Current and Future Strategies in Alzheimer’s Disease Treatment & Prevention

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Objectives

• To review the current state of diagnosis and treatment of AD
  – How far we have come
• To describe prominent research for treatments for AD symptoms and pathology
  – Where we are in experimental therapeutics
• To present the state of the science on Prevention of Dementia
  – Treating treatable conditions
  – Pharmacological and non-pharmacological approaches
Societal Trends and Dementia

- 65+ age group: fastest growing segment of US population
- Increasing number of elders results in greater incidence and prevalence of AD
- Increasing longevity with disease
- 3- to 5-year period of mild but significant cognitive impairment precedes diagnosis
- Changing technology required for routine activities carries high cognitive demand
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

Mild Cognitive Impairment

Hypothetical model of AD pathophysiological cascade

- Age Genetics
- Cerebrovascular risk factors
- Other age-related brain diseases
- Amyloid-β Accumulation
- Synaptic Dysfunction
- Glial Activation
- Tangle Formation
- Neuronal Death
- Brain and cognitive reserve
- Environmental factors

Graph showing follow-up time (years) with memory above and below cutoff.
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
Effects of galantamine in a 2-year, randomized, placebo-controlled study in Alzheimer’s disease

Survival Benefit

Cognitive Benefit

Patients at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1,021</td>
</tr>
<tr>
<td>Galantamine</td>
<td>1,024</td>
</tr>
</tbody>
</table>

Mean change ± SE in MMSE score

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo 906</th>
<th>Galantamine 905</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>888</td>
<td>873</td>
</tr>
<tr>
<td>Month 6'</td>
<td>891</td>
<td>874</td>
</tr>
<tr>
<td>Month 12'</td>
<td>891</td>
<td>874</td>
</tr>
<tr>
<td>Month 18'</td>
<td>891</td>
<td>874</td>
</tr>
<tr>
<td>Month 24'</td>
<td>891</td>
<td>874</td>
</tr>
</tbody>
</table>
Treatment benefits persist even for patients with moderate and severe disease.

**Figure 3.** Mean Scores on the Standardized Mini–Mental State Examination (SMMSE) and the Bristol Activities of Daily Living Scale (BADLS), According to Visit Week and Treatment Group.

Scores on the SMMSE range from 0 to 30, with higher scores indicating better cognitive function; scores on the BADLS range from 0 to 60, with higher scores indicating greater impairment. Shown are raw estimates of the mean score at each visit. Error bars denote the standard error.
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 1.1–3.0 million cases worldwide
• 184 000–492 000 cases in the USA
• Very little evidence that reducing these risks will benefit cognition
Finger Study: Inclusion Criteria

• aged 60-77 years
• dementia Risk Score 6 points or more
• one of the following criteria:
  – i) MMSE: 20-26 points
  – ii) word list memory task (3x10 words): 19 words or less
  – iii) delayed recall: 75% or less
FINGER Study

Control

• Study nurse gave oral & written information and advice on management of vascular risk factors & disability prevention
  – Healthy diet
  – Physical activities
  – Cognitive activities
  – Social activities.

Intervention

• Nutritionists: 3 individual & 7-9 group sessions.
• Physiotherapists individual program for muscle strengthening 1–3/wk & aerobic exercise 2–5/wk
• Psychologist led cognitive training: 72 individuals and 10 group sessions
• Social activities stimulated through numerous group meetings of interventions
Figure 2. Change in cognitive performance during the 2 year intervention. The figure shows estimated mean change in cognitive performance from baseline until 12 and 24 months (higher scores suggest better performance) in the modified intention-to-treat population. E...


A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

null, Volume 385, Issue 9984, 2015, 2255–2263

http://dx.doi.org/10.1016/S0140-6736(15)60461-5
PreDiva

- visits to a practice nurse in every 4 months, for 6 years (18 visits).
- Address cardiovascular risk factors:
  - smoking habits, diet, physical activity, weight, and blood pressure. Blood glucose and lipid concentrations were assessed every 2 years and when indicated otherwise.
- On the basis of these assessments, individually tailored lifestyle advice was given according to a detailed protocol conforming with prevailing Dutch general practitioner guidelines on cardiovascular risk management and supported by motivational interviewing techniques. If indicated, drug treatment for hypertension, dyslipidaemia, and type 2 diabetes mellitus was initiated or optimised.
Pre-Diva

- Open-label, cluster-randomised controlled trial,
- Individuals aged 70–78 years through participating general practices in Netherlands.
- Assigned (1:1), via a computer-generated randomisation sequence, to either a 6-year nurse-led, multidomain cardiovascular intervention or control (usual care).
- The primary outcomes: incidence of dementia and disability score (ALDS) at 6 years of follow-up.
- Secondary outcomes: incident cardiovascular disease and mortality.

ITT analyses
**Figure 2: Kaplan-Meier plot of cumulative incidence of dementia**

To allow participants recruited early into the trial to continue follow-up until the 6-year assessment of the last participant was completed, the study was extended for participants randomised early (ie, in 2006–07). The hazard ratio (HR) refers to an analysis including all participants, up to 8 years of follow-up. The period beyond the planned 6-year follow-up, concerning few participants, is shaded.
What about Specific Interventions

• Diet
• Exercise
• Cognitive Training
• Sleep
• Supplements
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, and 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 Martínez-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>0.005</td>
<td>+0.57 (+0.11 to +1.03)</td>
</tr>
<tr>
<td>CDT</td>
<td>5.31 (4.98–5.64)</td>
<td>0.001</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>0.001</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

A  Hippocampus

B  Caudate Nucleus

C  Thalamus

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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.
LIFE Study

• Sedentary men and women aged 70 to 89
• High risk for mobility disability based on low score on the
• Could walk 400 m (without assistance) within 15 minutes at baseline.
• Randomized to Health Education or Physical Activity
70 to 89 years who were at high risk for mobility disability

Based upon promising results from a pilot study among 424 sedentary older adults who were randomized to a physical activity intervention or a successful aging health education intervention, a Phase 3 multi-center randomized controlled trial is being conducted to compare a moderate-intensity physical activity program to a successful aging health education program in 1,900 sedentary older adults who are followed for an average of 2.7 years.

The primary aim is to assess the long-term effects of the proposed interventions on the primary outcome of major mobility disability defined as inability to walk 400 m.

Secondary aims focus on assessing the relative effects of the interventions on the following outcomes: cognitive function; serious fall injuries; persistent mobility disability; the combined outcome of major mobility disability or death; disability in activities of daily living; cardiovascular and pulmonary events; and cost.

**Graphs:**

- **Major mobility disability**
  - Proportion of Event-Free Participants
  - HR, 0.82 (95% CI, 0.69-0.98); P = .03
  - Follow-up Time, y

- **Persistent mobility disability**
  - Proportion of Event-Free Participants
  - HR, 0.72 (95% CI, 0.57-0.91); P = .005
  - Follow-up Time, y
LIFE Study: Incident MCI and Dementia

- Perhaps too little too late?

<table>
<thead>
<tr>
<th></th>
<th>Physical Activity</th>
<th>Health Education</th>
<th>OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI</td>
<td>70/686 (10.2)</td>
<td>62/682 (9.1)</td>
<td>1.14 (0.79-1.62)</td>
</tr>
<tr>
<td>Dementia</td>
<td>28/743 (3.8)</td>
<td>29/747 (3.9)</td>
<td>0.96 (0.57-1.63)</td>
</tr>
<tr>
<td>MCI or Dementia</td>
<td>98/743 (13.2)</td>
<td>91/747 (12.1)</td>
<td>1.08 (0.80-1.46)</td>
</tr>
</tbody>
</table>
• Age between 65 and 89 years old, inclusive
• Diagnosis of single or multi-domain amnestic MCI using clinical criteria as per
• MMSE: ≥24 for participants with 13 or more years of education; ≥22 for participants with 12 or fewer years of education
• CDR = 0.5
• Impaired delayed verbal recall as indicated by scores meeting at least ONE of the following criteria: Logical Memory II ≤ 7 Auditory Verbal Learning Test, Trial 7 ≤ 4
• Has an informant who knows the participant well, has at least weekly contact, and is available to accompany the participant to clinic visits
• Sedentary or underactive, determined by responses to the staff-administered Telephone Assessment of Physical Activity (TAPA) survey
Sleep Disordered Breathing (SDB)

- Snoring common in the elderly
  - 52.6% of men
  - 26.3% of women

- Associated with:
  - Increased body weight
  - Reduction in cognition
  - Earlier age of MCI

- CPAP may reduce the cognitive loss
Sleep-disordered breathing advances cognitive decline in the elderly

CPAP CAN HELP
Role of Depression in Predicting Time to Conversion to Mild Cognitive Impairment

(Am J Geriatr Psychiatry 2014; 22:727e734)
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); $P = .21$


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What about amyloid modification
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
  (Tobias, 2008)

- Prevalence of AD
  ~15 yrs
  (Tobias, 2008)
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
$^{18}\text{F-AV-45}$ Representative Images: Healthy Controls

Amyloid Negative HC

Amyloid Positive HC
Effect of amyloid on memory decline from preclinical to clinical Alzheimer’s disease
Solanuzamab

- Monoclonal antibody, binds to amyloid-β peptides; “ineffective” at plaque formation
- Minimally effective in AD
- Clinical trials moving to “milder AD” & asymptomatic individuals
Aducanumab
amyloid plaque reduction

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%

Trial Referral is an Underused Opportunity

Ever referred for an AD trial?
- 22%
- 78%

Have patients/caregivers approached about an AD trial?
- 39%
- 61%

Why Clinical Research Participations?

<table>
<thead>
<tr>
<th>Clinicians</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Low referrals, delay new diagnostics, and treatments</td>
<td>• Standardized evaluations as baseline</td>
</tr>
<tr>
<td>• Mutual referral relationships</td>
<td>• Access to up-to-date research initiatives</td>
</tr>
<tr>
<td>– Tertiary care research centers need referral options</td>
<td>• Potential for earliest access to medications</td>
</tr>
<tr>
<td>– Enhance practice credibility</td>
<td>• Support for family and friends</td>
</tr>
<tr>
<td></td>
<td>• Contribution from self to family, society***</td>
</tr>
</tbody>
</table>
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
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*
Conclusions/Considerations

• Cognitive loss and dementia are important problems with many stakeholders
• Progress has been made with diagnosis and modest interventions
• Prevention is a challenge that will require considerable, coordinated, commitment
• Lifestyle, environmental and pharmacological interventions will probably be required.
Information on AD Research

• 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