Hope on the Horizon: An Update on the Early Detection and Treatment of Alzheimer's Disease
Learning Objectives

• Update knowledge on the neurobiology and etiology of Alzheimer's disease and other dementias

• Assess for possible Alzheimer's disease and other dementias as early as possible in the course of illness

• Compare and contrast the utility of currently available treatments for various dementias

• Investigate the state of the research being performed to improve early diagnosis and develop novel treatments for Alzheimer's disease
Richard is an 81-year-old patient with Alzheimer's dementia. Seven years ago, he exhibited some symptoms of mild cognitive impairment. Biomarker testing of Richard 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
Dave is a 61-year-old man with familial Alzheimer’s disease. He carries a mutation in the amyloid precursor protein (APP) gene that causes increased production of amyloid beta. Which of the following enzymes are involved in the amyloidogenic processing of APP?

1. Alpha-secretase
2. Beta-secretase
3. Gamma-secretase
4. 1 and 2 only
5. 2 and 3 only
Fiona is a 37-year-old woman with a family history of Alzheimer’s disease. She and her 59-year-old father are interested in enrolling in one of the Alzheimer's prevention studies designed to test the efficacy of potential treatments. Treatments currently being investigated for Alzheimer’s include:

1. Intravenous human immunoglobulin
2. Active immunization with Aβ peptide
3. Passive immunization with antibodies against Aβ
4. All of the above
5. None of the above
• A disease of survivors
• 1 in 9 persons aged 65 and older has AD
• Every 67 seconds, someone in the US develops AD
• Cost exceeds that of cancer and equals that of heart disease
• Delaying institutionalization by 5 years saves half the cost
• Rivals heart disease and cancer as a cause of death

Death From AD Is on the Rise

Percentage Changes in Selected Causes of Death (All Ages) Between 2000 and 2013

- Breast cancer: -2%
- Prostate cancer: -11%
- Heart disease: -14%
- Stroke: -23%
- HIV: -52%
- Alzheimer's disease: +71%

Alzheimer's Pathology

- Extracellular plaques composed of amyloid β (Aβ)
- Intracellular neurofibrillary tangles composed of tau
- Synaptic dysfunction and neuronal cell loss
Amyloid Precursor Protein (APP) Processing: Non-amyloidogenic
Amyloid Precursor Protein (APP) Processing: Amyloidogenic

Amyloid Precursor Protein (APP) Processing:
Amyloidogenic

β-secretase

γ-secretase
(Presenilins)

Plaque formation

Why Do We Make Aβ?

- Antioxidant properties?
- Chelation of metal ions?
- Regulation of cholesterol transport?
- Vessel repair?
  - Throughout its lifespan, Aβ may act as a sealant at sites of injury or leakage on vessel walls
  - Protects from acute brain injury but may increase the risk of developing dementia in old age

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 for AD

- Apolipoprotein E4 (APOEε4) is a risk factor gene
  - APOEε4 homozygotes: 10x increase in 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
    - Chronic traumatic encephalopathy (CTE) in athletes and military personnel with repetitive head injuries

Decreased Risk for AD

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

Amyloid Cascade Hypothesis

- Increased production/reduced degradation of Aβ
- Plaque formation
- Hyperphosphorylation of tau
- NFT formation
- Synaptic dysfunction and neuron loss
- Memory loss/cognitive deficits

Biomarkers for Alzheimer's

- Hippocampal atrophy on MRI
- Temporoparietal 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

Functional MRI (fMRI)

• Indirect measure of neuronal activity (blood-oxygen level-dependent MR signal)

• During the encoding of new information, patients with AD show:
  – Decreased hippocampal activity
  – Increased prefrontal activity
    • Compensatory
    • May be a marker for impending neuronal failure

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

Herrmann N et al. Drugs 2011;71(15):2031-65;
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 ($2,600/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

Herrmann N et al. Drugs 2011;71(15):2031-65;
• Tau may be used as a surrogate marker of cognition
• Tracers may help predict cognitive decline and disease progression
• Several tau-PET tracers in development show promise
  – 18F-FDDNP
  – 18F-THK523
  – 18F-THK5105
  – 18F-THK5117
  – 18F-THK5351
  – 18F-T807
  – 18F-T808
  – 18F-N-methyl lansoprazole
  – 11C-N-methyl lansoprazole
  – 11C-PBB3

Biomarker Progression

- Aβ42 biomarkers may already be altered as many as 10 years before symptoms of AD manifest

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>PRECLINICAL</th>
<th>PRODROMAL (MCI)</th>
<th>DEMENTIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Features</td>
<td>Asymptomatic</td>
<td>Symptomatic/Non-demented</td>
<td>Symptomatic/Demented</td>
</tr>
<tr>
<td>↑ PET amyloid</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>↓ CSF Aβ42</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>↑ CSF tau</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>↓ FDG-PET</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>↑ MRI atrophy</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
</tr>
</tbody>
</table>
Alzheimer's Begins Years Before Symptoms Emerge

Who Will Progress From MCI to AD?

• Only ~60% of patients with MCI will progress to AD
  – 1/3 of patients with MCI will return to normal cognition

• Characteristics of patients with MCI who progress to AD
  – Impairment in episodic memory
  – Presence of neuropsychiatric or depressive symptoms
  – Temporoparietal hypometabolism (FDG-PET)
  – Aβ42 and tau CSF biomarkers
  – Aβ42 PET imaging

### Predicting Conversion to Dementia

Individuals >65 years old considered clinically "normal" (no MCI or dementia)

<table>
<thead>
<tr>
<th>STAGES OF PRECLINICAL ALZHEIMER’S DISEASE</th>
<th>Stage</th>
<th>Amyloid</th>
<th>Degeneration</th>
<th>10th Percentile Cogn Fnxn</th>
<th>% of Individuals</th>
<th>% Conversion Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>45</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>SNAP</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>20</td>
<td>7</td>
</tr>
</tbody>
</table>

SNAP: suspected non-amyloid pathology.

DIAGNOSING ALZHEIMER'S DISEASE
Dementia: Stages of Decline

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

- **Middle/moderate**: increased language problems; 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
Initial Diagnosis

• A detailed history should be obtained from the patient and a well-acquainted informant to determine onset, course, progression, and characteristics of cognitive and functional decline
  – Patients with AD do not usually complain of their own memory loss

**Determine risk factors**
- Previous vascular disease
- Hypertension
- Diabetes
- Lipid disorders
- Head trauma
- Family history of dementia

**Screen for alternate causes of cognitive deficits**
- Hyperthyroidism
- Vitamin B12 deficiency
- Depression
- Brain pathology (e.g., subdural hematoma, neoplasm, hydrocephalus)

# Brief Cognitive Screening Tests for Assessing Dementia

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</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, 11-item, 70-point scale 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>Clock Drawing</strong></td>
<td>Single test measuring multiple cognitive domains; requires minimal training; multiple scoring systems with proven validity</td>
</tr>
</tbody>
</table>

The Old Way of Diagnosing AD

• Neurological testing for tentative diagnosis
  – Limited by variability in individual performance and cultural, ethnic, and educational factors
  – Inter-individual comparison (compared to age-matched individuals)
  – Symptoms often overlap with other forms of dementia
  – Memory loss is a required symptom in the diagnostic criteria

• Postmortem evaluation of AD pathology to confirm diagnosis
- Asymptomatic preclinical phase
- Symptomatic pre-dementia (mild cognitive impairment (MCI))
- All-cause dementia
- Probable AD dementia
- Possible AD dementia
- Probable or possible AD dementia with evidence of AD pathophysiological process

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

- Cognitive/neuropsychiatric symptoms that interfere with ability to perform usual activities
- Decline from previous levels of functioning
- Not attributable to delirium or a major psychiatric disorder
- Cognitive impairment diagnosed through neuropsychological testing or patient informant
- Cognitive impairment involves 2 of the following:
  - Impaired ability to acquire/retain new information
  - Reasoning impairment
  - Visuospatial impairment
  - Changes in personality or behavior

POSSIBLE AD DEMENTIA

- Atypical course
- Etiologically mixed presentation

WITH EVIDENCE OF AD PATHOPHYSIOLOGY

- Positive for AD biomarkers
- Postmortem neuropathology

Dementia w/ Lewy bodies

Cerebrovascular disease

Frontotemporal dementia

AD DEMENTIA

- Postmortem AD neuropathology

Probable AD DEMENTIA

- Insidious onset
- History of worsening cognition
- Most prominent cognitive deficits include 1 of the following:
  - Amnestic presentation
  - Nonamnestic language presentation
  - Nonamnestic visuospatial presentation
  - Nonamnestic executive function
- No evidence of another form of dementia, medical comorbidity, or medication as the cause of cognitive deficits

WITH INCREASED LEVEL OF CERTAINTY

- Documented cognitive decline
- Genetic mutation in APP or PSEN

WITH EVIDENCE OF AD PATHOPHYSIOLOGY

- Positive for AD biomarkers

<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>
</tbody>
</table>

### Differential Diagnosis: Neuroimaging

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>VaD</th>
<th>DLB</th>
<th>FTLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Medial temporal lobe atrophy</td>
<td>Medial temporal lobe atrophy; white matter</td>
<td>Medial temporal lobe atrophy</td>
<td>Frontal/temporal lobe atrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDG-PET</td>
<td>Temporoparietal cortices</td>
<td>Fronto-subcortical networks</td>
<td>Parieto-occipital and temporoparietal cortices</td>
<td>Frontotemporal cortices</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 need to start here.

Too late?
TREATING ALZHEIMER'S DISEASE AND COMORBIDITIES
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
- In 2014, a once daily combination of donepezil and memantine was FDA-approved
- 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 Medications: Side Effects

• **Cholinesterase inhibitors**
  – Mainly GI (nausea, vomiting, diarrhea, anorexia)
  – Also leg cramps, runny nose, excessive salivation, dizziness, vivid dreams
  – Skin irritation with rivastigmine patch

• **Memantine**
  – Transient increase in confusion, dizziness, headaches, constipation

• Titration schedules are recommended to help to minimize side effects
Cholinesterase Inhibitors (ChEI)

**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 butyrylcholinesterase
- 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

Rivastigmine Actions

Rivastigmine Actions

Galantamine Actions

Galantamine Actions: Nicotinic Allosteric Modulation

Galantamine Actions: Nicotinic Allosteric Modulation

NMDA Receptor

Glutamate
Glycine

Mg

Ca²⁺

memory problems

free radicals

free radicals

Copyright
Memantine Actions

Ca$^{2+}$

Glutamate

Glycine

Mg$^{2+}$

memantine
## 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>

Donepezil is generally used first. 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

**PERFORM**
ongoing monitoring and evaluation

**MILD**
CONSIDER TREATMENT WITH ChEI

**MODERATE**
CONSIDER TREATMENT WITH ChEI + memantine

**SEVERE**
CONSIDER TREATMENT WITH memantine; add a ChEI as needed

**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 a patient on antideementia 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
- Dextromethorphan/quinidine

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

Antipsychotics in Elderly Patients With Dementia

- Conventional antipsychotics confer the greatest risk of mortality in this population

Medications That May Be Contraindicated in the Elderly Population

• Benadryl, tricyclics for sleep
• Oxybutynin for overactive bladder
• Cipro
• Benzodiazepines
• Debate over hormone replacement therapy in women with dementia
• Always pick the least anticholinergic drug
  – Example: Pepcid over Tagamet, Zantac
EMERGING TREATMENTS

We can now determine fairly reliably who will develop AD. What can we do about it?
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

Current Phase 2/3 Trials

- Intravenous human immunoglobulin
  - Gamunex (Phase 2/3)
- Active immunization with $\text{A}\beta$ peptide
  - CAD106 (Phase 2/3)
- Passive immunization with antibodies against $\text{A}\beta$
  - Gantenerumab (Phase 3)
  - Solanezumab (Phase 3)
  - Crenezumab (Phase 2)
  - Aducanumab (Phase 3)
  - Ongoing 18-month treatment of 1,350 people with MCI due to AD or mild AD (positive amyloid PET scan)
- PPAR$\gamma$ agonist/insulin sensitizer
  - Pioglitazone (Phase 3)

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.
  – CAD106 in homozygous ApoE4.

• **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.
  – 1,000 cases. 500 treatment/500 placebo. Solanezumab. May add BACE inhibitor arm later. Amyloid status is divulged.

• Ongoing 18-month aducanumab treatment of 1,350 people with MCI due to AD or mild AD (positive amyloid PET scan).

• **Tomorrow.** ApoE4 cases with risk polymorphism in TOMM40. Treated with pioglitazone.

Summary

• Our understanding of the etiology and pathogenesis of AD continues to expand
• There are currently 5 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
The Alzheimer's Prevention Initiative has provided an online registry for people interested in joining future Alzheimer's treatment trials
www.endalznow.org

The Alzheimer Research Forum is an excellent source of information regarding Alzheimer's disease research, treatments, and resources
www.alzforum.org