Prevention and treatment of dementia
Henry Brodaty
“My memory really sucks Mildred, so I changed my password to "incorrect." That way when I log in with the wrong password, the computer will tell me... “Your password is incorrect.”
Changing demographics: Australia

ABS: Population by Age and Sex, Australian States and Territories Jun 2010.
ABS: Population projections, Australia, 2006 to 2101.
How will we age ...????
Auguste Deter 51 yrs
100 years ago

Paul McCartney 69 yrs

John Howard 71 yrs

Hugh Hefner 84 yrs
Positive aspects of ageing
Older Australians...

**Independent**
- 94% of 65-84 yr olds & 74% of those 85 yrs and older live in private dwellings

**Carers**
- 24% of 65+ yr olds provide support to relatives outside their household

Older Australians...

Healthy

- 68% of 65+ year olds rate their health as good to excellent

Volunteers

- 31% 65+ yr olds do voluntary work

Patterns of disease over last 100 years

Death rates Australia (1907-2003): Infectious diseases

Magnus & Sadkowsky 2006. Cat. no. PHE 73. Canberra: AIHW.
Patterns of disease over last 100 years

Death rates Australia (1907-2003): Circulatory diseases

Magnus & Sadkowsky 2006. Cat. no. PHE 73. Canberra: AIHW.
Patterns of disease: 85+yr olds

Death rates Australia (1968-2003): nervous system diseases

Magnus & Sadkowsky 2006. Cat. no. PHE 73. Canberra: AIHW.
The paradox

• Positive – living longer & not dying as often from heart attacks, strokes
  vs
• Consequence – more prone to develop age associated conditions such as dementia, macular degeneration, gait disturbance

• The 21st Century is century of neurodegenerative disease
Is dementia inevitable?

- Biggest barrier to healthy, happy ageing is brain disease
- But not inevitably, dementia affects
  - >5% of people > 65 years but not 95%
  - 20% > 80 .... 80%
  - 30% > 90 .... 70%
Projections of a tripling of world’s dementia population by 2050

World Alzheimer Report, ADI, 2009

- 2020: 36 million
- 2030: 66 million
- 2050: 115 million
Tripling in Australia

Access Economics for Alzheimer's Australia, 2009
Rate in indigenous people several fold higher
Cost of care in Australia

- In 2009-10, Australian, state and territory government expenditure on aged care was around $11 billion
- two-thirds to residential aged care
- aged care spending increase from 0.8% GDP in 2010 to 1.8 % of GDP in 1 generation

Productivity Commission , Caring for Older Australians, 2011 Intergenerational Report 2010
COMING SOON RESIDENTIAL AGED CARE
WHY?

Epidemic of ageing by 2050
65yo + double
85yo + >4x increase
In Australia by 2050

• 85+ yrs projected to increase from 0.4m in 2010 to 1.8m (5.1% population)

• >3.5 million older Australians will access aged care services each year, ≈80% services delivered in community
Dementia is an umbrella term

- Cognitive *and* functional decline
- Over 100 causes
- Alzheimer’s is the most common
What goes wrong in the brain in AD?

• The adult brain weighs about 1.3 kg
• Dementia shrinks it to $\frac{1}{2}$ usual size
Amyloid plaque  Neurofibrillary tangle
Can Alzheimer’s disease be prevented?
Eugeria

- Took up fencing, aged 85
- Rode bicycle till 100
- Lived alone till 110
- Poured olive oil on food and rubbed onto her skin
- Port wine, 2 cigs/day, 1Kg chocolate every week
- Died 122 without dementia

Jeanne Calment
1875-1997

Prevention: Eliminate v Postpone

• Disease elimination
  – eg smallpox vaccination
  – best prospect is AD vaccine

• Disease postponement (Brookmeyer R, 1998)
  – delay AD onset by
  – 2 yrs \(\rightarrow\) ↓ prevalence by 20%
  – 5 yrs \(\rightarrow\) ↓ prevalence by 50%
What is new in prevention?

- Public campaigns to delay or prevent AD
- Whole of life approach
- Never too late
Alzheimer’s Australia – *Mind your Mind*

Dementia risk reduction signposts

– Mind your BODY
– Mind your BRAIN
– Mind your DIET
– Mind your HABITS
– Mind your HEAD
– Mind your SOCIAL LIFE
– Mind your HEALTH CHECKS – esp. BP

http://yourbrainmatters.org.au
Physical activity = protective

- Several studies show physical activity protective against cognitive decline, dementia, Alzheimer’s, vascular dementia
- More is better – puffed, weights
- At least 3x per week; > 150 mins/wk
- Check with your doctor

Walking 150’/wk for cognition

N = 138 memory complainers

Lautenschlager et al (2008) JAMA; 300(9):1027-1037

© DCRC/Brodaty 2010
The power of physical activity

Erickson et al., 2011
“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”
Mind your brain: Accumulating evidence for mental exercise/cognitive training
Mental Activity & Dementia ¹,²

- Meta-analysis of 22 studies, 29,000 people
- *Lifetime*: Education, occupation, IQ, leisure each reduce risk by about half
- *Late life*: ↑ complex mental activity ↓ risk of dementia by half
- Dose - response relationship evident
- Complex patterns of mental activity in early, mid- and late-life associated with ↓ dementia

## Computer cognitive training products

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Research</th>
<th>Multi-domain</th>
<th>User-friendly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Fitness Program 2.0</td>
<td>Posit Science Corp.</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Insight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><a href="http://www.HappyNeuron.com">www.HappyNeuron.com</a></td>
<td>Quixit Inc.</td>
<td>Yes</td>
<td>Yes</td>
<td>Mixed</td>
</tr>
<tr>
<td><a href="http://www.Mind">www.Mind</a> Fit</td>
<td>CogniFit Ltd</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><a href="http://www.mPowerBrainFitness">www.mPowerBrainFitness</a></td>
<td>Dakim Inc.</td>
<td>Yes</td>
<td>Yes</td>
<td>Mixed</td>
</tr>
</tbody>
</table>
Mind your diet

- Mediterranean diet
- Antioxidants
What is Mediterranean diet?

- Abundant plant foods
- Fresh fruit as typical daily dessert
- Olive oil as principal source of fat
- Dairy products (cheese and yogurt)
- Fish and poultry - low to moderate
- 0-4 eggs week
- Red meat - low amounts
- Wine - low to moderate amounts
- Total fat = 25% to 35% of calories
- Saturated fat ≤ 8% of calories
Foods rich in anti-oxidants

Small red beans
Blueberries
Red kidney beans
Pinto beans
Cranberries
Artichoke hearts
Berries: - black
Rasp- and Straw-

Dried prunes
Apples - Red delicious, Granny Smith, Gala
Pecans
Sweet cherries
Sweet cherries
Black plum, plum
Russet potato, cooked
Black beans
Nutrition / Supplements

- Alcohol ? moderate
- Fish/Seafood/ω3 ?
- Vitamin D ?
- Caffeine ??
- Vitamin E x
- Vitamin C x
B Vits reduce rate of brain atrophy

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

- Reduced homocysteine level
- Decreased rate of brain atrophy by 30%
- Effects greater in people with high homocysteine level
- ? Cognition effect

Smith AD et al, PLoS ONE, 2010
Smoking and AD

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

Anstey K. Am J Epidem 2008
Mind your health checks

✓ Blood pressure
✓ Sugar
✓ Cholesterol
Metabolic syndrome & dementia risk

- Diabetes/ raised fasting sugar
- Abdominal obesity
- High cholesterol
- High blood pressure

- 23% increased dementia risk for each component of metabolic syndrome

4895 older women
497 with metabolic syndrome

Attending to environmental factors

• Up to 50% 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

Barnes & Yaffe, 2011
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% cognitive inactivity/education#

Barnes & Yaffe, 2011
Natural therapies

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

Ginkgo leaves

Member of ginger family
Treatment of Alzheimer’s

• Symptomatic drugs
• Disease modifying drugs
• Non-drug treatments
Bill 70 y.o., m. architect 3C, 5GC

- Diagnosis = relief!
- Wife grateful
- Changes work duties
- Starts anti-Alzheimer Rx
- Enduring Power of Attorney ✅
- Enduring Guardianship ✅
- Will ✅ Advance Directive ✅
- Monitors driving
Bill’s story

- Establishes routine
- OT → compensatory strategies
- Regular exercise, diet
- Mental stimulation, computer training program
- Life priority decisions
  - more family time
  - golf with supportive friend
  - plans holiday abroad
- Considers drug trial
- → Positive Quality of Life
Drugs for AD

Four drugs approved
- all symptomatic, non curative

**Cholinesterase inhibitors** (boost acetyl choline)
- Aricept (donepezil)
- Exelon (rivastigmine)
- Reminyl (galantamine)

**NMDA receptor antagonist** (prevent flow of toxic chemicals into cells)
- Ebixa (memantine)
Souvenaid for AD (Nutricia)

- = multinutrient drink designed to improve synapse formation
- By precursor and supporting nutrients to act synergistically
- Some positive results

Scheltens P et al, 2009
Treatments that cure or modify pathology of Alzheimer’s disease
Amyloid plaque
Proteolytic Processing of APP Gives Rise to Aβ
Proteolytic Processing of APP Gives Rise to Aβ

sAPPβ  sAPPβ  sAPPα

Aβ  AICD  C83

Courtesy of Ron Petersen
Immunisation & Protection from Amyloid

12 Months

18 Months

18 Months immunized

1Schenk D et al, Nature 1999;400:173-77
AD Cures – graveyard

- Trimiprosate (Alzhemed)
- Flurbiprofen (tarenflurbil)
- Anti-inflammatory
- Rosiglitazone
- Statins
- Leuprolide
- Semagacestat ($\gamma$-secretase inhibitor)
- Celecoxib
- Dimebon
- Intravenous Ig
Under investigation

• Enzyme inhibitors
  – δ secretase
  – β secretase

• Immunotherapy
  – Active
  – Passive
    • antibody

• PBT2 (zinc, copper)
• Insulin nasal spray
• Tau protein (Rember)
AD Cures – graveyard or Holy Grail

• Economics of drug treatments
  – Aricept generated sales of $3.5 billion in year ending March 2009 (Reuters, 4/3/2010)
  – The market for a drug that slows or reverses Alzheimer’s could be $20 billion a year (Wall Street Journal, 5/8/2011)
Iceberg Phenomenon

- 25 yrs
- 5-10 yrs
Advances in biomarkers

- Genetics – ApoE ε4
- Cerebrospinal fluid
  - Amyloid β Protein (Aβ42) ↓
  - Tau Protein (τt and τp) ↑
- MRI scans – serial, fMRI
- SPECT scans + dopamine label
- PET Scans + amyloid ligands
  - PiB (Pittsburgh B), flurbetapir
Role of MRI in Diagnosis of Mild Cognitive Impairment and Alzheimer's Disease
PiB-PET Scans: AD vs MCI vs control

From the online newspaper of Prof Yasser Metwally
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
- Scarlet Road Study - Gantenerumab
Sydney Centre for Clinical Cognitive Research at POWH

• Recruiting (community, carer, MMSE range)
  – Referrals/questions to Lynne 9382 3733 or
  – lynne.seifman@sesiahhs.health.nsw.gov.au
“Natural therapies”
Natural therapies

- Turmeric
- DHA
- Fo-ti root
- Soy isoflavone
- Vit E & Selenium or memantine
- Folate, B6, B12
- Saffron
- Huperzine A: natural ChEI
Non-medical treatments
Cognitive training

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

Valenzuela & Sachdev (2009) Am J Geriatr Psychiatry 17(3)
Treatments of behavioural symptoms

- Carer education
- Music therapy
- Physical exercise
- Recreation
- Validation therapy
- Music
- Pet therapy
- Robotic pets
- Humour therapy
- Dance
- Children, babies

O’Connor et al, 2009; Int Psychogeriatr; 21(2):241-251
The future
If there is successful treatment for AD.....

Which part of AD journey will the cure prolong?

Cognition

Years
If there is successful treatment for AD....

Which part of AD journey will the cure prolong?

- Prevention
- Cognition

Years
Prolong early...
Prolong late...
And in meantime ... 

• Prevention message
• Better community care
• Better residential care
• Better management of behavioural and psychological symptoms of dementia (BPSD)
Research funding per $1 direct cost of care

<table>
<thead>
<tr>
<th>Condition</th>
<th>2000-01</th>
<th>2023</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>CVD</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.06</td>
<td>0.01</td>
</tr>
<tr>
<td>Dementia</td>
<td>0.01</td>
<td>0.005</td>
</tr>
</tbody>
</table>

$AUD
NHMRC funding 2010-2011

Bottom line

• Research leads promising
• Potential for AD modifying drugs
• In meantime..
  – Prevention
  – Better care
  – More research
Brain Stimulation and Cognitive Training

Recent brain stimulation research suggests that mild brain stimulation (i.e., tDCS) when given during performance of a cognitive (memory) task in a single session improves performance. Also patients who have had a stroke learn how to do certain 'hands-on' tasks better when participants receive a course of brain stimulation treatment. There is research that
Scope of CHeBA Research

- Epidemiology
  - Centenarians
  - Older twins
  - Memory and Ageing Study
- Better diagnosis
  - GPs
  - MRI scans
  - Proteomics/genomics
- Interventions
  - Drug trials for AD and for pre-AD
  - Cognitive training + exercise (SMART) + tDCS
- Nursing homes
  - SMILE study
  - Environment
For healthy brain ageing..

- Look after your brain and your body

- Centre for Healthy Brain Ageing
  [website](http://www.cheba.unsw.edu.au)

- [website](http://www.dementiaresearch.org.au)