Methodological Considerations Pertaining to the Prevention of Dementia

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Overview

- Life course perspective
- Timing of interventions
- Patient characteristics
- Risk Justification
Clinical Trial Design Challenges

• Potential interventions identified from the bench, observational studies and anecdotes
• “Lasix surgery effect”
• Feasibility seldom permits trials to recapitulate observed factors (when does life-style begin)
• Designs tend to cherry pick
  – Interventions
  – Outcomes
  – Populations/indications
Methodological Issues in Protocol Development

• Targets (Biology and symptoms)
• Patient Characteristics (Definition and diagnosis)
• Outcomes (What to measure)
• Timing (How long/How often)
• Technology (Where to assess)
• Analysis (Confounders and Missing Data)
Targets, Outcomes and Stages

Alzheimer’s Disease

Cognitive function

Preclinical

Is this really flat?

Years

Aging

MCI

Dementia

Icahn School of Medicine at Mount Sinai
Targets for Treatment

- Induction
- Latency
- Detection

- Etiology
- Maximizing Cognition
- Pathogenesis
- Stabilizing Cognition
- Symptoms
- Reversing Deficit
- Disease
Target Determines Design

• Many current targets are defining dementia symptoms with anti-amyloid targets
• Other targets may be relevant to “dementia” disease
• Synapse count provides the best correlation with cognition and dementia
  – Volumetric MRI? FDG PET?
  – Could this be a target across age and disease?
• May not be a transparent relationship between target and outcome
Trials for Non-Pharmacological Interventions

• Require:
  – Rigor in case selection
  – Fidelity in treatment delivery
  – Attention to outcomes
  – Awareness of safety assessment

• How will we find interventions for care beyond the trial
Outcomes

• Though biological target may be affected, trials need clinical outcome to recommend an intervention

• Interventions may affect multiple effects (on and off target) which may not all move the outcome in the same way. (safety seldom reported)
  – (e.g. physical leads to injury leads to pain management)
Target and outcomes
Increase in hippocampus volume in aerobic exercise group
Improved spatial memory in both groups

A Hippocampus

B Caudate Nucleus

C Thalamus

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

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Patient Characteristics

“Indication”

• Valid reason to recommend an intervention
• Selection for prevention studies is seldom he absence of symptoms
• “Risk selection” or add-on studies limit interpretation.
• Inclusion/exclusion criteria must be clinically recognizable
• Impact of requiring a study partner
Golden Rule for Inclusion/Exclusion Criteria

• The role of eligibility criteria is to insure efficacy can be measured and safety is maximized
  • Who is the target population?
  • How common is that outcome in the population?
  • Do known factors change the likelihood of outcome or safety of treatment?
• Every exclusion reduces the generalizability and applicability of findings
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
78.9 years of age
At high risk for mobility disability

STUDY OVERVIEW:
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 1,600 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.
### 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><strong>MCI</strong></td>
<td>70/686 (10.2)</td>
<td>62/682 (9.1)</td>
<td>1.14 (0.79-1.62)</td>
</tr>
<tr>
<td><strong>Dementia</strong></td>
<td>28/743 (3.8)</td>
<td>29/747 (3.9)</td>
<td>0.96 (0.57-1.63)</td>
</tr>
<tr>
<td><strong>MCI or Dementia</strong></td>
<td>98/743 (13.2)</td>
<td>91/747 (12.1)</td>
<td>1.08 (0.80-1.46)</td>
</tr>
</tbody>
</table>
Figure 2. Change in cognitive performance during the 2 year intervention. 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
Diet Affecting Cardiovascular Outcomes

• At risk for cardiovascular outcomes
• 7500 enrolled
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
How Many Subjects? How long to study?

- Sample size is determined by the frequency of the outcome measure in a given population.
- In general, sample size need increases as disease or symptoms decrease.
- \# Patient < \# At-risk < \# Healthy.
- Those with disease and symptoms are likely to progress rapidly; consequently shorter trial periods.
## 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>Dementia Patients</td>
<td>Symptom change</td>
<td>200-300</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>Slow Progression</td>
<td></td>
<td>1-2 years</td>
</tr>
<tr>
<td>MCI</td>
<td>Dementia</td>
<td>700-1000</td>
<td>3-4 years</td>
</tr>
<tr>
<td>Asymptomatic At-Risk</td>
<td>Memory Decline</td>
<td>1000-1500</td>
<td>4 yrs*</td>
</tr>
<tr>
<td>Healthy Elders</td>
<td>Dementia</td>
<td>2000-4000</td>
<td>5-7 years</td>
</tr>
</tbody>
</table>
Risk/Benefit and Type of Trial

- **Primary:** targets induction phase
  - Larger number of low risk people are treated
  - Low tolerance for adverse effects; risk/ benefit HAS to favor very low risk

- **Secondary:** targets latency phase
  - Smaller number of high risk healthy people treated
  - Higher risk/ benefit maybe justifiable,

- **Symptomatic Treatment**
  - Illness changes perception and tolerance of risk
Considerations

• Few methods to recapitulate life-long habits
• Interventions most often conducted in at-risk populations
• Risk reduction in one area may not capture risk in another area.
• What is a relevant outcome: Incidence, slope of change
• How do we interpret those changes