Disclosures

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Research: AstraZeneca, Avanir, Biogen, Eisai, Eli Lilly, Genentech/Roche, Janssen, Merck, Novartis, NIA, NIMH, DOD.

Consultant: Acadia, Neurim Pharmaceuticals.
ALZHEIMER’S DISEASE

Alzheimer’s disease (AD) is a brain disease. It is the most common cause of dementia.

“Dementia” describes the progressive loss of thinking, memory, and other cognitive abilities impairing daily function.

In people over the age of 65, Alzheimer’s disease accounts for over two-thirds of dementia cases.
MORE ON AD

The most common symptom of AD-related dementia is a gradual worsening of memory.

Other cognitive abilities such as logic and reasoning, geographical orientation and use of language also worsen over time.
Alzheimer’s Disease

- 5.3 million Americans currently live with Alzheimer’s and other related dementias
- 1 in 10 people over the age of 65
- 1 in 3 people over the age of 85
- Nearly 500,000 new cases will be diagnosed in 2018
- Lifetime risk at age 45: 10% for men and nearly 20% for women
- Health care costs exceed $250 Billion (2017)

*Alzheimer’s Association: 2017 Alzheimer’s Disease Facts and Figures*
### Projected Prevalence in our Aging Society

**Figure 4**

Projected Number of People Age 65 and Older (Total and by Age Group) in the U.S. Population with Alzheimer’s Disease, 2010 to 2050

<table>
<thead>
<tr>
<th>Year</th>
<th>Ages 65-74</th>
<th>Ages 75-84</th>
<th>Ages 85+</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>4.7</td>
<td>5.8</td>
<td>8.4</td>
</tr>
<tr>
<td>2020</td>
<td>5.8</td>
<td>7.1</td>
<td>10.6</td>
</tr>
<tr>
<td>2030</td>
<td>7.1</td>
<td>9.3</td>
<td>11.6</td>
</tr>
<tr>
<td>2040</td>
<td>9.3</td>
<td>11.6</td>
<td>13.8</td>
</tr>
<tr>
<td>2050</td>
<td>11.6</td>
<td>13.8</td>
<td></td>
</tr>
</tbody>
</table>

*Alzheimer’s Association: 2017 Alzheimer’s Disease Facts and Figures*
AD Prevalence

- Prevalence of AD increases with age
- Prevalence of AD is higher in minority populations

2017 Alzheimer’s Disease Facts and Figures.
Alzheimer’s Disease

• Initially presents with memory impairment followed by progressive cognitive decline over 5 to 10 years

• Pathologically, there is a shrinkage of brain volume, caused by regional loss of neurons and their connections
Clues from Pathology

- Neuronal loss
- Amyloid plaques
- Neurofibrillary tangles
- Neuroinflammation
- Vascular changes

Perl, 2010
Clues from Genetics

• Familial Alzheimer’s disease (FAD) occurs before the age of 65 and accounts for 1% of all cases

• Genes mutated in FAD are associated with increased production of the amyloid-β peptide, which is the primary constituent of amyloid plaques

• The “Amyloid Hypothesis” has largely dominated the field for over 20 years
We haven’t cured Alzheimer’s, but....

- Despite 15 years of clinical trials aimed at amyloid-β, the clearest “cause” of Alzheimer’s, we have not identified a cure.

- We know much more about genes and pathological processes in the disease: *There are many more targets to go after*.

- With neuroimaging and new biomarkers we can now track AD progression: *Provides early diagnosis and therapeutic efficacy*.
Categories in Cognitive Disorders Spectrum

- Cognitively Normal
- Mild Cognitive Impairment
- Dementia

Symptomatic Cognitive Impairment

• Distinctions are based on history and exam
Push Back Diagnosis so Intervention Starts as Early as Possible

Cognitive continuum of aging

**Normal**
- Thinking effectively but more slowly
- Forgetting a name or appointment but remembering later
- Occasionally misplacing things

**Presymptomatic**
- APOE-e4 risk gene
- Multiple protein or gene “barcodes”
- Family history
- Tau or amyloid in CSF or blood
- MRI, PET

**MCI**
- Subjective problem in memory or another domain, informant corroborated and measurable on tests
- Normal overall cognition and ADLs

**AD**
- Clear deficits in 2 or more core cognitive domains (memory, language, problem solving, visual interpretation)
- ADLs affected

ADLs, activities of daily living; APOE, apolipoprotein E; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography
What Should Evaluation Include?

- Competent history and neurological exam
- Bedside cognitive assessment versus neuropsychological testing
  - What is added value of neuropsychological testing?
- Standard laboratory testing as in dementia
- Standard imaging (MR, no contrast) as in dementia
Diagnostic Criteria of Dementia

A. Dementia

• Interferes with ability to function at work or at usual activities
• A decline from a previous level of functioning
• Not delirium or psychiatric disorder
• Diagnosed by history, examination
• Involves at least 2 cognitive domains:
  - Memory
  - Reasoning and judgment
  - Visuospatial
  - Language
  - Personality, behavior, comportment

Diagnostic Criteria of MCI

Clinical and Cognitive Criteria

• Concern about a change in cognition reported by patient or informant or clinician (historical or observed evidence of decline)

• Objective evidence of impairment in one or more cognitive domains, typically including memory (formal or bedside testing)

• Preservation of independence in functional abilities

• Not demented

Assess etiology of MCI consistent with AD pathophysiology

• Rule out vascular, traumatic, medical causes of cognitive decline

• Provide evidence of longitudinal decline in cognition

• Report history consistent with AD genetic factors

According to the 2011 National Institute of Aging/Alzheimer’s Association (NIA-AA) guidelines, Alzheimer’s disease diagnosis requires core criteria be met\textsuperscript{1,2}

1. Report of cognitive concern by patient, caregiver, or clinician
2. Gradual onset over months to years
3. Evidence of longitudinal cognitive decline
4. Differential diagnosis that rules out vascular, traumatic, and medical causes of cognitive decline

Objective evidence of impairment in ≥1 cognitive domains and maintains independence

MCI due to AD

Objective evidence of impairment in ≥2 cognitive domains and unable to function at work or usual activities

Dementia due to AD

Possible AD: Atypical course or etiologically mixed presentation

Probable AD: Insidious onset, history of progressive worsening, and no evidence of CVD, DLB, FTD, or aphasia

Proven AD: Meet widely accepted neuropathology criteria at autopsy

NIA-AA Alzheimer’s disease diagnosis criteria can also be accessed at http://www.alz.org/research/diagnostic_criteria/.\textsuperscript{3}

AD = Alzheimer’s disease; CVD = cardiovascular disease; DLB = dementia with Lewy bodies; FTD = frontotemporal dementia; MCI=mild cognitive impairment.

Biomarkers and Imaging

Jack et al. Lancet Neurology 2013
Biomarkers for AD: Blood

A blood-based biomarker represents the best avenue for preclinical AD

- Inexpensive
- Specialized equipment not required
- Readily obtained
- Minimal risk involved
- Suitable for large scale screening
What Are the Main Goals of Treatment?

- Disease arrest
- Slowed progression
- Symptomatic benefit
- No effect
## Treatment Domains

<table>
<thead>
<tr>
<th>Symptom improvement</th>
<th>Disease modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>• FDA-approved</td>
<td>• No FDA-approved medications, but clinical trials are in progress on a variety of mechanisms</td>
</tr>
<tr>
<td>- Acetylcholinesterase inhibitors</td>
<td>- Neuronal protection</td>
</tr>
<tr>
<td>- NMDA-receptor antagonist</td>
<td>- Protein synthesis or aggregation inhibition</td>
</tr>
<tr>
<td>• Experimental</td>
<td>- Immunologic priming with antibodies</td>
</tr>
<tr>
<td>- Multiple clinical trials underway</td>
<td>- Vaccines</td>
</tr>
<tr>
<td></td>
<td>- Secretase inhibition</td>
</tr>
</tbody>
</table>

NMDA = N-methyl-D-aspartate.
Approved Drugs Only Address the Symptoms of AD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>FDA Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Cholinesterase inhibitor</td>
<td>• Mild-to-severe Alzheimer’s dementia</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Cholinesterase inhibitor</td>
<td>• Mild-to-severe Alzheimer’s dementia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mild-to-moderate Parkinson’s dementia</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Cholinesterase inhibitor</td>
<td>• Mild-to-moderate Alzheimer’s dementia</td>
</tr>
<tr>
<td>Tacrine</td>
<td>Cholinesterase inhibitor</td>
<td>• Mild-to-moderate Alzheimer’s dementia</td>
</tr>
<tr>
<td>Memantine</td>
<td>NMDA antagonist</td>
<td>• Mild-to-severe Alzheimer’s dementia</td>
</tr>
<tr>
<td>Memantine and donepezil</td>
<td>Fixed-dose combination:</td>
<td>• Mild-to-severe Alzheimer’s dementia</td>
</tr>
<tr>
<td></td>
<td>NMDA antagonist and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cholinesterase inhibitor</td>
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</tbody>
</table>

Common Side Effects Associated with Available Therapies for AD

<table>
<thead>
<tr>
<th>Cholinesterase Inhibitors</th>
<th>Memantine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>Confusion</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Sedation</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>Dizziness</td>
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<tr>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td></td>
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<tr>
<td>Leg cramps</td>
<td></td>
</tr>
<tr>
<td>Ulcers</td>
<td></td>
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<tr>
<td>Cardiac arrhythmias</td>
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Alzheimer’s Disease: The Treatment Horizon

• Disease-modifying therapy
• Combination disease-modifying and symptomatic therapy
• Earlier recognition of AD
• Integration of biomarkers into clinical practice
  • Spinal fluid
  • Blood
  • Imaging
  • Genetics as well
• A host of unanswered questions
Questions?