Dementia: great expectations
Hope and realism
Henry Brodaty
Today’s topics

• Terminology
• Cause of AD
• Why this is important
• Diagnosis
• Prevention
• Drug treatment of AD – the silver bullet
• Behavioural and Psychological Symptoms
• Conclusions
Let’s get our terms straight

• Dementia/s = umbrella term
  – Alzheimer’s disease (AD)
  – The other (non-Alzheimer’s) dementias
    • Vascular dementia
    • Lewy body dementia
    • Fronto-temporal dementia
    • 100 others
• Mild Cognitive Impairment
• Cognition
Cause: Brain in AD

- Brain atrophy, loss of nerve synapses and branches
- Breakdown of APP releasing $\text{A}\beta$ protein $\rightarrow$ clumps $\rightarrow$ toxic to brain $\rightarrow$ plaques
- Phosphorylated tau $\rightarrow$ paired helical filaments $\rightarrow$ NFTs
- Chemicals in brain $\downarrow$ esp ACh
The cause of AD??

- Make excess $A\beta$ protein
  - Familial AD, mutations in APP, PSEN1 or 2
  - Onset in 40s, 50s.
- Decreased clearance of $\beta$- amyloid
  - Late onset AD, ApoE4
- Role of tau
- Many other pathways involved, eg...
Many other factors …

- Insulin resistance in brain
- Inflammation
- Support cells (astrocytes, glial cells) in brain
- Progranulin
- Repressor Element 1-Silencing Transcription factor (REST) protects neurons from oxidative stress and amyloid β-protein toxicity
  - decreased in AD and other dementias
Cause: realism

• For young onset autosomal dominant AD cause seems clear
• For late onset sporadic AD, we know risk factors and pathological paths but not cause
Why dementia is important ... globally?

- 47 million people → 131 m by 2050
  - 2/3 in developing countries
- ≈10m new cases per year, every 3.2 seconds
- Cost US$818 billion, 1.09% of global GDP
Why dementia is important in Australia?

- 413,000 in 2017 → 1.1 million by 2056
- 244 new cases of dementia each day in 2017
- Cost to community $14 billion in 2017
  - 61% direct costs, 38% opportunity costs
  - $28b by 2056
- If 5% ↓ number of people ≥ 65 developing dementia
  → save $5.7b from 2016-25 & $120.4b by 2056
- 28,000 under 65 years of age
- Aboriginal people have higher rate

1 The Economic Cost of Dementia in Australia 2016-2056, NATSEM 2017; 2 Dementia in Australia, AIHW, 2012
Why dementia is important?

• Because we fear it
Why dementia is important?

• Because we fear it
• Because we are getting older as a population
• Because we are living longer as individuals
• Because age is the major risk factor for dementia
• Because we have it OR we know someone who has it
• Because we see what dementia does
The hope

• Are numbers decreasing?
• Studies from Sweden, Denmark, Spain, Netherlands, USA show that the number of *new cases* per each age group has declined in the last 20 years
• Better education, health care, diet, lifestyle may be responsible
The realism

- Prevalence, number of existing cases, is ↑
  - Ageing of population outweighs decline in new cases
  - People with dementia are living longer
- Obesity & diabetes epidemics may ↑ incidence
- Developing countries are ageing rapidly
Diagnosing Dementia: the gap

- 2-3 year gap from Sx to Dx
- 50% of (mild) dementia undiagnosed in GP
- DTA, AA, LaTrobe and DCRC ‘Timely Diagnosis’
  - Aim to reach 5000 GPs
  - Face-face or online
Diagnosis: the revolution

**Tradition:** History + Examination + Tests $\rightarrow$ Dx

- **Neuroimaging**
  - MRI scans
  - PET imaging, now of amyloid & tau protein
- **Cerebro-Spinal Fluid (Lumbar puncture)**
- **Genetics** - advances but not yet for most
- **Blood test** - advances but not yet
PET amyloid imaging: normal vs AD

- 35% persons 60+ amyloid+
- ↑ risk clinical progression
- Will all amyloid +ve develop AD?
Lumbar puncture = Spinal tap

- Change in proteins in CSF
  - Decrease in amyloid beta protein and increase in tau and phospho-tau proteins
  - If all measures are normal in pt with mild memory disturbances almost excludes AD
Diagnosis of AD - realism

- Biggest challenge is in primary care
- No test 100% accurate yet
- No blood test sufficiently accurate to use yet
- The older the patient, the more likely brain will have multiple pathologies AD, α-synuclein, TDP43, vascular changes
- Predictive testing not accurate enough and not recommended
- Would you be tested today to see if you would develop AD in 2, 5 or 20 years?
Can we prevent dementia?

- **Disease elimination**
  - eg smallpox vaccination
  - best prospect is AD vaccine for those at risk

- **Disease postponement**: delay AD onset by…
  - 2 years, ↓ prevalence by 20%
  - 5 years, ↓ prevalence by 50%

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1 Brookmeyer et al. (1998)
Is early life the most important target?

• 60-70% of world dementia in developing countries
  – Low foetal birth weight
  – Poor or no education
  – Poor socio-economic environment

• 12.4% West Australia’s Kimberley Aboriginal people have dementia = 5.2x non-indigenous\(^1\)

Smith K et al, Neurology, 2008;71: 1470-1473
• Look after your heart
• Be physically active
• Mentally challenge your brain
• Follow a healthy diet
• Enjoy social activity

yourbrainmatters.org.au
Dosage effect

As cardiovascular risk factors accumulate, AD dementia risk increases

- Hypertension
- Smoking
- Hypercholesterolemia
- Obesity
- Diabetes
- Physical inactivity

Number of risk factors

Luchsinger et al 2005

Slide adapted from Michael Valenzuela
Statins to prevent AD

Two reviews in 2016 conflict:

• Good evidence that statins neither prevent nor increase risk of cognitive impairment or dementia

• Statins linked to reduced AD risk – differences by sex, race & statin

1 McGuiness B et al, 2016; CD003160 (1) Cochrane Database of Systematic Reviews

2 Zissimopoulos JM et al, 2016, JAMA Neurology
Physical activity
Can exercise protect against dementia?

- Preserve cognition and slow cognitive decline
- Decreased incident dementia
- 8/11 RCTs in healthy older persons: cognitive & fitness improved
  – especially cognitive speed and attention
- Biomarkers ↑ e.g. brain volume
- Animal studies – growth factors↑, BDNF↑, neurogenesis↑, inflammation↓, AD path. ↓

Graff-Radford NR, Alzheimer’s Research and Therapy 2011, 3:6
Physical activity

• Physical activity benefits older adults to prevent dementia: Never too late to start
• Moderate intensity (brisk walking) 30 min 5d/wk
• Evidence for specific exercise not clear; more than one type and more exercise may be better
• Resistance training better in SMART Trial$^2$
• More is better – puffed, weights
• $\geq$ 3x per week; $\geq$150 min/wk, e.g. Perth Study$^3$
• Combine with social and mental activity better?

The hope: physical activity ... 

- Improves fitness
- Improves physical health - ↓ heart disease, Hi BP, diabetes, some types of cancer, osteoporosis, sarcopenia
- Reduces morbidity & mortality
- Improves mental health
- Improves confidence, quality of life

http://www.mednwh.unimelb.edu.au/research/health_promotion.htm
Physical activity: the realism

- Reverse causality
- Effect size of physical activity
- Interaction of genetics and lifestyle
- Side effects possible if not done correctly
Mental Activity
Mental Activity & Dementia

- Meta-analysis of 22 studies, 29,000 individuals
- ↑ complex mental activity in late life = ↓ risk of dementia by half; OR = 0.54 (0.49-0.59)¹
- Dose - response relationship evident¹
- Results suggest complex patterns of mental activity in the early, mid- and late-life stages are associated with ↓ dementia incidence¹
- Results held when covariates in source studies were controlled for²

Cognitive training

• Systematic review of RCTs with longitudinal follow-up (>3mths) in healthy elderly¹
  – 7 RCTs met inclusion criteria, low quality
  – Strong effect size for cognitive exercise intervention vs wait-and-see controls
  – Longer FU duration (>2yrs) → ES no lower

• Review of cog. training or rehab in dementia²
  – 11 RCTs, no benefit

Valenzuela & Sachdev (2009) Am J Geriatr Psychiatry 17(3)
Realism mental training

- Reverse causality
- Which mental activity
  - Crosswords?? Sudoku??
  - Musical instrument? New language?
  - Computer cognitive training, are benefits:
    - Sustained?
    - Generalise beyond computer?
Diet
Mediterranean Diet Pyramid*  

Daily  
1. Vegetables  
2. Olive Oil  
3. Fish  
4. Eggs  
5. Poultry  
6. Sweets  

Red meat - a few times per month in very small amounts  
A few times per week  

* Adapted from Consumer Reports, Nov/94
Nutrition / Supplements

- Alcohol ? moderate
- Fish/Seafood/ω3 ?
- Vitamin D ?
- Caffeine ?
- Vitamin E ?
- Vitamin C x

*Food sources better than supplements*
Smoking and AD

- Current smoking
  - increase risk for AD
- Previous smoking
  - Risk not significantly increased

Anstey K. Am J Epidem 2008
Alcohol

• Some evidence benefit with moderate alcohol – i.e. abstinent → higher risk, j-shaped curve
• Not all studies confirm
• Interaction with ApoE4 – contradictory results?
• Heavy alcohol is risk factor
• Which alcohol – (red) wine? – Evidence not strong
• What is moderate?
Natural therapies

- Ginkgo biloba
- Turmeric, curcumin
- DHA, omega 3
- Fo-ti root
- Soy isoflavone
- Vitamin E, Selenium
- Folate, B6, B12
- Saffron
- Brahmi
- Huperzine A
Diet: realism

- Diet, exercise, vascular health, diabetes, obesity – all linked
- Obesity in mid-life is a risk factor; late life not
- RCTs for long periods impossible
Other factors

• HRT – neither harmful or beneficial close to menopause
• Hearing loss ↑risk RR 1.55-2.32
• Less ‘socialisation’
  – increases risk of cognitive decline/dementia
  – moderates effect of Alzheimer pathology on cognitive function
Environmental factors

• 30% of population attributable risk of AD cases from 7 environmental factors

• If 25% lower prevalence of these risk factors → 3 million fewer AD cases worldwide

• Highest estimated Pop\textsuperscript{u} Attributable Risk for AD
  – Global: low education (19·1%, 95% CI 12·3–25·6)
  – USA: physical inactivity (21·0%, 95% CI 5·8–36·6)
  – Europe and UK similar (20·3%, 5·6–35·6)

Barnes & Yaffe, 2011; Norton et al, 2014
Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)

- Diet
- Cognitive training
- Exercise – PMR and aerobic
- Manage metabolic and vascular risk factors
- Social activities
Mean change in cognition over 2 years

NTB Total Score

Executive Function

p=0.03

p=0.04
Mean change in cognition over 2 years

Processing speed

Memory

Prevention of Dementia By Intensive Vascular Care (preDIVA) trial

- Multicomponent intervention targeting vascular risk factors
- New cases of all-cause dementia and AD did not significantly differ between groups.
- Signif. less non-AD dementia in intervention (1%) vs control group (2%) (HR 0.37; p=0.007)
- Subgroup with untreated hypertension adherent to intervention, significantly fewer new dementia cases (4% vs 7%; HR 0.54; p .02)
Internet based prevention trials

- Healthy Aging Through Internet Counselling in the Elderly (HATICE) [http://www.hatice.eu/](http://www.hatice.eu/)
- **Maintain Your Brain**
  - NHMRC funded, 5 years, largest trial in world
  - 18,000 Australians 55-75 years old
  - Exercise, cognitive training, diet, depression
  - blood pressure, cholesterol, glucose
  - Tailored to individual risk factors
    - [www.cheba.unsw.edu.au](http://www.cheba.unsw.edu.au)
Drug prevention trials

- A4 Study - Clinically normal, Aβ positive
- DIAN – TU – Dominantly inherited AD
- Alzheimer Prevention Initiative (Colombia)

- Prevent MCI → AD
  - Tau therapeutics
  - β-secretase inhibitor
Drug trials = the hope
Strategies

• Anti-amyloid
  – Enzyme inhibitors
  – Immunotherapies – active, passive

• Anti-tau

• Neurotransmitter enhancers
  – Cholinesterase inhibitors
  – Memantine
  – Serotonin receptor antagonists

• Others: intranasal insulin, RAGE, NGF
Anti-amyloid therapies - 1

- Reduce production of Aβ protein
  - α-secretase upregulation
    - Etazolate (EHT-0202)
  - β-secretase inhibition
    - Rosiglitazone (stimulate PPARγ) - failed
    - Verubecestat Merck) – failed
  - γ-secretase inhibition
    - Semagecestat – worse than control
Anti-amyloid therapies - 2

- Immunisation to promote Aβ clearance
  - Active immunisation
    - AN-1792 → sterile meningoencephalitis
    - Shorter peptides to avoid T-cell activation
  - Passive immunisation with antibodies
    - Bapineuzumab – ceased, negative result
    - Solanezumab – primary outcome negative (Nov 2016)
    - Gantenerumab - trial stopped; but ↓PET plaque (ns) and ↓tau in CSF (signif)
  - IV immunisation with immunoglobulin - failed
Anti-amyloid therapies - 3

- Prevent Aβ aggregation
  - Tramiprosate (3APS) – ceased
  - PBT1 (clioquinol) – question eye toxicity
  - PBT2 – disrupts Zn, Cu required for aggregation
Anti-tau

• Modulation of phosphorylation
  – Glycogen synthase kinase 3β (GSK3β) & Cyclin dependent kinase 5 (CDK5) inhibitors
  – Activate phosphatase
• Tau-directed immunotherapy
  – Active or Passive
• Small molecule inhibitors of protein aggregation
  – Methylthioninium (methylene blue, Rember)
• Microtubule stabilisation Epothilone D (EpoD)
• Antisense oligonucleotides

Himmelstein DS et al Pharmacology & Therapeutics 2012
DeVos et al. Science Translational Medicine 2017
Promote neuronal function

- Mitochondrial dysfunction
  - Latrepirdine (Dimebon) - failed
- Nerve growth factors: Delivery to brain is barrier
  - Viral vectors
  - Nanotechnology
- Inhibit RAGE (receptor for advance glycation end-products)
- Anti-inflammatory treatments – TNF-α blocker
Other treatments

- 5-HT6 Receptor antagonist, idalopirdine
  - Encouraging results in 2014 (with donepezil)
  - Higher doses no benefit; lower doses ??
- Long acting intra nasal insulin
- Deep brain stimulation targeting limbic memory circuit in pts with mild AD
- Nerve growth factor
- Nutraceuticals – Axona, Souvenaid
AD Cures – graveyard

- Trimiprosate (Alzhemed)
- Flurbiprofen (tarenflurbil)
- Anti-inflammatory
- Rosiglitazone
- Statins
- Leuprolide
- Semagacestat ($\gamma$-secretase inhibitor)
- Bapineuzemab
- Verubecestat ($\beta$-secretase inhibitor)
- Celecoxib
- Dimebon
- Intravenous Immunoglobulin
Why failures despite Phase 1/2 trial success?

- Wrong time? Too late in disease process?
- Wrong target? Amyloid may not be the one
- Wrong patient? 30% of trial participants did not have AD as per amyloid PET Scans
- Wrong model? May need multiple drugs simultaneously eg TB, H. bacter, leukaemia
Realism – drug treatments

- No silver bullets
- Billions invested with no return
- Pharma still interested but some not
- Most trials for AD
- World Dementia Council aim for cure by 2025 unlikely

‘The mainstay of treatments for AD is supportive care from family ..’

1 Cummings J et al, 2016 Alz Research & Therapy
Behavioural and Psychological Symptoms of Dementia
BPSD
What are BPSD?

- Agitation
- Aggression
- Calling out/ screaming
- Disinhibition (sexual)
- Night time disturbance
- Shadowing
- Swearing
- Wandering

- Depression
- Anxiety
- Apathy
- Delusions
- Hallucinations
- Irritability
- Elation/euphoria
The bio-psycho-social framework

Socio-environmental

Interpersonal

Biological

Psychological
How to intervene: Environment

- Secure grounds
- Personalised space
- Non-institutionalised environment
- Home-like
- Colour, furnishings, architecture, lighting
- Resident mix
- Size of facility
- Aroma therapy
- Pets
- Robots
- Toys, dolls
Interpersonal

• Family carers can be effective therapists for people living in the community (ES 0.34)¹
• Person centred care training reduced agitation in NHs – sustained 4 months later & cost-effective²

²Chenoweth L et al, Lancet Neurology, 2009
Psychological

- Humour therapy ↓agitation, ↓depressⁿ, ↑QoL¹,²
- Tailored Activity Program³,⁴ – OT led
- Others – Volunteers, music, singing, dance therapy, Integrating kindergarten/ babies

¹Low LF et al BMJ Open 2013; ²Brodaty et al Am J Ger Psych 2014
³Gitlin L et al, Am J Ger Psych 2008 & ⁴Gerontologist, 2009
Key elements

- Engagement
- Understanding
- Time

Barriers

- Time
- Money
- Staff
- Attitudes
- Training
Pharmacological interventions
Rx for BPSD - summary

- Antipsychotics – effect on aggression, psychosis, agitation, but ↑risk of AEs, stroke, death
- Antidepressants – negative trials for depression
  - Citalopram effect on agitation, AEs - QTc↑, cog↓
- Analgesics – effect on agitation (paracetamol 3g/d)
- Anticonvulsants – no or little effect
- Benzodiazepines – risk of confusion, falls
- Cholinesterase inhibitors – effect on apathy
- Memantine ?benefit for agitation/aggression/delusions/hallucinations
HALT study: Deprescribing antipsychotics in NHs

- Identify residents on antipsychotics ≥ 3 m
- Permission from NHs, families & GPs
- Train nurse champions in nursing homes to teach other nurses how to manage BPSD
- Academic detailing of GPs
- ≈75% cease antipsychotics; remain off for 12m
- No re-emergence of behaviours
- No significant drug substitution
Conclusions

• Research on dementias - challenging & vibrant
• The more we know, the more we don’t know!
• Research focus on AD but strong groups working in Vascular dementia, LBD, FTD
• Research can drive drug Rx and improvements in diagnosis and care
• Australia has leading researchers in basic, diagnostic, translational, carer, residential areas
• Funding for research is major issue
• Australian Dementia Registry would boost care & research
Thank you

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