Prevention of Cognitive Decline and Dementia: Fiction or Reality?

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Chair Gerontopole
UMR INSERM 1027, University of Toulouse, France
Conflicts of Interest

• The Gerontopole have the mission to work, on Alzheimer’s drug development and have to work with any companies with potential interesting drug development (list available: Merck, Lilly, Biogen, Roche, Genentech, Avanir, Nestle, Astra..); However B Vellas have no stock options in any of these companies
Estimated population aged 60 years or older (2050)

Percentage of population (%)

- ≥30
- 20–29
- 10–19
- <10
- Data not available
- Not applicable

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Information, Evidence and Research (IER)
World Health Organization

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## Dependence

Prevalence of dependence/disability: 350 to 600 million

<table>
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<tr>
<th>Region</th>
<th>Year</th>
<th>Total population (millions)</th>
<th>Number of dependent people (millions)</th>
<th>Prevalence of dependence (%)</th>
<th>Increase in numbers (compared to numbers in 2000, %)</th>
<th>Dependency ratio* (%)</th>
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<td>Established Market Economies</td>
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<td>9337</td>
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</table>
The Freedom of *Healthy Ageing*

Dr John Beard
Director, Ageing and Life Course
"Healthy Ageing - the process of developing and maintaining the functional ability that enables wellbeing in older age."

“To shift the focus from disease to capacity”
Prevention of Cognitive Decline and Dementia: Fiction or Reality?

• I. Cognitive decline in older adults using precision medicine

• II. How can we prevent cognitive decline part of our clinical practice now and in the near future
I. Cognitive Decline in Older Adults

• Subjective Memory Complaints
• Vascular Cognitive Decline
• Cognitive Decline Related to Alzheimer’s Disease
• Cognitive Decline Related to Frailty

• To be effective intervention: targeted, strong and sustained
• Precision medicine, personalized therapy
Subjective Memory Complaints

- **Definition:** Subjective memory complaints, 60% normal cognitive functions (CDR 0), 40% objective cognitive decline, CDR 0.5, early M.C.I.
- **Advantages:** observance, frequent population
- **Disadvantages:** some of them will have no cognitive decline, some more likely to decline if recent (less than 5 years) and progressive complaint
- **Prevalence:** 60 % (MAPT), cultural influence
- **Intervention Studies:** GuidAge, MAPT
M.A.P.T: Multi-domain Alzheimer Preventive Trial

• Randomized, placebo control study
• 1680 subjects; 70yrs +, living in the community
• Inclusion criteria:
  • Subjective memory complaint, slow gait speed
• Three years Intervention + 2 years observation
  • Multi-domain Intervention plus placebo
  • Omega 3 (800 mg DHA)
  • M.I plus Omega 3
  • Placebo
• Primary End Point: Cognitive decline
• Secondary: SPPB, Frailty
• Brain MRI(500), Florbetapir PET (271), FDG (68)

M.A.P.T Multi-Domain Intervention

• Yearly Alzheimer Preventive Clinic Assessment

• Cognitive training:
  • Reasoning: strategies (8 sessions); S Willis (Seattle)
  • Mnemonic strategies (4 sessions); S Belleville (Montreal)
  • one session by month for 36 months

• Physical training
  • 150 minutes of moderately intensive physical activity per week; eg: walking (30 minutes per day).

• Nutrition Education
  
Good Sensibility for Cognitive Composite Score as Primary Criteria

**Composite Score:**
Episodic memory: FCRST (Free + total recall)
Orientation: 10 items MMSE
Executive Function: WAIS (DSSS)
Verbal Fluency (animals 2 mn)

Donohue et al (adapted, JAMA Neurology 2016)
Coley N, Andreiu S (Alzheimer Dementia 2016)
MAPT Results: Primary Criteria: ITT (N=1525)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean change from baseline to 36 months (95% CI)</th>
<th>Mean difference (95% CI) vs placebo</th>
<th>P value (raw)</th>
<th>P value (Hochberg)</th>
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<tbody>
<tr>
<td>Omega3 + Multid</td>
<td>0.02 (-0.04 ; 0.09)</td>
<td>0.09 (0.00 ; 0.18)</td>
<td>0.0473</td>
<td>0.1419</td>
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<tr>
<td>Omega3</td>
<td>-0.06 (-0.12 ; 0.01)</td>
<td>0.01 (-0.08 ; 0.10)</td>
<td>0.8121</td>
<td>0.8121</td>
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<tr>
<td>Multid</td>
<td>0.01 (-0.05 ; 0.07)</td>
<td>0.08 (-0.01 ; 0.17)</td>
<td>0.0896</td>
<td>0.1792</td>
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</table>

- Composite Score

![Diagram showing change in composite score over time for different groups with statistical values provided.]
MAPT: Sub-group, Early MCI: CDR 0.5

Population modified ITT

Group:
- **omega3+MI**
  - CDR=0.5
- **omega3**
  - CDR=0.5
- **MI**
  - CDR=0.5
- **control**
  - CDR=0.5

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
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<tr>
<td>M0:</td>
<td>n=151</td>
<td>n=160</td>
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<tr>
<td>M36:</td>
<td>n=115</td>
<td>n=119</td>
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</table>

Change in Composite score over time (months)
Low DHA Results From the MAPT Trial

3-year change from baseline on composite score in intervention and control groups in subjects with low baseline erythrocyte DHA+EPA% (defined as the lowest DHA+EPA% quartile) in the ITT population

<table>
<thead>
<tr>
<th>Intervention group:</th>
<th>Omega-3 + Multidomain</th>
<th>Omega-3 + placebo</th>
<th>Multidomain + placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in 3y change from baseline vs. control</td>
<td>0.21</td>
<td>0.19</td>
<td>0.16</td>
</tr>
<tr>
<td>95%CI</td>
<td>[0.02; 0.39]</td>
<td>[0.00; 0.38]</td>
<td>[-0.04; 0.35]</td>
</tr>
<tr>
<td>P (raw)</td>
<td>0.0339</td>
<td>0.0543</td>
<td>0.1170</td>
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<tr>
<td>P (adjusted for multiple comparisons)</td>
<td>0.1017</td>
<td>0.1086</td>
<td>0.1170</td>
</tr>
</tbody>
</table>
DO-HEALTH

- Vitamin D3 - Omega3 - Home Exercise – HeALTHy Aging and Longevity Trial

- Funded by the European Commission Framework 7 research programme and the University of Zurich.
- Europe’s largest healthy aging study.
- 2157 healthy seniors recruited at 7 centres in 5 countries.
- Study to establish whether vitamin D, omega-3 fatty acids and a simple home exercise program will prevent disease at older age.
DO-HEALTH -

• The 3 most promising interventions to impact on 5 key health endpoints

Evidence from large clinical trial is missing
Nolan Trial: Brain Protector Blend

The BPB was designed to **target known biological risk factors** for brain aging

- support brain physiology through B-vitamins
- reduce homocysteine
- reduce inflammation
- reduce oxidative stress
- increase blood flow
- support healthy neuronal structure

NOLAN Clinical Study to prove effects in humans

- Various rodent models
  - 2003
  - 2005
  - 2010
  - 2016

Research shows that the BPB improves cognition in

- aged dogs...
- ...and aged cats

**Above effects were observed after 8 (dog) and 2.5 (cat) months of intervention in the egocentric reversal learning task.** *p<0.05*
Four Large Type of Cognitive Decline

• Subjective Memory Complaints
• Vascular Cognitive Decline
• Cognitive Decline Related to Alzheimer’s Disease
• Cognitive Frailty, in Frail older adults
Vascular Cognitive Decline: Finger Trial

• Target Population: CAIDE: Cardiovascular Risk Factors, Aging and Dementia:
  • Age,
  • Sex,
  • Height and weight,
  • Serum cholesterol,
  • Systolic and diastolic blood pressure,
  • Physical activity status,
  • Years of education.

• Score $\geq 6$ and cognition at mean level or slightly lower than expected for age. (Alz & Dementia 2015)

• 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. ($N=1280$) (Lancet 2015)
Finger Trial: Effect on Cognition

In post-hoc analyses, we defined cognitive decline as decrease in NTB total score (overall decline) and NTB domain scores (decline per domain) between the assessments at baseline and at 24 months. Logistic regression analyses were used to assess risk of cognitive decline in the control group compared with the intervention group. Analyses are based on all participants with data available at both baseline and 24 months. NTB= neuropsychological test battery.

Table 2: Risk of cognitive decline from baseline to 24 months
Four Large Type of Cognitive Decline

• Subjective Memory Complaints
• Vascular Cognitive Decline
• Cognitive Decline Related to Alzheimer’s Disease
• Cognitive Frailty, in Frail older adults
Prevalence of Amyloid Phenotype in Normal Elderly Subjects
What We Have Learned from Drug Trials in Alzheimer?
(Jour Prev Alz Dis 2017, No3)

• 1990 – 2000: Dementia stage: too late
• 2000 – 2010: Early AD but no precision medicine, no good target (30% of those classified as mild Alzheimer in the solaneuzumap trial are amyloid negative and don’t progress after 4 years of follow up (NEJM 2016)
• 2010 – 2017: Prodromal to mild AD, precision medicine (biomarkers), specific therapy: however maybe not strong enough (doses) (NEJM 2017 in press), too late
• 2017: Same trials with higher dose, anti-tau, regenerative Medicine
• Early preventive trials eg A 3 with β-secretase inhibitors
Pro-dromal Alzheimer or MCI due to AD

- **Definition**
  - Objective cognitive decline: logical memory
  - CDR=0.5
  - Amyloid signature (PET or CSF)
  - spared ADL’s
- **Advantages**: conversion, observance
- **Disadvantages**: screening, cost, cut off for pour defining cognitive decline
- **End-Point**: CDR-SB
- **Prevalence**: 5 to 10% (MAPT)
Preclinical Alzheimer

- **Definition**
  - No objective cognitive decline
  - Amyloid or Tau Signature (PET or CSF)
  - Spared ADL

- **Advantages**: large target, early intervention
- **Disadvantages**: conversion, slow cognitive decline, cost
- **End-Point**: composite score, logical memory

- **Prevalence**: 20 to 30% with amyloid signature
Anti-Amyloid Treatment in Asymptomatic AD (A4) Study

- Secondary prevention trial in clinically normal older individuals (age 65-85) who have evidence of amyloid-β accumulation on screening PET imaging
- Phase 3 randomized, double-blind, placebo-controlled trial of solanezumab vs. placebo for 240w
- Trial N=1150 (N=575+ per treatment arm)
- Observational cohort of Aβ negative “screen fails” – LEARN study (funded by Alzheimer’s Association)
- Ethics component – Disclosure of amyloid status
EARLY (A5) Trial

• Industry sponsored trial of Janssen oral BACE inhibitor with academic collaboration
• EARLY is a more global study - launched in Europe, Australia, will start in US in fall 2016
• Amyloid eligibility by CSF or PET – same “amyloid positive” normals criteria as in A4
• Broader age range – 60-85 years old
  • Participants age 60-65 must have additional risk factor
• Broader cognitive range than A4
• Longer trial – up to 4.5 years
A3 Study

• A3 will leverage the A4 /A5 screening to identify people with “subthreshold” Aβ levels who are at high risk for continued amyloid accumulation

• Four year Phase IIb/IIIa 4 trial - BACE inhibitor

• Primary outcomes are biomarkers – rate of Aβ accumulation, tau spreading, MR atrophy

• Exploratory sensitive cognitive outcomes (iPAD)

• Public-private-philanthropic partnership (P4)
  • In process of selecting therapeutic agent
Aging & Rejuvenation Therapies

• Adults have a pool of stem cells in organs tissue that respond to exercise or injury – pumping out new cells to repair.

• Aging frailty can be considered as a depletion of endogenous stem cells contributing to a reduced ability to regenerate or repair organs and tissues.

• Cell-based, regenerative treatment strategy could ameliorate frailty and restore muscle and brain functions.
Effect of MSCs on Phenotypes of Frailty

<table>
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<tr>
<th>Frailty phenotypes</th>
<th>MSC response</th>
<th>Postulated mechanism of action</th>
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<tbody>
<tr>
<td>Weight loss</td>
<td>Maintains total caloric expenditure</td>
<td>↓ Inflammation which suppresses the onset of sarcopenia</td>
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<tr>
<td>Exhaustion</td>
<td>↑ Pulmonary function, ↓ chronic inflammation</td>
<td>↑ Endothelial function, ↓ markers of inflammation</td>
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<tr>
<td>Weakness</td>
<td>↑ Physical performance</td>
<td>↑ Mitochondrial transfer, ↑ endogenous stem cell function</td>
</tr>
<tr>
<td>Slow gait speed</td>
<td>↑ 6-minute walk distance</td>
<td>↑ Endothelial function, ↑ cardiac performance, ↑ skeletal muscle performance</td>
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<tr>
<td>Decreased activity level</td>
<td>↓ Chronic inflammation, ↑ quality of life</td>
<td>↓ TNF-α, ↓ IL-1β, ↑ IL-10</td>
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</table>

Notes: MSCs home to sites of injury and to enhance repair of damaged tissue (heart, joints, muscle, and blood vessels) and **exert their regenerative effects via paracrine signaling, mitochondrial transfer, direct cellular contact, and exosome excretion.**
Intravenous Delivery of Allogeneic Mesenchymal Stem Cells Reduces Chronic Inflammation in Frailty and Reverses Immunosenescence

Ana Marie Landin  International Conference Sarcopenia Frailty Research, April 2017, Barcelona

- **Intervention**: Administering allo-hMSCs by intravenous infusion in patients with aging frailty
- **Design**: Subjects (N=80) first randomized in a pilot phase that tested the dose effect of (20-, 100- and 200-million) allo-hMSCs. Twelve to 15 months after, subjects received a second infusion with 100-million allo-hMSCs

**Results**:
- Well tolerated.
- TNF-α significantly reduced at 6 months post 1st infusion in all patients.
- Immune risk phenotype significantly improved at 6 months post 1st infusion and was maintained throughout the study.
- Some clinical preliminary effects on physical and cognitive functions

**Comments**: systemic effects of stem cells, rejuvenation therapy
Prevention of Cognitive Decline and Dementia: Fiction or Reality

• Part II: How Can We Prevent Cognitive Decline in Clinical Practice:
  • Increase intrinsic capacity reserves in early aging
  • Monitor and Preserve functions in late aging
  • Restore functions as soon as possible
Increase Intrinsic Capacities Reserve in Early Aging

• WHO defines *intrinsic capacity* as the combination of the individual’s physical and mental – including psychosocial – capacities, and *functional*

• INSPIRE: INStitute for P revention of AgIng and REjuvenation
Population in the second half of life

Intrinsic Capacity

Increasing age group
Population in the second half of life

Intrinsic Capacity

High and Stable
Population in the second half of life

Intrinsic Capacity

High and Stable

Declining
Population in the second half of life

Intrinsic Capacity

High and Stable

Declining

Significant losses
Population in the second half of life

Intrinsic Capacity

High and Stable

Declining
We already monitor diet, sleeping patterns, physical exercise.
Voice emotion recognition and voice analysis for determining mental states

Healthy

ME-BYO

MIMOSYS

Sick

Stress and brain nerve damage can be monitored.

Daily, in real time.

MIMOSYS enables this.
Monitoring intrinsic capacity using self management

- Using mobile applications every day
- This plan is shared with the patient to involve their needs
Population in the second half of life

High and Stable | Declining | Significant loss

Intrinsic Capacity
Population in the second half of life

Intrinsic Capacity

High and Stable | Declining | Significant loss
Population in the second half of life

Intrinsic Capacity

High and Stable | Declining | Significant loss
Population in the second half of life

- Intrinsic Capacity
  - High and Stable
  - Declining
  - Significant loss
Population in the second half of life

Intrinsic Capacity

Functional Ability
Intrinsic Capacity

High and Stable  Declining  Significant loss
Prevention of Cognitive Decline and Dementia: fiction or reality

• What are the causes of cognitive decline in older adults

• How can we prevent cognitive decline ?:
  • Increase intrinsic capacity reserves in early aging
  • Monitor and Preserve functions in late aging
  • Restore functions as soon as possible
Monitor and Preserve Functions in Late Aging

Intrinsic Capacity

High and Stable

Declining

Significant losses
NMAPS: Results- Above (Younger transition matrix – 60 ≤ age ≤ 78 years), Below: Older 78 + (JNHA 2017)
COGNIGRAM™ digital cognitive assessment system received positive notification from the FDA

Boston, MA – July 2017:
Self-administered assessment that can be completed both in-clinic and at-home.

For prescription use
Can be used to assess cognition on a single occasion or cognitive change over periodic assessments.
Performance is unaffected by language, education, cultural background, or practice
Intervention to Maintain Functions in Late Aging

• Late Aging stable:
  • Multi-domain Intervention: Nutrition, physical and cognitive exercise
  • Vascular et metabolic risk factors
  • Brain Protector Blend?

• Decrease of cognitive functions: Precision Therapy
  • Amyloid related cognitive decline: β-secretase inhibitors?
  • If Amyloid biomarkers negative: Low DHA / EPA: Omega 3, Vit D, if chronic inflammation?
Prevention of Cognitive Decline and Dementia: fiction or reality

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• How can we prevent cognitive decline ?:
  • Increase intrinsic capacity reserves in early aging
  • Monitor and Preserve functions in late aging
  • Restore functions as soon as possible
Restore Cognitive Functions in Older Adults

• Amyloid Related: Amyloid monoclonal antibody, anti-tau, (Phase III in process), combinations?

• Regenerative Medicine? Stems cells?
## Perspective (2): P4 / Contemporary Medicine

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<th>Contemporary Medicine</th>
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<td>Proactive, predictive</td>
<td>Reactive</td>
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<tr>
<td>Precision medicine</td>
<td>Population</td>
</tr>
<tr>
<td>Participative: Wellness &amp; diseases</td>
<td>Only diseases</td>
</tr>
<tr>
<td>Personalized data clouds</td>
<td>Averaged patient population</td>
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<tr>
<td>Personalized data clouds for clinical trials</td>
<td>Averaged patient population for clinical trials</td>
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INITIATIVE EUROPÉENNE

EPAD
European Prevention of Alzheimer’s Dementia Consortium

REGISTRE DE SUJETS « A RISQUE »

COHORTE DE SUIVI

ESSAI THÉRAPEUTIQUE ADAPTATIF

Coordination Française :

Collaboration Centres Académiques/Partenaires Industriels
Prevalence of dependence/disability: de 350 - 600 M de 2010 à 2040

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<th>Region</th>
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