Alzheimer’s Disease: Where Are We Now?

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Disclosure

Speaker:
Nothing to disclose (honorarium, advisory group, etc.)
Objectives

- List the most common types of dementia
- State the role of medications, herbs, and nutritional supplements in the prevention and/or treatment of Alzheimer’s disease
- Describe the different mechanisms of action of FDA approved medications for the treatment of Alzheimer’s dementia
- Describe the molecular targets and future treatments of Alzheimer’s disease in late stage clinical trials
Are We There Yet?

Dr. Alois Alzheimer
5.3 million Americans have Alzheimer’s Disease
  - 5.1 million >64 years old

6th leading cause of death, 5th in Americans ≥ 65 y.o.

Between 2000-2013, deaths from Alzheimer’s Disease increased 71%

2015 total payments (health care, long-term care, and hospice) for people ≥ 65 y.o. with dementia expected to be greater than $225 billion

Defining Dementia

- Diagnostic and Statistical Manual of Mental Disorders, 5th ed
  - Symptoms must include decline in memory and at least one of the following cognitive abilities:
    - Ability to generate coherent speech or understand spoken or written language
    - Ability to recognize or identify objects, assuming intact sensory function
    - Ability to execute motor activities, assuming intact motor abilities and sensory function and comprehension or the required task
    - Ability to think abstractly, make sound judgments, and plan and carry out complex tasks
    - The decline in cognitive abilities must be severe enough to interfere with daily life

Common Types of Dementia

- Alzheimer’s disease (AD) – **Most Common**
- Vascular dementia
- Dementia with Lewy bodies (DLB)
- Mixed dementia
- Frontotemporal lobar degeneration (FTLD)
- Creutzfeldt-Jakob
- Normal pressure hydrocephalus
Characteristics of AD

- Difficulty remembering recent events and names
- Apathy
- Depression
- Impaired judgment and disorientation
- Confusion and behavior changes
- Difficulty speaking, walking, and swallowing
Changes in the Brain

- Accumulation of beta-amyloid protein (beta-amyloid plaques) outside neurons
- Accumulation of tau protein (tau tangles) inside neurons
Stages of AD

- **Preclinical (prodromal)**
  - Measureable changes in CSF composition, brain, and biomarkers without hallmark symptoms
    - area of current research and development

- **Mild Cognitive Impairment (MCI)**
  - Mild changes in the ability to think that is noticeable to family and self, but still able to perform activities of daily living

- **Dementia due to A.D.**
  - Memory, behavior, and impaired function in daily living

Genetics

www.amino-acid-therapy.com
Genetics: You Can’t Beat Your Genes...Yet

- 1% of patient’s with documented A.D. have 1 of 3 gene mutations (early onset A.D. - 30 y.o.)
  - Amyloid precursor protein
  - Presenilin 1 protein
  - Presenilin 2 protein (95% chance of A.D.)

Genetics

- Apolipoprotein E (APOE) Gene - cholesterol transport protein
  - 3 forms of APOE: ε2, ε3, ε4
  - ε3 most common: 60% of Americans having 2 copies
  - ε2: 10-20% have 2 copies (protective)
  - ε4: 20-30% have 1 copy; 2% have 2 copies
  - Risk for A.D.: ε4 > ε3 (40-65% of those with A.D. have 1 or 2 ε4 copies)
    - ε4: 1 copy, 3 fold > risk than those without ε4
    - 2 copies, 8-12 fold > risk

Risk Factors

- Advanced age
- Family history of AD (mutations, etc)
- Carrying Apolipoprotein E ε4 gene (risk gene)
- Mild Cognitive Impairment
- Cardiovascular disease risk factors (smoking, obesity, diabetes, hypertension, inc. cholesterol)
- Traumatic brain injury
- Lack of social engagement

Prevention/Progression Strategies

- Medications, Herbals, Diet????
  - Statins
  - NSAIDS, COX-2 Inhibitors
  - Vitamin E
  - Ginkgo biloba
  - Conjugated estrogens
  - Folic acid, Vitamin B12
  - Dietary Fats
  - Resveratrol
Naproxen and Celecoxib do not Prevent AD in Early Results from a Randomized Controlled Trial

- **Objective:**
  - To evaluate the efficacy and safety of naproxen and celecoxib for the primary prevention of Alzheimer’s disease

- **Randomized, placebo controlled trial of 2,528 patients > 70 years old and a 1st degree relative with probable AD.**

- **Conclusion:**
  - Hazard ratios were not statistically significant for either naproxen or celecoxib; p=0.14 and p=0.06

Neurology 2007; 68:1800-1808
Objective:
- To determine whether treatment with donepezil or vitamin E could delay the clinical diagnosis of AD in patients with mild cognitive impairment

3 year, double blind study of 769 patients with the amnestic subtype of mild cognitive impairment

Conclusion:
- 212 patients developed possible or probable AD.
- No difference in the probability of progression to AD in the vitamin E or donepezil group; p=0.91 and 0.42 respectively

Objective:

- To determine effectiveness of G. biloba vs placebo in reducing the incidence of all-cause dementia and Alzheimer’s disease in elderly individuals with normal cognition and those with mild cognitive impairment

Randomized, double-blind, placebo controlled trial involving 3,069 subjects over 74 years old for a median of 6 years

Conclusion:

- G. biloba was not effective in reducing either the overall incidence rate of dementia or incidence of AD (p=0.21 and p=0.11)

JAMA 2008;300(19):2253-2262
Current Pharmacotherapy

Medscape.com
Current Pharmacotherapy

- **Cholinesterase Inhibitors**
  - Tacrine (Cognex®, 1993) withdrawn from US market
  - Donepezil (Aricept®, 1996)
  - Rivastigmine (Exelon®, 2000)
  - Galantamine (Razadyne®, 2001)

- **NMDA Receptor Antagonist**
  - Memantine (Namenda®, 2003; Namenda XR®, 2014)
Cholinesterase Inhibitors

- **FDA Labeled Indication**
  - **Donepezil**
    - mild to severe Alzheimer’s disease dementia*
  - **Rivastigmine**
    - mild to moderate Alzheimer’s and Parkinson’s disease dementia
  - **Galantamine**
    - mild to moderate Alzheimer’s disease dementia
Donepezil

**Dosing**
- **Mild to Moderate AD Dementia**
  - 5 mg orally once daily; if suboptimal clinical response at 4 to 6 weeks, may increase to 10 mg daily.
- **Moderate to Severe AD Dementia**
  - Increase from 10 mg daily to 23 mg daily following 3 months.

**Adverse Events**
- **Common:** nausea, vomiting, diarrhea, insomnia
- **Serious:** torsades, AV block, syncope
Rivastigmine

- Acetylcholinesterase and butyrylcholinesterase inhibitor

- Dosing
  - **Mild to Moderate AD Dementia**
    - (dose adjustment for renal dysfunction)
    - Oral: 1.5 mg orally twice daily. If tolerated, increase dose by 1.5 mg every 2 weeks to a maximum of 6 mg twice daily.
    - Patch: 4.6 mg patch applied daily, increase in 4 weeks to 9.5 mg patch. ( < 6 mg/day oral = 4.6 mg patch)

- Adverse Events
  - **Common**: nausea, vomiting, loss of appetite
  - **Serious**: tachycardia, bronchospasm
Galantamine

• Dosing
  ○ Mild to Moderate AD Dementia
    (dose adjustment for renal dysfunction)
    ▷ Immediate release: 4 mg orally twice daily and increase every 4 weeks by 4 mg to max dose of 12 mg twice daily.
    ▷ Extended release: 8 mg orally daily and increase by 8 mg every 4 weeks to a maximum dose of 24 mg orally daily.

• Adverse Events
  ○ Common: Nausea, vomiting, diarrhea, loss of appetite
  ○ Serious: Thrombocytopenia, bradycardia
NMDA antagonist (N-methyl-D-aspartate)

Memantine

- **Mechanism of Action**
  - Noncompetitive NMDA, 5HT₃, and nicotinic acetylcholine receptor antagonist

- **FDA Labeled Indication**
  - Moderate to Severe Alzheimer’s Disease Dementia

- **Dosing** (dose adjustment for renal dysfunction)
  - Immediate release: 5 mg orally daily, increase by 5 mg weekly to 10 mg twice daily
  - Extended release: 7 mg orally daily, increase by 7 mg weekly to 28 mg daily

- **Adverse Events**
  - Common: Headache, syncope, hypertension
  - Serious: Renal failure, hepatitis, liver failure, Stevens-Johnsons
Biomarkers for AD

Florbetapir 18-month follow-up study

Cognitively normal

Aβ+ AD

Aβ- MCI

Aβ+ MCI

Neurology 2012;79:1636–1644
Hallmark brain/CSF abnormalities: β-amyloid plaques, tau protein, reduced glucose uptake, brain atrophy

- Brain amyloid-beta (Aβ) protein deposition
  - low CSF A β_{42} (cognitive changes?)
  - Positive PET amyloid imaging (Florbetapir F18; Flutemetamol F18)
Neuronal degeneration

- Increased CSF tau protein
- Decreased fluorodeoxyglucose uptake in temporoparietal cortex
- Disproportionate brain atrophy on MRI
Research Biomarkers Cont.

Biomarkers Cont.

**Evidence for Ordering of Alzheimer Disease Biomarkers**


- 401 patients in Alzheimer’s Disease Neuroimaging Initiative who were cognitively normal, who had MCI, or who had A.D. dementia

- CSF $\alpha$42, CSF total tau, adjusted hippocampal volume MRI

- **Findings:**
  - All biomarkers progressively abnormal as symptoms worsened
  - CSF $\alpha$42 levels declines while clinical asymptomatic
  - Total tau and hippocampal volume decline progressively as symptoms appear
  - Cognitive decline more closely associated with neuronal injury than amyloid load
Alzheimer’s Disease: Developing Drugs for the Treatment of Early Stage Disease
-Draft Guidance: February 2013

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Cognitive and Functional Tests

- Combo Assessment
  - Clinical Dementia Rating-Sum of Boxes (CDR-SB)
- Cognitive Assessments
  - Mini Mental Status Exam (MMSE)
  - Alzheimer’s Disease Assessment Scale-Cognitive (ADAS-Cog)
- Functional Assessment
  - Alzheimer’s Disease Cooperative Study-Activities of Daily Living (ADCS-ADL)
Research Underway

Intravenous Immune Globulin

Bapineuzumab – abandoned

Solanezumab
Intravenous Immune Globulin (IVIG)


- Phase III, double-blind, placebo controlled in 390 patients with probable mild-moderate A.D.
- 0.4 mg/kg, 0.2 mg/kg, or albumin placebo every 2 weeks
- Clinical assessments: baseline, every 3 months for 18 months
IVIG Continued

- **Assessments**
  - Volumetric brain MRI
  - Cerebral glucose metabolism (FDG PET)
  - Florbetapir F18 amyloid PET

- **Subgroup Assessment**
  - Aβ40 and 42 levels in CSF and plasma
  - Anti- Aβ antibody titers in plasma and CSF
  - Total and phosphorylated tau protein in CSF
IVIG Results

- **Primary Outcomes**
  - Change in ADAS-Cog and ADCS-ADL scores
    - No Significant Difference
    - Subgroup analysis in APOE-ε4 carriers and moderate A.D. demonstrated positive trend
  - Dose dependent decreases in amyloid β42 levels

- **Current IVIG studies:**
  - High dose IVIG
  - IVIG combined with plasmaphoresis
Bapineuzumab

- Anti-amyloid beta monoclonal antibody directed at precipitated amyloid beta
- Abandoned in 2012
Solanezumab

**EXPEDITION/EXPEDITION 2**

*Phase 3 trials of solanezumab for mild-to-moderate Alzheimer’s Disease*


- Failed to improve cognition and functional abilities
  - Pooled secondary analysis of mild A.D. patients showed slowing of cognitive decline by 34% for ADAS-cog and MMSE and slowing of functional decline by 18% in ADCS-iADL
  - Rise in plasma and CSF Aβ1-40 and CSF Aβ 1-42 total
  - No difference in CDR-SB, vMRI, CSF tau and p-tau

- **EXPEDITION 3**
  - Mild A.D.
Lilly Announces Change to Primary Endpoint of EXPEDITION3 Study

INDIANAPOLIS, March 15, 2016 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced a change to the primary endpoint for the EXPEDITION3 clinical trial, a Phase 3 study of solanezumab in people with mild Alzheimer's dementia.

The original study design included co-primary endpoints of cognition and function—measured by ADAS-Cog14 (Alzheimer's Disease Assessment Scale-Cognitive subscale) and ADCS-IADL (Alzheimer's Disease Cooperative Study- Instrumental Activities of Daily Living), respectively. Emerging scientific evidence supports the idea that cognitive decline precedes and predicts functional decline in Alzheimer's disease, particularly in earlier stages of the disease. Thus, Lilly has decided to amend the EXPEDITION3 trial to include a single primary endpoint of cognition (ADAS-Cog14). Functional outcomes will be measured during the trial in the same manner as previously designed, using both the ADCS-IADL and the FAQ (Functional Assessment Questionnaire). These two functional outcomes will now be considered key secondary endpoints for the EXPEDITION3 study.

It is important to note that the endpoint change affects the study's data analysis plan, but it does not affect anything related to the actual conduct of the trial. Lilly will continue to remain blinded to study data until after the database lock occurs in the fourth quarter of 2016.

Lilly understands that regulators globally will continue to view both cognitive and functional endpoints as necessary for clinical trials in people with mild Alzheimer's dementia, and regulatory guidance has been to include these as co-primary endpoints. Lilly is submitting the EXPEDITION3 amendment to all appropriate regulatory authorities.
More Ongoing Research

- γ-Secretase Inhibitors
  - Semagacestat
  - Avagacestat
- τ-Aggregation Inhibitor
  - Methylthioninium Chloride (methylene blue)
- Retinoid X Receptor Agonist
  - Bexarotene
γ-Secretase Inhibitors: Semagacestat

A phase III trial of semagacestat for treatment of Alzheimer’s Disease.


- 76 week, double-blind, placebo-controlled trial of 1537 patients with probable A.D. who were randomized to various doses of semagacestat

- Outcomes: ADAS-cog, ADCS-ADL
γ-Secretase Inhibitors: Semagacestat

- Study terminated after interim analysis

- Results:
  - Worsening ADAS-cog and ADAS-ADL scores in semagacestat group compared to placebo
  - Semagacestat groups had increased weight loss and statistically significant increases in skin cancer
γ-Secretase Inhibitors: Avagacestat

**Targeting prodromal A.D. with avagacestat—A randomized clinical trial**

Coric V, et al. JAMA Neur 2015; E1-10

- 104 week, randomized, placebo-controlled phase II trial involving 263 patients with MCI and biomarker positive

- Outcomes: ADAS-cog, ADCS-ADL
γ-Secretase Inhibitors: Avagacestat

- Study Terminated after 1 year

- Results:
  - No significant difference: ADCS-ADL or ADAS-cog, MMSE
  - Higher dose associated with significant weight loss, nausea, vomiting, and non melanoma skin cancers
τ-Aggregation Inhibitor- Methylthioninium

*Tau aggregation inhibitor therapy: An exploratory phase II study in mild or moderate Alzheimer’s Disease.*


- Randomized, double-blind, placebo-controlled dose finding study in 321 patients with mild and moderate cognitive impairment

- Outcomes:
  - ADAS-cog at 24 weeks and regional cerebral blood flow in a select subset
τ-Aggregation Inhibitor - Methylthioninium

- **Results**
  - Statistically significant improvement in ADAS-cog for moderate cognitive impairment (-5.42 pts, p=0.047) and cerebral blood flow in mild impairment (p<0.001) at middle dose at 24 weeks
  - 50 weeks: improvement in ADAS-cog with mild and moderate cognitive impairment groups
  - No improvement in low dose or high dose groups
Retinoid X Receptor Agonist-Bexarotene

ApoE-directed therapy rapidly cleared beta-amyloid and reversed deficits in Alzheimer’s Disease mouse models


- Bexarotene enhances ApoE levels and converts microglia into their active state which promotes Aβ phagocytosis
Results

- Aβ plaques reduced by 50% in 72 hours, 75% in 14 days.
- Reversed cognitive, social and olfactory deficits
- Continuous dosing caused reversion to previous state by 3 months?????
Retinoid X Receptor Agonist-Bexarotene

- Cleveland Clinic

A double-blind, placebo-controlled, randomized study to evaluate the efficacy and safety of bexarotene in patients with mild to moderate Alzheimer’s Disease.

Closed to new enrollment
Future

- Define and adopt biomarkers for prodromal AD
  - Risk stratification
  - Genes
  - Imagining
  - CDR-SB
  - Blood test
- Disease Modifying Agents