Expanding Research: Preventing and Treating Alzheimer’s Disease

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Disclosures

• In the past 12 months I have been a consultant/advisor to the following companies on topics of trial design and data analysis
  – Medpace,
  – Sanofi-Aventis,
  – Takeda,
  – Genentech,
  – Targaset,
  – Hoffman-LaRoche
  – Neurcog trials.
Today’s Topics

• How far we have come
  – Diagnosis
  – Treatment

• What we know about lifestyle
  – Treating your co-morbidities, diet, supplements
  – Activity: physical, mental, social

• Research: Taking the next step
Fear of Alzheimer’s Disease

Since 2006, the percentage of those who fear getting Alzheimer’s has increased more than the other illnesses.
What we know about Diagnosing and Treating Alzheimer’s Disease

• Improved confidence in diagnosis by clinical evaluation, imaging and biomarkers
• Known genetic risk of Apolipoprotein ε4
• Approved treatments for treating AD exist with robust though modest effects
• Functional benefit with Vitamin E demonstrated in mild and moderate disease
Cognitive Decline Precedes Dementia

Hypothetical model of AD pathophysiological cascade

- Age
  - Genetics
  - Cerebrovascular risk factors
  - Other age-related brain diseases

- Amyloid-β Accumulation
  - Brain and cognitive reserve
  - ? Environmental factors

- Synaptic Dysfunction
  - Glial Activation
  - Tangle Formation
  - Neuronal Death

- Cognitive Decline

Mild Cognitive Impairment

Memory above cutoff

Memory below cutoff

Follow-up Time (Years)
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

FDA APPROVED
**Biomarkers in the Cerebrospinal Fluid (CSF)**

### Table 2. Association Between CSF Aβ1-42/CSF P-Tau181P Mixture Model Classification and Diagnostic Follow-up Broken Down by Diagnosis at Baseline

<table>
<thead>
<tr>
<th>Diagnosis at Baseline</th>
<th>Mixture Model Classification</th>
<th>Latest Follow-up Diagnosis, No. (%)</th>
<th>P Value for Association&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td>MCI</td>
</tr>
<tr>
<td>Normal</td>
<td>AD</td>
<td>37 (91)</td>
<td>3 (8)</td>
</tr>
<tr>
<td></td>
<td>Healthy</td>
<td>71 (99)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>MCI</td>
<td>AD</td>
<td>2 (1)</td>
<td>100 (73)</td>
</tr>
<tr>
<td></td>
<td>Healthy</td>
<td>3 (6)</td>
<td>42 (82)</td>
</tr>
<tr>
<td>AD</td>
<td>AD</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Healthy</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

100% accuracy if you have AD  
35% of Normals were mislabeled AD  
Only 26% of MCI labeled AD had progressed
Apolipoprotein ε 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
Effects of galantamine in a 2-year, randomized, placebo-controlled study in Alzheimer’s disease

**Survival Benefit**

Days from randomization:

- Placebo: 1,021 947 816 699 633 552 492 411 332 3 0
- Galantamine: 1,024 943 811 715 639 571 512 432 356 7 0

**Cognitive Benefit**

Mean change ± SE in MMSE score:

- Baseline: Placebo 888, Galantamine 873
- Month 6*: Placebo 891, Galantamine 874
- Month 12*: Placebo 891, Galantamine 874
- Month 18*: Placebo 891, Galantamine 874
- Month 24*: Placebo 891, Galantamine 874

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Treatment benefits persist even for patients with moderate and severe disease.
From: Effect of Vitamin E and Memantine on Functional Decline in Alzheimer Disease: The TEAM-AD VA Cooperative Randomized Trial


Figure Legend:
Changes in Primary Outcome (ADCS-ADL Inventory Score) During the 4-Year Study Period, Compared With Baseline In this between-group comparison, lower scores indicate worse functioning. Data are least squares means at each time point. Values have been adjusted for baseline scores as a fixed effect and the study site as a random effect. ADCS-ADL indicates Alzheimer’s Disease Cooperative Study/Activities of Daily Living; error bars, 95% CIs.
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)
What Do we know about Lifestyle & Modifiable Risks

- Diet
- Sedentary lifestyle
- Stress
- Head injury
- Diabetes
- Hypertension
- Hypercholesterolemia
- Stroke
- Depression

- Epidemiological connection
- No clinical trial evidence
- Maybe an indirect path
- Maybe not independent risk factors
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 to 3 million cases worldwide
- 184,000–492,000 cases in the USA
- Very little evidence that reducing these risks will benefit cognition
Mediterranean Diet and Dementia
Diet Affecting Cardiovascular Outcomes

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

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.
Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial

Elena H Martínez-Lapiscina,1,2 Pedro Clavero,3 Estefania Toledo,1,4 Ramon Estruch,4,5 Jordi Salas-Salvadó,4,6 Beatriz San Julián,1 Ana Sanchez-Tainta,1 Emilio Ros,4,7 Cinta Valls-Pedret,4,7 Miguel Á Martinez-Gonzalez1

Table 4  Multivariable-adjusted means after a 6½-year follow-up and differences versus control (95% CIs) in each intervention group

<table>
<thead>
<tr>
<th></th>
<th>MedDiet+EVOO (n=224)</th>
<th>MedDiet+Nuts (n=166)</th>
<th>Control (low-fat diet) (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (95% CI)</td>
<td>p Value (vs control)</td>
<td>Mean (95% CI)</td>
</tr>
<tr>
<td>MMSE</td>
<td>27.73 (27.27 to 28.19)</td>
<td>0.005</td>
<td>27.68 (27.20 to 28.16)</td>
</tr>
<tr>
<td>Adjusted diff. versus control (95% CI)</td>
<td>+0.62 (+0.18 to +1.05)</td>
<td></td>
<td>+0.57 (+0.11 to +1.03)</td>
</tr>
<tr>
<td>CDT</td>
<td>5.31 (4.98–5.64)</td>
<td></td>
<td>5.13 (4.78–5.47)</td>
</tr>
<tr>
<td>Adjusted diff. versus control (95% CI)</td>
<td>+0.51 (+0.20 to +0.82)</td>
<td></td>
<td>+0.33 (+0.003 to +0.67)</td>
</tr>
</tbody>
</table>

Small but significant benefit in overall cognition
What about Physical activity to benefit 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
Increase in hippocampus volume in aerobic exercise group
Improved spatial memory in both groups

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

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The women of the Vakhegula Vakhegula soccer team, ranging in age from 49 to 84, warmed up before a game last month near Tzaneen, South Africa.
Supplement Benefit? Only in those with low intake?

- MIDAS study
  - AAMI
  - Low omega 3 diet
  - Treated with DHA
  - Benefit in learning

Docosahexaenoic Acid – DHA
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
Gbiloba 1545 1521 1458 1369 1254 1129 775 97

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


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Stress, Age and Word Recall

Stress, Age and Word Recall

Golier, Yehuda, Lupien et al.  
*Am J Psychiatry, 2002*
Cut down on distractions

- Focus on one thing at a time
- Give the item you want to learn or remember your full attention
- Remember that multi-tasking is for the young – not the young-at-heart
What is the A4 Study?

• A4 = Anti-Amyloid Treatment in Asymptomatic Alzheimer’s
• First-ever trial designed to prevent memory loss in people at a higher risk for AD but who have no symptoms
• Testing whether a new investigational treatment, called an anti-amyloid antibody, can prevent memory loss associated with AD
The Goal of the A4 Study

To determine whether we can prevent memory loss in people who may be at a higher risk for developing Alzheimer’s disease (AD) before they show symptoms.
A4 Fast Facts

100% voluntary
100% confidential
No cost to participants
Monetary compensation /transportation reimbursement* provided
Lasts for 3.5 years/requires monthly visits
Investigational medication or placebo delivered through monthly IV
Can withdraw any time
Anti-Amyloid treatment in Asymptomatic AD – The A4 Trial

- Older individuals (ages 65-85)
- Normal thinking and memory function
- Presence of amyloid on imaging
- May be at risk for developing Memory Loss
- Treatment with Solanezumab or placebo to reduce the rate of memory decline
$^{18}$F-AV-45 Representative Images: Healthy Controls

Amyloid Negative HC

Amyloid Positive HC
Cognition in Aβ Pos vs. Neg in HC > 70 years old

Florbetapir (¹⁸F AV-45) Phase II Study

Sperling R et al Neurobiology of Aging 2012
Preclinical Alzheimer’s Disease?

Prevalence of plaques in HC
(Davies, 1988, n=110)
(Braak, 1996, n=551)
(Sugihara, 1995, n=123)

Prevalence of PiB+ PET in HC

~15 yrs

Prevalence of AD
(Tobias, 2008)

Rowe C et al Neurobiology of Aging 2010
Subjective memory concerns associated with amyloid burden among “normal” elderly

Perrotin A et al Arch Neurology 2012
Effect of amyloid on memory decline from preclinical to clinical Alzheimer’s disease

AIBL data

Lim Y et al *Brain* 2014
The A4 Study

Anti-Amyloid Treatment

Cognition

Amyloid + Treated

Amyloid + Placebo
Solanuzamab

- Monoclonal antibody, binds to amyloid-β peptides; “ineffective” at plaque formation
- Minimally effective in AD
- Clinical trials moving to “milder AD” & asymptomatic individuals
Primary and Secondary Outcomes in EXPEDITION 2, Intention-to-Treat Population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean Change from Baseline to Wk 80 (95% CI)</th>
<th>Mean Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Solanezumab</td>
<td></td>
</tr>
<tr>
<td>ADAS-cog11 score†</td>
<td>6.6 (5.2 to 7.9)</td>
<td>5.3 (4.0 to 6.7)</td>
<td>−1.3 (−2.5 to 0.3)</td>
</tr>
<tr>
<td>ADAS-cog14 score†</td>
<td>7.5 (5.8 to 9.1)</td>
<td>5.9 (4.3 to 7.5)</td>
<td>−1.6 (−3.1 to 0.1)</td>
</tr>
<tr>
<td>ADCS-ADL score†</td>
<td>−10.9 (−12.7 to −9.1)</td>
<td>−9.3 (−11.2 to −7.5)</td>
<td>1.6 (−0.2 to 3.3)</td>
</tr>
<tr>
<td>CDR-SB score</td>
<td>1.9 (1.4 to 2.4)</td>
<td>1.6 (1.2 to 2.1)</td>
<td>−0.3 (−0.7 to 0.2)</td>
</tr>
<tr>
<td>NPI score</td>
<td>3.0 (0.8 to 5.1)</td>
<td>2.8 (0.7 to 5.0)</td>
<td>−0.2 (−1.8 to 1.5)</td>
</tr>
<tr>
<td>MMSE score</td>
<td>−2.8 (−3.6 to −2.0)</td>
<td>−2.1 (−2.8 to −1.3)</td>
<td>0.8 (0.2 to 1.4)</td>
</tr>
<tr>
<td>Free $\text{A}\beta_{40}$ in CSF — pg/ml</td>
<td>−649.0 (−2139.5 to 841.5)</td>
<td>−1258.1 (−2695.8 to 179.7)</td>
<td>−609.1 (−1228.4 to 10.2)</td>
</tr>
<tr>
<td>Free $\text{A}\beta_{42}$ in CSF — pg/ml</td>
<td>−35.1 (−129.5 to 59.3)</td>
<td>1.0 (−94.1 to 96.2)</td>
<td>36.1 (−1.0 to 73.3)</td>
</tr>
<tr>
<td>Total $\text{A}\beta_{40}$ in CSF — pg/ml</td>
<td>−876.4 (−4342.5 to 2589.8)</td>
<td>2156.8 (−1211.9 to 5525.4)</td>
<td>3033.1 (1628.4 to 4437.9)</td>
</tr>
<tr>
<td>Total $\text{A}\beta_{42}$ in CSF — pg/ml</td>
<td>323.8 (86.2 to 561.5)</td>
<td>726.6 (489.4 to 963.9)</td>
<td>402.8 (307.7 to 497.8)</td>
</tr>
</tbody>
</table>

* The methods used to analyze between-group differences in outcomes from baseline to week 80 were the same as those used in EXPEDITION 1. Measurements of $\text{A}\beta$ in the CSF were available at baseline and follow-up for 32 patients in the placebo group and 44 patients in the solanezumab group.

† The original primary outcomes were the changes from baseline to week 80 in scores on the ADAS-cog11 and the ADCS-ADL scale. After analysis of data from EXPEDITION 1, the primary outcome for EXPEDITION 2 was revised to the change in scores on the ADAS-cog14 in patients with mild Alzheimer’s disease.

Mild Alzheimer's Disease vs. Moderate Alzheimer's Disease
EXPEDITION 2, Intention-to-Treat Population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mild Alzheimer's Disease</th>
<th>Moderate Alzheimer's Disease</th>
<th>Test for Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Change from Baseline</td>
<td>Mean Difference (95% CI)</td>
<td>P Value†</td>
</tr>
<tr>
<td></td>
<td>to Wk 80</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td>solanezumab</td>
<td></td>
</tr>
<tr>
<td>ADAS-cog11 score</td>
<td>5.1</td>
<td>3.6</td>
<td>-1.5 (-3.0 to 0.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAS-cog14 score</td>
<td>5.8</td>
<td>4.1</td>
<td>-1.7 (-3.5 to 0.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADCS-ADL score</td>
<td>-8.9</td>
<td>-6.6</td>
<td>2.3 (0.2 to 4.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDR-SB score</td>
<td>1.6</td>
<td>1.3</td>
<td>-0.3 (-0.8 to 0.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI score</td>
<td>1.5</td>
<td>1.0</td>
<td>-0.5 (-2.4 to 1.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE score</td>
<td>-2.4</td>
<td>-1.8</td>
<td>0.7 (-0.1 to 1.4)</td>
</tr>
<tr>
<td></td>
<td></td>
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</table>

* Methods used to analyze between-group differences (solanezumab group minus placebo group) from baseline to week 80 were the same as those used for the primary analysis. In the placebo group, 325 patients had mild Alzheimer's disease and 194 had moderate Alzheimer's disease; in the solanezumab group, 322 patients had mild Alzheimer's disease and 199 had moderate Alzheimer's disease.
† The P value is for the comparison between the solanezumab group and the placebo group.
‡ The P value is for the comparison between patients with mild Alzheimer's disease and those with moderate Alzheimer's disease.

Mild Alzheimer's disease (MMSE score of 20 to 26 at visit 1)
Moderate Alzheimer's disease (MMSE score of 16 to 19 at visit 1)

A4 Study Synopsis

- Secondary prevention trial in clinically normal older individuals (age 65-85) who have evidence of amyloid-β pathology on PET imaging
- Randomized, double-blind, placebo-controlled trial of solanezumab vs. placebo for 168 weeks
- Trial N=1000+ (N=500+ per treatment arm)
- Observational cohort of amyloid negative “screen fails” – LEARN study
- Ethics component – Disclosure of amyloid status
Intranasal Insulin Therapy for Alzheimer Disease and Amnestic MCI

A

\[ P = .02 \]

\[ P = .003 \]

\[ P = .04 \]

\[ \text{Δlog Delayed Story Recall} \]

\[ \text{Δlog ADAS-cog} \]

Placebo  20 IU  40 IU  Placebo  20 IU  40 IU
STUDY OF NASAL INSULIN TO FIGHT FORGETFULNESS

SNIFF

• 12 months for 250 participants
• Mild Cognitive Impairment or mild AD
• 55-85 years of age
• No use of diabetic medications
What Can I Do To Minimize Cognitive Impairment?

• Treat your treatable conditions
  – High cholesterol  Hypertension
  – Diabetes  Depression

• Protect your brain
  – Seat belts  Helmet
  – Ladders  Falls

• Support Research
  – Participate  Be a study partner
  – Encourage funding
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%

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

• Our 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
<table>
<thead>
<tr>
<th>Status</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruiting</td>
<td>Progress of Mild Alzheimer's Disease in Participants on Solanezumab Versus Placebo</td>
</tr>
<tr>
<td></td>
<td><strong>Condition:</strong> Alzheimer's Disease</td>
</tr>
<tr>
<td></td>
<td><strong>Interventions:</strong> Drug: Solanezumab; Drug: Placebo</td>
</tr>
<tr>
<td>Recruiting</td>
<td>Study of the Safety and Effectiveness of Two Doses of Investigational Study Drug EVP-6124 in Subjects With Alzheimer's Disease</td>
</tr>
<tr>
<td></td>
<td><strong>Conditions:</strong> Alzheimer's Disease, Dementia</td>
</tr>
<tr>
<td></td>
<td><strong>Interventions:</strong> Drug: Drug: EVP-6124; Drug: Placebo</td>
</tr>
<tr>
<td>Recruiting</td>
<td>Efficacy and Safety Study of ELND005 as a Treatment for Agitation and Aggression in Alzheimer's Disease</td>
</tr>
<tr>
<td></td>
<td><strong>Condition:</strong> Alzheimer's Disease</td>
</tr>
<tr>
<td></td>
<td><strong>Interventions:</strong> Drug: ELND005; Drug: Placebo</td>
</tr>
<tr>
<td>Recruiting</td>
<td>Study of Lu AE58054 in Patients With Mild - Moderate Alzheimer's Disease Treated With Donepezil</td>
</tr>
<tr>
<td></td>
<td><strong>Condition:</strong> Alzheimer's Disease</td>
</tr>
<tr>
<td></td>
<td><strong>Interventions:</strong> Drug: Placebo; Drug: Lu AE58054</td>
</tr>
</tbody>
</table>

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