National Campaign on Alzheimer’s Disease: A Primary Care CME Initiative

Boston, MA

November 12, 2009
12:30 PM – 2:30 PM

Education Partner:
Mary S. Easton Center for Alzheimer’s Disease Research at UCLA
Session 4: National Campaign on Alzheimer’s Disease: A Primary Care CME Initiative

Learning Objectives
1. Describe appropriate management of AD at its various stages, including pharmacologic therapy.
2. Identify patients who are candidates to participate in research and discuss with them the importance of participation.

Faculty

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Co-Director, Alzheimer’s Disease Clinical and Research Program
Acting Director, Clinical Core, BU Alzheimer’s Disease Center
Co-Director, Center for the Study of Traumatic Encephalopathy
Boston University School of Medicine

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Massachusetts General Hospital
MassGeneral Institute for Neurodegeneration.

Faculty Financial Disclosure Statements
The presenting faculty reported the following:

Dr Gomez-Isla has nothing to disclose.
Dr Stern receives consulting fees from Elan Pharmaceuticals.

Education Partner Financial Disclosure Statement
The content collaborators at UCLA have reported that they have nothing to disclose.

Drug List

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Investigational</th>
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<tbody>
<tr>
<td>donepezil</td>
<td>Aricept</td>
<td>AN1792</td>
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<tr>
<td>rivastigmine</td>
<td>Exelon</td>
<td>bapineuzumab</td>
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<tr>
<td>galantamine</td>
<td>Razadyne</td>
<td>LY450139</td>
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<tr>
<td>memantine</td>
<td>Namenda</td>
<td>dimebolin</td>
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</table>

Acronym List

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAN</td>
<td>American Academy of Neurology</td>
<td>FDG</td>
<td>fluorodeoxyglucose</td>
</tr>
<tr>
<td>ACh</td>
<td>acetylcholine</td>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>AChE</td>
<td>acetylcholinesterase</td>
<td>MCI</td>
<td>mild cognitive impairment</td>
</tr>
<tr>
<td>AChEI</td>
<td>acetylcholinesterase inhibitor</td>
<td>MMSE</td>
<td>Mini Mental State Examination</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>ADAS-cog</td>
<td>Alzheimer’s Disease Assessment Scale- cognitive subscale</td>
<td>nAChR</td>
<td>nicotinic ACh receptor</td>
</tr>
<tr>
<td>ADL</td>
<td>activities of daily living</td>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>ADNI</td>
<td>Alzheimer’s Disease Neuroimaging Initiative</td>
<td>NINCDS-ADRDA</td>
<td>National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association</td>
</tr>
<tr>
<td>ADCS</td>
<td>Alzheimer’s Disease Cooperative Study</td>
<td>APP</td>
<td>amyloid precursor protein</td>
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<tr>
<td>APP</td>
<td>butyrophilinesterase</td>
<td>BuCh</td>
<td>NMDA</td>
</tr>
<tr>
<td>BuCh</td>
<td>butyrophilinesterase</td>
<td>NPI</td>
<td>N-Methyl-D-aspartate</td>
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<tr>
<td>CJD</td>
<td>Creutzfeldt-Jakob disease</td>
<td>PDD</td>
<td>neuropsychiatric inventory</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
<td>PET</td>
<td>Parkinson’s disease dementia</td>
</tr>
<tr>
<td>DIAN</td>
<td>Dominantly Inherited Alzheimer’s Disease Network</td>
<td>PiB</td>
<td>positron emission tomography</td>
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<tr>
<td>DLB</td>
<td>dementia with Lewy bodies</td>
<td>RAGE</td>
<td>Pittsburgh Compound B</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical</td>
<td>TSH</td>
<td>receptor for advanced glycation</td>
</tr>
<tr>
<td></td>
<td>Manual of Mental Disorders</td>
<td></td>
<td>end products</td>
</tr>
</tbody>
</table>

Session 4
Suggested Reading List


Boston University
Alzheimer's Disease Center
VA Boston Healthcare System
Neurology Service (127)
150 South Huntington Avenue
Boston MA 02130
Web site: http://www.bu.edu/alzresearch
Information Line: 1-888-458-2823 (toll free)
ADC e-mail: bmyoung@bu.edu

Massachusetts General Hospital/Harvard Medical School
Alzheimer’s Disease Research Center
Massachusetts General Hospital
114 16th Street, Room 2009
Charlestown, MA 02129
Web site: http://madrc.org
Information Line: 617-726-3987

Session 4
Recognizing, Diagnosing, and Treating Alzheimer’s Disease

Robert A. Stern, Ph.D.
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Co-Director, Alzheimer’s Disease Clinical and Research Program
Acting Clinical Core Director, BU Alzheimer’s Disease Center
Co-Director, Center for the Study of Traumatic Encephalopathy
Boston University School of Medicine

What is needed?
• Humor
• Hope
• New Research is providing much hope!
• And...use of cool new technology like Audience Response Systems

ARS Question
• Dementia is an inevitable part of growing old.
  1. True
  2. False

ARS Question
• I generally perform a brief screen with patients over the age of 65 for cognitive/memory impairment.
  1. True
  2. False

ARS Question
• I regularly inform/refer patients to the local services of Alzheimer’s Association.
  1. True
  2. False

ARS Question
• Even if I suspect Alzheimer’s disease as the cause of a patient’s dementia, I hardly ever tell a patient that they have “Alzheimer’s disease.”
  1. True
  2. False
ARS Question

- Even if I feel that a patient has Alzheimer’s disease, I hardly ever prescribe any medication for its treatment.
  1. True
  2. False

What is Dementia?

In a nutshell:
Dementia refers to a new loss of cognitive functioning that results in significant impairment in social or occupational functioning.

Used to be: “Senility”

What is Dementia?

- Describes a syndrome; does not describe a cause.

DSM Criteria for Dementia

- Cognitive impairment to 2 domains
  - Memory
  - And 1 of: aphasia, apraxia, agnosia, or disturbance to executive function
- Impairment to social or occupational function
  - Decline from previous level of function
  - No Delirium
  - Not due to depression, etc.


Alzheimer’s Disease

- Accounts for approximately 75% of dementia cases.
- AD Differential Diagnosis (4 D’s)
  - Depression
  - Delirium
    - Sudden and fluctuating cognitive impairment
    - Deficiency (e.g., thyroid, B12)
  - Other Progressive/Degenerative Dementias
    - Vascular Dementia, Dementia w/ Lewy Bodies (DLB), Frontotemporal Lobar Degenerations (FTLD), Chronic Traumatic Encephalopathy (CTE)

“Plaques and Tangles”

- Since Dr. Alzheimer first described the disease over 100 years ago, the hallmark features have been plaques and tangles seen in brain tissue.
- Plaques (senile plaques, amyloid plaques) are made up of a protein, called beta amyloid (Aβ42), and are found outside of the neurons.
- Tangles (neurofibrillary tangles) are made up of another protein, tau (phosphorylated), and are found inside neurons.
Amyloid Cascade:
Current, widely accepted view of the pathophysiological mechanism of AD is that of an "amyloid cascade:":
generation and deposition of Aβ42 (especially dimers and oligomers) leads to the generation and accumulation
of neurofibrillary tangles, oxidative stress, inflammation, and cell death.

The Amyloid Hypothesis is Not Dead
• Despite recent research underscoring how complex the mechanism is, as well as recent negative findings of a clinical trial for a drug aimed at decreasing amyloid, there is still overwhelming evidence that beta amyloid plays a central, early, and likely causative role in the development of AD.

AD Numbers
• Every 70 seconds, someone in the US develops AD.
• In US, around 5.3 million people now have AD.
• 13%, or 1 in 8 persons ≥ 65 have AD
• ~50% or 1 in 2 ≥ 85!!

By 2030, 7.7 million Americans are expected to have AD, a greater than 50% increase over current numbers.
• Baby Boomers! (in 2006 BB’s began turning 60 at a rate of 330 every hour)

AD Numbers: $$$$:
• The national cost of caring for people with AD is about $148 billion every year.
• In 2005, Medicare spent $91 billion on beneficiaries with AD or other dementia, expected to rise to $189 billion by 2015.
• Average lifetime cost for an individual with AD is $170,000.
• Costs to businesses for employees who are dementia caregivers is $37 billion/yr.

From: Alzheimer’s Association 2009 Facts & Figures
**Projected Cost of AD in US**

<table>
<thead>
<tr>
<th>Year</th>
<th>Cost (billions of U.S. $)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td><strong>2.0</strong></td>
</tr>
<tr>
<td>2006</td>
<td><strong>2.5</strong></td>
</tr>
</tbody>
</table>


**AD Clinical Presentation**

- Short term memory impairment
  - e.g., Repeatedly asking the same questions
  - Long-term memory (recall of old events/info) can be remarkably spared
- Impairments in visuospatial/navigational abilities
  - e.g., Getting lost
- Language impairments
  - Word finding difficulties
- Executive Functioning Deficits
  - Planning, organization, multi-tasking, abstraction, working memory, decision-making, judgment, *awareness and insight*

**Distinguishing AD from Aging**

<table>
<thead>
<tr>
<th>Normal Aging</th>
<th>Alzheimer’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrieval deficit (responds well to clues/multiple choice)</td>
<td>Amnestic memory impairment (little benefit from clues or reminders); Rapid Forgetting!</td>
</tr>
<tr>
<td>Insight retained</td>
<td>Insight loss</td>
</tr>
<tr>
<td>No change in IADLs</td>
<td>IADLs compromised</td>
</tr>
<tr>
<td>Minor delay in word finding</td>
<td>Anomia</td>
</tr>
<tr>
<td>Visuospatial function retained</td>
<td>Visuospatial function impaired (clock draw)</td>
</tr>
<tr>
<td></td>
<td>Apathy, withdrawal</td>
</tr>
</tbody>
</table>

*IADL, Instrumental activities of daily living.*


**AD Risk Factors**

- **Age**
  - The Most Dramatic Risk Factor!
- **Head Injury**
  - Increased risk, but unclear; CTE-NFL???
- **African American**
  - Many unclear issues, e.g., vascular risks, cultural effects on tests
- **Hispanic**
  - Again, unclear, but may be effected 6-7 years earlier than non-hispanics

**AD Risk Factors, continued**

- **Female**
  - Slightly greater risk in some studies.
  - Estrogen?
  - However, prevalence of AD among women is twice as high as men…simply because women live longer
- **Low Education**
  - Cognitive Reserve
- **Additional Possible Risk Factors**
  - High Blood Pressure
  - High Cholesterol
  - Diabetes

*In other words, what's bad for the heart is bad for the brain!*
Does it run in families?

Family History of Dementia increases relative risk 3-4 fold (at least up to age 80)

Genetics of AD

The two distinct types of AD: Early-Onset and Late-Onset

• Early-onset AD is rare, usually affecting people aged 30 to 60 and usually running in families.
• Mutations known in three genes that cause early-onset AD: Presenilin-1, Presenilin-2, APP
• Together < 2% of AD.

Genetics

• Late-onset AD is more common. It usually affects people over age 65 (though lower these days because of greater surveillance)
  – No single gene yet discovered that causes it.
  – Susceptibility Gene: ApoE:
    » Having the ApoE e4 allele (the "bad" form of the gene) does not on its own result in AD; it increases the susceptibility, along with other factors. Similar to BRCA1/BRCA2 genes.
      — e2 allele = protective
      — e3 allele = neutral
      — e4 allele = increases risk: e4/e3 3X; e4/e4 ~10X
• New Research: APOE status may impact efficacy of treatment and risk of side effects

ARS Question

• I feel confident about my ability to diagnose Alzheimer’s dementia.
  1. True
  2. False

Alzheimer’s Disease

NINCDS-ADRDA Research Diagnostic Criteria

• Definite AD
  – Characteristic neuropathology and clinical findings
• Probable AD
  – No alternative disorder present
• Possible AD
  – Contributing medical condition present
  – Single cognitive function affected
• Unlikely AD
  – Acute onset, focal signs, seizures, gait disturbance
Clinical Diagnosis of Alzheimer’s Disease

- Without looking at actual brain tissue, the diagnosis of AD is never completely certain.
- The diagnosis is based on
  - Clinical examination (including cognitive screening),
  - History (Listen to the Caregivers/Family)
  - Neuroimaging (CT, MRI, PET)
  - Laboratory tests (to rule out other Dx)
  - Neuropsychological evaluation

Screening

- Many patients with cognitive impairment of AD are not identified in primary care
- In a study of 1107 subjects screened (mean age 76.3)
  - 343 (31%) of study subjects scored ≤24 on the MMSE
  - Of these, only 42 had a diagnosis of dementia

Mini-Mental State Examination

- Brief, structured cognitive status examination
- 10 minutes to administer
- Typical deterioration of 3–4 points per year
- Sensitivity and specificity vary in different patient populations
- Adjustments for age, education and race may be necessary
- Beware: Many false positives and false negatives; does not make the Diagnosis!

Scores Range from 0–30

<table>
<thead>
<tr>
<th>Score</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥27</td>
<td>Normal</td>
</tr>
<tr>
<td>26 – 21</td>
<td>Mild Cognitive Impairment</td>
</tr>
<tr>
<td>20 – 11</td>
<td>Moderate Cog. Impairment</td>
</tr>
<tr>
<td>10 - 0</td>
<td>Severe AD</td>
</tr>
</tbody>
</table>

The AD8 Informant Interview

- Informant-based questionnaire that can be administered at home or in waiting room
- Detects change compared with previous level of function
  - No need for baseline
  - Patients serve as their own control
  - Minimally affected by education, race, gender
- Brief (<3 minutes), yes/no format
  - 2 or more “yes” answers highly correlated with presence of dementia
  - Sensitivity 85%, Specificity 86%

Rapid Screen for Cognitive Impairment: Mini-Cog

- 5 minutes to administer
  1) 3-word registration
  2) Simple clock drawing test
  3) 3-word recall
- Diagnostic value not influenced by education level or language
- Sensitivity 99%?
  Specificity 93%?

Formal Neuropsychological Evaluation

- Referrals for neuropsychological evaluation are useful in diagnostic workup
  - Tests that focus on (anterograde) memory may be most useful
  - May be particularly relevant in determining likelihood to progress from MCI to AD
  - Useful in distinguishing among dementias
  - Useful in distinguishing normal aging (with and without depression) from mild dementia
ARS Question

• I usually order neuroimaging as part of my dementia work-up.
  1. True
  2. False

Neuroimaging and Biomarkers Support a Diagnosis of AD

• MRI/CT
  – Rule out other causes
  – Hippocampal/Temporal lobe atrophy
• CSF Analysis
  – Decreased Aβ/Increased Tau
• PET/SPECT/fMRI
  – Bilateral temporal or parietal lobe hypo-function

Potential Treatment Outcomes in Alzheimer’s Disease

ARS Question

• There is nothing that can be done to prevent Alzheimer’s.
  1. True
  2. False

Prevention and Delay

• If we can delay the onset of AD by just FIVE years, we can cut in half the number of people with the disease!
• So, Prevention and/or Delay is critical.

Prevention: Decrease Heart Risk
Prevention: Diet?

• Polyphenols
• Antioxidants
• Flavanoids
• Omega-3 Fatty Acids
• Resveratrol

Prevention: Lose Weight

• Being fat in your 40s might raise your risk of developing dementia later in life.
• In a study published in the British Medical Journal (Whitmer et al., 2005), researchers found that the fatter people were, the greater their risk for AD. This was based on a study of more than 10,000 Californians who were followed for almost 30 years.
• Obesity, defined as a Body Mass Index of ≥ 30, was a particularly serious risk factor for women. Obese women were twice as likely to develop dementia than women of healthy weight, while obese men were only slightly more likely to develop the disease.

Prevention: Exercise

• In a report in Annals of Internal Medicine (Larson et al., 2006), regular exercise was found to delay the onset and reduce the risk of developing AD, and the more frail a person was, the more she or he benefited from exercise.

Alcohol and AD

• Recent research suggests:
  – Moderate alcohol consumption (1-2 drinks/day) may decrease risk of AD
    • ONLY if no other contraindications!
  – More than moderate drinking may INCREASE risk of AD
  – Once there is any cognitive impairment, continued drinking increases risk.
    • Sink et al., 2009, ICAD
Prevention: Exercise
• A mouse study suggests that exercise may prevent beta amyloid deposition, thereby lowering the risk of developing AD.
  – Adlard et al., J Neuroscience, 2005

Prevention: Intellectual Stimulation

Intellectual Stimulation: What seems to work best?
• Try new things and new ways.
  – Take up a new language.
  – Take a new route.
  – Try new recipes.
  – Read a different type of book.
  – Start a new hobby or rekindle an old one.
• Do the computerized “brain health” methods work?
  – Yes and No…it doesn’t hurt.

Prevention: OTCs
• “Alzheimer’s Cocktails”
  – Ibuprofen
  – Vitamin E
  – Glucosamine
  – Curcumin
  – Fish Oil – DHA ?
  – Ginkgo Biloba – Nope!
• No Evidence in Support

Prevention: Medication
  – NSAIDS – stay tuned – ADAPT study at BU
  – Statins – Unclear
  – Estrogen – Nope
  – Angiotensin Receptor Blockers– new findings by Wolozin ???

ARS Question
• Donepezil and other cholinesterase inhibitors have a direct impact on the underlying causes of Alzheimer’s disease.
  1. True
  2. False
Once Alzheimer’s Disease Begins...

• If the disease begins, there is no cure.
• But, there currently are prescription medications available that are geared specifically for AD.
• The three “somes” of current treatments
  -- some symptomatic relief
  -- some patients
  -- some duration.

Symptomatic Therapies

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Target (Action)</th>
<th>Dosing</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (tablets and orally disintegrating tablets)</td>
<td>ACe (inhibition)</td>
<td>5, 10 mg q.d.</td>
<td>Mild AD</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>ACe (inhibition) BuChE (inhibition)</td>
<td>1.5, 3, 4.5, 6 mg b.i.d. (with food)</td>
<td>Mild AD</td>
</tr>
<tr>
<td>Rivastigmine Patch</td>
<td>ACe (inhibition) BuChE (inhibition)</td>
<td>4.6 (5 cm²), 9.5 (10 cm²) mg/d</td>
<td>Mild AD</td>
</tr>
<tr>
<td>Galantamine ER</td>
<td>ACe (inhibition) nAChR (modulation)</td>
<td>5, 16, 24 mg q.d. (with food)</td>
<td>Mild AD</td>
</tr>
<tr>
<td>Memantine (tablets and oral solution)</td>
<td>NMDA Receptor antagonism</td>
<td>5, 10 mg b.i.d.</td>
<td>Moderate AD</td>
</tr>
</tbody>
</table>

Symptomatic Therapies Can Provide Long Term Benefit

Combination Therapy is Safe and Effective

Synergistic Effect of Combination Therapy

• Progression over time on the Blessed Dementia Scale is slowed with combination therapy relative to ChEI therapy alone and no AD meds

Approved Therapies for AD Delay Nursing Home Placement

1. Memantine + ChEIs
2. ChEIs alone
3. No dementia medication
Adverse Events

• Donepezil: Nausea, vomiting, diarrhea, anorexia, insomnia, muscle cramps, fatigue, syncope
• Rivastigmine: Nausea, vomiting, anorexia, weight loss, dyspepsia, asthenia, dizziness, fatigue, diarrhea, skin reaction (to patch); GI Sx less with patch
• Galantamine: Nausea, vomiting, anorexia, weight loss, dyspepsia, asthenia, dizziness, fatigue, diarrhea
• Memantine: Dizziness, headache, confusion, constipation, hypertension, coughing, vomiting, back pain, somnolence


Treatment Algorithm

Diagnosis of AD
First-line: AChEI therapy (titrate to maximal tolerated dose)

Switch AChEI therapy
No clinical benefit
Clinical benefit

Maintain AChEI therapy & monitor
No clinical benefit to ANY AChEI
No clinical benefit to AChEI monotherapy
Substitution of memantine in moderate AD
Addition of memantine in moderate AD
Treatment failure/loss of clinical benefit
Withdrawal of AChEI and/or memantine therapy


Cessation of Therapy

• Consult the family
  – Keep in mind: hope and placebo effects
• Monitor during withdrawal
  – Behavior
  – Function
  – Cognition
• Once meaningful social interactions are no longer possible


Behavioral Symptoms in AD

• Will occur in 90% of AD patients

Nonpharmacologic Strategies for Behavioral Symptoms

• Depression: maintain cheerful environment, encourage exercise and social interaction, redirect negative thoughts
• Agitation/aggression: identify potential triggers, establish calm environment, avoid arguing, be flexible, usefulness of touch/intimacy
• Repetitive behavior: ignore some repetitive questions, redirect attention
• Delusions/hallucinations/paranoia: avoid confrontation and reasoning, give noncommittal answers, understand the “reality” of the patient

MCI, mild cognitive impairment; NPI, neuropsychiatric inventory; Total NPI=any symptom.

Medical Recommendations for Behavioral Symptom Management
• Anti-AD meds may help behavioral symptoms
• SSRIs have supportive data
• Tricylics and benzodiazepines should be avoided
• Conventional and atypical antipsychotics
  – Mixed efficacy results, mostly for agitation
  – Safety considerations (stroke and death)


Patient/Family Education and Support
• Integrate medical care and support
  – Do not try and manage all of the patient’s and family’s needs alone.
  – Alzheimer’s Association (800) 272-3900
    • www.alz.org
  – Geriatric Care Managers
  – Be aware of caregiver stress and limitations
• Discuss diagnosis and treatment
• Involve early stage patients
• Discuss progression
• Discuss decisional capacity and end-of-life decisions

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ARS Question
• Mild Cognitive Impairment (MCI) is a meaningful clinical diagnosis.
  1. True
  2. False

Mild Cognitive Impairment (MCI)
• Now clear that AD disease process begins years or decades prior to symptoms and diagnosis
• MCI is a clinical construct that distinguishes a patient from their age cohort
  – Memory complaint
  – Objective impairment for age
  – No impairment of activities of daily living
• High likelihood of progression to AD
• May not progress and may improve
• Can progress to other dementia (~30%)

ARS Question
• I will regularly perform the MMSE or another cognitive screen in patients over the age of 75.
  1. True
  2. False

MCI Management
• MCI “should be recognized and monitored for cognitive and functional decline due to increased risk for subsequent dementia” AAN
• To date, no clinical trial has demonstrated efficacy on a primary endpoint for treatment of MCI
• To date, no treatment study has demonstrated delayed progression from MCI to dementia

ARS Question

• I will regularly perform the MMSE or another cognitive screen in patients over the age of 65.
  1. True
  2. False

ARS Question

• I will inform patients of the services of offered by the Alzheimer’s Association.
  1. True
  2. False

ARS Question

• I routinely refer my patients with Alzheimer’s disease to centers conducting clinical research.
  1. True
  2. False

Research In Alzheimer’s Disease: Cause for Hope and Referral

Teresa Gomez-Isla MD, PhD
Massachusetts General Hospital
MassGeneral Institute for Neurodegeneration.

ARS Question

• I have previously referred an Alzheimer’s patient for participation in research.
  1. True
  2. False

ARS Question

• What factors keep you from referring patients to Alzheimer’s research?
  1. Nothing, I refer all the time
  2. I don’t want to lose my patient
  3. There’s nothing out there that can help the patient more than I can
  4. It’s inconvenient to me
  5. It’s inconvenient to my patient
  6. I lack information for proper referrals
Growth of AD Population

![Growth of AD Population](image)

Projected Cost of AD

![Projected Cost of AD](image)

Research May Be the Answer

Goals in Alzheimer's Disease Research
1. Earlier diagnosis – Biomarkers of disease
   a. MRI
   b. CSF
   c. PET/fMRI
   d. Amyloid (and other disease marker) imaging
2. Disease modifying therapies
3. Better symptomatic therapies

Low Subject Recruitment Hinders Research Progress

Reason for lost days [toward deadline for clinical trial completion]

![Low Subject Recruitment Hinders Research Progress](image)

Older Patients in Clinical Trials

- Age distribution should reflect that of the target disease
- Efforts to include the “very elderly” should be addressed
- Sufficient numbers of elderly and very elderly to assess
  – Safety
  – Risks
  – Benefits

Ethics of Elderly Inclusion

- Those who bear the inconvenience and risk associated with research participation must be representative of those who will benefit
- Elderly candidates for research are rarely encouraged to participate
- Upper age limits should be excluded or thoroughly justified in research protocols


**Patient Safeguards**

- Institutional Review Board (IRB)
- Informed consent
  - Document
  - Process

**Benefits of Participation**

- Active role in own health care
- Access to new treatments before they are widely available
- Specialist medical care and cutting edge technologies at academic institutions
- Help others by contributing to medical research
- Often free of charge
- High satisfaction rating

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**Human Clinical Trials: The Limiting Factor**

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**Trial Referral is an Underused Opportunity**

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**Trial Awareness is a Missing Link**

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**Why Refer Clinical Research Participants?**

- Without referrals, new medications, diagnostic tools, and cure will be delayed
- Research participation is not a substitute for routine clinical care - subjects continue to see own physician
- Opportunity for mutual referral relationships
  - Tertiary care research centers cannot see patients in primary clinical capacity and need referral options
  - Enhance practice credibility
Early Diagnosis is Important

- Initiate treatment
- Delay decline
- Allow advance directives
- Allow “last” events

Research is Leading to Earlier Diagnosis

Proposed Research Diagnostic Criteria
1. Episodic memory impairment
2. Biomarker for AD
   - MRI
   - FDG PET
   - PIB PET
   - CSF $A\beta$ / Tau

Research Suggests Amyloid Protein is Central to AD


Amyloid Imaging Shows Amyloid in the Brain in AD


Amyloid Imaging Shows Amyloid in Some MCI and Some Normal Elderly


Other Biomarkers Identify Early AD

- MRI: hippocampal volume, cortical thickness mapping
- CSF: decreased $A\beta$, increased Tau
- PET: bilateral temporal or parietal hypometabolism
Hippocampal Atrophy is a Marker for AD

CSF Levels Predict Progression from MCI to AD

- Pathological CSF:
  - Aβ42: <530 ng/L
  - T-tau: >350 ng/L
- Sensitivity: 95%
- Specificity: 83%

MCI population:
- Peterson criteria
- Memory complaint
- Excluded causes of impairment but not white matter changes or depression

FDG PET Hypometabolism in aMCI and AD

ADNI study of 74 probable AD, 142 aMCI subjects, and 82 NC

AD and aMCI show hypometabolism in:
- Posterior cingulate
- Precuneus
- Parietotemporal cortex
- Frontal cortex

Alzheimer’s Disease Neuroimaging Initiative (ADNI)

- Five year study (inception: Oct 1 2004)
- Examine rate of change
  - Cognition
  - Function
  - Brain structure and function
  - Biomarkers
- 200 elderly controls, 400 MCI, 200 AD
- Public access of clinical and imaging data
- www.adni-info.org www.loni.ucla.edu/ADNI/

Genome Wide Association Study

- NIA-funded project among AD centers
- Currently 95% complete
- Allows for study of whole genome or individual genes of interest
  - More than 620,000 markers available
- Linked to neuroimaging and other biomarker data
- Available to all investigators www.loni.ucla.edu/ADNI

Dominantly Inherited Alzheimer’s Network (DIAN)

- International partnership to study familial form of AD
- Rare form (~2% of all cases)
- Caused by genetic mutations to APP, PS1, PS2 genes
- Expected to provide information important to sporadic AD

New Treatments Are Evolving That May Prevent or Treat AD

- Anti-amyloid drugs
- Anti-amyloid antibodies
- Neuroprotective

All studies need patients in trials.

Current Therapies in Phase III Development

- Bapineuzumab: Passive immunization with humanized monoclonal antibodies against Aβ42
- LY450139: Gamma secretase inhibitor
- Dimebolin: Mitochondrial pore stabilizing agent

Vaccination in Human Patients (AN1792)

Dimebolin Treatment Preserved Cognition and Memory for 18 Months

Receptor for Advanced Glycation Endproducts (RAGE) and Aβ

- RAGE is a cell-surface receptor expressed by many CNS cells including neurons
- RAGE binds Aβ
  - Promotes inflammation and glial activation
  - Feeds forward (further increase in RAGE expression)
  - Aβ transport at the BBB
  - AGEs may be neurotoxic and increase oxidative stress
- Blocking RAGE may decrease pathologic events in AD

Alzheimer’s Disease Cooperative Study (ADCS)

- Formed in 1991
- Partnership between NIA and UCSD
- Facilitate discovery, development, testing of new drugs for treatment of AD
- Part of the Alzheimer’s Disease Prevention Initiative
- www.ADCS.org
Summary

• Tremendous ongoing research efforts
  – Better diagnosis
  – Better treatments
• Research can not move forward without participants
• Primary care providers are well positioned to facilitate research advances through participant referral

Interaction Between Primary Care and Academia is Critical to Helping Patients

• Patients and providers want better treatments
• Patient participants are critical to research advances
• With research, better diagnosis and treatment will be available

ARS Question

• I intend to inform patients with Alzheimer’s disease of the opportunities to participate in research
  1. True
  2. False