Alzheimer’s Disease: From Recognition to Prevention

Pierre N. Tariot, MD
Director, Banner Alzheimer’s Institute
Co-Director, Alzheimer’s Prevention Initiative
Research Professor of Psychiatry
University of Arizona

Consulting fees: Abbot Laboratories, AbbVie, AC Immune, Auspex, Boehringer-Ingelheim, Brain Test, Inc., California Pacific Medical Center, Chase Pharmaceuticals, Clintara, CME Inc., GliaCure, Insys Therapeutics, T3D.
Consulting fees and research support: AstraZeneca, Avanir, Lilly, Lundbeck, Merck and Company, Roche, Takeda.
Research support only: Elan, Functional Neuromodulation (f(nm)), GE, Genentech, Novartis, Roche, Targacept.
Other research support: NIA, Arizona Department of Health Services, Alzheimer’s Association.
Patents: contributor to a patent owned by the University of Rochester, “Biomarkers of Alzheimer’s Disease.”
Stocks: I own stock options in Adamas Pharmaceuticals.
Disclosure

Off label use of medications will be discussed for the treatment of Alzheimer’s Disease.

Objectives

• Review the epidemiology of dementia
• Summarize the clinical presentation, evaluation, and differential diagnosis of dementia
• Review the use of FDA approved medications and summarize the clinical evidence for use of unapproved psychotropics for treatment of symptoms of dementia
• Understand nonpharmacological approaches to management of dementia
• Summarize new developments in experimental therapeutics for Alzheimer's disease
• Review the rationale and design of new Alzheimer's prevention trials
Alzheimer’s Disease Statistics

- Most common cause of dementia\(^1\)
- About 5.3 million people affected now in US\(^1\)
- Prevalence of AD doubles for every 5 years beyond age 65\(^2\)
- A leading cause of death among elderly
- By the year 2050, up to 16 million Americans are expected to have AD\(^2\)
- Estimated annual cost $1.2 trillion by 2050
- 50% of caregivers will become ill or depressed

---

**From: Alzheimer Disease in the US Population: Prevalence Estimates Using the 2000 Census**

Prevalence of severe (Mini-Mental State Examination score, \(\leq 9\)), moderate (Mini-Mental State Examination score, 10-17), and mild (Mini-Mental State Examination score, \(\geq 18\)) Alzheimer disease, in each of 3 age groups, in the community population providing data for these estimates.
What is “dementia?”

- This is a syndromal term, not a diagnosis
  - Like saying “cancer”
  - Does not say what lies ahead or how to treat
- Always characterized by progressive loss of thinking and memory
- Results in inability to function on a daily basis
- Almost always results in changes in emotions and personality
- Eventually causes neurological dysfunction
  - Examples: incontinence, swallowing problems, balance and walking problems
- There are many causes of this syndrome, not just Alzheimer’s
  - But Alzheimer’s is the most common cause

Clinical Presentation of Dementia
Hypothetical Course of Cognitive Function in a Patient with Dementia

The Clinical Evaluation

**Routine**
- History
  - Evolution of illness: cognition, function, behavior
  - Social, developmental
  - Medical/surgical
  - Medications
  - Allergies
  - Habits
  - Family illnesses
- Mental Status Exam
- Neurological Exam
- Office neuropsychological testing
  - MOCA, fluency, clock
- Labs
- CT/MRI

**Optional**
- Syphilis serology
- Sedimentation Rate
- Chest X-Ray
- Electrocardiogram
- Urinalysis
- Drug Levels
- HIV testing
- Lyme Serology
- EEG
- PET/SPECT
- APOE genotyping
- CSF (Aβ42/tau: done rarely)
- Biopsy, autopsy

Pierre N. Tariot, MD
In-Clinic Cognitive Testing

- No standard
- Practitioner preference
- Should include:
  - Attention
  - Orientation
  - Short and long term memory
  - Language
  - Visuospatial abilities
  - Executive functioning

Common Cognitive Tools

<table>
<thead>
<tr>
<th>Tool</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE1,2</td>
<td>Screens for cognitive impairment; does not evaluate executive functioning or capture impairments in ADL; scores 10–26 generally considered as mild to moderate AD and &lt;10 as severe AD</td>
</tr>
<tr>
<td>Clock- Drawing Test3,4</td>
<td>Patient is asked to draw the face of a clock indicating the time of 2:45; scoring criteria include closed circle, numbers in correct position, all 12 numbers correct, and clock hands in correct positions</td>
</tr>
<tr>
<td>Mini-Cog5</td>
<td>Combines 3-word recall and clock drawing task</td>
</tr>
</tbody>
</table>


MMSE = Mini-Mental State Examination
today is going to be a good day
for me & my husband.
MRI Brain: Normal vs. AD

FDG-PET Scan: Glucose Uptake in Brain

Amyloid Imaging and Clinical symptoms

Preferential uptake in the parietal, frontal, and temporal lobes.


Differential Diagnosis of Dementia

Vascular dementias
- Multi-infarct dementia
-Binswanger's disease

Other dementias
- Frontal lobe dementia
- Creutzfeldt-Jakob disease
- Corticobasal degeneration
- Progressive supranuclear palsy
- Many others

Dementia with Lewy bodies
- Parkinson's disease
- Diffuse Lewy body disease
- Lewy body variant of AD

Alzheimer's Disease
- 5%
- 10%
- 65%

AD and dementia with Lewy bodies
- 5%
- 7%
- 8%

Criteria for Alzheimer’s Dementia

- Insidious onset with progressive decline
- **Impaired social or occupational functioning**
- Memory loss
- Cognitive loss in at least 1 other domain
  - Language
  - Calculations
  - Orientation
  - Judgment
- Deficits not due to other systemic disease
- Deficits not in the setting of a delirium

Triggers for a Non-AD Diagnosis

- Vascular Dementia: Stepwise progression, Ataxia
- Creutzfeldt-Jakob Disease: Rapid course, Myoclonus
- Dementia With Lewy Bodies: Hallucinations, Fluctuations in cognition, Parkinsonism, EPS
- Hydrocephalus: Ataxia, Intontinence
- Frontal Lobe Dementia: Bizarre behaviors, Aphasia
- Focal Atrophies: Early and prominent behavioral and language dysfunction
- Hereditary Tauopathies: Family history
- B-12 Deficiency: Ataxia, Nystagmus, Ophthalmoplegia

# Current Medication Treatment Goals

- Improve memory
- Improve functional status
- Improve behavioral symptoms
- Slow progression of symptoms

## Pharmacologic Treatments for AD

<table>
<thead>
<tr>
<th>MOA</th>
<th>Cholinesterase Inhibitors</th>
<th>NMDA-Receptor Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indication</td>
<td>Mild-moderate AD; severe AD</td>
<td>Mild-moderate AD</td>
</tr>
<tr>
<td>Initial dose</td>
<td>Tablet: 5 mg qd</td>
<td>Tablet/oral solution: 4 mg bid</td>
</tr>
<tr>
<td>Maximal dose</td>
<td>Tablet: 10 mg qd</td>
<td>Tablet/oral solution: 12 mg bid</td>
</tr>
</tbody>
</table>

ER = extended-release; MOA = mechanism of action; NMDA = N-methyl-D-aspartate.

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

www.banneralz.org/

Memantine Therapy for AD*

**Disease Severity**

- **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

www.banneralz.org/
Pharmacologic Treatments for AD: Common Side Effects

<table>
<thead>
<tr>
<th>Cholinesterase Inhibitors</th>
<th>NMDA-Receptor Antagonist</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>


1-Year, Placebo- Controlled Trial of Donepezil: Slowing of Cognitive Decline

Winblad et al. 2001

MMSE Mean Change from Baseline

Clinical Improvement

Clinical Decline

Weeks

0 12 24 36

Donepezil HCl

Placebo

*P = .0005
†P < .05
‡P = .001
Practical Issues in Antidementia Treatment

- Use individual patient target symptoms by domain
- Monitor:
  - cognition (MOCA, other)
  - behavior (NPI items, e.g., depression, psychosis, agitation, apathy)
  - functioning (basic/instrumental ADLs)
  - side effects
- Train family to be your "eyes and ears"
  - Side effects
  - Target symptoms
  - Use of e-mail, phone

Practical Issues in Antidementia Treatment (cont’d)

- Monitor/treat intercurrent medical conditions
- Look for
  - Noticeable improvement in major domains
  - Stabilization
  - Decline slower than expected
- Watch for sudden decline if antidementia treatment is stopped!
Causes of Excess Disability= Opportunities to Relieve Distress

- Delirium
- Medical illness
- Pain, other discomfort
- Sensory deprivation
- Too hot, cold, dark or light
- Confusion
  - Give simple explanations
- Fatigue, use of rest
- Caregiver approach (e.g. don’t over-explain!)
- Boredom
- Lack of routine, or change
- Overstimulation
- Excessive demand
- Focus on comfort
- Use distraction/redirection

What is the unmet need?

---

2004 Consensus Guidelines for Treatment of Psychiatric and Behavioral Symptoms in AD

- Use antidementia agents first
  - Emerging data with AChEIs
  - Memantine trial showed antiagitation effect
- Atypical antipsychotics: first line for psychosis with or without agitation
- No first-line recommendation for agitation without psychosis: consider antipsychotic alone or with other agent, or other agent alone
  - Mood stabilizers
  - Serotonergic compounds
  - Trazodone: negative trials but positive clinical experience
  - Sertraline: anecdotes only
  - Citalopram: preliminary evidence for possible effect
  - Escitalopram: by inference

General Approach to Managing Illness: What You Would Want for Your Mother But Is Rarely Offered

- Render an accurate diagnosis: it matters!
- Optimize physical, social, intellectual stimulation
- Monitor for delirium
  - Aggressive treatment of medical problems
- Anticipate/mitigate possible changes in emotions and behavior
- Review driving safety
- Discuss medical, legal, financial issues
- Review relevant community resources
- Discuss coping strategies
- Discuss availability of clinical trials
- Establish ongoing monitoring plan
AD Genetics 101

- **Increased risk**
  - Family history of late onset AD alone: 3-4 fold
  - APOE e4 alleles (APOE e3 neutral)
  - Autosomal dominant AD
    - About 500 families worldwide
    - 100% penetrant
    - APP mutations
    - Presenilin 1,2 mutations

- **Decreased risk**
  - APOE2 alleles
  - APP/BACE mutation, even in presence of APOE e4

Alzheimer’s is a malignant pathogenic process that damages and destroys brain neurons and the connections between them.
The Main Changes in the Brain

- Amyloid plaques
- Neurofibrillary tangles
- Death of brain cells (neurons)
- Shrinkage of the brain
- Inflammation

What amyloid deposits in the brain look like
A Proposed Temporal Progression Of Alzheimer’s Disease

**Genetic Factors**
- APP mutations
- Presenilin 1,2 mutations
- APOE alleles
- Family history
- APOE2 alleles protect
- APP/ACE regulation protects

**Environmental Factors**
- Head Injury
- Toxins

**Age**
- Diet
- Cardiovascular risk factors
- Smoking
- Education
- Menopause
- Physical/Mental Activity

**Endogenous Factors**
- Genetic
- APP mutations
- Presenilin 1,2 mutations
- APOE4 alleles
- APOE2 alleles protect

**Protective Factors**
- Drugs?
- Anti-inflammatory

**Net effect = stress and vulnerability to stress**

**Molecular Phenotype**
- **INITIAL STRESSORS**
  - Proximal Apoptosis
  - APP dysregulation
  - Impaired neurotrophic function
  - Inflammatory stress

- **FAILED STRESS RESPONSE**
  - Cell cycle dysregulation
  - Cell cycle arrest
  - Proionic dysfunction
  - Protein misfolding

**Cell Injury**
- Inflammation
- Apoptosis
- Synaptic dysfunction
- Mitochondrial damage

**Cell Death**
- Distal apoptosis
- Neurotransmission failure

**Neuropathology**
- Normal
- Tangles, Plaques
- Normal

**Clinical Phenotype**
- Normal
- Mild Cognitive Impairment
- Dementia

---

*The figure depicts apparently continuous processes, though they are likely to be asynchronous.*

Yaari and Tariot 2008

---

**We can use information from multiple sources to improve diagnosis and assess treatment**

- **Neuronal Activity**
  - FDG PET

- **Fluid Biomarkers**
  - PIB-PET

- **Cognitive Reserve**
  - fMRI

- **Brain Atrophy**
  - Structural MRI

- **Genetic Risk Profile**
- **Cognitive, Functional Profile**
The Search for **New** Alzheimer’s Therapies

- Retool existing drugs
- Nutraceuticals
- Neurotransmitter-based therapies
- Neuroprotective drugs
- Nerve growth factor approaches
- Amyloid modulating drugs and biologics
- Tau modulating drugs and biologics
- Other approaches

www.banneralz.org/

---

Amyloid-related disease-modifying strategies

- APP gene
- Production
- APP
- Antisense
- Secretase inhibitors & modulators
- Aβ Monomer
- Aggregation
- Aβ Oligomer
- Fibrillogenesis modulators
- Aβ Fibril
- Diffuse Plaque
- Senile Plaque
- Immunotherapy
- Cu²⁺ Chelator

Courtesy of Dr. Norman Relkin, Weill Cornell Medical School, New York, NY.
**Why start treatment earlier, and why start studies now?**

- A “preclinical” stage of AD exists during which silent changes occur
  - Including changes in the amyloid cascade
- Earlier treatment may slow the progression of AD along this continuum
  - Maybe starting treatment before the brain is heavily damaged is better
- We have plausible experimental therapies to study
  - Like those that attack the amyloid protein
- We have clinical and biomarker measures of Alzheimer’s disease progression
- The urgent need

**Our plan to accelerate the study of “preclinical” (prevention) treatments for Alzheimer’s disease**

- Alzheimer’s disease prevention trials in people with normal memory who, based on their age & genetic background, are at very high risk for showing Alzheimer’s symptoms soon
  1. Early onset mutation carriers within 15 years of their estimated mean age at clinical onset
    i. *This is where we began, in partnership with Dr. Francisco Lopera, in Colombia*
    ii. *Initial funding from the National Institutes of Health*
  2. *APOE ε4* carriers close to their estimated age at clinical onset
  3. More trials to follow

*Reiman et al, Biomarkers Med 2010; Reiman et al, J Alzheimers Dis 2011*
When we planned the study, we had a number of challenges to deal with.
First, these genetic mutations are rare. How do we find people at high risk?
Antioquia, Colombia: a genetically isolated area with strong founder effect for an autosomal dominant mutation causing early onset AD.

A family tree with AD associated with a specific mutation, *E280A*, in the gene that codes for “*Presenilin 1*”

Source: Lopera et al, JAMA 1997
How do changes in memory and thinking occur over time? And how can we measure subtle changes before symptoms emerge?

The onset age of each stage of AD in the Colombian PSEN1 E280A families. (Acosta et al Lancet Neurology 2011)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Median Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-MCI Asymptomatic**</td>
<td>35.00</td>
</tr>
<tr>
<td>Pre-MCI Symptomatic#</td>
<td>38.01</td>
</tr>
<tr>
<td>MCI (Petersen)</td>
<td>44.01</td>
</tr>
<tr>
<td>Dementia</td>
<td>49.01</td>
</tr>
<tr>
<td>Death</td>
<td>59.01</td>
</tr>
</tbody>
</table>

CI 95% = Confidence Interval bootstrap 95%  
*Age range in years, according to exact survival time  
** objective cognitive impairment, no subjective symptoms  
# objective cognitive impairment, with very mild subjective symptoms
If we want to block the bad amyloid proteins from developing, when should we start treatment? At what age do these proteins show up?

Kindred ~ 25 known families with common ancestry
- N = 5000 living individuals
- 1000 with the E280A (Glu280Ala) Presinilin1 mutation
- Autosomal dominant, 100% penetrance
- Median age of MCI = 44 years old, dementia = 49 years old
When to treat? AD biomarkers vs age in PSEN1 E280A mutation carriers

Fleisher et al, Lancet Neurol 2012; JAMA Neurol (in press)

These families were willing to be studied, but they did not want to know whether or not they carry the gene that causes early onset Alzheimer’s disease in their families. How could we design a study to assure that?
Double-blind, placebo-controlled trial for up to 60 months crenezumab given as subcutaneous injections every 2 weeks

Primary endpoint: change in the API composite cognitive score
Also amyloid PET, FDG PET, MRI, CSF & cognitive/clinical endpoints

300 PSEN1 E280A kindred participants from Colombia

Launched 2nd half 2013 in partnership with Genentech

The Generation Study: Collaboration among academia, government and industry

- March 2014: Novartis was selected as API partner by an independent treatment selection
- July 2014: Collaboration agreement between Banner and Novartis signed
- Sept. 2015: Novartis entered co-development agreement for BACE-1 inhibitor with Amgen
- Additional philanthropic support obtained by Banner

* NIA award 1UF1AG046150, PI's Reiman, Tariot

54 | Generation Study | 4 Dec 2015 | DMC Kick-off meeting | Business Use Only
Why we are studying genetic disclosure in the APOE4 trial?

- Imagine a world in which testing for genetic risk for AD is widespread
  - To help decide about whether expensive diagnostic testing is needed
  - If any preclinical therapies are shown to delay the onset of symptoms due to Alzheimer's

1st API 1 trial in Colombia

At risk for early onset, familial AD

2nd API trial in people with 2 copies of the APOE 4 gene

At risk for late onset AD

Age 60-75

A4 (current)

At risk for late onset AD because of positive amyloid brain scan

Age 65-85

TOMMORROW

Age, APOE4, TOMM40

Closed to enrollment
Alzheimer’s Prevention Registry

- Launched in May 2012 to accelerate enrollment into prevention studies and raise awareness about Alzheimer’s prevention research
  - Intended to be a shared resource
  - IRB exempt
- Enrollees provide minimal information at sign-up. Receive emails with study opportunities; searchable Study Opportunities page
- Modeled after recruitment registries for other diseases (Army of Women, Fox Trial Finder)
- Complements other internet-based (Alzheimer’s Association TrialMatch, Brain Health Registry) and local registry efforts
- ClinicalTrials.gov Identifier: NCT02022943

www.endALZnow.org
GeneMatch

Novel program to conduct in-home genotyping for genetic risk for AD (APOE4 genotype)

- Online consent
- No genetic disclosure
- Information used to help match people to research studies; if study requires disclosure, disclosure and counseling provided via the particular study
- Presages era of possible widespread APOE genotyping if prevention trials are successful

RESOURCES

- Alzheimer's Prevention Registry
  - [www.endALZnow.org](http://www.endALZnow.org)
  - 1-888-STO-P-ALZ
  - info@endALZnow.org

- Banner Alzheimer's Institute
  - For research: 602-839-6500
  - For clinic appointment: 602-839-6900
  - [www.banneralz.org](http://www.banneralz.org)
## Acknowledgements of Support to API

**National Institute on Aging**  
RF1 AG041705, 1UF1AG046150, R01 AG031581, P30 AG19610, AMP (pending)

**Industry**  
Genentech, Avid/Eli Lilly, Novartis

**Foundations**  
Banner Alzheimer’s Foundation, FBRI, Nomis Foundation, Alzheimer’s Association,  
Flinn Foundation, Forget Me Not Initiative & Geoffrey Beene Foundation

**Colciencias**  
1115-408-20512, 1115-408-20543

**State of Arizona**  
Arizona Alzheimer’s Consortium

Our colleagues, collaborators, & supporters
Our valued research participants

---

### Can we DO anything to reduce risk? Possible Protective Factors for Dementia

- Mental activity
- Mid-life smoking cessation
- Aerobic exercise
- Diet low in animal fat  
  - Role of unsaturated
- Fish consumption
- Moderate wine intake
- Avoid head trauma
- Control blood pressure, cholesterol, diabetes

- Anti-inflammatory drugs?
- Antioxidants?  
  - Estrogen? (estradiol)
- Statins?
- Antihypertensives
- Antidiabetic agents?