Dementia – where are we?

Henry Brodaty

Dementia: Where are we now?

Prevalence
Projections of dementia worldwide


Statistics New Zealand (2009) Impact of structural population change

Life expectancy at birth in NZ 1985–2009

Statistics New Zealand; Ministry of Social Development
≈ 400–500 Centenarians in NZ, 2011 → triple by 2050
Estimated population aged 100+ years
1950–2006

Source: Statistics New Zealand

Dementia in NZ 1,2

• 2011 ≈ 48,000
• 2050 ≈ 147,000
• Maori, Pacific Island, Asian over-represented.
• NZ$955m cost to NZ

1 Dementia Economic Impact Report 2011
2 Alzheimers NZ 23.08.14

Assumptions about constant incidence and prevalence

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Is number 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

Gu et al. Neurology 2013;80:1866–1884

Implications of reduced prevalence

- Environmental factors
  - Better education?
  - Better attention to lifestyle factors?
    - Cardiovascular?
    - Diet?
    - Perinatal and early childhood?
Where are we with prevalence?

- Ageing world especially developing world
- 2-3x increases in prevalence by 2050
- Higher rates than expected in East Asia and Sub Saharan Africa which outweighs....
- Less increase than forecast in UK, Scandanavia
- Dementia remains a global and national health priority

Population predictions: China


Definitions: Dementia & AD
- DSM IV
- ICD 10
- Dubois criteria
- DSM 5
- (ICD 11 coming)
Alzheimer's disease without dementia

- Biomarker led diagnosis
  - CSF ↓β, ↑tau and phospho-tau
  - PET amyloid imaging
  - Serial MRIs – hippocampal atrophy, white matter lesions, cingulate gyrus, tracts
  - Genetic markers
  - Blood markers

Dubois criteria (in brief)

- AD Incorporates pre-dementia & dementia
- Prodromal AD (pre-dementia AD)
  - Clinical symptoms (eg memory loss) but they do not interfere with IADLs
  - Biomarker evidence from CSF or imaging
- AD dementia
  - Cognitive symptoms interfere with IADLs, social function
    - Change in episodic memory & ≥ 1 other domain

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
  - Usual definition; recognises non-amnestic presentations – PCA, Logopenic, Executive
- 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, typically involving ≥ 2 SDs below appropriate norms (ie < 3rd.) on formal testing or equivalent clinical evaluation
• Cognitive deficits interfere with independence (ie requiring minimal assistance with IADL)
• Cognitive deficits not exclusively in the context of delirium and not primarily attributable to another mental disorder (eg, major depression, schizophrenia)

DSM-5 Minor Neurocog. Disorder

• Modest cognitive decline ≥ 1 domain based on concerns of individual, knowledgeable informant or clinician
• Decline in neurocognitive performance - typically 1-2 SDs < appropriate norms on formal testing or equivalent
• Cognitive deficits insufficient to interfere with independence (IADLs preserved eg more complex tasks, paying bills, meds.), but > effort, compensatory strategies or accommodation required
• Cognitive deficits not exclusively in the context of delirium and not primarily attributable to another mental disorder (eg major depression, schizophrenia)

Where are we with definition?

• Still in flux
• Lack of gold standard
• Biomarkers = advance
• Clinical diagnosis remains cornerstone
• Choice of definition will affect
  – Prevalence
  – Reimbursement
  – Treatment
  – Genetic counselling
Diagnosis by GPs

- 2-3 year gap between symptoms & diagnosis in primary care
- GPs miss 50-90% of mild cases\(^1\,^2\)
- 10% of PWD receive diagnosis in Low and Middle Income Countries (LMIC)
- 40% ................................. in High Income Countries (HIC)

\(^1\)Valcour et al Archives Int Med 2000;160:2964-8
\(^2\)Boustani et al J Ger Int Med 2005;20:572-7

Role of cognitive screening

- 50-80% of dementia are undiagnosed, screening could redress this
- At least 50% of mild & moderate dementia cases are missed by physicians, improves for moderately advanced dementia
- Target of screening should be those with risk factors (age, family history, genotype) – Not just those who present to medical centres for other reasons

Controversy about screening

• No clear evidence for or against the benefits of screening in primary care ¹
• No evidence for benefits of screening for preclinical dementia ²
  – Risks of over-diagnosis
  – No drugs that prevent progression
• My position – targeted screening and
  – screen +ve ≠ diagnosis → further assess


High tech diagnosis

- CSF
- MRI
- PET, PET-PiB etc.
- DaT SPECT scans
- Genetics
- Blood tests

Benefits
- Useful for research
- Diagnostic challenges

Disadvantages
- Cost
- Accessibility limited
- Not 100% accurate
**PiB-PET Scans: AD vs MCI vs control**

From the online newspaper of Prof Yasser Metwally

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**Dopamine Transporter (DaT) SPECT scan**

More and hotter colour = more dopamine

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**New blood test for AD?**

1. A set of 10 LIPIDS from blood predicted conversion to either amnestic MCI or AD within 2–3 yrs, > 90% accuracy
2. A set of 10 PROTEINS (AIBL study)
3. MicroRNA (AIBL study)

Mostly defined samples, 80-90% sensitivity and specificity, not large samples, await replication

- Doecke JD et al, Arch Neurology 2012
- Cheng et al, Molecular Psychiatry, 28/10/2014, 1-9
Strategies for GPs

- GPCOG – web based assessment of cognitive impairment \(^1,2\)
- E-training modules
- Prompts for desk top computers
- GP Pathways
- Incentives for GPs (eg $$)
- GPs specialising in elder care?
- Practice nurses assessing
- Targeted screening - controversial

\(^1\) [www.gpcog.com.au](http://www.gpcog.com.au)
\(^2\) Brodaty et al, JAGS, 2002

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Where are we with diagnosis?

- Major public health target:
  - \(\uparrow\) Proportion diagnosed, \(\downarrow\) time to diagnosis
- Initiatives needed to improve GP Dx & Mx
  - Training – academic detailing, e-modules, Small groups, case based,
  - GP tools eg GPCOG, computer prompts
- Biomarkers including neuroimaging improve diagnostic accuracy but limitations
- Marginal benefit versus cost of new tests

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Prevention AD
50% of population attributable risk of AD from 7 environmental factors:
- 2% diabetes mellitus (type 2)
- 2% midlife obesity
- 5% midlife hypertension
- 10% depression
- 13% physical inactivity
- 14% smoking
- 19% cognitive inactivity/education

25% ↓ → 3m ↓ dementia cases globally

Re-analysis Norton S et al, Lancet 2014
- Highest estimated PAR 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)
- Adjusting for association between risk factors, Global PAR 49% → 28-2% (95% CI 14-2-41-5) = 9-6/33.9m attributable cases (95% CI 4.8-14.1m)
- ≈30% for USA, Europe, UK
Re-analysis Norton S et al, Lancet 2014

- Assuming a causal relation and intervention at correct age for prevention, relative reductions of 10% per decade in the prevalence of each of the seven risk factors could reduce the prevalence of AD in 2050 by 8-3% worldwide
- After accounting for non-independence between risk factors, around 1/3 of AD worldwide may be attributable to potentially modifiable risk factors

Physical activity

- Evidence from observational & control studies
- Physical activity benefits older adults to prevent dementia: Never too late to start
- Moderate intensity (brisk walking) 30 min 5d/wk
- No evidence for a specific exercise, but > 1
  - > exercise may be better; aerobic + resistance?
- Combine with social and mental activity better?

Can aerobic exercise protect against dementia?

- Preserve cognition and slow cognitive ↓
- 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
The power of physical activity

Erickson et al., 2011

Physical activity & change in hippocampal volume

• 18 month follow-up of 97 cognitively intact older adults
• Low risk = no APOE e4 allele
• High risk = APOE e4 allele

Smith JC et al. 2014 Frontiers in Aging Neuroscience
doi: 10.3389/fnagi.2014.00061

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 interventions healthy older adults & people with MCI

- 20 RCTs with healthy adults
  - Memory improvements in 17/20
- 6 RCTs with MCI
  - Memory improvements in 4/6
- Unclear whether these improvements generalise to everyday activities


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)
Bahar-Fuchs, Clare, Woods – Cochrane Database Syst Rev. 2013 Jun

Causality? Reverse causality?

Do leisure, mental or physical activity lower risk of dementia?
  Or
Are those with better cognitive function and lower risk of dementia more likely to participate?
  Or
Could prodromal dementia influence activities?
Mind your diet
- Mediterranean diet
- Antioxidants

Nutrition / Supplements
- Alcohol ? moderate
- Fish/Seafood/ω3 ?
- Vitamin D ?
- Caffeine ?
- Vitamin E ?
- Vitamin C x
  Food sources better than supplements

B Vitamins reduce rate of brain atrophy
- ↓ homocysteine level
- ↓ brain atrophy rate by 30%
- Effects greater in people with high homocysteine level
- No effect if normal HCy
- Cognition better too

- Folic acid 0.8mg/day
- Vitamin B6 20mg/d
- Vitamin B12 0.5mg/d
- In people 70+ w. MCI

Smith AD et al, PLoS ONE, 2010
Systematic review - negative

- Ford AH¹, Almeida OP.
- Effect of homocysteine lowering treatment on cognitive function: a systematic review and meta-analysis of randomized controlled trials.

Vitamin D and dementia

- Vit D deficient older adults have increased risk of dementia
- 1,658 65 yo+ in US Cardiovascular Health Study without dementia followed for = 6y
- 171 → dementia; (including 102 with AD)
- Those with low vitamin D levels (<50nmol/L) almost 2x as likely to develop dementia & AD
- Assoc'n betw. Vit D level & cognition, AD risk

¹TJ Littlejohns Neurology, 2014

Vitamin D

- Vit D receptors in brain, including hippocampus
- Vit D regulates neurotrophin expression and enhances the survival of brain cells
- Vit D can stimulate brain cells that may play a role in clearing amyloid beta plaques.
- > 50% of Australians and ≤ 95% of people in residential aged care are Vit D deficient
- No evidence that taking Vit D improves cognition or reduces risk
NSAIDs, fish, circumin

- Anti-inflammatories – mixed epidemiological evidence
- Fish oil – some evidence (epidemiological)
- Circumin – some evidence (laboratory)

Herbal & vitamin medications

- Turmeric
- DHA
- Fo-ti root
- Soy isoflavone
- Vit E & Selenium
- Omega-3
- Saffron
- Huperzine A: natural ChEI
- Folate, B6, B12 - Optima group → evidence

Can Ginkgo biloba Prevent Dementia?¹

RCT double-blind, 7 years follow-up
1545 Ss on Ginkgo, 1524 on placebo

¹DeKosky et al, JAMA. 2008; 300(19):2253-2262
Where are we with prevention?

- Increasing evidence but not conclusive
- Physical & mental exercise, diet, BP, etc
- Attractive proposal to government and public
- Benefits body, heart, muscles, bones, mood as well as cognition
- No significant adverse effects
- Strong campaigns by Alz Associations
  – Raises awareness
  – Start preventative strategies younger

Prevention of AD and VaD

- Low education √
- Blood pressure √
- Diet ?
- Cholesterol ? √
- Sugar, diabetes √
- Head injury ?
- Socialisation ? √
- Supplements ?? to X


Parallel session 1.30 pm today with Stephen Iliffe and Glenn Rees
Drug treatments for dementia

Rx for AD
Symptomatic:
• ChE Inhibitors
• Donepezil
• Galantamine
• Rivastigmine
• Memantine
• Nutraceuticals - Souvenaid

Disease modifying drugs
None proven

Disease modifying drugs

- Amyloid as target
  - Beta and gamma secretase inhibitors
  - Immunotherapy
  - Block aggregation of Aβ protein
- Phosphorylated tau as target

AD Cures – graveyard

- Trimiprosate (Alzhemed)
- Flurbiprofen (tarenflurbil)
- Anti-inflammatory
- Rosiglitazone
- Statins
- Leuprolide
- Semagacestat (γ-secretase inhibitor)
- Bapineuzumab
- Celecoxib
- Dimebon
- Intravenous Immunoglobulin

AD Cures – graveyard
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  
Where are we now?

- 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

Non-pharma treatments for dementia
Non pharmacological for dementia

- Exercise
  - 4 trials analysable and only 2 provided data
- Cog. training or rehab in dementia
  - 11 RCTs, no benefit
- Further research needed

1 Forbes D et al. 2013 Cochrane Database of Systematic Reviews
DOI: 10.1002/14651858.CD006489.pub3.
2 Bahar-Fuchs, Clare, Woods – Cochrane Database Syst Rev. 2013

Cognitive training

- Review of cog. training or rehab in dementia
  - 11 RCTs, no benefit

Bahar-Fuchs A, Clare L, Woods R – Cochrane Database Syst Rev. 2013

BPSD
Where are we: Rx for BPSD?

- Lack of effect of antidepressants for depression in dementia 1,2
- Ltd benefit + side effects of antipsychotics
  - Risk of stroke, falls, cog decline, death


Sertraline for treatment of depression in AD: Wk-24 Outcomes (DIADS-2)

- 67 Sertraline, 64 placebo; 12 wk RCT + 12 wk
- No between-groups diff. in depression response
  - in CSDD score
  - remission rates
  - secondary outcomes
- SSRI associated > adverse events of diarrhoea, dizziness, dry mouth, pulmonary SAE (pneumonia)


HTA-SADD Trial

- Mirtazapine 15 mg & sertraline 50 mg; 1-3/day
- N = 507

Banerjee S, HTA-SADD trial, Lancet, 2011
Effects of citalopram on BPSD

- Improve hallucinations and delusions (= antipsychotics)
- Improve agitation
- 60% ↓ irritability and apathy (but n.s.)
- ↓ hallucinations (statistical but ?clinical significance)


CitAD RCT – citalopram & agitation

- Significant better with citalopram
- Cognitive & cardiac adverse effects may limit effectiveness at 30mg/day

Effects of antipsychotics

- Meta-analysis from 13 studies\(^1\):
  - Mean ES in Rx = 0.45
  - Mean ES in placebo = 0.32
- Effect sizes of atypical antipsychotics for BPSD are medium, not statistically better than placebo
- Increased rate of stroke\(^2\)
- Increased mortality\(^3\)
- Increased AEs in general

\(^1\) Yury C. & Fisher J, Psychotherapy and Psychosomatics 2007
\(^2\) Brodaty H et al, J Clin Psychiatry 2003
\(^3\) Schneider L, 2005

Continuing vs stopping neuroleptics in dementia patients?

- 12 months RCT
- Continuous use of neuroleptics vs placebo
- For most AD patients withdrawal had no overall detrimental effect
- Continuers – worse verbal fluency (p<.002) and higher mortality
- Subgroup of pts with more severe symptoms (NPI ≥ 15) might benefit from continued Rx

Ballard et al 2008 PLOS Medicine, 5:587-599

DART-AD – mortality associated with continuous Rx

\(^1\) Ballard et al, 2009 Lancet Neurology, 8, 151–157
Analgesics

- No analgesic or low dose paracetamol → 3g/day paracetamol (n = 120, 69%)
- Full dose paracetamol or low dose morphine → 5mg bd morphine (n = 4, 2%)
- Low dose buprenorphine or unable to swallow → buprenorphine patch 5-10μg/h (n = 39, 22%)
- Neuropathic pain → pregabaline 25-300mg /d (n = 12, 7%)

Husebo BS et al, BMJ, 2011;343:d4065 doi: 10.1136/bmj.d0465

Legal consent for psychotropics

- Depending on jurisdiction a Person Responsible must give consent
- Survey of 3 NHs; 77 residents without capacity to give informed consent; on psychotropics¹
  - Only 6.5% written consent
  - + 6.5% partial or attempted consent

¹ Rendina N et al, 2009

Where are we: psychosocial treatment for BPSD?

- Person Centred Care ¹
- Humour therapy ², ³
- Caregiver delivered interventions ⁴

¹ Chenoweth L et al Lancet Neurology 2010
² Low LF et al, BMJ Open 2013;
³ Brodaty H et al, Am J Ger Psych 2013
Dementia Care Mapping & Person Centred Care for agitation

Cost for PCC
≈ $6 to reduce a point on CMAI

Chenoweth et al. Lancet Neurology 2009

Humor therapy: SMILE study

- 20% reduction in agitation
- Effect size = antipsychotic medications for agitation
- Adjusting for dose of humour therapy
  - Decreased depression
  - Improved quality of life

Low LF et al BMJ Open 2013
Brodaty et al Am J Ger Psych 2014
Low LF et al JAMDA 2014

Family caregivers

- Family carers as therapists for people living in the community
- Systematic review
  - ES 0.34 for decreasing BPSD
  - ES 0.15 for decreasing caregiver “stress”

Novel strategies

- Volunteers
- Montessori
- Music, singing, dance therapy
- Integrating kindergarten/ babies

Robotic pets, toys, dolls

BPSD: where are we?

- Major advances in psychosocial treatment
  - PCC
  - Engagement and stimulation
  - Working with caregivers and with staff
- Drug Rx – disappointing
  - indicated in some cases
Summary … d’oh!

- Drug treatments limited benefit and
to side effects – yet 30% of residents
in Australia are on antipsychotics
and half on ≥1 psychotropics
- Most drug Rx given without required
consent¹
- Psychosocial and environmental
therapies beneficial with effect size
> drug Rx

Rendina N et al, IJGP, 2009

Summary … d’oh!

- So why are nursing homes not
engaging more?
- Why is the knowledge not being
translated into practice?
  - Training – too little?
  - Cost – too much?
  - Time – not enough?
  - Residents, families, system??

Other major issues
Other major issues 1

- Family carers
- Acute hospital care
- Technology and design
- Dementia friendly communities
- Residential Care
- End of life care
- Workforce

Other major issues 2

- Stigma
- Research funding
- Policy

Research

LMIC: woeful
HIC: Improving by long way to go
Where are we on 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

- Supra-national
  - ADI Policy Brief for Heads of Government G8
  - Also: G20, WHO, UN

Conclusions
Dementia – where are we?

Looking back
Looking forward

Dementia – the where are we?

• Huge progress in last 30 years but huge gaps
• Improvements uneven globally
• Fight dementia – multiple fronts
  – Policy and funding
  – Clinical services – diagnosis → end of life
  – Research – cause, cure and care
  – Prevention implementation
  – Stigma - public and professional attitudes
• Dementia – the future is NOW!

References

• Brodaty H, Connors M, Pond D. Dementia: How to Treat. Australian Doctor, 2014 In Press
Thank you

- www.dementiaresearch.org.au
- www.cheba.unsw.edu.au
- www.alz.co.uk
- h.brodaty@unsw.edu.au

Thanks to Megan Heffernan for help with slides