Alzheimer’s Disease: Current and Future Therapies

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Disclosures

- Consultant/Advisory Boards:
  - AstraZeneca, Lilly, Merck, Rivermend

- Clinical Trials:
  - Baxter, Elan, Janssen, Novartis, Pfizer
Overview

- How have we come to this period in the history of AD?
- AD: a process or continuum, not a “state”
- Understanding brain changes leads to therapeutic strategies at each stage
- Biomarkers (spinal fluid, neuroimaging, blood)
- Medicines may work in one phase but not another
- Therapeutic strategies emerging for symptomatic AD, MCI, and prevention (delay) of onset of symptoms
From the Clinic to the Community: characterizing the clinical picture of AD

Alois Alzheimer
Germany, 1907:

- single case report
- rare, unusual disease of middle-aged
- “pre-senile dementia”

Martin Roth and colleagues
Newcastle, 1964:

- community survey
- fairly common disease of elderly
- “senile dementia”

Majority of cases of dementia in late life are AD, with many cases showing additional co-morbidities
1976 Katzman editorial: an alarm is sounded


- Predicted a massive increase in the number of cases of Alzheimer’s Disease in the 21st century

- No clear difference between presenile and senile onset with respect to symptoms or pathology

- Stimulated research in aging and AD brain

- Cholinergic deficit discovered by several laboratories in the UK
Current Therapies for AD

- Neurotransmitter enhancement for acetylcholine, which is involved in memory and decreased in AD
- Donepezil, Rivastigmine, Galantamine
- Neurotransmitter receptor regulation for glutamate
- Memantine

These medications improve cell communication but do not alter the neurodegenerative process

- They have mild effects but proved that AD can be treated
<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Stages</th>
<th>Form</th>
<th>Initial dose</th>
<th>Titration interval</th>
<th>Therapeutic dose</th>
<th>ADR</th>
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<tbody>
<tr>
<td>donepezil</td>
<td>Aricept</td>
<td>mild-severe</td>
<td>Tablet</td>
<td>5 mg bedtime</td>
<td>4-6 weeks</td>
<td>5 mg, 10 mg, 23 mg daily</td>
<td>N/V/D, appetite loss</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Immediate-release tablet</td>
<td>4 mg twice daily with food (Immediate release)</td>
<td></td>
<td>8-12 mg twice daily (Immediate-release)</td>
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<td></td>
<td>4 weeks</td>
<td>16-24 mg daily (extended-release)</td>
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<tr>
<td></td>
<td></td>
<td>mild-moderate</td>
<td>Extended-release capsule, liquid solution</td>
<td>8 mg daily in morning with food (extended release)</td>
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<td></td>
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<tr>
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<tr>
<td>rivastigmine</td>
<td>Exelon</td>
<td>mild-moderate</td>
<td>Tablet</td>
<td>1.5 mg twice daily with food</td>
<td>4 weeks</td>
<td>3-6 mg twice daily</td>
<td>N/V/D, appetite loss</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Patch</td>
<td>= TDD &lt;6 mg</td>
<td></td>
<td>9.5 mg/24 h patch</td>
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<td>= TDD 6-12 mg</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>moderate-severe</td>
<td>Tablet</td>
<td>5 mg daily (Immediate-release)</td>
<td>1 week</td>
<td>10 mg twice daily (Immediate-release)</td>
<td>headache, constipation, dizziness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 mg daily (extended release)</td>
<td></td>
<td>daily (extended-release)</td>
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Therapy for Alzheimer’s (and other Neurodegenerative Diseases)

Current: Symptomatic treatments Neurotransmission

Emerging: Disease modification based on pathophysiology

Future: Mechanisms that promote synaptic plasticity, Disease prevention based on risk factors, Disease prevention based on targets from genetics

Image courtesy of Samantha L. Budd, AstraZeneca
So, let’s talk neuroscience…
The ‘inflammatory surround’ consists of distorted and degenerating synaptic processes, activated microglia, and astrocytic processes.

Defining AD Pathology: Neurofibrillary Tangles & Amyloid (Neuritic) Plaques

Neurofibrillary tangles
Inflammatory surround
Compacted amyloid core
Mechanisms in Neurodegeneration

**Biological Cascade**

- genetic predisposition
- Environmental factors
- altered protein metabolism
- oxidative stress
- mitochondrial dysfunction
- protein aggregation
- apoptosis
- Synapse loss and cell death

**Clinical Status**

- Time
  - asymptomatic
  - preclinical
  - symptomatic (detection)
  - advanced disease

**Plaques, NFT**
What influences AD onset and course?
Risk Factors in Alzheimer’s Disease

• Genetic
  ◦ Causative mutations: APP, PS1, PS2
  ◦ Risk alleles: APOE4 is most powerful risk

• Environmental “protective” factors
  ◦ Education
  ◦ Cognitive activities
  ◦ Physical Activities
  ◦ Social networks
  ◦ Engagement in games/activities
# Genetics: 3 Mutations CAUSE AD and *all 3 disrupt amyloid metabolism*

<table>
<thead>
<tr>
<th>Location</th>
<th>Gene Product</th>
<th>Effect on Amyloid</th>
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<tbody>
<tr>
<td>Chromosome 21</td>
<td>amyloid precursor protein (APP)</td>
<td></td>
</tr>
<tr>
<td>Chromosome 14</td>
<td>Presenilin 1 (PS1)</td>
<td><em>All 3 mutations raise serum levels of APP and Aβ</em></td>
</tr>
<tr>
<td></td>
<td>(transmembrane protein; part of γ-secretase complex)</td>
<td></td>
</tr>
<tr>
<td>Chromosome 1</td>
<td>Presenilin 2 (PS2)</td>
<td></td>
</tr>
<tr>
<td>(Volga German Kindreds)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(65% homology with PS1)</td>
<td></td>
</tr>
<tr>
<td>Increased Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>1.5x normal gene dose</td>
<td><em>Serum levels of APP &amp; Aβ are increased 1.5x</em></td>
</tr>
<tr>
<td>(Down Syndrome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk Alleles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromosome 19</td>
<td>apolipoprotein E (apoE)</td>
<td><em>Diminished Aβ Clearance. Gene dose effect: 3 &amp; 8-12x risk for het and homozygotes</em></td>
</tr>
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APOE and Alzheimer’s Disease

**ALLEL FREQUENCY:**

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<thead>
<tr>
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<th>normal Caucasian population:</th>
<th>in AD:</th>
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<tr>
<td>E2</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>E3</td>
<td>79%</td>
<td>40-50%</td>
</tr>
<tr>
<td>E4</td>
<td>14%</td>
<td>40-50%</td>
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</table>

**Potential mechanisms:**
- Impaired removal of beta amyloid
- Diminished neural regeneration

Can it be used to speed trials? Identify at-risk cases for prevention? (API is now preparing to test this)
Disease-Modifying Mechanisms: The Key to Slowing or Preventing AD

- Medications that slow primary pathology of amyloid plaques, formation of neurofibrillary tangles, inflammation, and other mechanisms
- Lifestyle changes associated with lowering risk of AD: exercise, diet, cognitive activity
- Prevention starts with midlife health activities
Can treatment of vascular factors decrease AD risk?

...all of these are associated with increased risk

- Hypertension
- Hypercholesterolemia
- Diabetes mellitus
- Obesity
- Lack of exercise
- Inflammatory states, increased CRP
- Homocysteine elevation
- Carotid & Circle of Willis atherosclerosis
Studies in Autosomal Dominant AD

- Dominantly Inherited Alzheimer’s disease Network (DIAN)
  - Gantenerumab (Roche) and Solanezumab (Lilly)

- Alzheimer’s Prevention Initiative (API)
  - Colombia: extensive FAD family to be studied
  - Crenezumab (Genentech)
  - USA: additional prevention trials with APOE4 carriers; medications not selected yet
What is the course of the brain changes?

And how do we interrupt them?

Let’s discuss the two pathologies Alzheimer identified: amyloid plaques and neurofibrillary tangles (NFT)
Amyloid Metabolism:

Normally we “cut the grass” [corte el césped]

Amyloid Precursor Protein (APP)

soluble APPα

γ-cleavage site

soluble APPβ

(BACE-1) β site

α site

CELL MEMBRANE

Pero en la enfermedad de Alzheimer…
Amyloid Metabolism: “cut the grass”

Amyloid plaques, Inflammation, Neuron loss

Monomers → Dimers → Oligomers

soluble APPα

soluble APPβ

(BACE-1) β site

α site

Amyloid Precursor Protein (APP)

β & γ cleavage

Aβ domain

Presenilin 1/2
APH-1
PEN-2
Nicastrin

Amyloid Metabolism: “cut the grass”
Nerve cells communicate via their Axons (red arrow). Information and proteins move up and down it, like a railroad track. NFT disrupt this.
NFT are made of altered Tau Protein (Microtubule Associated Protein, or MAP): Cutting the “Railroad Ties”
Spread of neurofibrillary pathology in AD

Alzheimer’s Disease: A Continuum of Pathological & Clinical Progression

Clinical State:
- Normal
- Pre-symptomatic AD
- Mild Cognitive Impairment
- AD

Disease Progression
Alzheimer’s Disease: A Continuum of Pathological & Clinical Progression

**Clinical State**
- Normal (No Disease, No Symptoms)
- “Pre-symptomatic” AD (Early Brain Changes, No Symptoms)
- Mild Cognitive Impairment (AD Brain Changes, Mild Symptoms)
- AD (Mild, Moderate, or Severe Impairment)

**Brain Pathologic State**
- Primary Prevention
- Early Treatment
- Treatment

**Intervention**
- Early Treatment
- Treatment

**Disease Progression**
- Normal
- “Pre-symptomatic” AD
- Mild Cognitive Impairment
- AD
Evolution of Neuroimaging in AD

- Computed Tomography
- MRI (magnetic resonance)
- Volumetric MRI
- Co-registration of MRI
- Functional MRI
- FDG Glucose PET
- Amyloid Imaging

PIB PET in AD and Control

University of Pittsburgh
PET Amyloid Imaging Group
Imaging Amyloid \textit{in vivo} in Humans

- Amyloid Cascade Hypothesis:
  - Amyloid deposition begins years before clinical sx

- Ability to image brain amyloid will impact:
  - Diagnosis (sensitivity and specificity TBD)
  - Prognosis (different patterns of progression?)
  - Monitoring anti-amyloid therapeutic interventions
  - Efficiency of drug development

- Current ligands:
  - Florbetapir (\textit{Amyvid} / Lilly), approved by FDA in 2012
  - Flutametamol (PiB) (\textit{Vizamyl} / GE), approved by FDA in 2013
  - Florbetaben (\textit{Neuroceq} / Piramal) approved by FDA in 2014
PiB Imaging in MCI

Average MCI group deposition of PiB is significantly greater than controls.

In INDIVIDUAL CASES, PiB deposition is either elevated or in the range of normal controls.

Mean Cortical PIB Binding in Nondemented Controls and AD (N=41)

Mintun et al, 2006, Neurology
Heterogeneity of Amyloid Binding in Asymptomatic Normal Elderly

Courtesy of Reisa Sperling, Harvard Univ.
The best markers across a broad range are MRI and FDG-PET. Amyloid imaging is the diagnostic marker.
Overview of AD Therapies

- **Symptomatic improvement** (cognitive and behavioral)
- **Non-specific** therapies
  - Antioxidants, Anti-inflammatory agents, others
  - None so far successful
- **Specific** therapies:
  - Anti-amyloid therapy
  - Anti-neurofibrillary tangle strategies
  - Neurotrophins
  - APOE modifiers (make E4 act like E3)
- Genetics-guided interventions: stem cells? Transformed cells? Virus vectors with appropriate therapy?
Anti-Amyloid Mechanisms in AD Medications

- **Enzyme inhibitors:**
  - Beta secretase inhibitors (in trials)
  - Gamma secretase inhibitors or modulators
    - (failed trials)

- **Passive immunotherapy**
  - Monoclonal antibodies (some have failed; several others in trials)
  - Immunoglobulin G (trial failed)

- **Active immunotherapy**
  - Immunize with beta amyloid or a fragment of it
  - Several types under evaluation or entering trials

- **Anti-aggregation compounds**
Negative Phase III AD Trials

- Xaliproden (5HT1A agonist with neurotrophic effects in vitro)
- Tramiprosate (GAG anti-aggregant)
- Tarenflurbil (R-flurbiprofen, gamma secretase modulator)
- Rosiglitazone (Peroxisome proliferators activated receptor PPAR-γ)
- Leuprolide (LHRH endocrine)
- Dimebon (5HT6 antagonist, H1 antagonist + mitochondrial transition pore)
- Semagacestat (gamma secretase inhibitor)
Negative Phase III Trials

- Bapineuzumab (passive immunotherapy; monoclonal Ab N-terminal)
- Solanezumab (passive immunotherapy; monoclonal mid domain Ab) (but positive results on combination of 2 trials)
- IVIG (passive immunotherapy; polyclonal pooled Abs)
- Subcutaneous injection of antibody - new modality for administration
- Over 100 compounds in progress from preclinical to proof of concept trials
Can we remove amyloid from the human brain?

- Yes [AN1792 Vaccine trial, Bapi trial]
- Does it matter? How much is enough? All?
- Probably not suitable as a treatment for symptomatic AD
- Better suited to pre-symptomatic therapy: remove plaque before symptoms occur
- Symptoms do not occur for a decade or more after plaques form—so there is adequate time to remove amyloid plaque
- May take a long time to remove (years)
- Trials would be long and extremely expensive
Plaques in untreated AD Subjects

Plaques in Immunized Subject

Nicoll et al., 2003
Phase II Bapineuzemab Study

“Due to varying doses and a lack of statistical precision, this Class II ascending dose trial provides insufficient evidence to support or refute a benefit of bapineuzumab.”

Salloway et al., 2009
**11C-PiB PET assessment of change in amyloid-β load in patients with AD treated with bapineuzumab:**

a phase 2, double-blind, placebo-controlled, ascending-dose study

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Rinne et al., Lancet Neurology 2010
Loss of amyloid on PET Scan—how much is enough?

Rinne et al., Lancet Neurology 2010
Anti-Tau/NFT Strategies

- NFT result from excessively processed tau protein, which is hyperphosphorylated and extensively **cross-linked** (bound to itself) and is inactive
  
  Therefore:

  - Administer drugs that block phosphorylation and inhibit cross linking
  - Utilize compounds that bind to tau and block its auto-cross linking
  - Dissolve formed tangles
  - Inhibit spread of NFT from one neuron to another

  All these mechanisms are under study. One is in clinical trials now (methylene blue)
Newest Biomarkers: In Vivo Tau Imaging: 18F-T807 PET in AD

Healthy
Mild MCI MMSE=26
MILD AD MMSE=21
Severe AD MMSE=7

58 yo 69 yo 88 yo 72 yo

rSUV Target/Cerebellum
Images 80-100 min post injection

Courtesy of Mark Mintun, Avid Pharmaceuticals
Dementia Prevention Objectives

- Identify presymptomatic persons at elevated risk
- Take action (public health measures) to prevent dementia or significantly delay its onset, e.g., exercise, diet
- Treat asymptomatic persons with disease-modifying medications to delay onset of symptoms of dementia
- All prevention trials either negative (Ginkgo GEM trial; DeKosky et al, 2009) or stopped for toxicity (ADAPT, NSAIDs; WHIMS (estrogen, estradiol)
- Barring breakthrough in design, such studies will take years to complete
- Regulatory agencies are easing the restrictions to allow more rapid answers to emerge
Newer Prevention Initiatives

- **API (Alzheimer Prevention Initiative)**
  - PS 1 families in Antioquia, Columbia (F. Lopera)
  - APOE ε4 carriers, Arizona

- **DIAN (Dominantly Inherited Alzheimer Network)**
  - Familial, early-onset AD (North America)

- **A4 (Anti-Amyloid Treatment in Asymptomatic Alzheimer’s)**
  - Normal subjects with positive amyloid scan, 2 years
  - Primary outcome: cognition; β-amyloid, hippocampal atrophy

- **AD-4833/TOMM40**
  - Pioglitazone prevention trial

- **MAPT, FINGER, others**
  - 3 year follow-up, requirements for frailty, cardiovascular risks;
    interventions: food supplements, nutritional, strength training, aerobic exercise, cognitive training, socialization, management of metabolic & vascular risk factors
Therapy for Alzheimer’s (and other Neurodegenerative Diseases)

Image courtesy of Samantha L. Budd, AstraZeneca