Emerging global knowledge – Dementia ‘prevention’ and the translation of clinical trials

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Today...

1. The new dementia and especially ‘dementia prevention’ (published)
2. Clinical trials EU vs. US (published first analysis)
3. Translations EU, US, Brazil (work in progress)

Ethical reflection: Does it matter how (and where) science knowledge is translated into recommendations?

In reality risk reduction and not prevention
I. Dementia prevention, the “new dementia”

“One Third of Dementia Cases May Be Preventable”

Lancet Report (Livingston et al. 2017): 9 factors

Close to one in two cases of dementia could be preventable in low- to middle-income countries (Mukadam et al. 2019)

Main explanations:

- Dementia increasingly merging with aging
  Richards and Brayne (2005: 865), In older age groups, AD seems to be a diffuse clinical syndrome representing the gradual accumulation of multiple pathologies, arising from multiple interlocking risk factors over the life course.

- Pharma – meds don’t work
The “new dementia”: opening up the “cognitive paradigm”*

<table>
<thead>
<tr>
<th>‘Old’ dementia</th>
<th>‘New’ dementia</th>
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<tbody>
<tr>
<td>Focus on cognitive impairment*</td>
<td><strong>BPSD</strong> (Behavioral and Psychological Symptoms of dementia)</td>
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<td>Prevention = brain training (‘use it or lose it’)</td>
<td><strong>Early detection + early intervention, biomarkers, MCI (mild cognitive impairment)</strong></td>
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<td><strong>Prevention: Brain is body – esp. cardiovascular risk factors (see Lancet and others); The merging of vascular dementia and Alzheimer’s disease</strong></td>
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<td>Genetic explanation (1990 - )</td>
<td>“brain is body” (risk factors, microbiome...), genetics weaker explanation</td>
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* German Berrios (1987, 1989): ‘Cognitive paradigm’ – “the view that an impairment of cognition (in practical terms, a memory deficit) is sufficient to define dementia.” ‘Neurocentrism’ (e.g., Vidal & Ortega [2017] Being Brain: Making the Cerebral Subject)
Preventing Dementia?
Critical Perspectives on a New Paradigm of Preparing for Old Age

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II. Situated clinical trials

Situatedness

• Less essentialist than ‘culture’

• Chandler and Munday (2011): situatedness is “[t]he dependence of meaning (and/or identity) on the specifics of particular sociohistorical, geographical, and cultural contexts, social and power relations, and philosophical and ideological frameworks, within which the multiple perspectives of social actors are dynamically constructed, negotiated, and contested.”

• Donna Haraway (1991): ‘situated knowledge’ – responsibility and accountability toward multiple existing (or possible) moral narratives
In some (richer) regions of the world dementia prevalence and incidence rates are declining, for instance in the US (Manton, Gu and Ukraintseva 2005), Holland (Schrijvers et al. 2012), Sweden (Qiu et al. 2013), England (Matthews et al. 2013), and Germany (Doblhammer et al. 2015). (health care system)

The turn toward integrating pre-clinical phases into the definition of the dementia syndrome itself will happen more likely on the North American continent. (science discourse)

Media images: once passive victims of the disease, have since come to be seen as active agents of self-care in some contexts. (public images/lived experience)

Critiques regarding prevention campaigns in general. “a focus on the individual is ethically questionable, ineffective and ignores relevant research that suggests systemic factors, not individual choices, are behind the epidemic ...” (Mayes, 2016) (problematizing public health recommendations)
# Situating prevention clinical trials: US versus EU, 2017

<table>
<thead>
<tr>
<th>US-American</th>
<th>Intervention</th>
<th>European</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>Disease Prevention in Clinical Practice Base on Patient Specific Physiology</td>
<td><strong>Lifestyle modification</strong></td>
<td>Norway: Anthocyanins as Dementia Prevention?</td>
<td>Plant-based medication</td>
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<tr>
<td><strong>... Prevention of MCI and Eventual Alzheimer’s Disease Using F18 Futemetamol</strong></td>
<td>2 drugs (anti-depressants) and placebo</td>
<td>France, Italy, Netherlands, Spain, Sweden, Switzerland, United Kingdom: European Prevention of Alzheimer’s Dementia (EPAD) Longitudinal Cohort Study (LCS)</td>
<td>Personalized drugs or multiple drugs in development</td>
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<tr>
<td>GeneMatch: A Program of the Alzheimer’s Prevention Registry to Match Individuals to Studies Based on APOE Genotype</td>
<td>Get a pool of individuals for future preventive clinical trials (first study using the pool sponsored by Novartis)</td>
<td>Germany: Physical Activity and Cerebral Metabolism in the Elderly: a Randomised Controlled Trial</td>
<td>Aerobic training</td>
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Main source: ClinicalTrials.gov
## Larger trials US vs. EU, cont.

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<th></th>
<th>USA</th>
<th>Europa</th>
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<tr>
<td><strong>A4 trial (Anti-Amyloid Treatment in Asymptomatic Alzheimer’s)</strong></td>
<td>... whether an anti-amyloid antibody can slow memory loss caused by Alzheimer’s disease.</td>
<td>FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability)</td>
</tr>
<tr>
<td><strong>One drug</strong></td>
<td></td>
<td>A 2-year multidomain intervention including nutritional guidance, physical activity, cognitive training, increased social activity, and intensive monitoring and management of metabolic and vascular risk factors</td>
</tr>
<tr>
<td><strong>Autosomal Dominant Alzheimer's Disease (ADAD) Trial</strong></td>
<td>This study focuses on whether two investigational drugs – an active immunotherapy (CAD106) and a BACE (beta-secretase 1) inhibitor (CNP520) – can prevent or delay the onset of Alzheimer’s symptoms.</td>
<td>PREVENT Dementia study</td>
</tr>
<tr>
<td><strong>One drug</strong></td>
<td></td>
<td>UK study: research focuses on people in middle age to identify biological and psychological factors which may increase the risk of dementia in later life. Once identified, we would like to select those people at high risk and intervene in this process. These interventions might be lifestyle changes or measures to affect the risk of an individual developing dementia.</td>
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Lifestyle/cardio-vascular
The participants [from the US] receive solanezumab, an antibody-based drug that aims to reduce brain amyloid-beta, which recently failed to improve mild Alzheimer’s dementia. Despite the failure, researchers speculate the drug may be effective in preventing dementia in people who have amyloid-beta aggregates in the brain (Kegel 2017).

Recent research suggests changes in the brain may precede symptoms of Alzheimer’s disease by many years. (...) Our research (...) focuses on people in middle age to identify biological and psychological factors which may increase the risk of dementia in later life. Once we have identified which factors are changing we would like to select those people at high risk and intervene in this process. These interventions might be lifestyle changes or measures to affect the risk of an individual developing dementia. (PREVENT n.d., UK)
Pharma-dominated major prevention initiatives

- **The UK-based Dementia Discovery Fund**: “Our goal is to invest over $200m over fifteen years to support the creation of novel disease-modifying drugs for dementia... “The Department of Health, the charity Alzheimer’s Research UK and ... six pharmaceutical firms have raised $100m (£65m) to invest in early-stage, novel treatments for (...) dementia (...) [T]he company is joined by the US drugmakers Johnson & Johnson, Biogen, Eli Lilly and Pfizer, and Japan’s Takeda.”

- **The (US based) Global Alzheimer Platform**: “the GAP Foundation is joining together leading academic researchers, pharmaceutical companies, nonprofit organizations and foundations, and governments around the world to reduce the time, cost and risk of Alzheimer’s clinical trials, in order to speed innovative medicines ...”

- Today most clinical trials are pharma-based
III. Different messages?

• https://www.youtube.com/watch?v=xQwbsAywZrl

• http://www.euronews.com/2017/07/20/nine-steps-to-dementia-prevention

• Many researchers believe successful treatment will eventually involve a "cocktail" of medications aimed at several targets, similar to current state-of-the-art treatments for many cancers and AIDS.” (US Alzheimer’s Society)
Example 1: AD drug aducanumab (2015 - )

• Logic: treatment needs to start at a very early stage + amyloid hypothesis

• “fast track designation” from the FDA, based on earlier studies that seemed to show that the compound could switch off the production of amyloid (Aβ) in the brain.

• 3200 patients

• Biogen/Eisai announced in March 2019, patients treated with this experimental drug, a monoclonal antibody that was tested on people with mild or moderate AD, showed no cognitive improvement after 18 months.
Reactions to the failure of the Phase 3 EMERGE and ENGAGE studies (PRIME is the name of the European equivalent study)

• Source: Alzforum 2019 (professional discussion list)

• (A) those who believe that the antibody tested was not the right one, but that a similar antibody will be a solution, and that the current Aβ model (or tau) is not yet dead;

• (B) those who think that still earlier stages of AD need to be considered and that the current target of either β amyloid or tau or both is still valid;

• (C) Criticizing Amyloid-hypothesis; prevention is seen at the moment as the only possible pathway
Cont.

• Even though this trial was in the early symptomatic phase of AD, it is still in the phase when Aβ is no longer likely to be the driving process but where tau and inflammation probably are. I think Aβ is still a good target for the primary and maybe secondary prevention trials of AD, before tau and inflammation have started driving the disease (David Holtzman, USA).

• The failure of the Phase 3 aducanumab trial is another warning that the field must take a different approach. Some authors have already called for a rejection of the amyloid hypothesis (...) AD is a multifactorial condition (...) we need to remind ourselves that a third of AD cases are strongly dependent on the concerted activity of modifiable factors (...) It is time to take up the challenge of complexity (Stefan Sensi, Italy).
• It has been known for many years that the amyloid hypothesis cannot be correct; the reason it survives is because it is appealingly simple and offers a one-sided treatment strategy that pharma can pursue easily by antibodies and inhibitors. (...) Unfortunately, these people include, because of the paradigm's previous popularity, major opinion-leaders and big pharma with a responsibility for listening to only some key opinion makers of the dominating paradigm in the time of its sunset (Kasper Kepp, Denmark).

• Might they work prior to the development of symptoms? Maybe, but with no symptomatic signal, it is risky to continue in that space. We clearly need other targets, and tau is the leading candidate for now.” (Ron Petersen, USA)
Example 2: exercise is prevention!: Brazil or, when “the structural” goes wrong
Possible moral narratives / framing

Donna Haraway: *possible* moral narratives: etiology and translations

Epistemic cultures? Not clear-cut, but worth studying

Individualizing or structural?
Pharma benefits, profit?

“Americans break down at an earlier age than Europeans, especially from nervous ailments, and he (Dr. Hamilton) attributes this to their struggles for the rapid accumulation of wealth, to the competition and ambition which are largely stimulated by agitational newspapers... to hustling, over-eating, insufficient exercise and luxurious living general.”

Thank you / danke / תודה

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