FDA-Approved Treatments for Alzheimer’s Disease: The Good, The Bad, and the Ugly

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I have an interest in relation to several organizations that could be perceived as a possible conflict of interest in the context of this presentation, as summarized below:

<table>
<thead>
<tr>
<th>Interest</th>
<th>Name of organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grants</td>
<td>National Institute on Aging (RF1 AG041705, 1UF1AG046150, R01 AG031581, R01 AG055444, P30 AG19610)</td>
</tr>
<tr>
<td>Advisory board</td>
<td>Abbvie, AC Immune, Acadia, Athira, Corium, Cortexyme, Eisai, Genentech, ImmunoBrain, Merck, Novo Nordisk,</td>
</tr>
<tr>
<td>Consulting fees</td>
<td>Acadia, Lundbeck, Merck, Otsuka &amp; Astex, T3D Therapeutics</td>
</tr>
</tbody>
</table>
The Main Changes in the Brain in Alzheimer’s Disease

- Amyloid plaques
- Neurofibrillary tangles (tau)
- Inflammation
- Change in biochemicals and neurotransmitters
- Shrinkage of the brain (atrophy)

Cummings, NEJM, 2004
A Proposed Temporal Progression of Alzheimer’s Disease(s)

Genetic Factors
- APP mutations
- Presenilin 1,2 mutations
- APOE4 alleles
- Family history
- APOE2 alleles protect
- APP/BACE mutation protects

Environmental Factors
- Head Injury
- Toxins

Age

Endogenous Factors
- Diet
- Cardiovascular risk factors
- Diabetes
- Smoking
- Education
- Menopause
- Physical/Mental Activity

Protective Factors
- Estrogen?
- Anti-inflammatory Drugs?

Net effect = stress and vulnerability to stress

Molecular Phenotype

INITIAL STRESSORS
- Proximal Apoptosis
- APP dysregulation
- Impaired neurotrophic function
- Oxidative stress
- Excitotoxicity

FAILED STRESS RESPONSE
- Cell cycle dysregulation
- Kinase/phosphatase dysfunction
- Protein misfolding
- Altered DNA repair
- Vascular/membrane dysfunction

CELL INJURY
- Inflammation
- Cytoskeletal dysfunction
- Synaptic dysfunction
- Mitochondrial damage

CELL DEATH
- Distal apoptosis
- Neurotransmitter failure

Neuropathology

Normal

Clinical Phenotype

Normal

Clinical Phenotype

Normal

Mild Cognitive Impairment

Dementia

The figure depicts apparently continuous processes, though they are likely to be asynchronous. Yaari R, Kumar S, Tariot PN. Expert Opinion 3(7):745-760, 2008.
Types of Interventions

- **“Symptomatic” therapy:**
  - Interventions that improve cognition, defer functional decline, or ameliorate behavioral symptoms without altering the underlying disease processes that comprise AD pathogenesis and without producing enduring changes that persist when the treatment is withdrawn.

- **Disease modifying therapy:**
  - Interventions that produce an enduring change in the clinical progression of AD by interfering in the underlying pathophysiological mechanisms of the disease process that lead to cell death as demonstrated by biomarkers
Initial FDA-Approved Medications for Alzheimer’s Disease Dementia

- **Cholinesterase-inhibitors**: donepezil, rivastigmine, galantamine, tacrine*
  - All FDA approved for treatment of *mild to moderate* AD dementia
  - Donepezil is FDA approved for treatment of *severe* AD dementia (2006)
  - 1/week donepezil patch approved by FDA 3/22
  - Galantamine available as a generic since 2009; donepezil & rivastigmine since 2010
  - Rivastigmine available as 1/day patch
- **NMDA (glutamate) receptor antagonist**: memantine
  - FDA approved for treatment of moderate to severe AD dementia (generic 2015)
    - Alone or in combination with a cholinesterase inhibitor

*No longer used clinically*
Pharmacology of Acetylcholinesterase Inhibitors

- Block the action of the enzyme responsible for the breakdown of the neurotransmitter acetylcholine
- Enhance cholinergic neurotransmission in the brain
Cholinesterase Inhibitor Therapy in AD

Disease Severity

MCI
- Benefits cognition?

Early-Stage Dementia
- Benefits cognition

Moderate Dementia
- Benefits cognition
- Preserves global status
- Preserves ADLs
- Benefits behavior?

Severe Dementia
- Benefits cognition
- Preserves global status
- Preserves ADLs
- Benefits behavior?

Class approved for mild-moderate AD
Donepezil and rivastigmine also approved for severe AD
1-Year, Placebo-Controlled Trial of Donepezil: Slowing of Cognitive Decline in Mild-Moderate AD Dementia

Winblad et al. 2001
Pharmacology of Memantine

- Moderate affinity, reversible uncompetitive NMDA antagonist (glutamatergic neurons)
- Renal dosing required for severe renal impairment
Memantine Therapy for AD*

- **MCI**
  - Role unknown

- **Mild-Moderate Dementia**
  - Inconsistent effects

- **Moderate-Severe Dementia**
  - Benefits cognition
  - Preserves global function
  - Preserves ADLs
  - Benefits behavior

*Approved for moderate-severe AD, alone or in combination with cholinesterase inhibitors*
Memantine Monotherapy in Severe AD Dementia

- Clinical benefit for moderate to severe AD
  - Cognition
  - Performance on ADLs
  - Behavior and mood
- Irrespective of taking a cholinesterase inhibitor
- No benefit in people with mild AD
- Moderate-certainty evidence suggesting no benefit for agitation


Memantine/Cholinesterase Inhibitor (AChEI) Add-On Therapy

• One clearly positive trial (see graph)
  • Primary outcome was a cognitive measure
• Meta-analysis suggested that, compared with AChEIs alone, M+AChEIs showed a greater reduction in behavioral disturbances and a trend toward cognitive improvement
# Dosing for AChEIs and Memantine (from Prescribing Information for each drug)

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>STARTING DOSE</th>
<th>DOSING RANGE</th>
</tr>
</thead>
</table>
| Donepezil                         | 5 mg/d for 4–6 weeks                               | 5–15 mg/d  
After 3 months, can consider 23-mg dose formulation, approved for mod-severe only  
Note: new 1/week TD formulation available late 2022 |
| Rivastigmine                      | 1.5 mg BID, increasing by 1.5 mg every 2 weeks    | 6–12 mg/d                                                                    |
| Rivastigmine Patch                | 4.6 mg/d for 4 weeks                               | 9.5 mg/d; if worsening, consider 13.3-mg maximum dose                       |
| Galantamine                       | 4 mg BID (8 mg once daily for XR) for 4 weeks      | 8–24 mg/d                                                                    |
| Memantine (immediate release)     | 5 mg/d, increasing by 5 mg every week              | 10–20 mg/d                                                                   |
| Memantine XR($$)                  | 7 mg/d, increasing by 7 mg every week              | 14–28 mg/d                                                                   |
| Donepezil/Memantine ($$)          | 7mg/10 mg memantine HCl XR/donepezil HCl daily     | 7 mg/10 mg; 14 mg /10mg ; 21 mg/10 mg;  28mg/10 mg daily                   |
# Pharmacologic Treatments for AD: Common Side Effects

<table>
<thead>
<tr>
<th>Cholinesterase Inhibitors</th>
<th>Memantine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nausea</td>
<td>• Dizziness</td>
</tr>
<tr>
<td>• Vomiting</td>
<td>• Headache</td>
</tr>
<tr>
<td>• Diarrhea</td>
<td>• Constipation</td>
</tr>
<tr>
<td>• Weight loss</td>
<td>• Confusion</td>
</tr>
<tr>
<td>• Loss of appetite</td>
<td></td>
</tr>
<tr>
<td>• Muscle weakness</td>
<td></td>
</tr>
</tbody>
</table>

One Clinical Practice Guideline for Symptomatic Drugs*

- Newly diagnosed patients with mild AD should be treated with AChEi.
- Addition of memantine:
  - Newly diagnosed patients with moderate AD
  - Patients who progress from mild to moderate AD
- Newly diagnosed patients with severe AD should be treated with memantine (an AChEi can be added)
- In mild AD:
  - Memantine monotherapy may be used when AChEi is not tolerated
  - Combination with AChEi should be considered when the disease is progressing rapidly
- Patients with mixed dementia may be treated according to AD guidelines
- Treatment may be discontinued in patients who advance to “profound” disease and who have lost all cognitive and functional abilities
- AD therapy should be continued during acute illness / hospitalization unless contraindicated

Cummings J et al 2023. DOI: 10.1002/trc2.12385
Why Amyloid Matters

- Amyloid plaques are a pathological hallmark of Alzheimer’s disease
- Amyloid fragments are toxic in many animal models
- Amyloid buildup predicts future dementia
- The rare causes of familial Alzheimer’s all involve abnormal processing of amyloid
- A rare mutation blocks the pathological amyloid cascade and prevents AD (Icelandic mutation: Jonsson 2012)
- Can we block this cascade with drugs/biologics?
- When is the right time to intervene?
- Note: most early anti-amyloid agents failed
Current Monoclonal Antibodies (MAB) in AD - Overview

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration, Frequency</th>
<th>Phase</th>
<th>Status</th>
<th>Prevention Trial?</th>
<th>ARIA Rates %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aducanumab</td>
<td>Intravenous, every 4 weeks</td>
<td>Phase 4</td>
<td>Accelerated Approval</td>
<td>No</td>
<td>25-35</td>
</tr>
<tr>
<td>Lecanemab</td>
<td>Intravenous, biweekly</td>
<td></td>
<td>Traditional Approval</td>
<td>Phase 3, AHEAD 3-45 enrolling, also in DIAN</td>
<td>13</td>
</tr>
<tr>
<td>Gantenerumab</td>
<td>Subcutaneous, every 4 weeks</td>
<td>Phase 3, active, not enrolling</td>
<td>Breakthrough Designation</td>
<td>Phase 3, SKYLINE, enrolling, also in DIAN</td>
<td>29</td>
</tr>
<tr>
<td>Donanemab</td>
<td>Intravenous, every 4 weeks*</td>
<td>Phase 3, active, not enrolling</td>
<td>Breakthrough Designation</td>
<td>Phase 3, TRAILBLAZER-ALZ3, enrolling</td>
<td>30</td>
</tr>
</tbody>
</table>

*It worked!
Aducanumab Phase Ib: Reduced brain amyloid after 1 year

Aducanumab

Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer’s Disease


- Two parallel trials – EMERGE (Europe) and ENGAGE (USA)
  - Primary outcome of Clinical Dementia Rating – Sum of Boxes (CDR-SB)

- Futility Analysis
  - “50% of the participants (whose data were used) had the opportunity to complete week 78”

- Assumption violations per authors:
  - 1) treatment effect similar in both studies
  - 2) treatment effect would not substantially change during the study
## Aducanumab, cont’d

### Table 2. Primary and secondary endpoints at week 78

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>EMERGE</th>
<th></th>
<th></th>
<th>ENGAGE</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Placebo decline ± SE (n=548)</td>
<td>Difference vs placebo (%)</td>
<td>95% CI</td>
<td>Placebo decline ± SE (n=545)</td>
<td>Difference vs placebo (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low dose (n=543)</td>
<td>High dose (n=547)</td>
<td></td>
<td>Low dose (n=547)</td>
<td>High dose (n=555)</td>
</tr>
<tr>
<td>CDR-SB*</td>
<td>1.74±0.11</td>
<td>-0.26 (−15%)</td>
<td>-0.39 (−22%)</td>
<td>1.56±0.11</td>
<td>-0.18 (−12%)</td>
<td>0.03 (2%)</td>
</tr>
<tr>
<td></td>
<td>-0.57, 0.04</td>
<td>-0.69, −0.09</td>
<td></td>
<td></td>
<td>-0.47, 0.11</td>
<td>-0.26, 0.33</td>
</tr>
<tr>
<td></td>
<td>0.090</td>
<td>0.012</td>
<td></td>
<td></td>
<td>.225</td>
<td>.833</td>
</tr>
</tbody>
</table>

### Table 3. Summary of adverse events

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>EMERGE</th>
<th></th>
<th></th>
<th>ENGAGE</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Low dose</td>
<td>High dose</td>
<td>Placebo</td>
<td>Low dose</td>
<td>High dose</td>
</tr>
<tr>
<td>Safety MRI population</td>
<td>n=544</td>
<td>n=537</td>
<td>n=541</td>
<td>n=532</td>
<td>n=545</td>
<td>n=554</td>
</tr>
<tr>
<td>ARIA-E</td>
<td>13 (2)</td>
<td>140 (26)</td>
<td>181 (35)</td>
<td>16 (3)</td>
<td>141 (26)</td>
<td>199 (36)</td>
</tr>
<tr>
<td>ApoE ε4 carriers</td>
<td>7/371 (2)</td>
<td>109/366 (30)</td>
<td>156/362 (43)</td>
<td>9/371 (2)</td>
<td>114/390 (29)</td>
<td>159/378 (42)</td>
</tr>
<tr>
<td>ApoE ε4 noncarriers</td>
<td>6/173 (4)</td>
<td>31/171 (18)</td>
<td>32/179 (18)</td>
<td>7/161 (4)</td>
<td>27/155 (17)</td>
<td>40/176 (23)</td>
</tr>
<tr>
<td>Brain microbleeds</td>
<td>37 (7)</td>
<td>57 (16)</td>
<td>105 (20)</td>
<td>34 (6)</td>
<td>89 (16)</td>
<td>104 (19)</td>
</tr>
<tr>
<td>Brain microbleeds in participants without ARIA-E</td>
<td>35 (7)</td>
<td>30 (8)</td>
<td>32 (9)</td>
<td>32 (6)</td>
<td>24 (6)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>Localized superficial siderosis</td>
<td>14 (5)</td>
<td>52 (10)</td>
<td>73 (13)</td>
<td>10 (2)</td>
<td>51 (9)</td>
<td>89 (16)</td>
</tr>
<tr>
<td>Localized superficial siderosis in participants without ARIA-E</td>
<td>9 (2)</td>
<td>9 (2)</td>
<td>7 (2)</td>
<td>6 (1)</td>
<td>7 (2)</td>
<td>5 (1)</td>
</tr>
</tbody>
</table>
Aducanumab, cont’d

- Monthly infusions
- Titration required
- May slow down cognitive/functional decline by about **22%**
- About **35%** of patients on high dose experienced reactions in the brain, called “Amyloid-Related Imaging Abnormalities” or ARIA
  - Most were asymptomatic
  - Dose- and ApoE4-genotype related
- Frequent MRI is required during titration to monitor for ARIAs
- Not covered by insurance company Medicare, VA, etc.
  - Uptake has been very low
- Placebo-controlled efficacy trial still required for traditional FDA approval
ARIA-E: Vasogenic Edema

• Reprinted from Alzheimer’s & Dementia, 7/4, Sperling RA, Jack CR Jr, Black SE, Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer’s Association Research Roundtable Workgroup, 367-385, copyright 2011, with permission from Elsevier
Lecanemab

- Key Inclusion Criteria
  - 50-90 years old
  - MCI or mild dementia
  - Amyloid+ by PET or CSF
  - Episodic memory impairment
    - 1 SD below age-adjusted mean on Wechsler Memory Scale IV-Logical Memory
Lecanemab

- 27% Slowing of decline on the CDR-SB
  - 1.66 decrease in placebo
  - 1.21 decrease in treatment group

- FDA granted full approval 2023
Lecanemab

Table 3. Adverse Events.

<table>
<thead>
<tr>
<th>Event</th>
<th>Lecanemab (N=898)</th>
<th>Placebo (N=897)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall—no. (%)</td>
<td>798 (88.9)</td>
<td>735 (81.9)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event related to lecanemab or placebo†</td>
<td>401 (44.7)</td>
<td>197 (22.0)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>126 (14.0)</td>
<td>101 (11.3)</td>
</tr>
<tr>
<td>Death</td>
<td>6 (0.7)</td>
<td>7 (0.8)</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation of the trial agent</td>
<td>62 (6.9)</td>
<td>26 (2.9)</td>
</tr>
</tbody>
</table>

ARIA:

- **ARIA-E** — no. (%)
  - Symptomatic ARIA-E — no. (%) 25 (2.8)
  - ApoE ε4 noncarrier — no./total no. (%) 4/278 (1.4) 0/286
  - ApoE ε4 carrier — no./total no. (%) 21/620 (3.4) 0/611
  - ApoE ε4 heterozygote 8/479 (1.7) 0/478
  - ApoE ε4 homozygote 13/141 (9.2) 0/133

- **ARIA-H** — no. (%)
  - ApoE ε4 noncarrier 15/278 (5.4) 1/286 (0.3)
  - ApoE ε4 carrier 98/620 (15.8) 14/611 (2.3)
  - ApoE ε4 heterozygote 52/479 (10.9) 9/478 (1.9)
  - ApoE ε4 homozygote 46/141 (32.6) 5/133 (3.8)

ARIA according to ApoE ε4 genotype — no./total no. (%)

ARIA-E 12.6%  
- Symptomatic ARIA-E 2.8%

ARIA-H 17.3%  
- Symptomatic ARIA-H 2.8%

Higher risk in APOE4 carriers  
- Highest in homozygotes
Clinical Use Guidelines for Lecanemab

Cummings et al, Meaningful use guidelines for lecanemab. J Prev Alz Dis 2023; Published online March 27, 2023, http://dx.doi.org/10.14283/jpad.2023.30
Phase 3 Trial of Donanemab in Early Alzheimer’s Disease

- Different anti-amyloid antibody
- Earlier Phase 2 trial was 1st to show a disease modifying effect
  - Selected patients with medium level of tau tangles (“sweet spot”)
- Primary focus was patients with low-medium tangle burden
- Rapid reduction of brain amyloid
Donanemab in Early Alzheimer’s Disease – Phase 3 Topline Results

<table>
<thead>
<tr>
<th>Population</th>
<th>Intermediate Tau</th>
<th>Combined Intermediate &amp; high Tau</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative % Slowing</td>
<td>P-value</td>
</tr>
<tr>
<td>iADRS</td>
<td>35%</td>
<td>p&lt;0.000004</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>37%</td>
<td>p&lt;0.000005</td>
</tr>
<tr>
<td>ADCS-iADL</td>
<td>40%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>ADAS-Cog13</td>
<td>32%</td>
<td>p&lt;0.00005</td>
</tr>
</tbody>
</table>

In the overall donanemab treatment group, ARIA-E occurred in 24.0% of treated participants, with 6.1% experiencing symptomatic ARIA-E.
Data Suggest that Amyloid mAbs that Do Not Clear Plaques Do Not Work Clinically (Even When Given Pre-symptomatically)
Blood Tests for soluble forms of Tau and Amyloid in Alzheimer's Disease: Not quite ready for the clinic (but CSF tests are)
Where do we go from here?

• Refining currently available monoclonal antibodies such as subcutaneous administration
  • Lecanemab subcutaneous in ongoing trials.
  • Aducanumab considering subcutaneous study.
  • Donanemab follow-on compound in ongoing trials.
• Development of next generation of antibodies with less adverse events and more efficacy
  • Remternetug: “2nd generation” donanemab
• Start treatment before symptoms onset in participants who already have amyloid plaque → **Secondary prevention**
  • Lecanemab (AHEAD), donanemab (TRAILBLAZER 3)
Backup
Mild Cognitive Impairment – Treatment

- **None of the neurotransmitter-based drugs are FDA-approved**
  - Clinical trials results bottom line: “the glass is half-full”
  - NIH-funded Petersen trial of donepezil is considered most informative
    - Primary outcome was negative: delayed progression to dementia at year 3
    - Secondary: Delayed progression to dementia at 1 year, better cognitive performance for 2+ years
  - Best practice per AAN is to discuss pro’s/con’s of cholinesterase inhibitors (but not memantine)

- New disease modifiers ARE FDA-approved for MCI
- Consider clinical research/trial referral
  - Explosion in number of therapeutic targets being tested
  - Most are putative disease modifiers
Where do we go from here?, cont’d

- Lifestyle interventions trials (e.g., BP, sleep, metabolic syndrome, exercise, etc.)
  - **U.S. POINTER** (The Alzheimer's Association U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk): physical activity, nutritional guidance, cognitive training, social activities and management of heart-health risk factors
- **Middle Path**: Hypertension intervention in mid-life (Jeremy Pruzin et al)
  - Further prevention trials in Colombia
- Anti-tau monoclonal antibody therapies have not panned out yet
  - **BIIB080** first antisense oligonucleotide (ASO) targeting tau expression in Phase 2 trial
- Other mechanisms: too soon to say (microbiome-directed, inflammation, neuroprotection, membrane stabilization, etc.)
- **Combination treatments?**
  - Different anti-amyloid mechanisms: e.g., immunotherapy followed by oral agent
  - Anti-amyloid and anti-tau
  - Other: Lifestyle intervention/risk factor reductions plus amyloid &/or tau-directed therapies