Preventing and Treating Alzheimer's Disease: Recruiting Patients for Clinical Trials

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Goals and Learning

Objectives.

• Current thinking about the biology of Alzheimer's Disease that can be targeted for treatment and prevention;
• Trial designs and demands in Alzheimer disease studies;
• Methods for referring patients to clinical research
Hypotheses about Plaques & Tangles

- **Risk Factors**
  - Altered proteolysis of APP
  - Extracellular secretion of A beta peptide
- **Plaques & Tangles**
  - Diffuse amyloid plaques
  - Neuritic plaques
  - Amyloid plaques
  - Neurofibrillary tangles
- **Inflammatory Response**
  - Microglial activation/astrocytosis
  - Oxidative stress
  - Increased cytokine release
  - Kinase/phosphatase effects
  - Intracellular effects?
  - Intraneuronal effects?
  - Physical damage?
What is Cognitive Decline

Mild Cognitive Impairment
The Good News

- Evidence of reduced incidence of dementia and cognitive decline
  - Better education
  - Higher standard of living
  - Better detection in prevalence studies
## Education and Dementia

<table>
<thead>
<tr>
<th></th>
<th>Education Expenditure*</th>
<th>Incidence**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2005</td>
</tr>
<tr>
<td>Indonesia</td>
<td>8.1</td>
<td>191</td>
</tr>
<tr>
<td>Thailand</td>
<td>20</td>
<td>71.4</td>
</tr>
<tr>
<td>Malaysia</td>
<td>27</td>
<td>20</td>
</tr>
</tbody>
</table>

* % of 2002 National Budget; **cases/1000

The Controversy

7 Risks for 50% of AD

- Diabetes,
- Midlife hypertension,
- Midlife obesity,
- Smoking,
- Depression,
- Cognitive inactivity/ low educational attainment
- Physical inactivity.

Can we really reduce risk?

- 10–25% reduction in all risk factors could potentially prevent as many as 1·1–3·0 million cases worldwide
- 184 000–492 000 cases in the USA
• Insufficient evidence to support… use of pharmaceutical or dietary supplements to prevent cognitive decline or AD
• Promising research is under way
  (e.g. antihypertensive medications, omega-3 fatty acids, physical activity, and cognitive engagement)
ADNI Conversion Rates

**NB** 229

**MCI** 398

**AD** 192

<table>
<thead>
<tr>
<th>Year</th>
<th>Normal → MCI</th>
<th>MCI → AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>1.4% (0.0-3.2)</td>
<td>16.0% (11.3-20.4)</td>
</tr>
<tr>
<td>1-2</td>
<td>2.4% (0.0-4.7)</td>
<td>23.9% (19.0-29.5)</td>
</tr>
<tr>
<td>2-3</td>
<td>0.0% (0.0-3.4)</td>
<td>9.5% (5.8-13.5)</td>
</tr>
</tbody>
</table>
CSF Levels Predict Progression from MCI to AD

- Pathological CSF:
  - $A\beta_{42}$: <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

100% accuracy if you have AD
35% of Normals were mislabeled AD
Only 26% of MCI labeled AD had progressed
Finding the Best Measure to Predict Disease

Best outcomes across a broad range are MRI and FDG-PET

Best screening marker rises early

AD Progression

Pre-Symptomatic, eMCI, lMCI, Dementia

TIME

ABNORMAL

NORMAL

CSF Aβ42
Amyloid imaging
FDG-PET
MRI hipp
CSF tau
Cog
Fxnl

Function (ADL)

CSF abeta42
FDG PET
Amyloid Imaging
MRI Hippocampal Volume
CSF Tau
Cognitive Performance
Apolipoprotein E for AD Risk

- Risk of AD increased by presence of e4
  - OR=3.2 (95% CI, 2.9–3.5) 1 allele
  - OR=11.6 (95% CI, 8.9–15.4) 2 allele

- Recommendation for use:
  - Only as within clinical work up in symptomatic cases
    » JAMA 1995
  - Reconsideration in prodromal or non-symptomatic?
    » Alzheimer & Dementia 2011
Use of Florbetapir-PET for Imaging - Amyloid Pathology

High correlation between imaging and neuropathology

Does not rule out other pathology

Requires PET technology and proximity to ligand manufacturer
Caveat

• All prognostic markers of dementia depend on neuropsychological deficit

• To date no evidence that biomarkers in the presence of intact cognition predict dementia
  – Predict worsening, but not dementia

• Stay tuned: as drug discovery moves forward using new criteria, this will matter
Limitations of Biomarker studies

- All done in pristine populations
- >95% are Caucasian, college educated, at tertiary medical centers
- Little is known about prediction in the presence of co-morbidity and in the hands of general practice providers
Translational Medicine: *How we know what to test*

- Observational and epidemiological studies provide hints to risk factors, protective factors and potential treatments.
- The laboratory discovers the mechanisms of pathology and models for intervention.
- Clinical Trials provide the ultimate test of efficacy and safety.
Translating to Treatments
not so straight forward

Cocktail lounge, Norway:
   LADIES ARE REQUESTED NOT TO HAVE CHILDREN IN THE BAR.

Instructions for using a hotel air conditioner, Japan:
   IF YOU WANT TO BE COOL IN YOUR ROOM, PLEASE CONTROL YOURSELF.

Hotel lobby, Bucharest:
   THE LIFT IS BEING REPAIRED FOR THE NEXT DAY. DURING THAT TIME WE REGRET THAT YOU WILL BE UNBEARABLE.

On the front desk of a hotel, Colombia:
   IF THIS IS YOUR FIRST VISIT TO OUR COUNTRY, YOU ARE WELCOME TO IT.

• Epidemiological data
• Laboratory Results
• Animal Models
• Biomarkers
• Testimonial
# Why we need to do the Trials

<table>
<thead>
<tr>
<th>Observation Hint</th>
<th>Treatment Trials</th>
<th>Secondary Prevention</th>
<th>Primary Prevention</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-inflammatory</td>
<td>No effect in AD</td>
<td>No effect of COX II</td>
<td>ADAPT</td>
<td>Safety issues</td>
</tr>
<tr>
<td>Estrogen</td>
<td>No effect in AD</td>
<td>?</td>
<td>No effect</td>
<td>Safety issues</td>
</tr>
<tr>
<td>Anti-oxidant</td>
<td>Mild effect in AD</td>
<td>No effect of vitamin E</td>
<td>No effect</td>
<td>Safety issues</td>
</tr>
<tr>
<td>Statins</td>
<td>Mild effect in AD</td>
<td>?</td>
<td>No effect</td>
<td>Need more studies</td>
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</tbody>
</table>
### Clinical Trials in Dementia

**How many, How Long**

<table>
<thead>
<tr>
<th>Group</th>
<th>Outcome</th>
<th>Sample Size</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD Patients</td>
<td>Symptom change Slow Progression</td>
<td>200-300</td>
<td>6 months</td>
</tr>
<tr>
<td>MCI</td>
<td>Dementia</td>
<td>700-1000</td>
<td>3-4 years</td>
</tr>
<tr>
<td>Healthy Elders</td>
<td>Dementia</td>
<td>2000-4000</td>
<td>5-7 years</td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td>15,000</td>
<td>7-10 yrs</td>
</tr>
</tbody>
</table>
Diet Affecting Cardiovascular Outcomes

- Unpredicted result
- Favoring higher fat intake
- Simple design
- Few exclusions
- 7500 enrolled
- Consider other outcomes

![Graph showing the incidence of cardiovascular outcomes and total mortality across different diet groups.](image.png)

**Figure 1.** Kaplan–Meier Estimates of the Incidence of Outcome Events in the Total Study Population.

Panel A shows the incidence of the primary end point (a composite of acute myocardial infarction, stroke, or death from cardiovascular causes), and Panel B shows total mortality. Hazard ratios were stratified according to center (Cox model with robust variance estimators). CI denotes confidence interval, EVOO extra-virgin olive oil, and Med Mediterranean.
Homocysteine Lowering in AD with Folate and B vitamins

5 mg Folate 1 mg B12, 25 mg B6

- Some increase in depression
- Perhaps nutritional patterns provide maximum effect

- Folate in grain and Use of multi-vitamins
Docosahexaenoic acid (DHA)

• Omega-3 fatty acid
• Important component of cell membranes
• *Found in all tissues*; most abundant in *neural, retinal* and *CV conducting tissue*
• Important in infant development and cardiovascular health
Change in Primary and Secondary Outcome Measures in the Alzheimer’s Disease Cooperative Study (ADCS) Docosahexaenoic Acid (DHA) Supplementation Trial

Quinn, J. F. et al. JAMA 2010;304:1903-1911

Copyright restrictions may apply.
MIDAS Study

**Goal**
- Evaluate the effects of algal DHA on cognitive outcomes in healthy elderly (≥55 yrs.) with a mild memory complaint

**Trial Design**
- Study Population: Age-related Cognitive Decline
- Multi-center (19 U.S. sites)
- Randomized, double-blind, placebo-controlled, parallel, stratified by age (55-69; ≥70)
- Oral Dose: 900 mg/day algal DHA or placebo (corn/soy)
- Study Treatment: 6 months
- Sample Size: 485 subjects
- Primary Endpoint: cognitive test of memory & learning as measured by the CANTAB™ Paired Associate Learning (PAL) test
- Secondary Endpoints: other cognitive tests, activity of daily living skills, plasma phospholipid fatty acid levels, safety and tolerability

![Change Score Diagram](image)
Cognitive Function Over Time in the Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT) NonSteroidal Trial
No benefit on protection of cognition
No reduction of dementia
Dementia Prevention Trial

Ginkgo Biloba vs. Placebo

HR, 1.12 (95% CI, 0.94-1.33); P = .21

No. at risk
Placebo 1524 1485 1423 1342 1243 1148 792 81
G. biloba 1545 1521 1458 1369 1254 1129 775 97

No. with incident dementia
Placebo 13 26 40 50 51 36 30
G. biloba 10 26 47 66 60 40 27

Understanding the Role of Lifestyle and Nutrition in AD

- Caloric Restriction in animals
  - Reduces amyloid
  - Increases longevity
  - Protects against motor slowing
Low BMI and Risk of dementia

- Religious Order Study
- 5.5 yrs of follow-up
- N=822
- Incident AD associated with Baseline BMI and with declining BMI
- Effect persists after adjustment for prevalent cases

Buchman et al 2005
What about Physical activity to improve cognition in healthy elders

• Eleven studies of aerobic physical activity programs for healthy people (55+ yrs).
• Eight of these 11 studies
  – Aerobic exercise increased fitness of the trained group
  – Improved at least one aspect of cognitive function.
  – Cognitive speed, auditory and visual attention.
  – No consistent benefit on any domain
  – Majority of comparisons yielded no significant results.

Cochrane Collaboration
Stretching and Aerobic Exercise Improved Spatial Memory

*Only Aerobic Exercise Increased Hippocampal Volume

Erickson K I et al. PNAS 2011;108:3017-3022

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Leisure Activities

- Board Games*
- Reading*
- Musical Instruments*
- Crossword Puzzles*
- Writing
- Group Discussions
- Dancing*

- Individual activities seem to have some benefit
- 1 cognitive activity /1 day/ week = 7% reduced risk
- 11 activities/day = 63% reduced risk
- *Now we need the randomized trials*
Does Memory Training Help?

- Memory training may provide immediate help with specific material.
- Little evidence of generalizability.
- Tends to improve self esteem and reduce complaint in those without serious memory problems.
- In the presence of serious memory problems consider the risk of frustration.
Long-term Effects of Cognitive Training on Everyday Functional Outcomes in Older Adults

- Elders: >65yr community dwelling, non-demented
- 10 session Training & Booster
  - Memory, Reasoning
  - Processing Speed, Control
- 5 year follow-up
- Retained learning
- No Self reported IADL except in Reasoning group

*JAMA 2006 296; 2805-2814*
Home Based Assessment: Background

• Develop efficient/effective methods for Primary Preventions Trials in dementia using new technologies
• Will Home Based Assessment (HBA) improve:
  • Recruitment of diverse elders?
  • Retention and reduce study costs?
  • Participation of those who find clinic-based assessment interferes with lifestyle?
• Aims:
  • Establish feasibility of HBA
  • Assess acceptability and efficiency of new methods of assessment
Proposed Technologies and Domains

- Mail In Administration & “tester administered” phone-based cognitive assessment (MIP)
- Telephone Assessment, automated presentation with vocal and key pad response (IVR)
- Computerized Assessment for presentation and response capture (KIO)

- Cognitive
- Functional
  - IADL
  - Performance-based Medication Compliance****
- Global
- Behavioral
- Quality of Life
- Pharmaco-economic
Dissatisfaction with Technologies

- “so ugly”
- “takes up so much room”
- “glow disturbs sleep”
- “interference of phone line”
- “static on line”
600 Non-Demented Community dwelling “real world” Elderly (≥75) 20% minority
In-Person Baseline Evaluation

Mail-in and Telephone Cognitive Battery Written Med diary (N=200)

Automated Telephone Assessment Phone Med diary (N=200)

Computerized Assessment & Medtracker (N=200)

4-Year Follow-Up Period

25% Receive an In-Person Evaluation

In-Person Diagnostic Evaluation Upon Trigger

All Receive In-Person Evaluations at 4-Year Endpoint
Entry Criteria

Inclusion

– Age $> 75$
– MMSE $> 26$
– Independently living
– Study partner desirable but not required

Exclusion

• Dementia
• Use of prescriptive cognitive-enhancing
• Use of non-study multi-vitamins
• Other conditions causing cognitive impairment
• Life expectancy $< 5$ years

1 in 5 enrollees were required to be “Minority”
All assessments were available in-home
Participant Flow

Screened
N = 713

Screen Fail
N = 73

Randomized
N = 640

MIP
N = 211

IVR
N = 214

KIO
N = 215

Dropout
N = 4 (2%)

Dropout
N = 18 (8%)

Dropout
N = 37 (17%)

Less education than randomized cohort

Randomization
N = 640

Baseline
N = 581

All pairwise comparisons significant

N = 207

N = 196

N = 178
### Demographic and Clinical Characteristics of Baseline Cohort: All Arms Combined

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>N</td>
<td>581</td>
</tr>
<tr>
<td>Age</td>
<td>80.9 (4.4)</td>
</tr>
<tr>
<td>Education</td>
<td>15.6 (2.9)</td>
</tr>
<tr>
<td>% Female</td>
<td>67</td>
</tr>
<tr>
<td>% Racial/ethnic minority</td>
<td>22</td>
</tr>
<tr>
<td>% Married</td>
<td>42</td>
</tr>
<tr>
<td>% History of hypertension</td>
<td>59</td>
</tr>
<tr>
<td>% Cardiovascular disease</td>
<td>74</td>
</tr>
</tbody>
</table>

*No differences between baseline cohort and cohort that passed screening and discontinued after randomization*
Demographic and Clinical Characteristics of Baseline Cohort: All Arms Combined (cont’d)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>581</td>
</tr>
<tr>
<td>% Self-Report Current Memory Problem</td>
<td>28</td>
</tr>
<tr>
<td>% Self-Report Current Memory Problem is a Change from Before</td>
<td>21</td>
</tr>
<tr>
<td>% Self-Report Current Memory Problem worse than age peers</td>
<td>3</td>
</tr>
<tr>
<td>% MCI, by assessment</td>
<td>19</td>
</tr>
<tr>
<td>% APOE 4 (N = 471)</td>
<td>25</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.8 (1.2)</td>
</tr>
</tbody>
</table>
### Who Refused and Why?

<table>
<thead>
<tr>
<th>Drop Out By Arm And Frequency</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MIP Annual</td>
<td>4 /105</td>
<td>4%</td>
</tr>
<tr>
<td>MIP Quarterly</td>
<td>0/106</td>
<td>0%</td>
</tr>
<tr>
<td>IVR Annual</td>
<td>7/107</td>
<td>6%</td>
</tr>
<tr>
<td>IVR Quarterly</td>
<td>11/107</td>
<td>10%</td>
</tr>
<tr>
<td>KIO Quarterly</td>
<td>16/109</td>
<td>15%</td>
</tr>
<tr>
<td>KIO Monthly</td>
<td>21/106</td>
<td>20%</td>
</tr>
</tbody>
</table>

**Nature of complaints:**
- Inconvenience of the equipment
- Too much time to participate
## Efficiency

<table>
<thead>
<tr>
<th></th>
<th>IVR</th>
<th>KIO</th>
<th>MIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days to Baseline</td>
<td>39.2</td>
<td>55.7</td>
<td>33.5</td>
</tr>
<tr>
<td></td>
<td>(25.8)</td>
<td>(42.3)</td>
<td>(25.5)*</td>
</tr>
<tr>
<td>Training Time</td>
<td>39.1</td>
<td>76.7</td>
<td>25.6</td>
</tr>
<tr>
<td></td>
<td>(20.6)</td>
<td>(60.1)</td>
<td>(15.2)*</td>
</tr>
<tr>
<td>Preparation Time</td>
<td>24.0</td>
<td>141.4</td>
<td>18.6</td>
</tr>
<tr>
<td></td>
<td>(20.6)</td>
<td>(140.8)</td>
<td>(17.1)*</td>
</tr>
<tr>
<td>Time at Baseline w/o Testing</td>
<td>11.1</td>
<td>73.4</td>
<td>8.44</td>
</tr>
<tr>
<td></td>
<td>(16.8)</td>
<td>(235.6)</td>
<td>( 23.77)*</td>
</tr>
<tr>
<td>Testing time</td>
<td>NA</td>
<td>NA</td>
<td>31.2</td>
</tr>
<tr>
<td>Total Time</td>
<td>72.0</td>
<td>280.4</td>
<td>79.1</td>
</tr>
<tr>
<td></td>
<td>(37.7)</td>
<td>(314.5)</td>
<td>(39.0)*</td>
</tr>
</tbody>
</table>

*P<0.001

- Longer time from Screen to Baseline for KIO
- Longer Training time for KIO and IVR
- Longer Preparation Times for KIO
Summary/Considerations

• HBA trial enrolled a diverse, elderly cohort

• High technology assessment methods
  – Acceptability not affected by subject demographic and clinical characteristics
  – Require more time at study initiation

• Inconvenience of equipment and assessment frequency associated with non-participation

• Cognitive and functional assessments demonstrate adequate range to observe change over time
Fear of Alzheimer’s Disease in the United States.

Since 2006, the percentage of those who fear getting Alzheimer’s has increased more than the other illnesses.
What can you do to prevent cognitive loss and dementia

- Treat treatable conditions
- Protect the brain
- Maximize physical activity
- Maintain cognitive stimulation
- Insure social engagement
- Support research
Whose job to support research

• Clinicians
  – Know how to refer to research,

• Volunteers (w or w/o disease)
  – Discuss with your family
  – Support the decision, be a study partner

• Everyone
  – Support public funding
  – Make your contribution
Low Subject Recruitment Hinders Research Progress

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

- Difficulty in recruiting patients: 85-95%
- Other: 5-15%

Trial Referral is an Underused Opportunity

Ever referred for an AD trial?
- Yes: 22%
- No: 78%

Have patients/caregivers approached about an AD trial?
- Yes: 39%
- No: 61%
Why Participate in Research

• Standardized evaluations even for the healthy
• Access to up-to-date research initiatives
• Potential for earliest access to new medications
• Support for family and friends
• Contribution from self to family, society***
Not all studies for all participants

• Inclusion criteria:
  – Insure safety
  – Limitations by age co-morbidities other medications
  – Insure the ability to measure efficacy
  – Hearing / visual difficulties make

• How to Choose:
  – Select by interest
  – Work with those you trust
  – Be honest about how much you can do
  – Ask questions

Remember, you can always change your mind
Information on AD Research

• My ADRC:
  – Mount Sinai: 212-241-8329

• Alzheimer’s Association: National Site
  – 800-272-3900 (24 hr help line)
    – www.alz.org

• Alzheimer Disease Education and Referral Center
  – 800-438-4380
    www.alzheimers.org

• Clinical Trials
  – www.clinicaltrials.gov