Alzheimer's Disease and Dementia Treatment Update
Marketa Marvanova, PharmD, PhD, BCGP, BCPP, FASCP
Dean and Professor
Pacific University School of Pharmacy, Hillsboro, Oregon
OSHP Annual Seminar 2023
April 22, 2023

Disclosure

• Dr. Marvanova has no relevant financial relationships with ineligible companies to disclose.

• None of the planners for this activity have relevant financial relationships to disclose with ineligible companies.

Learning Objectives

1. Define dementia and Alzheimer’s disease and be familiar with the major pathological hallmarks of Alzheimer’s disease.
2. Understand Alzheimer’s disease continuum and clinical presentation and treatment goals.
3. Know currently available medications and their formulations for management of Alzheimer’s disease and their place in therapy
4. Compare and contrast newly FDA-approved disease modifying therapies, aducanumab and lecanemab.
5. Given a specific clinical scenario, recommend appropriate treatment plan.
Pre-Test Question 1 and Answers

Which of the following is the major pathological hallmark of Alzheimer’s disease?

A. Lewy bodies
B. Apolipoprotein E inclusions
C. Beta amyloid plaques
D. Hypo-phosphorylated tau

Pre-Test Question 2

Which of the following represents a general phase in the Alzheimer’s disease continuum characterized by presence of cognitive impairment that does not impact individual function?

A. Preclinical Alzheimer’s disease
B. Mild cognitive impairment
C. Mild dementia due to Alzheimer’s disease
D. Radiographic Alzheimer’s disease

Pre-Test Question 3

Which of the following is true about donepezil?

A. It modifies disease progression and disease biology
B. It cannot be combined with memantine due to safety issues
C. It can be safely used in individuals with bradycardia and heart block
D. It is available in a weekly patch formulation
Pre-Test Question 4

Which of the following is true about lecanemab?

A. It has high affinity to insoluble fibril and plaques and minimal no affinity to protofibrils
B. It is administered as 10 mg/kg once monthly IV infusion after a baseline MRI
C. It demonstrated ability to significantly reduce cognitive and functional decline compared to placebo
D. The risk of ARIA associated with edema and/or hemorrhage seems higher than with aducanumab

Pre-Test Question 5

• A 75-year-old individual was just diagnosed with moderate AD dementia. She and her spouse inquired about treatment options to manage the disorder. She no longer denies her issues with memory. She is no longer able to manage the household and feels a loss of independence.
• PMH: hemorrhagic stroke, diabetes, hypertension, and in the past 12 months she experienced 2 transients ischemic attacks, active peptic ulcer disease
• VS: BP 130/89 mm Hg, HR 59 bpm, respiratory rate 14 bpm

Which of the following would be the most appropriate recommendation for her at this time?

A. Memantine  B. Donepezil  C. Aducanumab  D. Lecanemab

Longitudinal Case: Meet Mary

Mary is a 57-year-old married female currently employed as a kindergarten teacher.
• She complains of recent insomnia, fatigue, increased appetite, weight gain, increased guilt, and no longer enjoys her gardening or playing piano. This has persisted for the past 2 months. In addition, she started experiencing some difficulty with concentration and memory and noticed it takes her longer to plan her teaching lessons and feels like she thinks slower.
• PHM: hypertension, hyperlipidemia, and overactive bladder
• VS: 135/85 mm Hg; RR 14 bpm, HR 72 bpm; BMI 29.5 kg/m²
• Current medications:
  • Diphenhydramine 25 mg PO qhs; Lisinopril 10 mg PO once daily; Atorvastatin 20 PO mg once daily; Oxybutynin 3.9 mg/day patch twice weekly
**DEMENTIA**
Major Neurocognitive Disorder

a clinical syndrome = spectrum of brain disorders or conditions represented by decline in COGNITION with significant impact on function

- Cognitive impairment/decline interferes with functioning:
  1. Instrumental activities of daily living (IADL)
  2. Activities of daily living (ADL)

Different etiologies and clinical presentation

**IRREVERSIBLE**
- Alzheimer’s disease (AD)
- Vascular dementia (VaD)
- Dementia with Lewy bodies (DLB)
- Parkinson’s disease dementia (PDD)
- Frontotemporal dementia (FTD)
- Creutzfeldt-Jakob Disease (CJD)

**REVERSIBLE**
- Normal pressure hydrocephalus (NPH)
- Medical conditions including depression (pseudodementia), hypothyroidism, anemia
- Medication-induced cognitive impairment
- Vitamin B deficiencies (B1, B12, folic acid)

Alzheimer’s Disease (AD)

- Chronic IRREVERSIBLE neurodegenerative disorder with progressive clinical course:
  - AD tends to develop slowly and gradually worsens over several years
  - Eventually, AD pathology affects most brain areas
- AD affects at least 6.5 million Americans aged 65 years and older
  - Every 65 seconds, a new person develops AD in the U.S.
  - The 6th leading cause of death in the U.S.
- Prevalence of sporadic AD increases with advanced age
**AD Pathological Hallmarks: Primary Hypothesis**

**A)** Beta-amyloid (Aβ) plaques
- Extracellular location
- Amyloid precursor protein (APP) cleavage patterns by secretases
- Aβ 1-42 easily aggregate
  - Monomers (soluble)
  - Oligomers (soluble)
  - Protofibrils (soluble)
  - Fibrils (insoluble)

**B)** Tau tangles (neurofibrillary tangles)
- Intracellular location
- Hyper-phosphorylation of tau
- Decrease affinity to microtubules
- Aggregation and deposits in cytosol

**AD Continuum and Clinical Course**

<table>
<thead>
<tr>
<th>Preclinical AD</th>
<th>MCI due to AD</th>
<th>Mild Dementia due to AD</th>
<th>Moderate Dementia due to AD</th>
<th>Severe Dementia due to AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No noticeable symptoms</td>
<td>Very mild cognitive symptoms that do not interfere with memory, activities and function preserved</td>
<td>Early stage AD</td>
<td>Moderate stage AD</td>
<td>Severe stage AD</td>
</tr>
<tr>
<td>Functions relatively independent; may feel if it's or isn't getting memory better</td>
<td>Cognitive symptoms are more pronounced impacting ADLs and may require assistance</td>
<td>Problems with memory and thinking begin to impact IADL</td>
<td>Symptoms interfere with usual everyday activities and need for 24/7 care</td>
<td>Inability to interact with the environment; Movement and communication becomes difficult</td>
</tr>
</tbody>
</table>

**AD Treatment Management Intro**

- AD is a growing public health emergency
- Since age is the biggest risk for AD development and we expect the older adult population to grow
  - AD will potentially affect up to 13.8 million people by 2060
- Terminal diagnosis: **NO CURE AVAILABLE**
- Survival from onset: ~8-12 years (5-20 years)

- What treatment/management options do we have at this time?
Longitudinal Case: Continuation 1

Mary is very happy to learn that her cognitive impairment was not caused due to AD but to her current medications and presence of moderate depression.

She reads and hears a lot about Alzheimer’s disease on social media and is afraid of getting it. She inquires about anything now she could do to potentially decrease her risk and is willing to buy any herbal or nutritional supplements that might be recommended for prevention.

- PHM: hypertension, hyperlipidemia, overactive bladder, and depression
- VS: 135/85 mm Hg; RR 14 bpm, HR 72 bpm, BMI 29.5 kg/m²

Can We Prevent/Delayed Sporadic AD?

- Hypertension, diabetes and dyslipidemia
- Smoking and excessive alcohol consumption
- Sedentary life-style and excess body weight/obesity
- Education (cognitive reserve)

AD Pharmacotherapy and Goals

1. **Disease modifying therapy** (amyloid beta-directed antibody)
   - **Goal:** AD biology modification and slow down the disease progression

2. **Symptomatic improvement of core cognitive symptoms** (acetylcholinesterase inhibitors and NMDA receptor antagonist)
   - **Goal:** cognitive symptoms improvement or stabilization without AD biology modification

3. **Symptomatic improvement of core non-cognitive symptoms** (behavioral and psychiatric symptoms of dementia; BPSD)
   - Acetylcholinesterase inhibitors (i.e., galantamine, rivastigmine, donepezil)
   - NMDA receptor antagonist (i.e., memantine)
   - Select psychostimulatory medications (e.g., antidepressants, antipsychotics)
**Longitudinal Case: Continuation 2**

Mary is now 69-year-old and recently retired. She reports starting to have some issues with recalling recent events but compensates by writing notes. She also has issues misplacing of her glasses and getting lost more easily in known places. She is trying to hide these issues but she more often makes mistakes in payments, shopping and medication management that her husband has noticed. She was seen by her physician, underwent neuropsychiatric testing and was diagnosed with mild AD dementia with MMSE of 22/30.

- PH: hypertension, hyperlipidemia, depression, and overactive bladder
- VS: 126/85 mm Hg; RR 14 bpm, HR 74 bpm, BMI 27 kg/m²
- Current medications:
  - Lisinopril 10 mg once daily; Atorvastatin 20 PO mg once daily; Mirabegron 50 mg PO once daily

**Disease Modifying Treatment: Amyloid Beta-Directed Antibody**

Major Neurocognitive Disorder (Dementia) due to AD

<table>
<thead>
<tr>
<th>Predilection</th>
<th>MCI due to AD</th>
<th>MCI due to AD</th>
<th>Moderate Dementia due to AD</th>
<th>Severe Dementia due to AD</th>
</tr>
</thead>
</table>

MCI=mild cognitive impairment

**Monoclonal Antibodies (Accelerated FDA Approval)**

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Target</th>
<th>Administration</th>
<th>Efficacy</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aducanumab</td>
<td>4-1G10</td>
<td>IV xig weekly</td>
<td>↓ Aβ in CSF 15% and parenchyma</td>
<td>All-cause mortality and ARIA-E, ARIA-H, and ARIA-N</td>
</tr>
<tr>
<td>Lecanemab</td>
<td>L10A</td>
<td>SC xig bimonthly</td>
<td>↓ Aβ in CSF, CSF tau, and tau aggregates</td>
<td>ARIA-E, ARIA-H, and ARIA-N</td>
</tr>
<tr>
<td>Leqembi</td>
<td>A3B3</td>
<td>SC xig bimonthly</td>
<td>↓ Aβ in CSF</td>
<td>ARIA-E, ARIA-H, and ARIA-N</td>
</tr>
</tbody>
</table>

Acute reactions: headache, injection site reaction and pain, flu-like symptoms, nasopharyngitis, diarrhea, increased blood creatine kinase, and parosmia.

Adverse reactions: urinary tract infection, constipation, respiratory tract infections, anxiety, and constipation.

The incidence of ARIA-E, ARIA-H, and ARIA-N were lower in Leqembi (13.5% and 17.0%) vs. Aducanumab (15.5% and 19.6%).
Clarity AD: A Study to Confirm Safety and Efficacy of Lecanemab in Participants With Early Alzheimer’s Disease

- N=1,795 individuals (lecanemab arm N=898/placebo arm N=897) randomized to receive IV lecanemab 10 mg/kg biweekly or placebo for 18 months [core study] and up to 60 months (extension)
- Inclusion criteria similar to previous Phase 2 study:
  - Males or females aged 50-85 years who meet the National Institute of Aging - Alzheimer’s Association (NIA-AA) core clinical criteria for MCI due to AD - intermediate likelihood or probable AD dementia
  - Objective impairment in episodic memory (at least 1 SD below age-adjusted mean in the Wechsler Memory Scale - IV Logical Memory II)
  - Positive for brain amyloid load validated by PET or CSF
  - Global Clinical Dementia Rating (CDR) score of 0.5 to 1.0
  - CSF Aβ1-42 level below 100 ng/mL
- Exclusion criteria:
  - Concomitant use of anticoagulants or other medications known to interfere with CYP450 enzymes
  - Known history of acute or chronic infection
  - Known history of cancer

Clarity AD confirmatory Phase 3 study results:
- Compared to placebo, lecanemab (10 mg/kg biweekly) produced significant slowing of clinical (CDR-SB, -0.45 points; 27%), cognitive (ADAS-Cog, -1.44 points; 29%) and functional (ADAS-Cog, +2.0 points; 27%) decline
- 280 subjects receiving lecanemab showed significant increases in mean CBF 642 levels at 18 months (+282 pg/mL) compared to baseline. No significant changes were noted with placebo-treated subjects.
- Brain amyloid reduction by an average of 72% compared to baseline in a sub-study of 658 individuals

What is Next Regarding Disease-Modifying Treatment?

- Despite the FDA-approvals, use of aducanumab and lecanemab, access to care continues to be an issue
- New agents in development (e.g., donanemab, crenezumab, solanezumab)
- Several studies are ongoing with aducanumab and lecanemab
  1. Underway: Clarity AD Open Label Extension: Comparing lecanemab 10 mg/kg biweekly administered as IV infusion to 720 mg weekly administered as subcutaneous injection
  2. Underway: A Study to Evaluate Safety and Tolerability of Aducanumab in Participants with Alzheimer’s Disease Who Previously Participated in the Aducanumab Studies 221AD205, 221AD301, 221AD302, 221AD303, 221AD304
  3. Currently recruiting: AHEAD 3-45 Study: A Study to Evaluate Efficacy and Safety of Treatment With Lecanemab in Participants With Preclinical Alzheimer’s Disease and Elevated Amyloid and Also in Participants With Early Preclinical Alzheimer’s Disease and Intermediate Amyloid
  - IV lecanemab: 5 mg/kg every 2 weeks from week 0 to 8, then 10 mg/kg every 2 weeks from weeks 8 to 54, then every 4 weeks from week 56 to 216
  - Subcutaneous lecanemab: 5 mg/kg every 4 weeks from week 0 to 4, then 10 mg/kg, administered as IV infusion, every 4 weeks from week 8 to 216

Appropriate Use Recommendations of Lecanemab and Aducanumab

- Indication/Diagnosis: Clinical criteria for MCI due to AD or mild dementia due to AD
- Amyloid status: Amyloid positive PET or CSF findings consistent with AD
- Genetic testing: ApoE genotyping should be discussed and preference should be assessed. Most clinicians will recommend testing prior to use
- Concomitant medications: ACHEIs are allowed
- Exclusion (examples): Patients on anticoagulants or evidence of acute or subacute hemorrhage, macrohemorrhage, cortical or lacunar infarction (>1.5 cm) (baseline MRI)
- Follow-up scans/labs: Requires recent (within one year) brain MRI prior to initiating treatment and periodic monitoring with MRI
Symptomatic Treatment: AChEIs and NMDA Receptor Antagonist

Major Neurocognitive Disorder (Dementia) due to AD

<table>
<thead>
<tr>
<th>Predilection AD</th>
<th>MCI due to AD</th>
<th>Moderate AD</th>
<th>Severe AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Rivastigmine</td>
<td>Galantamine</td>
<td>Namenda</td>
</tr>
<tr>
<td>ER/donepezil</td>
<td></td>
<td></td>
<td>Memantine</td>
</tr>
</tbody>
</table>

MCI=mild cognitive impairment

Exelon
Rivastigmine
Galantamine
Razadyne
Namenda
Memantine
Donepezil
Lexicomp

Aduhelm Prescribing

MCI=mild

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269s000lbl.pdf.

Aduhelm

Mary decides not to pursue the currently FDA-approved disease modifying treatment due to difficulty obtaining the treatment as well as the cost and uncertainty of its efficacy and long-term benefits. She is also a homozygous carrier of APOE4 allele and her risk for ARIA is significantly higher.

She inquires what other options she has.

Longitudinal Case: Continuation 3

FDA-Approved AD Symptomatic Treatment

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand/ Formulations</th>
<th>Frequency</th>
<th>Dosage/Day</th>
<th>Therapeutic</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Aricept Aricept ODT Aricept patch</td>
<td>Daily/4hrs</td>
<td>10 mg/23 mg</td>
<td>Most commonly prescribed</td>
<td>Memantine ER/donepezil capsule cannot be opened and the contents sprinkled on an amount of pudding or applesauce</td>
</tr>
<tr>
<td>Memantine ER / Donepezil</td>
<td>Namenda</td>
<td>Daily</td>
<td>28 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Exelon Exelon sol. Exelon patch</td>
<td>BID (AM, PM)</td>
<td>6 mg-12 mg</td>
<td>Oral formulations have the highest incidence of gastrointestinal adverse effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily (24 hrs)</td>
<td>5 mg-12 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9.5 mg-13.3 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galantamine</td>
<td>Razadyne</td>
<td>BID</td>
<td>15 mg-24 mg</td>
<td>Racial clearance 9-13 mL/min: max 16 mg</td>
<td>Moderate hepatic impairment: max 16 mg</td>
</tr>
<tr>
<td></td>
<td>Razadyne sol.</td>
<td>BID</td>
<td>15 mg-24 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Razadyne sol.</td>
<td>Daily (AM)</td>
<td>15 mg-24 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memantine</td>
<td>Namenda</td>
<td>Daily</td>
<td>28 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Namenda IR</td>
<td>BID</td>
<td>20 mg</td>
<td>Memantine IR capsule can be opened and sprinkled on a small amount of pudding or applesauce</td>
<td></td>
</tr>
</tbody>
</table>
AChEIs and Memantine Clinical Use and Effectiveness

- Memantine can be used as monotherapy (especially when AChEI are not safe or contraindicated) or combination therapy with AChEI
- Before AChEI initiation assess HR and BP, drug interactions
- Slow AChEI titration to decrease risk for adverse effects (gastrointestinal)
- MODEST EFFECT on:
  1. Stabilization of cognitive function
  2. Stabilization or improvement of BPSD
- Further assessments on a 6-monthly basis to determine ongoing efficacy and response with the predetermined treatment goals

Longitudinal Case: Continuation 4

After a long conversation, Mary is initiated on donepezil tablet 5 mg once daily with instructions to increase the dose in 6 weeks to 10 mg once daily. Her husband will assist with the titration if needed. Her baseline BP is 126/85 mm Hg; and HR 74 bpm.

She was instructed to take it in the evening with her dinner and to report if she experiences any intolerable GI adverse effects. She was also instructed to continue to take her BP and monitor her HR, and was instructed to use acetaminophen instead of NSAID for pain or fever.

Conclusions

- AD is currently an incurable disorder and its prevalence increases with advanced age
- AD population is growing and there is need for prepared health workforce to provide care to these individuals
- Multiple symptomatic therapies are available and it is important to understand their place of therapy and clinical use
- In the past several years, new disease-modifying therapies were approved, however their access is still very limited
- Need to understand more about the disease modifying therapies
- There are still unmet needs in management of AD and increasing quality of life
Post-Test Question 1 and Answers
Which of the following is the major pathological hallmark of Alzheimer’s disease?
A. Lewy bodies
B. Apolipoprotein E inclusions
C. Beta amyloid plaques
D. Hypo-phosphorylated tau

Post-Test Question 2 and Answers
Which of the following represents a general phase in the Alzheimer’s disease continuum characterized by presence of cognitive impairment that does not impact individual function?
A. Preclinical Alzheimer’s disease
B. Mild cognitive impairment
C. Mild dementia due to Alzheimer’s disease
D. Radiographic Alzheimer’s disease

Post-Test Question 3 and Answers
Which of the following is true about donepezil?
A. It modifies disease progression and disease biology
B. It cannot be combined with memantine due to safety issues
C. It can be safely used in individuals with bradycardia and heart block
D. It is available in a weekly patch formulation
Post-Test Question 4 and Answers

Which of the following is true about lecanemab?

A. It has high affinity to insoluble fibril and plaques and minimal no affinity to protofibrils
B. It is administered as 10 mg/kg once monthly IV infusion after a baseline MRI
C. It demonstrated ability to significantly reduce cognitive and functional decline compared to placebo
D. The risk of ARIA associated with edema and/or hemorrhage seems higher than with aducanumab

Post-Test Question 5 and Answers

• A 75-year-old individual was just diagnosed with moderate AD dementia. She and her spouse inquired about treatment options to manage the disorder. She no longer denies her issues with memory. She is no longer able to manage the household and feels a loss of independence.
• PMH: hemorrhagic stroke, diabetes, hypertension, and in the past 12 months she experienced 2 transients ischemic attacks, active peptic ulcer disease
• VS: BP 130/89 mm Hg, HR 59 bpm, respiratory rate 14 bpm

Which of the following would be the most appropriate recommendation for her at this time?

A. Memantine  B. Donepezil  C. Aducanumab  D. Lecanemab