziness	5%-7%	1%
	Drowsiness	3%	1%-2%
	Fatigue	2%	1%
	Hallucination	3%	2%
	Headache	6%	3%-5%
	Pain	3%	1%
Endocrine & metabolic	Weight gain	3%	1%
GI	Abdominal pain	2%	1%
	Constipation	3%-5%	1%-3%
	Diarrhea	5%	4%
	Vomiting	2%-3%	1%-2%
Genitourinary	Urinary incontinence	2%	1%
Infection	Influenza	4%	3%
Neuromuscular & skeletal	Back pain	3%	1%-2%
Respiratory	Cough	4%	3%
	Dyspnea	2%	1%

*, incidence < 10%; ª, observed with extended-release product.

Clinical Drug Information LLC. Drug Facts and Comparisons: Memantine. Updated August 1, 2018. Accessed November 19, 2018.

Memantine/Placebo in Patients Receiving Donepezil



Tariot PN, et al. *JAMA*. 2004;291(3):317-24.

Namzaric (Memantine ER + Donepezil)

- Indicated to be taken in the evening, with or without food
- Do not divide/chew/crush
- Available dosage forms
  - 7 mg memantine ER/10 mg donepezil
  - 14 mg memantine ER/10 mg donepezil
  - 21 mg memantine ER/10 mg donepezil
  - 28 mg memantine ER/10 mg donepezil

- *Patients must be stable on donepezil 10 mg before starting this combination*
  - *Patients will need to be titrated up to donepezil 10 mg to be eligible for this combination*

Clinical Drug Information LLC. Drug Facts and Comparisons: Memantine and donepezil. Updated October 31, 2018. Accessed November 19, 2018.

AWP of AD Medications

Drug Formulation	Dosage units/day	AWP/day
Aricept 5 mg tab	1	$20.24
Aricept 10 mg tab	1	$20.24
Aricept 23 mg tab	1	$18.10
Donepezil 5 mg tab	1	$0.11-$8.66
Donepezil 10 mg tab	1	$0.11-$8.66
Donepezil 23 mg tab	1	$10.41-$11.36
Donepezil ODT 5 mg tab	1	$7.79-$8.66
Donepezil ODT 10 mg tab	1	$7.79-8.66
Exelon 4.6 mg/24 hours patch	1	$25.88
Exelon 9.5 mg/24 hours patch	1	$25.88
Exelon 13.3 mg/24 hours patch	1	$25.88
Rivastigmine 4.6 mg/24 hours patch	1	$16.20-$16.90
Rivastigmine 9.5 mg/24 hours patch	1	$16.20-$16.90
Rivastigmine 13.3 mg/24 hours patch	1	$16.20-$16.90
Rivastigmine 1.5 mg cap	2	$1.40-$9.32
Rivastigmine 3 mg cap	2	$1.40-$9.33
Rivastigmine 4.5 mg cap	2	$1.40-$9.34
Rivastigmine 6 mg cap	2	$1.40-$9.35
Razadyne 4 mg tab	2	$12.80
Razadyne 8 mg tab	2	$12.80
Razadyne 12 mg tab	2	$12.80
Galantamine 4 mg tab	2	$6.10-$6.36
Galantamine 8 mg tab	2	$6.10-$6.36
Galantamine 12 mg tab	2	$6.10-$6.36
Galantamine 4 mg/ml solution	2-6	$7.50-$22.50
Razadyne 8 mg ER cap	1	$12.81
Razadyne 16 mg ER cap	1	$12.81
Razadyne 24 mg ER cap	1	$12.81
Galantamine 8 mg ER cap	1	$6.10-$6.36
Galantamine 16 mg ER cap	1	$6.10-$6.37
Galantamine 24 mg ER cap	1	$6.10-$6.38

Drug Formulation	Dosage units/day	AWP/day
Namenda Titration Pack	1 - 2	$8.89-$17.78
Memantine Titration Pack	1 - 2	$6.10-$12.20
Namenda 5 mg tab	1 - 2	$8.90-$17.78
Namenda 10 mg tab	1 - 2	$8.90-$17.78
Memantine 5 mg tab	1 - 2	$6.09-$12.20
Memantine 10 mg tab	1 - 2	$6.09-$12.20
Memantine 2 mg/ml soln	2.5 - 10	$4.40 - $20.50
Namenda XR titration Pack	1	$16.98
Namenda XR 7 mg cap	1	$16.98
Namenda XR 14 mg cap	1	$16.98
Namenda XR 21 mg cap	1	$16.98
Namenda XR 28 mg cap	1	$16.98
Memantine ER 7 mg cap	1	$15.26-$15.28
Memantine ER 7 mg cap	1	$15.26-$15.29
Memantine ER 7 mg cap	1	$15.26-$15.30
Memantine ER 7 mg cap	1	$15.26-$15.31
Namzaric Titration Pack (Memantine (7/14/21/28 mg and Donepezil 10 mg)	1	$16.90
Namzaric 7-10 mg	1	$16.90
Namzaric 14-10mg	1	$16.90
Namzaric 21-10 mg	1	$16.90
Namzaric 28010 mg	1	$16.90

Clinical Drug Information LLC. Drug Facts and Comparisons: Memantine and donepezil. Updated October 31, 2018. Accessed November 19, 2018.;
Lexicomp, Inc. Donepezil. Updated October 31, 2018. Accessed November 19, 2018.;
Lexicomp, Inc. Galantamine. Updated October 31, 2018. Accessed November 19, 2018.;
Lexicomp, Inc. Memantine. Updated October 27, 2018. Accessed November 19, 2018.;
Lexicomp, Inc. Rivastigmine. Updated November 16, 2018. Accessed November 19, 2018.

Management of Confusion, Agitation, and Behaviors

- Assess pain, aggression, delusions, delirium, depression, hallucinations, paranoia, wandering, apathy, anxiety, sleep, disinhibition
- Pharmacological interventions
  - Treatments for behaviors
    - *Non-drug approaches*
    - Antidepressants, anxiolytics, antipsychotics, antiepileptic drugs
  - Treatments for sleep changes
    - TCAs, benzodiazepines, sedative/hypnotics, antipsychotics
  - *Avoid anticholinergic, benzodiazepines, sedative/hypnotics*
    - Chronic use of sedatives and psychoactive agents in the confused patient should be avoided unless persistent extreme agitation hampers care
  - Antipsychotics black box warning (2004):
    - Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death
      - Consistent across all antipsychotics (3.5% vs 2.3% placebo; NNH = 83; NNT = 5-14; for every 9-25 helped, 1 death)
    - Use the lowest possible doses and treat for the shortest time possible
    - Consider anticholinergic, EPS/TD, metabolic, sedation, orthostasis cerebrovascular, and cardiovascular side effects

Iowa Geriatric Education Center. IA-ADAPT. https://igec.uiowa.edu/ia-adapt. Accessed November 18, 2018.
Press D, Alexander M. Management of neuropsychiatric symptoms of dementia. Up to Date. Updated November 9, 2018. Accessed November 18, 2018.

EPS, extrapyramidal symptoms; NNH, number needed to harm; NNT, number needed to treat; TD, tardive dyskinesia.

Additional Antipsychotics: Adverse Effects

Antipsychotic	Sedation	EPS	Anticholinergic	Orthostasis	Weight gain	Prolactin
Aripiprazole	+	+	+	+	+	+
Asenapine	+	++	+/-	++	+	+
Chlopromazine	++++	+++	+++	++++	++	+++
Clozapine	++++	+	++++	++++	++++	+
Fluphenazine	+	++++	+	+	+	++++
Haloperidol	+	++++	+	+	+	++++
Iloperidone	+	+/-	++	+++	++	+
Olanzapine	++	++	++	++	++++	+
Palperidone	+	++	+	++	++	++++
Perphenazine	++	++++	++	+	+	++++
Quetiapine	++	+	+	++	++	+
Risperidone	+	++	+	++	++	++++
Thioridazine	++++	+++	++++	++++	+	+++
Thiothixene	+	++++	+	+	+	++++
Ziprasidone	++	++	+	+	+	+

Crismon M, et al. In Dipiro JT, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach.* 9th ed.; 2014.

Management of Confusion, Agitation, and Behaviors: Non-Pharmacological Approaches

- Provide structure and routine
- Follow regular, predictable routines
- Encourage pleasant activities that the person knows and enjoys
- Participate in activities that patient has enjoyed in the past
- Keep things simple
- Break down complex tasks into many small, simple steps that the person can handle

Redirect, distract, be flexible, soothe, reassure

Alexopoulos GS, et al. *Postgrad Med Special Report.* 1998;April:1-88.;
Iowa Geriatric Education Center. IA-ADAPT. https://igec.uiowa.edu/ia-adapt. Accessed November 18, 2018.;
Press D, Alexander M. Management of neuropsychiatric symptoms of dementia. Up to Date. Updated November 9, 2018. Accessed November 18, 2018.

How to Find Clinical Trials

- U.S. National Library of Medicine database: https://www.clinicaltrials.gov
- TrialMatch service: https://www.alz.org/alzheimers-dementia/research_progress/clinical-trials/about-clinical-trials

Emerging Therapies

- Agents that enhance cholinesterase inhibitors
  - Serotonergic drugs
  - Histamine antagonists
- Riluzole, a small molecule glutamatergic agent, is FDA-approved for the treatment of amyotrophic lateral sclerosis and is currently under investigation for the treatment of early AD

Ferreira-Vieira TH, et al. *Curr Neuropharmacol*. 2016;14(1):101-15.;
Wang R, Reddy H. *J Alzheimers Dis*. 2017;57(4):1041-8.

FDA, U.S. Food & Drug Administration.

Emerging Therapies

- Antisense technology
  - Evidence indicates that protein misfolding is a disease characteristic in the development and progression of AD
  - One agent currently under investigation addresses protein misfolding with consideration of its prion-like disease progression
    - Based on antisense technology, IONIS-MAPTRX, has been engineered to bind to mRNA and reduce tau protein production in the brain
    - This agent is currently in clinical trials to determine its safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with mild AD

CCDR Highlights. *Canadian Family Physician*. 2015;61:692.;
Ionis Pharmaceuticals. Pipeline. http://www.ionispharma.com/pipeline/. Accessed August 3, 2018.

Emerging Therapies

- Anti-inflammatory agents
  - Neuroinflammation leads to:
    - β-amyloid aggregate formation
    - Hyperphosphorylation of the tau protein
    - Neuronal damage/ neuronal death
- In AD, factors normally involved with inflammatory processes become hyper-reactive leading to changes in the immediate environment of the β-amyloid plaques
  - Changes in morphology in AD engage multiple processes including synaptic dysfunction, homeostatic imbalances, neurovascular dysfunction, changes in the normal three-dimensional network, and blood brain barrier dysfunction
  - Studies have shown no clinical impact in AD
- Some of the agents in clinical trials include TNF-α inhibitors, microglia inhibitors, PPAR gamma antagonists, agents used in the treatment of diabetes, and statins

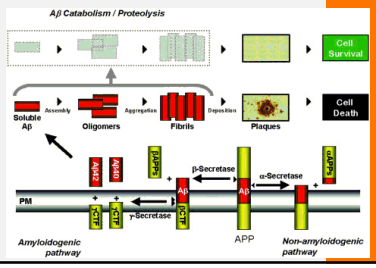
Ardura-Fabregat A, et al. *CNS Drugs.*2017;31(12):1057-82.; Bronzuloi MR, et al. *J Inflamm Res.* 2016;9:199-208.

PPAR, peroxisome proliferator-activated receptors; TNF, tumor necrosis factor.

Emerging Therapies

- Drugs affecting the amyloid pathway
  - Monoclonal antibodies: aducanumab, solanezumab, crenezumab, and gantenerumab
  - Bace1 inhibitors: initial studies in mice revealed significant reductions in the production of β-amyloid plaques when BACE1 deficiency was produced
    - Due to the development of liver toxicity, some BACE1 inhibitor agents have failed in clinical studies
    - Agents currently under investigation include: elenbecestat, lanabecestat, CNP250, JNJ-54861911, and verubecestat
  - Gamma-secretase inhibitors

Biogen. Media release. https://www.businesswire.com/news/home/20171221005195/en/Adaptive-Phase-II-Study-BAN2401-Early-Alzheimer's. Published December 21, 2018. Accessed August 3, 2018.; Endpoints news. Media release. https://endpts.com/roche-is-bringing-back-gantenerumab-from-the-dead-taking-another-stab-at-alzheimers-phiii/. Published March 7, 2017. Accessed August 3, 2018.; Gamage KK, Kumar S. *J Neurosci.* 2017;37(17):4430-2.; Jacobsen JS, et al. *NeuroRx.* 2005;2(4):612-26.; Kastanenka K, et al. *J Neurosci.* 2016;36(50):12549-58.; Merck. Media release. http://investors.merck.com/news/press-release-details/2017/Merck-Announces-EPOCH-Study-of-Verubecestat-for-the-Treatment-of-People-with-Mild-to-Moderate-Alzheimers-Disease-to-Stop-for-Lack-of-Efficacy/. Published February 14, 2017. Accessed August 3, 2018.; Ostrowitzki S, et al. *Arch Neurol.* 2012;69(2):198-207.; Roche Pharmaceuticals. Media release. https://www.roche.com/investors/updates/inv-update-2014-07-16.htm. Published July 16, 2014. Accessed August 3, 2018.; Siemers ER, et al. *Alzheimers Dementia.* 2016:12(2):110-20.; U.S. National Library of Medicine. Clinical trials database. https://www.clinicaltrials.gov/ct2/home. Accessed August 3, 2018.; Yan R. *Transl Neurodegener.* 2016;5:13.



Emerging Therapies

- Drugs affecting tau aggregates
  - Stabilize the structural formation of the intracellular microtubules
  - Prevent tau aggregates by introducing tau aggregation inhibitors
  - Enhance the clearance of phosphorylated-tau by the use of active immunotherapy
- Research in this area is ongoing
  - Many agents tested in clinical trials have either failed to meet endpoints and are associated with serious adverse events or have not yet reached advanced stages of clinical study

Yan R. *Transl Neurodegener.* 2016;5:13.

Emerging Therapies

- RAGE inhibitor
  - Inhibits a receptor protein that is thought to be involved in the development of AD: the receptor for advanced glycation endproducts (RAGE)
  - RAGE is a family of proteins present on the surface of several types of cells in the brain
    - It has several partner proteins, one of which is the advanced glycation endproduct (AGE)
    - Accumulation of AGE in cells and tissues occurs naturally during aging but is accelerated in AD
- Azeliragon
  - In April 2018, the Steadfast trial was terminated due to failure to meet its co-primary endpoint

Alzforum. Therapeutics: azeliragon. https://www.alzforum.org/therapeutics/azeliragon. Accessed November 18, 2018.

Role of Managed Care Pharmacists in AD

- Current direct costs of AD in the U.S. are estimated to be $172 to $200 billion annually
  - Predicted to increase to $1.1 trillion annually by 2050
- $341,840 is the estimated lifetime cost for an individual living with dementia
- A treatment that slows the rate of functional decline would reduce the average per-person lifetime costs by $4122 (2017 USD)
- A treatment reducing behavioral/psychological symptoms by 10% would reduce average per-person lifetime costs by $722 (2017 USD)
- A treatment introduced in 2025 that delays the onset of AD by 5 years would reduce total healthcare payments by 33% and out-of-pocket payments by 44% in 2050
- For individuals aged 70 years and older in 2050, delaying onset by 1, 3, or 5 years would lead to 14%, 27%, or 39% decreases in total healthcare payments

Average Annual Per-Person Payments for Health Care and Long-Term Care Services Provided to Medicare Beneficiaries Age 65 and Older, with and without Alzheimer's or Other Dementias, in 2017 Dollars

Service	Beneficiaries with Alzheimer's or Other Dementias	Beneficiaries without Alzheimer's or Other Dementias
Inpatient hospital	$10,862	$3,509
Medical provider*	5,729	3,569
Skilled nursing facility	6,750	462
Nursing home	15,462	749
Hospice	2,017	153
Home health care	2,525	367
Prescription medications†	3,436	2,947

*"Medical provider" includes physician, other medical provider and laboratory services, and medical equipment and supplies.

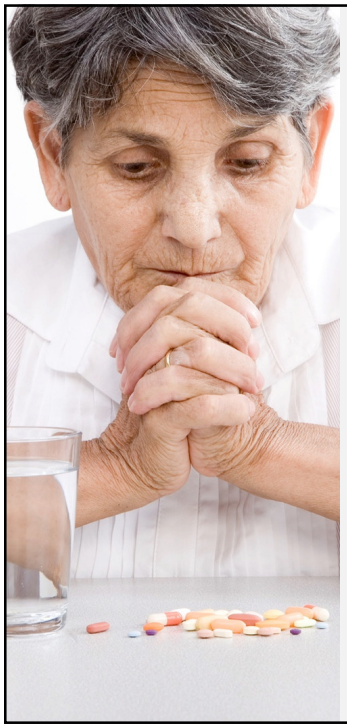
†Information on payments for prescription medications is only available for people who were living in the community, that is, not in a nursing home or an assisted living facility.

Created from unpublished data from the Medicare Current Beneficiary Survey for 2011.[427]

Alzheimer's Association. *Alzheimers Dement.* 2018;14(3):367-429.; Hebert L, et al. *Neurology*. 2013:80(19):1778-83.

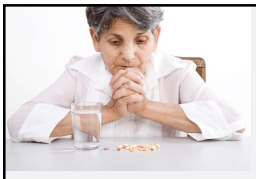
Role of Managed Care Pharmacists in AD

- Pharmacists participate in therapeutic decisions in AD, medication therapy management, disease state management programs, formulary management, adherence monitoring, and the institution of practices and processes that detect unsafe medicines to ensure patient safety
  - Prior authorization processes
  - Appropriate first-line and alternative treatments for large patient populations
  - "Criteria for use" for newly approved pharmacologic agents, particularly if there are concerns regarding cost
- The role of the managed care pharmacist is especially important in AD
  - Several investigational agents are currently under development that may significantly influence the standard of care and impact costs



Question & Answer

Please enter your questions in the *Ask a Question* area of you player



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- Also, in about 45 minutes, you will receive an e-mail with a link to the post-test and evaluation
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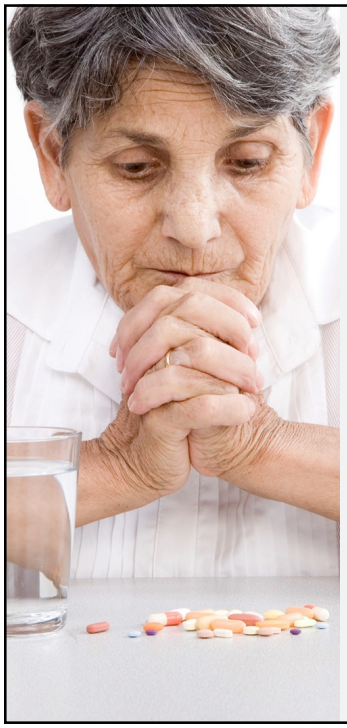

Thank You!