Benefits of early detection & long-term management of Alzheimer’s disease

Henry Brodaty

Dementia around the world

- 35 million people worldwide with dementia
  - 70% in developing countries
- Set to double every 20 years to more than 100 million in 2050
  - 71% in developing countries
  - Rate of increase 3 – 4 times higher in developing countries

Projections of a tripling of world's dementia population by 2050

World Alzheimer Report, ADI, 2009

Cost of dementia


Global Cost of Dementia

- Total estimated cost worldwide US$604 billion in 2010
- If dementia were...
  - a country, it would have the world's 18th largest economy
  - a company, it would be the world's largest by annual revenue

World Alzheimer Report, ADI, 2010
Philippines

- Prevalence estimate by age group:
  - 11.5% 60-69 yrs old
  - 15.6% 70+ yrs

- People with dementia estimate by year:
  - 2005: 169,800
  - 2020: 316,300
  - 2050: 1,158,900

- Estimated cost in 2009 1270.9 (millions US$)

Detection

- 2-3 year gap between symptoms & diagnosis in primary care
- Longer for
  - Young Onset Dementia
  - Culturally and Linguistically Diverse

GP/PCP diagnosis of dementia

- 74% of people consult a GP/PCP first after noticing symptoms of cognitive decline, and ...
- 79% consider GPs/PCPs to be easily accessible\(^1\)
- GPs/PCPs are in the best position to identify dementia early
- However, GPs/PCPs miss up to 91% of mild cases\(^2,3\)

Barriers to diagnosis and management

<table>
<thead>
<tr>
<th>Patient or family</th>
<th>GP/PCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal unawareness</td>
<td>Dementia not diagnosed</td>
</tr>
<tr>
<td>Personal reluctance to seek help</td>
<td>Non referral</td>
</tr>
</tbody>
</table>

\(^{3}\) Boustani et al. J Ger Int Med 2005;20:572-7
Ten reasons for early diagnosis

1. Reversible cause possible
2. A relief!
3. Legal planning
4. Financial planning
5. Medical planning
6. Life planning
7. Work
8. Driving
9. Relations with the family
10. Medication

Reasons why early diagnosis does not occur

1. Personal unawareness
2. Personal reluctance to seek help
3. Dementia not diagnosed
4. Non referral
5. Lack of management plan
6. Medication not prescribed
7. No evidence that early diagnosis improves outcome

Dubois criteria (in brief)

- Alzheimer’s disease
  - Incorporates predementia & dementia phase
- Prodromal AD (predementia AD)
  - Clinical symptoms (eg memory loss) but they do not interfere with IADLs
  - Biomarker evidence from CSF or imaging show AD pathology

Dubois criteria (in brief)

- AD dementia
  - Cognitive symptoms interfere with IADLs, social function
  - Change in episodic memory & at least one other domain


Alzheimer’s Association criteria

- Symptoms are gradual, not sudden & represent decline from previous level
- Preclinical AD: measurable change in biomarkers & poor cognitive performance
- MCI due to AD: noticeable changes in memory/cognitive abilities but do not interfere with daily function
- Dementia due to AD: changes in at least domains & interferes with daily function

McKhann et al. Alzheimer’s & Dementia. 2011; doi:10.1016/j.jalz.2011.03.005

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 $\geq 1$ domain based on concerns of individual, knowledgeable informant or clinician
- Decline in neurocognitive performance 1-2 SDs <appropriate norms (ie between 3rd and 16th %s) on formal testing or equivalent clinical evaluation
- Cognitive deficits insufficient to interfere with independence (IADLs, like more complex tasks, paying bills, meds, preserved), but > effort, compensatory strategies or accommodation required
- Cognitive deficits not exclusively in the context of delirium and not primarily attributable to another mental disorder (e.g., major depression, schizophrenia)

**Investigations**

**Assessment: Routine investigations**

- FBC, ESR
- Clinical chemistry *including calcium*
- Thyroid function tests
- B12, folate
- CT scan of brain *(without contrast)*
- Fasting BSL, Lipids, Homocysteine
Assessment: Elective Ix
- ECG
- CXR
- EEG
- micro-urine
- fasting glucose
- serology for $, AIDS
- neuropsychological assessment
- MRI
- PET scan

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), florbetapir
**Issue is incremental gain**

- Many biomarkers have about 90% sensitivity and specificity for AD
- Question how much benefit beyond good history and basic investigations?

**Will biomarkers replace cognitive screening tests?**

- Neuropsychological tests (99%) and structural MRI (88%) were most accurate at identifying AD
- CSF (78%) and FDG-PET (81%) were less accurate
  - Did not significantly add to accuracy of neuropsychological tests or MRI
  - Especially so for those older than 75 years
**Incremental gain**

- Conversion from MCI to AD (over 3 years)
- Best single predictors
  - Right entorhinal cortex (68.5%)
  - TMT-B (64.6%)
- Best multi predictor model
  - Combination CSF, MRI and neuropsychological tests (64%)


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**Early diagnosis**

- As drug trials for AD have failed, field moving to earlier treatment
  - Patients with MCI or prodromal AD

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**Assessment is more than diagnosis**

- Deficits
- Comorbidity – physical, psychological, sensory
- Assets
- Carer
Management is more than drug treatment

Management: General Principles I
- Dementia is not global
  - (until late in the disease)
- Quality of life for person with dementia
- The hidden second patient

Management: General Principles II
The burden of being a family carer
- Psychological (e.g. depression or anxiety)
- Physical
- Financial
- Social (isolation) strain
- Use of health services
**Management: General Principles III**

- Dementing not demented
  - the evolving ever-changing picture
- Dementia - the long haul.
  GP, patient, carer & services should form a partnership for the “long haul”
- Increased vulnerability of PWD
- Liaison with other services
- Patients who can’t consent: medico-legal issues

**Management: General Principles IV**

- Enjoyment does not require memory
- Last in, first out (and vice versa)
  - What is learnt most recently is most easily forgotten
  - reverse holds - FIRST IN, LAST OUT
  - certain types of memory - music, dancing, playing games - more resistant to decay
  - aim to get most enjoyment out of each day
  - one day at a time, one activity at a time

**Management: General Principles V**

- Regression occurs in dementia
  - Skills are lost sequentially in the reverse order to which they were acquired through childhood
- Solve problems creatively, e.g. Velcro instead of buttons for dressing dyspraxia
- Adapt the environment, not the person,
  - eg secure grounds not chemical straitjackets for wandering
Management: General Principles VI

- Create a sense of importance and mastery
  - structure activities so that the affected person feels useful
  - optimise assets
  - avoid using childish motivators eg sweets
  - compliments more effective when immediate
- Families influence dementia symptoms

Management: General Principles VII

- Maintain healthy lifestyle
  - Exercise
  - Mental stimulation
  - Social engagement
- Attend to/ maintain general health
  - Medical care
  - Foot and oral health
  - Eyes, ears
  - Pain management

Why intervene with Caregivers?

- Psychosocial effects
- Effects on CGs are main predictor of nursing home placement
- CGs’ and patients’ psychological state linked

1 Brodaty & Doniken (in Dementia 4th Ed, 2010); 2 Brodaty, McGilchrist, Harris & Peters (1993); 3 Brodaty & Luscombe (1998)
Caregivers and rate of decline

- Slower cognitive decline or disease progression
  - High levels of closeness
  - Carer is spouse
  - Positive caring strategies

Norton MC et al 2009 Journal of Gerontology
Tschanz JT et al 2012 Am J Ger Psychiatry

Negative Effects of Caregiving

- Psychological (e.g. depression)
- Physical (e.g. immune function, BP↑)
- Social (e.g. isolation)
- Financial
- ↑ use of health services

Brodaty & Doniken in Dementia 4th Ed, 2010

Legal Issues

- Enduring Power of Attorney
- Enduring Guardianship
- Advance Directives
- Informed consent for medical treatment
- Capacity to drive
- Capacity to work
Enduring Power of Attorney

• PoA relates to money and estate, not health, etc
• Recommend for all persons diagnosed with dementia (and for all persons >50)
• Tests for capacity?
• EPoA applications vary by jurisdiction
• May come into effect immediately or when triggered

Enduring Guardianship

• Proxy decision maker for services, accommodation, health
• Triggered by loss of decision making capacity
• Flexible: 1 or more guardians, severally or jointly, different guardians different powers
• Prudent to arrange early in dementia
• Prudent for us all to consider this

Advance Directives

• Treatment
• Withholding treatment
• Participation in research
• Disposal of body, tissue donation at death, funeral arrangements
Informed Consent for Medical Treatment

- Person must understand
  - the nature of the treatment
  - the possible effects
  - the potential side effects
  - the alternatives
- Understanding varies with complexity
- Person must be able to communicate understanding and wishes

Informed Consent for Medical Treatment

- Dementia will affect understanding; holding information in head while weighing up pros & cons; and communication
- Loss of capacity is a point on a sliding slope
- If unable to give consent, then proxy consent
- Who can give proxy consent varies by jurisdiction. In NSW = person responsible
- If no proxy, Guardianship Tribunal may appoint Public Guardian or similar

Capacity to Drive

- Mentally incompetent can be danger to self and others
- Level of cognitive impairment poor correlation with capacity to drive
- Best test is on road
- “Co-pilot”, familiar routes only, day time only – help but not sufficient
Capacity to Drive

- All pts with dementia will lose ability at some time
- If person already obviously incompetent cancel licence immediately.
- Approach 1: cancel licence immediately
- Approach 2: graded restrictions and warning about cessation “later”
- Approach 3: send for On-road Assessment
  Note: Poor correlation between cognitive testing and driving performance
- Austroads 2012 – if dementia, cannot have unconditional licence. Notify insurance.

Capacity to Work

- Capacity vs Competency
- Capacity vs Safety
- Decision for employer usually
- May become legal matter
  – doctor, lawyer, architect
  – judge, politician

Referral to Alzheimer’s Association

- Alzheimer’s Disease Association of the Philippines
- St Luke’s Medical Center
  Medical Arts Bldg, Rm 410
  E Rodriguez Sr Avenue, Quezon City
  Philippines
  Tel/fax: +632 723 1039
  Email: info@alzphilippines.com
  www.alzphilippines.com
Current medications approved

4 drugs approved - all symptomatic
• Aricept (donepezil)
• Exelon (rivastigmine)
• Reminyl (galantamine)
• Ebixa (memantine)

Donepezil

• Licensed in Australia in 1997;
• Available on PBS 2/2001
• Statistically significant benefit in mild to moderate Alzheimer’s disease in cognitive and global outcomes
• Patents expired in Australia for donepezil, galantamine, memantine
• Rivastigmine patch a few years more
Benefits of ChEIs

- Period of modest cognitive enhancement
- Symptomatic treatments not cures
- 2 in 3 maintain baseline or improve
- Functional and behavioural benefits
- Mean 38 to 52 weeks before patients cross baseline of cognitive decline

Brain AChEIs - what differences?

- Acetyl cholinesterase inhibition - all
- Butyryl cholinesterase - rivastigmine
- Nicotinic receptors - galantamine
- Efficacy? No difference
- Side effects, may be differences
- Duration of action - about same
- In Australia donepezil has over 60% of market

Adverse effects of cholinesterase inhibitors

- Nausea
- Anorexia
- Vomiting
- Insomnia
- Dizziness
- Muscle cramps
- Nightmares
**Contraindications**
- Active peptic ulcer
- Bradyarrhythmias eg sick sinus syndrome
- Asthma?
- Previous adverse response

**Realistic expectations**
- Maintain cognition for period of time
- Eventual decline
- Responders stay about a year ahead of where they would be on placebo

**How long for?**
- Uncertain
- Nearly all trials only for 6 – 12 months
- Unethical to ask patients to be on placebo for longer than 3 months
- Open label trials indicate less institutionalisation and mortality
When to stop?

- Side effects
- Patient declining rapidly
- Not if other change occurs eg NH admission
- Benefits in nursing home study with low MMSE
- Trial reduction for 2 weeks 10mg → 5 mg
- If stepwise decline, reinstitute previous dose
- If no worse, cease for 2 weeks
- If stepwise decline, reinstitute previous dose

Benefits continued Donepezil treatment

- Double blind, RCT; moderate or severe AD
- N = 295, community dwelling
- 4 groups:
  - Donepezil discontinued + placebo memantine
  - Donepezil discontinued + active memantine
  - Donepezil continued + placebo memantine
  - Donepezil continued + active memantine
- Continued donepezil = cognitive benefits

Donepezil

- Use of donepezil in late stage dementia
- Severe AD (n = 176), double blind RCT
- Greater efficacy vs. placebo on measures of cognition & global function


Donepezil

- Withdrawal in people who show no apparent response; AWARE trial
- Mild to moderate Alzheimer’s disease
- Those who showed no benefit of donepezil and were switched to placebo performed worse in measures of cognition & behaviour cf those who continued donepezil

Johannsen et al. CNS Drugs 2006; 20 (4): 311-325

AWARE study design

Tmt difference donepezil vs. placebo
Long term benefit

• N = 565 community dwelling
• Mild to moderate AD
• Better cognition & BADLS over the first 2 years.
• No significant benefits at 3 years
  – institutionalisation (42% vs 44%; p=0.4)
  – progression of disability (58% vs 59%; p=0.4)
  – But numbers very small by 3 years


Long term benefit

• Observational study; N = 135 probable AD
• 1 year follow-up
• Outcomes: cognitive & functional status, nursing home admission & death


Long term benefit

• Probable AD, N = 943
• Time to NH admission & death
• Mean follow-up = 62.3 (35.8) months
• ChEls delayed NH admission
• ChEls + memantine increased this delay
• No effect on time to death

Cohort 1

Cohort 2

**Benefits on BPSD**
- Apathy
- Hallucinations
Cochrane review 2012 (Birks J)

- The three cholinesterase inhibitors are efficacious for mild to moderate AD
- Despite the slight variations in the mode of action of the three cholinesterase inhibitors no evidence of any differences between them with respect to efficacy
- One large trial shows fewer adverse events with donepezil vs (oral) rivastigmine (Bullock R et al, 2001)

Memantine

- NMDA receptor antagonist
- Less glutamate and Ca** excitotoxicity
- Approved for moderately severe to severe AD
- Less decline in cognition and function compared to placebo
- Benefits on agitation, aggression, hallucinations, cluster
- Donepezil + Memantine > Donepezil + PBO (Tariot)

Disease modifying drugs for AD

- None yet shown to be effective for AD or MCI
Failed or withdrawn AD drug Rx

- Bapineuzumab (Janssen/Pfizer/Wyeth)
- Solanezumab (Lilly)
- Ponezumab (Pfizer)
- Active immunisation ACC-001 (Elan)
- Semagecastat
- Dimebon
- Tramiprosate
- Rosiglitazone
- Leuprolide
- Anti-inflammatory
- Celecoxib
- Statins

Drugs Rx for AD under trial

- β-secretase inhibitor (Merck)
- Histamine3 antagonist (Servier)*
- Curcumin
- PBT-2 (Prana)
- Rember (Tau therapeutics)*
- Intranasal insulin
- Gantenerumab (Roche)*
- IV IG (Baxter)
- No data
- Etanercept (Enabril)

Souvenaid

- Nutriceutical
- Combination of vitamins and lipids
- 2 trials (12w) and 24wks) show improvement in memory in mild AD
Nutrient | Amount in Souvenaid NHMRC recommend NHMRC upper level of daily intake
---|---
UMP | 625 mg
Choline | 400 mg
Phospholipids | 106 mg
DHA+EPA | 1,500 mg
Folic Acid | 400 μg
Vitamin B6 | 1 mg
Vitamin B12 | 3 μg
Vitamin C | 80 mg
Vitamin E | 40 mg
Selenium | 60 μg

Non-pharmacological approaches to treatment of dementia

Non-pharmacological approaches to prevention
- Exercise
- Computer cognitive training
- Combined computer cognitive training & exercise
- Diet
- Cholesterol lowering drugs - statins
- Antihypertensive treatment
- Diabetes prevention
- Head injury
- Social engagement

Non-pharmacological approaches to prevention
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**50% of PAR for AD from environmental factors?**

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

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**Less Strong Evidence**

**Risk factors**
- Cardiovascular factors – hi BP, AF, high cholesterol
- Other genetic factors
- Diabetes
- Obesity, inactivity

**Protectors**
- Education
- Medications?
- Diet/ Supplements?
- Lifestyle
  - Physical exercise
  - Diet
  - Alcohol?

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**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  \(\downarrow\) prevalence by 20%
  - 5 yrs  \(\downarrow\) prevalence by 50%
Preventative/ treatment strategies

- Physical exercise
  - ≥150 mins/ week walking
  - More is better – puff & sweat
  - Weights as well as aerobic
- Mental exercise
  - Computer cognitive training
  eg Lumosity, Posit Science, MindFit

The power of physical activity

Hippocampus

Erickson et al., 2011

Alzheimer’s Australia

- [http://yourbrainmatters.org.au](http://yourbrainmatters.org.au)
Prevention

- Physical exercise
- Avoid or treat hypertension
- Mental stimulation
- Diet
- Avoid or treat high cholesterol
- Avoid Obesity
- Avoid type 2 Diabetes
- Avoid head injury
- No smoking

Danger of over-treating

- hypertension
- obesity

Can Ginkgo biloba prevent dementia?

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

DeKosky et al., JAMA. 2008; 300(19):2253-2262
**Other natural therapies**
- Turmeric
- DHA
- Brahmi
- Fo-ti root
- Soy isoflavone
- Vit E & Selenium or memantine
- Folate, B6, B12
- Saffron
- Huperzine A: natural ChEI

**Caregiver interventions**
- Counselling
- Training courses
  - Carers therapists
- Tailored activity program

**The Dementia CGs’ Program¹**
- Ten day program for patients and CGs
- Intensive, comprehensive
- Psychological counselling
- Information, education
- Skills training
- Involvement of patient
- Involvement of extended family
- Follow-up contact and telephone booster sessions over one year

¹Brodaty and Gresham (1989), Brit Med J; 299: 1375-1379
Dementia Carers Program: survival at home over 7 years

Odds ratio 5.03, 1.73-14.7

Meta-Analysis of Psychosocial Interventions (Brodaty et al. 2003)

- 30 studies (34 interventions) included
- Setting: home or non-institutional
- Participants: Informal CGs
- Primary outcome measures:
  - Psychological morbidity and burden

Meta-Analysis of Psychosocial Interventions (Brodaty et al. 2003)

- Significant benefits for
  - CG psychological distress
  - knowledge
  - any main CG outcome
  - patient mood
- No difference to CG burden
- 4 studies showed delayed NH admission
Meta-Analysis of Psychosocial Interventions (Brodaty et al. 2003)

Common elements of successful programs:
- Involvement of patient as well as CG
- Involvement of the whole family
- Intervention of sufficient duration and intensity
- Anecdotally, having consistency and flexibility when helping the CG

The three country study: Aricept + counselling

Manchester, UK - Alistair Burns

New York, USA - Mary Mittelman

Sydney, Australia - Henry Brodaty

3 Country Study

- 156 CR-CG dyads, ≈ 50+ per site
- RCT, all patients on donepezil
- 50% of CGs receive 1# of individual and 4# of family counselling
- Follow-up 3 monthly for 12 m and then 6 monthly for further 12 months
Counselling intervention for carers

Results: CG depression

Mittelman, Brodaty, Burns (2008) AJGP

BDI II Score

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<tr>
<th></th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>18</th>
<th>24 mths</th>
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<td>CG</td>
<td>10</td>
<td>9</td>
<td>8</td>
<td>7</td>
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Control group
Counselling group
5 sessions of counselling

The Three Country Study (3CS)
Participants still at home in AUS, UK & USA (≤ 5y)

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<tr>
<th></th>
<th>Treatment</th>
<th>At Home</th>
<th>control</th>
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<tbody>
<tr>
<td>AUS</td>
<td>13 (50%)</td>
<td>6 (23%)</td>
<td>7 (50%)</td>
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<tr>
<td>UK</td>
<td>12 (44%)</td>
<td>14 (58%)</td>
<td>10 (75%)</td>
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<tr>
<td>USA</td>
<td>19 (73%)</td>
<td>20 (77%)</td>
<td>17 (75%)</td>
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χ²: df=1, p=0.044
χ²: df=1, n.s.

Long term management

- Whose responsibility – in Australia GP, neurologist have little or no contact after diagnosis
- If specialist contact than geriatrician or psychogeriatrician
- Long haul – partnership between patient, family, GP, specialists, community services
Long term management

- Continued support for family and patient
- Management of BPSD
- Community care
- Respite care
- Placement in residential aged care facility

Questions

- [www.dementiaresearch.org.au](http://www.dementiaresearch.org.au)
- [www.alzheimers.org.au](http://www.alzheimers.org.au)
- [www.alz.co.uk](http://www.alz.co.uk)
- [h.brodaty@unsw.edu.au](mailto:h.brodaty@unsw.edu.au)