Prevention Trials in Alzheimer’s Disease*

Posner, Harvey, Schneider, multi-chairs
ISCTM fall meeting
Marina del Rey, CA
October 16, 2018

*or do we mean dementia?
Disclosures

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Options and considerations for Alzheimer’s prevention trials

- Background
- Recap TOMM40 piaglitazone trial
- Review (some of) the ISCTM work to date for a prevention paper
- (Promised) selected topics:
  - Subject selection, time course, detection with performance-based instruments
  - Discuss whether the detection of amyloid is a viable selection criterion for trials
- Plan and write an ISCTM-branded paper
The one goal of workshop:
Establish plans to write an ISCTM paper
Risk factors for dementia affect trials

- Non-modifiable
  - Age
  - APOE genotype
- Modifiable
  - Education
  - Hearing loss
  - Hypertension
  - Obesity
  - Smoking
  - Depression
  - Physical inactivity
  - Social isolation
  - Diabetes

- Other potential modifiables
  - Air pollution
  - Pesticides
  - Head trauma
  - Retirement age
  - Being French

Drop in cognitive performance as a function of drop in employment rate between men 50-54 and 60-64 years old.20
Subject selection: Age-specific incidence/prevalence of dementia

- AD diagnoses are uncommon/rare before age 70
- Peak prevalence in the 80s
- Mean ages in trials: 70 - 78

Mean (min, max) numbers of individuals with AD in the US, 1997. Brookmeyer et al 1998

Age partly determines phenotype and clinical course
Genotypes or biomarkers have age-dependent meanings

Kawas C et al. Neurology 2000;54:2072-2077
Risks, with and without biomarkers?

### 10-year risks %: (95% CI) by age of AD dementia for females based on amyloidosis (A), neurodegeneration (N), and MCI (Brookmeyer et al 2018)

<table>
<thead>
<tr>
<th>Age</th>
<th>Normal state 1</th>
<th>A state 2</th>
<th>N state 3</th>
<th>A &amp; N state 4</th>
<th>MCI &amp; A &amp; N state 5</th>
<th>MCI &amp; N state 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>0.2 (0.06–0.8)</td>
<td>1.3 (0.6–2.2)</td>
<td>3.6 (1.1–14.2)</td>
<td>7.1 (4.3–10.9)</td>
<td>99.3 (91.1–95.0)</td>
<td>57.2 (48.2–67.9)</td>
</tr>
<tr>
<td>65</td>
<td>0.5 (0.14–1.8)</td>
<td>2.5 (1.2–4.9)</td>
<td>4.3 (1.4–15.0)</td>
<td>10.7 (6.8–16.2)</td>
<td>91.7 (89.7–93.5)</td>
<td>55.4 (46.6–65.8)</td>
</tr>
<tr>
<td>70</td>
<td>1.1 (0.34–3.5)</td>
<td>4.7 (2.4–8.7)</td>
<td>5.5 (2.0–16.6)</td>
<td>15.5 (10.0–22.8)</td>
<td>88.6 (85.8–90.6)</td>
<td>52.2 (43.8–62.4)</td>
</tr>
<tr>
<td>75</td>
<td>2.2 (0.74–6.5)</td>
<td>7.8 (4.1–14.0)</td>
<td>7.3 (2.9–19.0)</td>
<td>20.8 (13.7–29.7)</td>
<td>83.8 (80.1–86.2)</td>
<td>47.4 (39.6–57.0)</td>
</tr>
<tr>
<td>80</td>
<td>3.7 (1.3–9.8)</td>
<td>11.1 (6.0–18.7)</td>
<td>9.3 (3.9–20.9)</td>
<td>24.4 (16.4–33.8)</td>
<td>75.8 (72.2–78.7)</td>
<td>40.0 (33.1–48.6)</td>
</tr>
<tr>
<td>85</td>
<td>4.7 (1.8–11.0)</td>
<td>11.5 (6.5–18.5)</td>
<td>9.7 (4.3–19.3)</td>
<td>23.1 (15.8–31.2)</td>
<td>63.7 (59.6–67.2)</td>
<td>30.0 (24.5–37.2)</td>
</tr>
<tr>
<td>90</td>
<td>5.8 (1.5–2.2)</td>
<td>8.2 (4.7–12.9)</td>
<td>7.1 (3.3–15.3)</td>
<td>16.8 (11.5–21.6)</td>
<td>46.7 (42.7–50.2)</td>
<td>19.1 (15.3–24.3)</td>
</tr>
</tbody>
</table>

The lifetime risk estimates shown below represent the proportion of people expected to develop Alzheimer’s disease by age 65, 75, and 85. These values are based on people of European descent. Lifetime risk estimates are not available for people of other ethnicities.

#### Genetic result: Sex

<table>
<thead>
<tr>
<th></th>
<th>Age 65</th>
<th>Age 75</th>
<th>Age 85</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>Men</td>
<td>&lt;1%</td>
<td>3%</td>
</tr>
<tr>
<td>General population</td>
<td>Women</td>
<td>&lt;1%</td>
<td>3%</td>
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</table>

#### No e4 variants

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Age 65</th>
<th>Age 75</th>
<th>Age 85</th>
</tr>
</thead>
<tbody>
<tr>
<td>No e4 variants</td>
<td>Men</td>
<td>&lt;1%</td>
<td>1-2%</td>
<td>5-8%</td>
</tr>
<tr>
<td>No e4 variants</td>
<td>Women</td>
<td>&lt;1%</td>
<td>1-2%</td>
<td>6-10%</td>
</tr>
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</table>

#### One copy of e4 variant

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Age 65</th>
<th>Age 75</th>
<th>Age 85</th>
</tr>
</thead>
<tbody>
<tr>
<td>One copy of e4 variant</td>
<td>Men</td>
<td>1%</td>
<td>4-7%</td>
<td>20-23%</td>
</tr>
<tr>
<td>One copy of e4 variant</td>
<td>Women</td>
<td>&lt;1%</td>
<td>5-7%</td>
<td>27-30%</td>
</tr>
</tbody>
</table>

#### Two copies of e4 variant

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Age 65</th>
<th>Age 75</th>
<th>Age 85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two copies of e4 variant</td>
<td>Men</td>
<td>4%</td>
<td>28%</td>
<td>51%</td>
</tr>
<tr>
<td>Two copies of e4 variant</td>
<td>Women</td>
<td>2%</td>
<td>28%</td>
<td>60%</td>
</tr>
</tbody>
</table>
‘Preclinical AD:’ criteria for a prevention trial?
(Aβ prevalence by lifetime risk for AD by APOE genotype)

Prevalences of Aβ positivity in participants with normal cognition are plotted against lifetime risks for AD–type dementia by APOE genotype.

Inclusion criteria for ‘prevention’ trials:
Practical examples of ‘preclinical’ or at-risk conditions

• ADAPT ‘at risk’ criteria (NSAIDs)
  – Ages >= 70 years
  – At least one 1st degree relative with AD
  – Normal cognitive tests

• GEM (ginkgo biloba, Egb 761)
  – Ages >= 75 years
  – Normal cognition or MCI, CDR = 0 or 0.5

• A4 trial (solanezumab)
  – Ages 65 - 85
  – MMSE score, 25 - 30
  – Global CDR = 0
  – Logical Memory II, 6 -18
  – Florbetapir PET with amyloid pathology

• TOMMORROW (pioglitazone, TOMM40)
  – Ages 65 - 83
  – MMSE 25-30
  – CDR = 0
  – ‘Enriched’ for AD risk by an age/ APOE/ TOMM40 genotype ‘device’
  – 9 of 10 neuropsychological tests normal, both memory tests normal

• GENERATION, API ApoE 4/4 (CAD106 vaccine)
  – Ages 60 - 75
  – ApoE 4/4
  – Other criteria [median age of onset = 69]
“TOMMORROW” prevention trial

- Single global registration trial (Takeda/Zinfandel)
  - 60 sites: US, Europe (Italy, UK, Switzerland, Germany), Russia, Australia
- 5200 3400 cognitively normal (65-83 yr)
  - Enriched for AD risk with an algorithm of APOE/TOMM40 genotype and age (4622 2450 in the high-risk group)
- Treatment: pioglitazone SR, 0.8 mg
- Duration ≈ 4 y, 440 200 events in high-risk group
- Outcome: MCI/AD by clinical assessment
  - Supported by CDR ≥ 0.5, fails 1 memory and ≥ 1 other NP test on 2 exams
- Interim analysis: 70 outcomes
“Tommorrow” trial stopped

- AD-4833/TOMM40 301
- Biomarker Qualification for Risk of MCI due to AD and Safety and Efficacy Evaluation of Pioglitazone in Delaying its Onset
- N = 3494, 56 sites, 25,000 subjects screened
- Recruitment: Aug 2013 to Dec 2015
- Last subject out, July 2019
- Futility analysis: Jan 2018
- Limited follow up: 2 to 4 years
- 76 events
- Trial stopped
### Prevention trials, circa 1997

#### Prevention Protocols for Alzheimer Disease

**Position Paper from the International Working Group on Harmonization of Dementia Drug Guidelines**

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#### 1990s

| **Whom to treat** | **Braak and Braak (1994) -- preclinical changes may occur 20-30 years before clinical expression.**  
**Two basic strategies:**  
(1) treat all elderly individuals, would result in more generalizable data, would require larger numbers of subjects to obtain statistically significant treatment differences.  
(2) Identify high-risk populations. Age (Bachman et al., 1993), +FH (van Duijn and Hofman, 1992), and APOE4 (Corder et al., 1993) account for = 45% of attributable risk |
| **When to treat** | **Trial design** |
| **Sample size** | **5000 would allow for an 80% Power to detect a 30% decrease** |
| **Entry criteria** | **Free of diagnosable dementia. Requires clinical exam by a skilled clinician. In reality, individuals who become demented during a primary prevention trial with a 5-year follow up already have neuropathologic evidence of AD** |
| **Outcomes and endpoints** | **Endpoint must be dementia (e.g., NINCDS/ ADRDA or DSM-IV)** |
| **Stat. analysis** | **“Survival” models** |
| **Interventions** | **Require preliminary data supporting potential efficacy: Can be observational, epidemiologic, or markers of disease expression, such as decline on NP tests, changes in biomarkers such as Abeta. Likely that a primary prevention trial would be preceded by a “preliminary” trial examining the effects of the drug on progression in AD or conversion from MCI to dementia. Administered to a healthy population, safety is primary concern. 90% of subjects will not develop clinical disease, Frequent monitoring for AEs should not be necessary. There must be:**  
  - Supporting epidemiologic or observational data;  
  - Strong preclinical data justifying its use;  
  - Adequate information on dosing; and  
  - Adequate information on safety |
| **Classes of drugs** | **Hormones, estrogens, anti-inflammatory drugs, antioxidants, and vitamins. WHIMS, plans to randomize more than 8000 cognitively intact women between 50 and 79 years of age to determine incident dementia in women older than 75 years** |
| **Regulatory** | **Regulatory agency may need to rely on factors such as internal consistency. With an already marketed or approved drug, regulatory guidelines may not be necessary because the weight of the evidence from the trial itself may be sufficiently compelling to affect clinical practice. Nevertheless, trial design and methods should be reviewed by regulatory agencies and by a large group of experts to gain sufficient consensus that proposed trial can achieve its intended goals** |
| **Unresolved issues** | **A significant study would only allow the claim that the test drug reduced incidence of the onset of the clinical expression of disease and could not address a drug’s potential symptomatic effects or potential for altering disease expression Will one trial suffice, given the cost and magnitude of such a trial, or will a replicate trial be required? Would internal consistency within a single trial be sufficient to support a claim for primary prevention? A second less critical issue is the mechanism of action. Does an agent that delays incident dementia work by altering the underlying disease process, or could a prolonged symptomatic effect be operative? How would these possibilities be separated?**
**Prevention? What’s that?**

Multiple population-based studies in different countries: Incidence of dementia, and AD specifically, is declining. Some studies suggest rising levels of education account for part of this. Neuropathology: AD pathology rarely occurs in isolation; often with vascular problems. More aggressive treatment of hypertension and hypercholesterolemia may be behind the decline. Can we learn anything about possible intervention studies from observation of this phenomenon?

**Abstract**

<table>
<thead>
<tr>
<th>Intro</th>
<th>Methods</th>
<th>Results</th>
<th>Discussion</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series of ongoing prevention trials underway covering genetic and sporadic AD</td>
<td>Offer great hope and at the same time, as a field we always need to think strategically and learn from everything we do so as to continually improve.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Review of current studies**

Short review of current studies (maybe a table is best for this).

**Main ideas:**

What are we preventing?

- MCI? Dementia? A specific illness?
- Change in biomarkers?
- Amyloid deposition?
- Genomics? 1st relative with AD or MCI
- Performance-based metrics?
- High-risk populations? Genomics/dense pedigree

Who are the candidates for prevention trials? How do we select participants?

What do we target?

Eligibility criteria

Enrichment of participants

Other interventions

Outcomes to assess?

Intermediate

Endpoints. What is an “endpoint?” Diagnosis: MCI, mild AD, death?
### Sample sizes
Progression from normal to MCI or MCI to AD takes very large sample sizes. Cognitive and functional measures also take large sample sizes. Small signal, lots of noise. Both between-person and within-person noise. Can frequent measures help? Can computerized testing (processing speed, e.g.) reduce noise? Need evidence that testing results are relevant to function.

### Efficacy? Definition?
Something favorable and meaningful

### Composite endpoints –
Functional questions generally interrogate a single construct either with individual questions or groups of questions, such that to what extent should the statistics that are applied to their analysis be left solely to the researcher who generated them versus considered and optimized by people conducting clinical trials, as long as the decision is pre-specified prior to database lock and unblinding. What is validated during a validation study, the construct the questions/answers represent or the statistics as well? There are many ways to combine endpoints in a composite and why not allow this to be specified for the individual trial.)
The need to understand the assumptions underlying the components and decisions within studies.

### Surrogate marker (ENDPOINT) criteria
- High signal-to-noise ratio for change: between- and within-person noise.
- 2 Change in marker correlates with relevant clinical change. (Hard to show if clinical change noisy?). 3 Change in marker differs for treated and untreated participants.
- 4 Hardest to show: Change in marker following treatment tracks with clinical impact.

### Analysis and Stat models
Change in a performance-based index / psychometrics that do not necessarily reflect impairment?
- Worsening in the LASSI or UPSA?
- Other?
  - Ropacki: ensure that the assessments are being used correctly. Ex. Only use logical memory 2 instead of alternate forms. Also, MMSE, global CDR. Should be a composite.

### Progression to greater impairment, not necessarily diagnosable?
- Episodic memory performance? ADL challenges?

### Options for overall study designs?
- Controls? Head to head? Some length of placebo?

### Biomarker
- Amyloid (too late?); TAU (too late?)

### High risk conditions
- Down syndrome

### Industry and FDA perspective
New ideas: Down syndrome, other endpoints biomarkers vs cognition vs. combo of cognition and function/performance etc.

### Advances

### Regulatory paths
What do regulators do? What do they want?

### Feasibility

### Problems
Wrong drugs, wrong patients

### What we don’t know
What are the issues first

Lon: write a relatively short paper that lays out some prevention guidelines

Henry: Best practices are...
  • How would we do this right now?

Larry Adler: How are you defining primary prevention?
  • Population-based approach

How to define secondary prevention? This is a must to define the population we are talking about
  • Those with an identifiable risk factor.

How define AD?
  • The criteria define a mixed criteria depending on what you use (small hippocampus). And, there may be other dementia pathophysiology of other ilks concurrently. And, are following the biomarkers that one started with.

Raeanne: NIH is interested in what we can do for people starting at age 30

Mike R: could have different papers on different stages. Need to specify the stage at the onset.

The majority of studies now are secondary prevention unless talk about vaccine trials (primary prevention).

Mads Lundbeck: the state of the art. The most advanced thinking. With the FDA guidelines etc. defining new more sens scales: beyond the MMSE, ADAS, and CDR etc.

Primary prevention: family history / genetic risk
• Holly S. – are we really ready to conduct prevention trials? (Abbvie)
  • Pts may not have AD path. declining may be due to other issues & co-morbidity
  • Perfect world, tool would id the pathology: tau amyloid etc
  • Would need to follow the biomarker negative patients
  • Not just talking about AD.
• Lon: primary and secondary prevention can blur together
  • 60- 70 year 30-40% amyloid positive, over 5 years that 5-7% of the amyloid negatives. And other things are happening to people. Apply the intervention to all, and see who benefiting and how.
• Raeanne: need to define the population explicitly

• Lundbeck (Helle): more to consider than interventional drug treatment. There are the lifestyle factors that impact rate of decline.
• Definitions are first: primary vs secondary (one or two papers)
• Those with the highest risk of developing AD.
  • High genetic load highest risk (Lon’s table of life time risk for men and women from either general pop’n or had 1 or 2 apoE4 alleles. With one allele had a somewhat increased risk by age 75 is x % and higher than with no alleles.
  • This could be the main topic or at least a big message: Also confounds that in a 5 year study, the other risks that are modifiable, may well be getting modified by the participants. And, if other factors are influencing these modifiable. Things we don’t recognize rae impacting and dooming our trials. How can new technology help? And, identifying them and accounting for them and designing for them in the paper
• Implicit requirements outlined by the two papers
• From what perspective are we coming into this.
  • What you should do!
  • Or, how to take the guidances that exist and how you use them in a trial

• Goal: of the paper
• Rosie C. (U Miami): Are we prevention AD or dementia?
• Lon:
  • Lundbeck (Helle): which compounds is being taken into the trial also is a huge factor for how the study is designed.
  • Targeting: modifiable risk factors vs. a target drug intervention, vs a more general intervention (hyperbaric o2, ultrasound guided...)
  • Takeda TOMMOROW (Kathleen): what are the considerations going into a study being designed today. Where is the clinic to get normal people. What is the recruitment, what is the endpoint, how to enrich, risk and benefit or each age cohort’s inclusion,
• Who is the audience of the paper: leverage what is known and go beyond the for the future.
• M Ryan: not yet ready to do a post mortem on the current trials. He also is a proponent of having multiple kinds of designs since knowledge of best practice can come from unexpected locations.
• generation trial: a portion of the alpha goes to Time to event outcome. Another portion of the alpha went to the cogn outcomes. Lon: it’s an innovation for dementia trials, but not for interventional trials. This could be discussed in a position paper: don’t use one outcome. Relooking at efficiency in a trial.
• M Ropacki: Advocacy for data sharing for improving future designs.

• (KAthleen): to Lon’s question: what are we going to learn. The cohorts are so different. Heterogeneity will allow us to look at subgroups. The wealth of the data together will help drive the future

• Kim: Frequentist approach to Alzheimers trials. Moving away from p values and toward bayesian methodology. Models and predictions.

• M Walton: depends on having access to the patient level data from prior studies.

• Takeda: who is in the studies. Who stays in? Who are we really treating? Add in the tools (technology) to be able to capture the data for the subjects who left the study and maybe keep people in longer. (Not be left with the idiosyncratic group who made it through the trial).

• There are companies that pull data from EMRs.
  • Need to get consent for this and probably need to reconsent for this and some countries don’t permit it regardless.

• There is often the statistical assumption that the drop out rate is random, but it is not.

• Lon: can comment on the system (health care) and what is a standard treatment? For oncology: they randomize to standard care or another treatment or add a new one on top.

• M Walton: this doesn’t exist in primary care as much. In oncology one would go to the oncologist not the PC

• Tony (Sunovion): Resources: need to comment. N=3000, n=14,500 can’t do this sort of n. So, how to design a study that can be done by smaller company? What would a study be that a smaller company can run?
• Tony, Sunovion: What do we need to know about the compound before putting it into a bigger secondary prevention study?

• Kathleen (TOMMORROW): biggest reason for early termination: people feel threatened when they feel their cognition is slipping. Passively capturing this information would help. They planned from ADAPT. If can keep them in longer need fewer people.

• M Ropacki: IMI ePAD does this. Seamless adaptive trial with Bayesian modeling sharing risks. Tony: we need to refer to this / touch on this.

• Before you do a prevention trial, show proof of concept. Question: what is the current state of the art on how to design a good proof of concept study.

• Alz Research Roundtable for proof of concept position paper exists: about 6 years ago.

• Mads: bapi trial – PET ab is coming close to being a surrogate. Working precompetitively to qualify a surrogate would be a tremendous step forward.

• Larry Adler: Repurposing a medication that is already out there. All of our discussion has applied to new chemical entities.

• Charles: Cognex, FDA asked to submit with phase 2.

• Lon - summary: talk to secondary prevention and deal with the issues involved in that. Touch on primary prevention in passing.
• Mads: maybe use the FDA stage 1 2 3 framework instead of secondary v primary prevention
• Travis: why not look at treatment responders vs non-responders. And, try not include the predictors of non-response.
• Kathleen: some of the goal of ePAD is for this. (ropacki)

• Holly.posner@pfizer.com