Early Detection and Emerging Treatments in Alzheimer's Disease
Learning Objectives

• Update knowledge on our current understanding of the neurobiology and etiology of Alzheimer's disease

• Make informed decisions regarding the use of clinical tools and biomarkers in the screening, diagnosis, and management of Alzheimer's disease

• Recognize and manage comorbid conditions in patients with Alzheimer's disease
Betty is an 82-year-old patient with Alzheimer's dementia. Seven years ago, she exhibited some symptoms of mild cognitive impairment. Biomarker testing of Betty during this prodromal period would likely have revealed:

1. Increased CSF Aβ42
2. Increased brain Aβ42 using PET imaging
3. Both of the above
4. Neither of the above
A disease of survivors

1 in 10 is 65 years or older; 40% are 85 years or older across nation

Rivals heart disease and cancer as a cause of death

Most costly disease; cost estimated at $200 billion US, $15 billion Florida; nationally exceeds cancer and equals heart disease

Delaying institutionalization by 5 years saves half the cost

Alois Alzheimer (1907)

- "A woman 51 years old showed jealousy towards her husband. Soon a rapidly increasing loss of memory could be noticed. She could not find her way around her own apartment." (comments on Auguste D.)
- "I feel I have lost myself." (comment from Auguste D.)
- Originally reserved for only those cases with onset before 65 Y; presenile dementia; common pathology has extended the definition to all ages
Alzheimer's Pathology

- Autopsy of Auguste D. revealed 2 key features when stained with silver
- Neuritic plaques outside cells
- Neurofibrillary tangles inside cells
**Alzheimer A.** 37th meeting of psychiatrists from south Germany in Tübingen, 1906


12 patients
10 controls, 10 psychosis, 45 neurosyphilis
Cholinergic Hypothesis (1980s)

• Finds that aged people with dementia also have Alzheimer-type pathology
• Finds early declines in acetylcholine in Alzheimer brain
• Leads to drugs that boost acetylcholine, like Aricept
Amyloid Hypothesis (1990s)

• A protein breakdown product called Aβ forms fibrils that aggregate outside cells; these plaques attract "dystrophic neurites" from neurons, disrupting function
• Causes inflammatory reaction of glial cells
• Presumably leads to neurodegeneration
• Mutations causing Alzheimer's (rare; 1% of cases) increase production of long Aβ (42 vs. 40 amino acids)
• In mouse models, memory is lost, but degeneration is not present with amyloid plaques
• Amyloid deposition occurs 10-20 years before symptoms
Alzheimer's Pathology

- Extracellular plaques composed of amyloid β (Aβ)
- Intracellular neurofibrillary tangles composed of tau
- Synaptic dysfunction and neuronal cell loss

Pathology Progression

1. Entorhinal cortex
2. Hippocampus/amygdala
3. Parahippocampus
4. Temporal neocortex
5. Neocortical association areas
Amyloid Precursor Protein (APP) Processing: Non-amyloidogenic
Amyloid Precursor Protein (APP) Processing: Amyloidogenic

- **β-secretase**
- **γ-secretase** (Presenilins)
- **Aβ**
- Plaque formation

Aβ also acts as a transcription factor; binding to the Aβ-interacting domain (AβID) of APP and β-amyloid cleaving enzyme (BACE) genes increases the expression of both APP and β-secretase.

Tau Filaments: Tangle Hypothesis (2000s)

- Normally tau is in neuronal axons; in Alzheimer's disease (AD), it is found in dendrites and cell bodies.
- Tau can aggregate within neurons, forming neurofibrillary tangles.
- Tangles are virtually indestructible; leave "tombstone tangle" after neuron dies.
- Tau mutations cause frontal lobe dementia (distinct from AD); also involved in supranuclear palsy, Pick's disease, corticobasal degeneration.
Tau Protein

- Located primarily in axons
- Normally promotes tubulin assembly into microtubules
- Tubulin binding of tau is regulated by its phosphorylation state
  - Kinases phosphorylate tau
  - Phosphatases dephosphorylate tau

Hyperphosphorylated Tau

- Aβ activates many of the kinases that phosphorylate tau
- Intracellular trafficking is disrupted
- Hyperphosphorylated tau aggregates into neurofibrillary tangles (NFTs)
- Density of NFTs is correlated with dementia severity

# Genetics of Alzheimer's Disease

<table>
<thead>
<tr>
<th>Type of Alzheimer's</th>
<th>Age of onset</th>
<th>Inheritance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial (1%)</td>
<td>40s-50s</td>
<td>Autosomal dominant</td>
<td>Mutations in amyloid precursor protein, presenilin-1, or presenilin-2 account for most cases; Down syndrome has extra gene dosage</td>
</tr>
<tr>
<td>Inherited risk (30-50%)</td>
<td>60s-70s</td>
<td>Not dominant</td>
<td>Apolipoprotein E4 allele increases risk (earlier age of onset); pathology more severe; inflammation genes TREM2</td>
</tr>
<tr>
<td>Sporadic (50-70%)</td>
<td>70s-80s</td>
<td>None identified</td>
<td>Increased risk: head trauma, aluminum(?); Decreased risk: cigarettes, education</td>
</tr>
</tbody>
</table>
Increased Risk Factors for AD

• Apolipoprotein Eε4 (APOEε4) is a risk factor gene
  – APOEε4 homozygotes: 10x increase lifetime risk
  – APOEε4 heterozygotes 3x increase
  – Still, some APOEε4 cases never develop dementia
  – Increases risk for heart disease and other neurodegenerative disorders

• Other risk factors include:
  – Diabetes
  – Depression
  – African American race
  – Cardiovascular disease
  – Head injury

  • AD is 19-fold more common in NFL players
  • Dementia pugilistica in boxers; CTE primarily tau

Decreased Risk for AD

- Amyloid precursor protein polymorphism that reduces BACE cleavage
- Exercise
- Moderate and healthy dietary practices
- Long-term use of NSAIDs
- Education results in later onset
- Social engagement

Emerging View of Alzheimer's Pathology (2010s)

- Because of age, life events, and/or genetics, amyloid deposits form within the brain over decades (before disease)
- Amyloid can affect memory but does not alone destroy neurons or the connections between them (synapses); amyloid initiates the formation of tau filaments (tangles) within neurons
Biomarkers for Alzheimer's

• Hippocampal atrophy on MRI
• Temporal-parietal hypometabolism on FDG-PET
• Positive amyloid PET
• CSF tau:Aβ ratio (increased tau, decreased Aβ)
• Genetic mutation in presenilin genes (early onset AD)
• Eye tests for amyloid
Magnetic Resonance Imaging (MRI)

• Detects regional (medial temporal lobe) atrophy in AD
  – Entorhinal cortex, hippocampus, amygdala, and parahippocampus

• Even mildly affected individuals have:
  – 20-30% loss in entorhinal cortex volume
  – 15-25% loss in hippocampal volume
  – Ventricular enlargement

• Atrophy patterns can overlap with other diseases, and AD may have an atypical presentation

18F-2-Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography (FDG-PET)

- Indirect measure of synaptic activity (glucose metabolism)
- FDG-PET abnormalities in AD may reflect:
  - Expression of specific genes
  - Mitochondrial dysfunction
  - Oxidative stress
  - Aberrant synaptic plasticity
  - Excitotoxicity
  - Glial activation and inflammation
  - Reduced cerebral blood flow
  - Synapse loss and/or cell death
- Predictive of ultimate development of AD in cognitively normal individuals

Amyloid Imaging

• In vivo surrogate for Aβ pathology

• Utilizes PET imaging of tracers that bind to Aβ
  – Pittsburgh Compound B (PiB)
  – Florbetapir
  – Florbetaben
  – Flutemetamol

• Stabilize at the prodromal stage despite continued cognitive decline

• Amyloid binding is seen in 20-40% of cognitively normal elderly; indicative of impending AD?

• Cost and availability are the major deterrents to the widespread use of amyloid tracers in clinical practice

Florbetapir F18 (Amyvid)
FDA-Approved for Clinical Use

• To be used to rule out—not diagnose—Alzheimer's disease
  – A negative scan indicates that no Aβ plaques are present; thus, AD is not the cause of cognitive decline
  – A positive scan does not necessarily establish a diagnosis of AD

• Inter-reader reliability is being improved by a binary method of reading the scans as well as a 3-hour online training program for radiologists and nuclear medicine physicians

• Compared to other Aβ tracers
  – Faster kinetics enables shorter imaging procedures
  – Longer half-life allows for regional preparation and shipping of doses

• Cost ($2600/injection just for radioligand) may limit its use; currently not covered by Medicare

Cerebrospinal Fluid (CSF) Biomarkers

- Aβ42 levels are lower in the CSF of patients with AD
  - Increased deposition of Aβ42 into plaques?
  - Decreased synaptic activity or cells producing Aβ?
- Tau and phospho-tau levels are increased in the CSF of patients with AD
  - Increased neurodegeneration

Alzheimer's Begins Years Before Symptoms Emerge

People considered clinically "normal." No MCI or dementia over 65 Y.

<table>
<thead>
<tr>
<th>STAGES OF PRECLINICAL ALZHEIMER'S DISEASE</th>
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<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>-------</td>
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<tr>
<td>0</td>
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<tr>
<td>1</td>
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<td>2</td>
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<tr>
<td>3</td>
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<tr>
<td>SNAP</td>
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</tbody>
</table>

Amyloid: either PET positive or CSF ELISA below cutoff

Degeneration: atrophy of HC/CX on MRI, increased tau/p-tau by CSF-ELISA, or decreased HC/CX signal by FDG-PET

Cognitive Function: score 10th percentile or lower for age group on tests of memory function

From AAIC 2013 presentations by Vos et al and Knopman et al
DIAGNOSING ALZHEIMER'S DISEASE
What is Dementia?

• A syndrome of *acquired, persistent* intellectual impairment

• Characterized by memory loss

• Must have deficits in at least 1 other cognitive function (aphasia, apraxia, agnosia, executive dysfunction)

• Produces occupational or social disability
Many Causes of Dementia

- **Cerebral neuronal degenerations**
  - Alzheimer's disease
  - Frontotemporal dementia/Pick's disease
  - Lewy body dementia
  - Parkinson's disease and Parkinson's plus syndromes
  - Huntington's disease

- **Acquired cerebral disorders**
  - Vascular dementia
  - Multiple sclerosis
  - Intracranial neoplasms
  - Trauma
  - Hydrocephalus
  - Transmissible spongiform encephalopathies

- **Other disorders** (some potentially reversible)
  - Drugs/pharmaceuticals, alcohol, B12/vitamin deficiencies, endocrinopathies (thyroid)
  - AIDS, tertiary syphilis, tuberculosis, cryptococcal meningitis, encephalitis
  - Carbon monoxide, irradiation, heavy metals, organics (paint fumes)
  - Major depression (AKA "pseudodementia")
Dementia: Making a Diagnosis

- Good clinical history gathered from a close observer of the patient
- Patient interview and examination (mental status, neuro, physical)
- Lab data
- Imaging (MRI, CT, PET) and other biomarkers
- Neuropsych testing
Major Paradigm Shift in the Definition of Alzheimer's (2011)

- **Stage 1: Preclinical**
  - Positive biomarkers but no symptoms

- **Stage 2: Mild cognitive impairment (MCI)**
  - Short-term memory problems without functional impairment

- **Stage 3: Dementia**
  - Memory loss plus other cognitive loss, functional decline

### Brief Cognitive Screening Tests for Assessing Dementia

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short Blessed Test (SBT)</strong></td>
<td>6-item weighted version of the Information–Memory–Concentration Test; usually completed in 5 min; good correlation with AD pathology</td>
</tr>
<tr>
<td><strong>Mini-Mental Status Examination (MMSE)</strong></td>
<td>19 items measuring orientation, memory, concentration, language, and praxis; most widely used screening test</td>
</tr>
<tr>
<td><strong>Alzheimer's Disease Assessment Scale—cognitive subscale (ADAS-cog)</strong></td>
<td>A 20-minute, 70-point scale with 11-14 items that tests memory, language, orientation, and praxis</td>
</tr>
<tr>
<td><strong>7-Minute Screen</strong></td>
<td>4 tests (orientation, memory, clock drawing, and verbal fluency)</td>
</tr>
<tr>
<td><strong>General Practitioner Assessment of Cognition (GPCOG)</strong></td>
<td>A 6-item screening test similar to the SBT, a clock drawing, and a 5-item informant questionnaire</td>
</tr>
<tr>
<td><strong>Montreal Cognitive Assessment (MoCA)</strong></td>
<td>An 8-item, 20-minute evaluation measuring attention, concentration, executive function, language, conceptual thinking, and orientation; 30 points total with 26 or above considered normal</td>
</tr>
</tbody>
</table>

Symptomatic Pre-dementia (Mild Cognitive Impairment (MCI))

- Concern regarding cognition
  - Patient-, informant-, or clinician-observed

- Impairment in 1 or more cognitive domains
  - Memory, executive function, attention, language, and visuospatial skills

- Preservation of independence in functional abilities

- Failure to meet criteria for dementia

- Other systemic causes and medical conditions ruled out

All-Cause Dementia

- Patient must exhibit at least 2 of the 5 following criteria:
  - Impaired reasoning or handling of complex tasks
  - Impaired visuospatial abilities
  - Impaired language
  - Impaired ability to retain new information
  - Changes in personality

Probable AD Dementia

- Patient must meet criteria for all-cause dementia plus all 4 of the following criteria:
  - Gradual onset of symptoms
  - History of worsening cognition
  - Initial and most prominent cognitive deficits are impairment in learning and recall, language impairment, visuospatial deficits, and executive function disruption; at least 2 cognitive domains must be present
  - No evidence of substantial cerebrovascular disease
Probable Dementia With Increased Level of Certainty

- Probable AD dementia with documented decline
- Probable AD dementia in a carrier of a causative genetic mutation (APP, PSEN1, PSEN2)
- Probable AD dementia with evidence of AD pathophysiological process
  - Biomarkers of AD deposition (CSF Aβ or PET Aβ imaging)
  - Biomarkers of neurodegeneration (CSF tau)
  - Biomarkers of metabolic dysfunction in temporoparietal regions (FDG-PET)
Dementia: Stages of Decline

• **Early/mild**: forgetfulness; short-term memory loss; misplaces items; trouble with complicated tasks; searches for words

• **Middle/moderate**: increased language problem; forgets major events; may need help dressing, cooking; may have a decrease in personal hygiene

• **Late/severe**: verbal communication dwindles; needs help eating, bathing; significant long-term memory loss; decline in motor abilities; does not recognize family members
Possible AD Dementia

• Meets core clinical criteria of AD dementia but has an atypical course or an etiologically mixed presentation
  – Sudden onset of cognitive impairment
  – Insufficient historical detail of impairment
  – Evidence of objective progressive decline
  – Concomitant cerebrovascular disease
  – Features of dementia with Lewy bodies
  – Clinical evidence of another neurological disease, medical comorbidity, or medication use that could affect cognition

• As with probable dementia, biomarkers and genetic information provide increased certainty of the diagnosis

## Differential Diagnosis: Clinical Presentation

<table>
<thead>
<tr>
<th>Normal Aging</th>
<th>AD (Alzheimer's disease)</th>
<th>VaD (Vascular dementia)</th>
<th>DLB (Dementia w/ Lewy bodies)</th>
<th>FTLD (Frontotemporal lobe dementia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Reduced speed of mental processing and choice reaction times</td>
<td>• Short-term memory loss, impaired executive function, difficulty with activities of daily living, time and spatial disorientation, language impairment, personality changes</td>
<td>• Impaired abstraction, mental flexibility, processing speed, and working memory</td>
<td>• Visual hallucinations</td>
<td>• Progressive behavioral and personality changes that impair social conduct (apathy, disinhibition, etc.)</td>
</tr>
<tr>
<td>• Benign forgetfulness that is mild, inconsistent, and not associated with functional impairment</td>
<td>• Verbal memory is better preserved</td>
<td>• Slower cognitive decline</td>
<td>• Spontaneous parkinsonism</td>
<td>• Language impairment</td>
</tr>
<tr>
<td></td>
<td>• Dementia occurs within several months of a stroke</td>
<td>• Memory impairment is not as severe</td>
<td>• Cognitive fluctuations</td>
<td>• Possibly preserved episodic memory</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Visuospatial, attention, and executive function deficits are worse</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Earlier presentation of psychosis and personality changes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• REM sleep disturbances</td>
<td></td>
</tr>
</tbody>
</table>

Differential Diagnosis

<table>
<thead>
<tr>
<th>MRI</th>
<th>AD</th>
<th>VaD</th>
<th>DLB</th>
<th>FTLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial temporal lobe atrophy</td>
<td>Medial temporal lobe atrophy; white matter abnormalities</td>
<td>Medial temporal lobe atrophy</td>
<td>Frontotemporal lobe atrophy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FDG-PET</th>
<th>AD</th>
<th>VaD</th>
<th>DLB</th>
<th>FTLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporoparietal cortices</td>
<td>Fronto-subcortical networks</td>
<td>Parieto-occipital and temporoparietal cortices</td>
<td>Frontotemporal cortices</td>
<td></td>
</tr>
</tbody>
</table>

- The clinical presentation, volume loss (MRI), and metabolic deficits (FDG-PET) of each disorder have characteristic patterns but often overlap, making differential diagnosis difficult.
- Amyloid imaging and the use of CSF biomarkers can provide key information for making a differential diagnosis.

Why Bother With Early Diagnosis?

• There is currently no effective treatment for AD; however, early diagnosis can improve planning regarding safety issues (e.g., driving), finances, advance directives, and living arrangements

• Early detection allows for more effective and efficient testing of potential therapeutic interventions

• When treatment options do become available, early intervention will likely be imperative
  – By the time clinical symptoms manifest, AD pathology has progressed significantly, and treatment is likely too late

Treatment: Present and Future

Increased production/reduced degradation of Aβ

Plaque formation

Hyperphosphorylation of tau

NFT formation

Synaptic dysfunction and neuron loss

Memory loss/cognitive deficits

Diagnosis and treatment usually start here

Too late?
Currently Available Treatments for Alzheimer's Disease

- **Cholinesterase inhibitors**
  - Increase the availability of ACh to compensate for lost cholinergic neurons
  - Donepezil, rivastigmine, and galantamine

- **N-methyl-D-aspartate (NMDA) antagonist**
  - Memantine
    - Approved for moderate to severe AD

- At best, available treatments provide moderate symptom benefit but do not modify clinical course

- Can delay institutionalization up to 2 years

Geldmacher DS. JAGS 2003;51:937.
Alzheimer's Meds: Side Effects

• **Cholinesterase inhibitors**: mainly GI (nausea, vomiting, diarrhea, anorexia)
  – Also leg cramps, runny nose, excessive salivation, dizziness, vivid dreams
  – Skin irritation with Exelon Patch

• **Namenda**: transient increase in confusion, dizziness, headaches, constipation

• All the drugs have a titration schedule that helps to minimize side effects
**Donepezil**
- Reversible, long-acting, selective inhibitor of acetylcholinesterase
- Available as a once-daily formulation
- Mostly transient gastrointestinal side effects
- Approved for mild to severe AD

**Rivastigmine**
- Pseudo-irreversible, intermediate-acting inhibitor of neuronal acetylcholinesterase and glial butrylcholinesterase
- Most common side effects are gastrointestinal
- Side effects can be reduced with transdermal formulation
- Approved for mild to moderate AD

**Galantamine**
- Inhibitor of acetylcholinesterase
- Also a positive allosteric modulator of nicotinic cholinergic receptors
- Available as a once-daily formulation
- Approved for mild to moderate AD

Donepezil Actions

AChE: acetylcholinesterase
BuChE: butyrylcholinesterase

Donepezil Actions

central ACh neuron

AChE

glial cell

BuChE

donepezil

AChE

NMDA Receptor

Glutamate

Glycine

Ca$^{2+}$

memory problems

free radical
Memantine Actions

Mg$^{2+}$

Glutamate

Glycine

Ca$^{2+}$
## Cholinesterase Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Doses Per Day</th>
<th>CYP 450 2D6</th>
<th>BuChE Inhibition</th>
<th>Nausea</th>
<th>Vomit</th>
<th>Diarrhea</th>
<th>Anorexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>1</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>2</td>
<td>-</td>
<td>+</td>
<td>++++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Galantamine</td>
<td>1 or 2</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Aricept is generally used first. Surprisingly, if not effective, another cholinesterase inhibitor can benefit the patient in 50% of cases. Therapeutic failure is not a class effect with these drugs.
Nonpharmacological Treatments

• Cognitive training to teach strategies and skills aimed at improving cognitive functioning
  – Moderate effect size in patients with AD

• Reality orientation and cognitive stimulation therapy
  – Benefits in cognition and quality of life have been shown in patients with AD

• While improvements in tasks similar to the tests are observed, there is presently no evidence for modifying the rate of disease change or the risk of developing the disease

Treatment Algorithm

**SCREEN**
all elderly patients with memory complaint

**DIAGNOSE AND TREAT**
- Evaluate cognition, function, and behavior
- Treat at time of diagnosis
- Consider implementing nonpharmacological interventions

**SCREEN**

**CONSIDER**
- MILD
  - CONSIDER TREATMENT WITH ChEI
- MODERATE
  - CONSIDER TREATMENT WITH ChEI + memantine
- SEVERE
  - CONSIDER TREATMENT WITH memantine; add a ChEI as needed

**PERFORM**
on-going monitoring and evaluation

**RE-EVALUATE**
within 2 months and monitor every 6 months

**COUNSEL**
patients and caregivers about treatment expectations

**CONSIDER**
potentially reversible causes of cognitive impairment if patient on anti-dementia therapy is showing rapid decline

**PROVIDE**
geriatric care management and counseling and refer patients and caregivers to AD support groups

**DISCONTINUE TREATMENT**
when patients advance to loss of all cognitive and functional abilities

Common Secondary Behavioral Symptoms of AD

- Behavioral and psychological symptoms of dementia are frequent among patients with AD
  - Agitation and aggression
  - Hallucinations and delusions
  - Depression and apathy
  - Incontinence

- These are often the most disturbing symptoms to family and caregivers and the most common reason for institutionalization

- Agitation/aggression may be triggered by pain, fecal impaction, medical illness, boredom, loneliness, depression, or social/environmental stress

Managing Aggression/Agitation in AD

• Carbamazepine
• Trazodone
• Antipsychotics
  – Black box warning for use in patients with dementia
  – Use lowest possible dose for short term
  – Avoid use in patients with cardiovascular or pulmonary disease
• Anxiolytics and hypnotics
  – May increase confusion
• Valproate
• Benzodiazepines
  – Not generally recommended, but short-term use for episodes of agitation/anxiety may be useful

Managing Mood Symptoms in AD

• Methylphenidate may be useful for apathy

• Antidepressants
  – Data is limited
  – Choose an antidepressant with minimal anticholinergic effects, such as sertraline or citalopram

Avoid BAD MEDS for OLD PEOPLE!

• Benadryl, tricyclics for sleep
• Oxybutynin for overactive bladder. NO!
• Cipro for "everything"
• Benzodiazepines
• Debate over HRT in women with dementia
• Always pick the least anticholinergic drug!
  – Example: PEPCID over Tagamet, Zantac
We can now determine fairly reliably who will develop AD. What can we do about it?

EMERGING TREATMENTS
Treatment Strategies

- **Block Aβ production**
  - Promote α-secretase
  - Inhibit β-secretase
  - Inhibit γ-secretase

- **Decrease Aβ aggregation**

- **Increase Aβ clearance**

- **Decrease tau phosphorylation or aggregation**

- **Other**
  - Modulate glutamate receptor function
  - Enhance mitochondrial function
  - Decrease inflammation
  - Lower cholesterol
  - Enhance neuroprotection/growth

Treatments on Trial

Immunization: The Most Promising Treatment in Development?

- Intravenous human immunoglobulin (Gammagard)
  - Phase 2-3 study failed to show benefit

- Active immunization with Aβ peptide
  - Halted due to meningoencephalitis

- Passive immunization with antibodies against Aβ
  - Bapineuzumab
    - Humanized mouse monoclonal antibody against amino terminal of Aβ
    - Phase II trials indicate that APOE ε4 carriers require a lower dose
  - Solanezumab
    - Humanized mouse monoclonal antibody against midportion of Aβ; 25% slowing in mild AD patients
  - Crenezumab
    - Humanized mouse monoclonal antibody that binds Aβ oligomers and fibrils with high affinity and monomers with lower affinity
    - IG4 backbone causes less microglial activation

Prevention Studies in Alzheimer's

- **Alzheimer's Prevention Initiative (API)**. Familial AD all with same mutation in extended South American family.
  - 300 cases. 100 mPS1+ given crenezumab; 100 mPS1+ given placebo; 100 mPS1- given placebo. Genotype not divulged.

- **Dominantly Inherited Alzheimer Network (DIAN)**. Mixed mutations in 4 countries. Genotype not divulged.
  - 160 cases. 3 drugs and 1 placebo. 2 of 3 drugs are antibodies: solanezumab and gantenerumab.

- **Anti-amyloid Treatment in Asymptomatic Alzheimer's (A4)**. Cognitively normal cases over 70 positive for an amyloid biomarker.
  - 1000 cases. 500 treatment/500 placebo. Solanezumab. May add BACE inhibitor arm later. Amyloid status is divulged.

Summary

• Our understanding of the etiology and pathogenesis of AD continues to expand

• There are currently 4 options available for the treatment of cognitive symptoms of AD and numerous options available for the treatment of comorbid behavioral symptoms

• Recent advancements in neuroimaging and CSF biomarkers have dramatically improved our ability to detect AD early in the course of the disease and make a differential diagnosis

• Early detection (prior to the onset of clinical symptoms) is essential so that potentially disease modifying treatments can be utilized before too much pathology has accumulated

• Many novel therapeutic strategies, including immunization, are in development
Appendix

• The Alzheimer's Prevention Initiative has provided an online registry for people interested in joining future Alzheimer's treatment trials

  http://www.endalznow.org/

• An excellent source of information regarding Alzheimer's disease research, treatments, resources, etc. is the Alzheimer Research Forum

  http://www.alzforum.org