What's new in dementia?
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What I will talk about....

- Diagnosis
- Epidemiology
- Prevention
- Drug treatments
- Psychosocial care
- Policy
- The next 5-10 years
- OTs, dementia and research
Diagnosis of AD

Biomarker developments

- PET PiB and Florbetapir imaging
- CSF Aβ↓ and τ(tau)↑
- MRI – serial MRIs, connectivity
- Blood tests – not yet
- Many biomarkers have about 90% sensitivity and specificity for AD

PiB-PET Scans: AD vs MCI vs control

From the online newspaper of Prof Yasser Metwally
Alzheimer’s disease without dementia!? Dubois criteria (in brief)

- AD incorporates pre-dementia & dementia
- Prodromal AD (pre-dementia AD)
  - Clinical symptoms (e.g., memory loss) but do not interfere with IADLs
  - Biomarker evidence from CSF or imaging
- AD dementia
  - Cognitive Sx interfere with IADLs, social funct
  - Change in episodic memory & ≥ 1 other domain

Dubois et al. Lancet Neurol 2010; 9: 1118-1127

Alzheimer’s Association USA Alz & Dementia 2011

- Jack C et al; Sperling R et al
- Albert M et al – MCI due to AD
- McKhann G et al – Alzheimer’s disease
  - Non-amnestic presentations – Posterior Cortical Atrophy, Logopenic, Frontal variant
- Degrees of certainty:
  - Probable
  - Possible
  - Probable with biomarker positive
**DSM-5 Major Neurocog. Disorder**

- Substantial cognitive decline > 1 domain based on concerns of individual, knowledgeable informant or clinician
- Decline in neurocognitive performance
- Cognitive deficits interfere with independence
- Cognitive deficits not exclusively in the context of delirium and not primarily attributable to another mental disorder (e.g., major depression, schizophrenia)

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**Where are we with definition?**

- Still in flux; Lack of gold standard
- Biomarkers for AD are an advance
  - many ≈ 90% sensitivity & specificity
- Q: How much benefit beyond good history and basic investigations?
- Clinical diagnosis remains cornerstone
- Choice of definition will affect
  - Prevalence
  - Reimbursement
  - Treatment
  - Genetic counselling

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**Reappraisal of epidemiology**

Assumptions about constant incidence and prevalence


Do projections of dementia worldwide

.... but is % of people with dementia ↓?

- UK: Cohorts 1: c 1990 & 2: c. 2010
  - Based on 1990 Cohort, estimated dementia prevalence in 2010 was 8.3%
  - Actual prevalence 6.5%
- Sweden: Cohorts 1: c 1990 & 2: c. 2005
  - Fewer new cases
- Denmark: Cohorts 1 born 1905 (assessed at 93y) and 2, born 1915 (assessed at 95 yrs)
  - 1915 performed better in cognitive measures
Prevention

How much AD can be attributed to environmental factors?

- 2% diabetes mellitus (type 2)
- 2% midlife obesity*
- 5% midlife hypertension
- 10% depression
- 13% physical inactivity*
- 14% smoking
- 19% low education#


### Developmental & early life

- Nutrition: Indirect evidence for early life nutrition & development
- Education: Consistently protective, in large number cohort studies & across cultures
- Occupational status: Effects attenuated when controlling for education. Protective effect may not be causal


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### Psychological factors - midlife

- Depression: meta-regression indicates smaller effects for longer follow-up periods. Limited evidence for midlife exposure.
- Anxiety: One cohort study, possible risk
- Psychological distress: Indirect evidence using personality type


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### Psychological factors - late life

- Depression: strong & consistent association across many studies – reverse causality?

Lifestyle factors

- Smoking: late life studies support hypothesis. Midlife exposure in cohort studies may underestimate the effect.
- Physical: few long term cohort studies, mixed results.
- Cognitive stimulation: supportive case control studies (possible bias). Only 1 long term study.


Lifestyle factors – late life

- Smoking: Dose effect for AD
  - possible effect for VaD & any dementia.
- Alcohol: mod drinkers lower risk AD cf abstainers
  - Unclear if causal.
  - Safe limit of ‘moderate’ drinking unclear.
- Nutrition: few RCTs, often poor quality.
- Physical: difference in follow-up lengths contributes to contradictory results. Need RCTs to clarify.
- Cognitive stimulation: Consistent risk reduction but...
  - … lack RCTs to determine causality.


Cardiovascular risk factors - midlife

- Hypertension: consistent evidence
  - Stronger for any dementia & VaD than AD.
- Obesity: inconsistent for midlife BMI.
- Cholesterol: inconsistent. Main support from 2 long-term Finnish studies.
- Diabetes: evidence indirect from linkage studies.
  - Only one long-term cohort study (no association).

**Cardiovascular risk factors – late life**

- Hypertension: decline in BP predicts AD but unlikely to be causal. RCTs suggest no cog" benefit/harm to treating hypertension
- Obesity: Several studies, no association.
  - Decline in BMI from mid life predicts dementia but unlikely to be causal
- Cholesterol: no effect of statins on cognition
- Diabetes: consistent evidence for diabetes & incident dementia, AD & VaD. Strong for VaD


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**Prevention trials**

- Lifestyle (mainly European)
  - 55 yo+ with risk factors
  - Combine exercise, cognitive training, diet, cardiovascular care, social activities ± ω3
    - MAPT, HATICE, FINGER
- Pharmacological (mainly USA)
  - Biomarker positive, Antibodies to β-amyloid
    - A4 trial, Alz Prevent® Initiative, DIAN
  - Supplements – Ginkgo biloba

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**FINGER study**

- Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)
- First large, long term RCT of multi-domain interventions aimed at improving cognition
- Eligibility: 60-77 yrs, CAIDE dementia risk score ≥6; cognition at or slightly below mean for Finnish norms (eg, ≤ 26 MMSE)

Ngandu et al. The Lancet. 2015; http://dx.doi.org/10.1016/S0140-6736(15)60461-5
Executive Function

NTB Total Score

Mean change in cognition over 2 years

Processing speed

Memory

Drug treatments

Ngandu et al.  The Lancet. 2015; http://dx.doi.org/10.1016/S0140-6736(15)60461-5

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

Symptomatic:
- ChE inhibitors
- Donepezil
- Galantamine
- Rivastigmine
- Memantine
- Nutraceuticals - Souvenaid

AD Cures – graveyard
- Trimiprosate (Alzhemed)
- Flurbiprofen (tarenflurbil)
- Anti-inflammatory
- Rosiglitazone
- Statins
- Leuprolide
- Semagacestat (γ-secretase inhibitor)
- Bapineuzumab
- Celecoxib
- Dimebon
- Intravenous Immunoglobulin
- H3 receptor antagonist CL2-38093-012 (Servier)

Under investigation
- Enzyme inhibitors – β secretase
- Immunotherapy
  - Active
  - Passive
    - Antibody – eg gantenerumab
    - solanezumab
- PBT2 (zinc, copper)
- Insulin nasal spray
- Tau protein (Rember)
Disease modifying treatments

- NEJM 1986 tacrine for AD
- Still no disease modifying Rx for AD
- Despite billions of dollars invested
- Lure of success → continued efforts and …
- … promising leads – watch this space
- If next 5 years negative: is amyloid right target?
- Other approaches – tau, insulin, TNF, stem cells
- Some research in Fronto-temporal Dementia
- Less in Lewy Body Dementia

Maybe Rx has been too late

- New trials moving to treat earlier
- Even before diagnosis of Alzheimer’s disease dementia, ie when …
- .. evidence of Alzheimer’s pathology + minor impairment but not dementia
- Gantenerumab(Roche), Solanezumab (Lilly)
- β-secretase inhibitor (Merck, Lilly)

Alzheimer’s is an iceberg

- 5-10 yrs
- 25 yrs
Better research on psychosocial care

**CADRES:**
Caring for Aged Dementia Care Resident Study

- Prospective RCT comparing
  - DCM
  - Person-centred care (PCC)
  - Usual care (UC)
- 4 months intervention, 4m F/Up
- Primary outcome = CMAI

Professor
Lynn Chenoweth

Chenoweth et al. Lancet Neurol; 2009

**Effects of DCM and PPC on CMAI**

Chenoweth et al. Lancet Neurology 2009
SMILE Project

- **Sydney Multisite Intervention of LaughterBosses and ElderClowns**
- Cluster RCT, 36 NHs
- 12 wk intervention
- 2h/wk + Laughterboss

SMILE Results

- Agitation decreased significantly over time with humour therapy compared to usual care
  - mean adjusted change difference between baseline and follow-up being 2.6 points.
- CMAI difference between Rx & control across 3 RCTs of risperidone was 3.00 (95% CI 4.22, 1.78)
- Adjustments for “dosage” of humour therapy & engagement → benefits on depression, behavioural disturbance and self-reported dementia quality of life

Clinically significant?

- 20% reduction in agitation symptoms in SMILE
- The same effect size as is achieved by antipsychotic medications used to treat agitation

OR
Tailored Activity Program

- Home based OT intervention
  - 8 sessions over 4 months
  - Identify capabilities, previous roles, habits & interests of PWD
    - Activities identified based on this personalised info & train families
- Results: reduces behavioural symptoms, caregiver burden


Environment

- Dementia Enabling Environments Project (DEEP)
- Aimed at facilitating the creation of supportive environments for people with dementia.
- It is an Australian-first project to translate research into practice for dementia enabling environments.


Policy
G8 commitment, Dementia Council

- 2013 G8 dementia summit created World Dementia Council
- March 2015 UK announced $100 million Dementia Discovery Fund
  - Targets preclinical research to develop new drug targets

Policy

- 13 national plans for dementia and growing
  - Variable quality
  - Better ones have measurable targets
  - Policies not transportable: eg India, USA, UK
  - ? Correlation of outcome with expenditure
Australian Policy

- Community Aged Care Packages – 4 levels
- Consumer Directed Care
- www.myagedcare.gov.au

$200m for dementia research

- Australian government policy
  - $200m over 5 yrs
  - Dementia prevention & cure
- Aims
  - Expand research capacity
  - Prioritise funding
  - Ensure research translation
  - Invest in dementia research infrastructure

What’s going to change in the next 5-10yrs?
What’s going to change in the next 5-10yrs?

- Diagnosis – possible blood markers
- ICD 11 – 2017
- Prevention trials around the world
- Drug treatments
  - If amyloid hypothesis fails….
    - Other targets
  - Other dementias
- Psychosocial care

What’s going to change in the next 5-10yrs?

- Policy
  - Roll out of $200m
    - National Dementia Research Institute
    - Dementia Team Grants
    - Development Fellowshios
  - National Framework for Dementia Care
  - NSW Service Plan for Dementia

Change in the next 5-10yrs?

- International multidisciplinary perspective
- Research
  - Assessment; falls – Jacki Wesson
  - Nursing homes – Sofia Venuti
  - Community – TAP program; falls & dementia – Lindy Clemson
  - FTD – Claire O’Connor
  - Going to stay at home; bidets; etc - Meredith Gresham
- Professional interest group – IPA
  www.ipa-online.org
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Conclusion

- Much progress in last 10 years, still a long way to go
- Demographics and costs continue to make dementia attractive area for work & research
- ... and, so many unanswered questions ????

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