Facts, Fiction, Snake Oil and Wishful Thinking: an update on dementia research and practice

Susan Kurrle

Geriatrician

Hornsby Ku-ring-gai and Eurobodalla Health Services
Curran Professor in Health Care of Older People,
Faculty of Medicine, University of Sydney

susan.kurrle@sydney.edu.au
Dementia

• “de mens” – without mind

• progressive irreversible syndrome of impaired memory, intellectual function, personality and behaviour, causing significant impairment in function
Types of dementia

- Alzheimer’s Disease
- Vascular Dementia
- “Mixed” Dementia (Alzheimer’s Disease and Vascular Dementia)
- Dementia with Lewy Bodies
- Frontotemporal Dementia (aka Frontotemporal Lobar Degeneration)
- Parkinson’s Disease with Dementia
- Others – CJD, ARBD
Dementia in Australia

• **2017**: 414,000 people with dementia
• **2050**: 900,000 people with dementia
• approx 1800 new cases per week diagnosed
• at age 65: 1 in 12 people have dementia
• at age 80: 1 in 4 people have dementia
• At age 90: 1 in 2 people have dementia
• 2\textsuperscript{nd} highest cause of death after heart disease
• Highest cause of disability in >65 years group

• approx 25,000 under age 65 with dementia
Is dementia inevitable if we live long enough?
Madame Jeanne Calment

- Took up fencing, aged 85
- Rode bicycle till 100
- Lived alone till 110
- Port wine, 2 cigs/day, 1kg dark chocolate every week
- Gave up smoking at 120
- Poured olive oil on food and rubbed onto her skin
- Outlived husband, child and grandchildren
- Died 122 without dementia
Modifiable risk factors for developing AD

- Up to 1/3 of cases of Alzheimer’s disease are related to 7 modifiable risk factors:
  - 4% type II diabetes
  - 7% midlife obesity
  - 7% low cognitive activity
  - 8% midlife hypertension
  - 11% depression
  - 11% smoking
  - 21% physical inactivity

- Combined adjusted risk 31%

Barnes 2011; Norton 2014
Non-modifiable risk factors for developing AD

• older age: 9% aged over 65 years, 22% aged over 80 years
• Down syndrome (APP)
• family history
• other genetic factors:
  – ApoE4 allele (risk for late onset AD)
  – Mutations – Presenilin 1,2, TREM2 variants
Other possible risk factors for AD

- head injury (chronic traumatic encephalopathy)
- cerebrovascular disease
- ischaemic heart disease
- environmental factors
- excess alcohol intake
- benzodiazepine use
- smaller head size
- low Vit D

Llewelyn 2010; Billioti de Gage 2012; Littlejohns 2014
Prevention: what can we do?

• Look after cardiovascular health

• Exercise
  – physical
  – mental

• Social interaction

• Diet

• Habits

• (Medication and supplements)
Prevention: does it work?

• FINGER study (Lancet 2015):

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

• Findings from this study suggest that a multi domain intervention may improve or maintain cognitive functioning in at risk older people

Ngandu 2015
Prevention of dementia: the FINGER study

- 1260 people aged 60 to 77 with a CAIDE score of 6 or more indicating increased risk for developing dementia
- Randomised to control (general health advice) or intervention (nutritional advice, exercise, cognitive training, monitoring of metabolic and vascular risk factors)
- Adherence of between 85% and 100% to the 4 intervention domains
- At 2 year follow up there was a significant improvement in overall cognition (p=0.030) and also in executive functioning and processing speed

Ngandu 2015
Prevention: does it work?

• Evidence from the Framingham Study (US), Rotterdam study (The Netherlands), the Kungsholmen study (Sweden), CFAS study (UK) and a study from Denmark, all comparing 2 cohorts of older people a decade or more apart, indicates a stable prevalence of dementia and a decreasing incidence of dementia

• Thought to be due to amelioration of risk factors, and increased education

• HOWEVER the pre-DIVA study from the Netherlands did not show a reduction in dementia over a 6 year period with attention to cardiovascular risk factors

Schrijvers 2012; Qiu 2013; Christenson 2013; Matthews 2016; Moll van Charante 2016
Prevention

• Physical Exercise
  – Aerobic exercise: at least 30 mins 5X per week,
  – resistance training: weights, therabands
  – balance training: Tai Chi, balance exercises

  – Regular aerobic exercise improves cognitive function, stimulates BDNF, increases brain size, and decreases amyloid in the brain and body

Erickson 2011; Alz Aust 2013
Resistance exercises
Prevention

• Mental exercise
  – Higher level education
  – Ongoing complex mental activity – new language, musical instrument, chess, computer games

ACTIVE 2002; Fratiglioni 2000
Prevention

• Social activity: increase social interaction after retirement: U3A, Men’s Shed
  – (Get married - “living in a couple relationship is one of the most intense forms of social and intellectual stimulation .....”)

Hakansson 2009
Prevention

• Habits:
  – Stop smoking
  – Lose weight
  – Moderate alcohol intake

• Diet
  – Avoid high fat diets
  – Mediterranean diet (moderate to good adherence)
  – Curries containing curcumin (turmeric)
  – Concept of “culinotherapy”

Scarmeas 2009: Tsivgoulis 2013
The culinotherapy approach to prevention

- regular fish intake (omega-3 fatty acids)
- regular curries containing curcumin
- alcohol (resveratrols) 2-3 drinks/day
- dark chocolate (resveratrols)
- green tea (polyphenols)
- Mediterranean diet:
  - “avocados and olive oil”
  - Fresh fruit and vegetables
  - Legumes, complex carbohydrates, lower red meat intake

Scarmeas 2009; Tsivgoulis 2013; Morris 2015
Prevention

• Hormone replacement therapy
  – Epidemiological and in vitro studies indicate that oestrogen is likely to be protective against Alzheimer’s disease
  – WHIMS study showed increased risk of AD (and breast cancer) in older women
  – Later studies indicate HRT from menopause decreases mortality, heart disease (CCF and IHD) with no increase in cancer, VTE, stroke

• Nonsteroidal anti inflammatory drugs

• Vitamins and supplements
  – B group vitamins – slow brain atrophy
  – Vit D – deficiency assoc with cognitive impairment

Douaud 2013; Littlejohns 2014; Schierbeck 2012
Research results

• Cause of AD still unknown
• Most “research breakthrough” headlines relate to mice and rat populations
• Multiple (> 100) negative trials at Phase 3 levels in humans
• Aducanamab and Anavex 2-73 in trials in Aust
• Positive results:
  – Vit E 2000 IU daily slows functional decline in AD
  – Exercise delays functional decline in dementia

Dysken 2014
Snake Oil

• Etanercept using para-spinal injection approach
  – TNF alpha blocking agent (anti-inflammatory)
  – RCT of 41 people with mild to mod AD using 50mg etanercept weekly by subcut injection
  – Greater rate of decline in placebo group

• Coconut oil (caprylic acid)
  – Anecdotal evidence only for temporary benefit (effect of ketones as brain fuel)
Wishful thinking

• Ultrasound to the brain to clear amyloid – works well in mice (with thin skulls)
• “Young” blood for Alzheimer’s disease (in mice)
Evidence based care for people with dementia

- First evidence based guidelines developed
- Approved by NHMRC so considered “gold standard”
- 109 recommendations covering dementia from diagnosis to death, in all settings
- Released March 2016

Examples of recommendations:

### Care

<table>
<thead>
<tr>
<th>EBR</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>People with dementia living in the community should be offered <strong>occupational therapy</strong> interventions which should include: environmental assessment and modification to aid independent functioning; prescription of assistive technology; and tailored intervention to promote independence in activities of daily living which may involve problem solving, task simplification and education and skills training for their carer(s) and family.</td>
</tr>
<tr>
<td>68</td>
<td>People with dementia should be strongly encouraged to <strong>exercise</strong>. Assessment and advice from a physiotherapist or exercise physiologist may be indicated.</td>
</tr>
<tr>
<td>103</td>
<td>PP</td>
</tr>
<tr>
<td>104</td>
<td>EBR Low</td>
</tr>
<tr>
<td></td>
<td>Health and aged care professionals should provide carers and families with information regarding how to join a mutual support group. Individual preferences for group composition may vary and groups of the preferred composition should be available.</td>
</tr>
</tbody>
</table>
LIVING WELL WITH DEMENTIA AND REHABILITATION SERVICES

People with dementia will benefit from maintaining a healthy and active lifestyle to contribute to overall health and wellbeing.

This includes:

- doing regular exercise
- maintaining a healthy diet
- regularly monitoring weight and seeking help if there are changes in weight
- maintaining good oral health through regular dental appointments
- keeping engaged in activities that are meaningful and enjoyable
- maintaining a regular routine
- Remaining socially engaged and connected
- managing other health conditions (comorbidities).

A multidisciplinary care team which specialises in providing services for people with dementia (involving a medical practitioner, nurse and allied health staff) is best placed to provide a comprehensive assessment and treatment plan.

QUESTIONS TO ASK ABOUT A HEALTHY LIFESTYLE

- What can I do to remain as active and independent as possible?
- How can I create a safe home environment?
- What activities will help me maintain fitness, strength, balance and flexibility?
- What should I do if I have put on weight or lost weight?
- How do I maintain good oral health?

Many treatments have been trialled to reduce the symptoms of dementia. However, while some may be heavily marketed, the scientific evidence does not necessarily support recommending their use:

- Brain training programs aim to reduce decline in memory and thinking skills. Overall, the current research evidence does not show that regular use of these programs leads to better cognitive skills or levels of independence.
- Nutritional drinks are currently being investigated to reduce the symptoms of mild cognitive impairment and dementia, of which one, at the time of publication (Souvenaid®) is marketed in Australia. There is currently insufficient evidence to recommend the routine use of Souvenaid® in people with mild Alzheimer’s disease. Souvenaid® should not be recommended for people with moderate or severe Alzheimer’s disease.
1. When patient or family raise concerns about memory/cognition, do not dismiss as “old age”

2. Be alert to cognitive decline in older patients especially those aged 75+ - routinely ask about difficulties

3. Take history regarding cognition and function from informant
   a. Clinical history – onset, progression, medications, other illnesses, behavioural & psychological symptoms
   b. Interview informant, assess carer needs
   c. Activities of daily living (ADL), instrumental ADLs, mood, driving, safety

4. Assess cognition if any indication or suspicion of impairment
   a. MMSE\(^\text{^A}\) and Clock Drawing Test, GPCOG\(^\text{^B}\) or RUDAS\(^\text{^C}\) (for culturally and linguistically diverse groups)
   b. If uncertain, repeat over time

5. Conduct mental state and physical examination
   a. Look for specific conditions that mimic dementia (depression, delirium, drugs) or that can aggravate dementia e.g. cardiac failure, use of anti-cholinergic drugs
   b. Check nutrition, hygiene, visual or hearing impairment

6. Investigate for causes of cognitive decline
   a. Rule out rare, but reversible causes e.g. abnormal thyroid, calcium or Vit B12; tumour

7. Diagnose cause - exclude depression and delirium, diagnose type of dementia
   a. Type of dementia – 90% Alzheimer’s, vascular or mixed dementia; then Lewy body and frontotemporal dementia

8. Refer to specialist if ... unsure of diagnosis; patient is young or atypical; symptoms and signs are atypical; psychotic or severe behavioural disturbance occur; multiple, complex co-morbidities exist; or considering medication

9. Inform patient and family of diagnosis, management plan and prognosis

10. Discuss key issues with patient and family
    a. Legal issues – Enduring Power of Attorney, Enduring Guardianship, advance care planning, driving and work - particularly for licensed machinery operators
    b. Medication for Alzheimer’s if appropriate
    c. Lifestyle – regular exercise, mental stimulation, establish routine
    d. General health – blood pressure, other health conditions

11. Develop care plan (include legal/financial matters) and make follow-up appointments

12. Refer patient and family for further information and support to Alzheimer’s Australia (Phone 1800 100 500 National Dementia Help Line) and to community services

13. Manage physical and psychological co-morbidities and maintain optimal health – be alert to delirium

14. Regularly review care plan

\(^A\) Mini Mental State Examination \(^B\) General Practitioner Assessment of Cognition \(^C\) Rowland Universal Dementia Assessment Scale
# 14 Essentials for Good Dementia Care in General Practice

1. When patient or family raise concerns about memory/cognition, do not dismiss as “old age”
2. Be alert to cognitive decline in older patients especially those aged 75+ - routinely ask about difficulties
3. Take history regarding cognition and function from informant
   - a. Clinical history – onset, progression, medications, other illnesses, behavioural & psychological symptoms
   - b. Interview informant, assess carer needs
   - c. Activities of daily living (ADL), instrumental ADLs, mood, driving, safety
4. Assess cognition if any indication or suspicion of impairment
   - a. MMSE$^\text{a}$ and Clock Drawing Test, GPCOG$^*$ or RUDAS$^*$ (for culturally and linguistically diverse groups)
   - b. If uncertain, repeat over time
5. Conduct mental state and physical examination
   - a. Look for specific conditions that mimic dementia (depression, delirium, drugs) or that can aggravate dementia e.g. cardiac failure, use of anti-cholinergic drugs
   - b. Check nutrition, hygiene, visual or hearing impairment
6. Investigate for causes of cognitive decline
   - a. Rule out rare, but reversible causes e.g. abnormal thyroid, calcium or Vit B12; tumour
7. Diagnose cause - exclude depression and delirium, diagnose type of dementia
   - a. Type of dementia – 90% Alzheimer’s, vascular or mixed dementia; then Lewy body and frontotemporal dementia
8. Refer to specialist if ... unsure of diagnosis; patient is young or atypical; symptoms and signs are atypical; psychotic or severe behavioural disturbance occur; multiple, complex co-morbidities exist; or considering medication
9. Inform patient and family of diagnosis, management plan and prognosis
10. Discuss key issues with patient and family
    - a. Legal issues – Enduring Power of Attorney, Enduring Guardianship, advance care planning, driving and work - particularly for licensed machinery operators
    - b. Medication for Alzheimer’s if appropriate
    - c. Lifestyle – regular exercise, mental stimulation, establish routine
    - d. General health – blood pressure, other health conditions
11. Develop care plan (include legal/financial matters) and make follow-up appointments
12. Refer patient and family for further information and support to Alzheimer’s Australia (Phone 1800 100 500 National Dementia Help Line) and to community services
13. Manage physical and psychological co-morbidities and maintain optimal health – be alert to delirium
14. Regularly review care plan

---

$^\text{a}$ Mini Mental State Examination  
$^*$ General Practitioner Assessment of Cognition  
$^*$ Rowland Universal Dementia Assessment Scale
Legal issues

• Planning in advance:
  – Enduring power of attorney
  – Enduring guardianship
  – Advance care directive (living will)

• Working:
  – Consider simpler tasks
  – Work part time and retire

• Driving:
  – People with diagnosis of dementia may continue to drive but need to notify RMS and have a conditional or restricted licence
  – On road tests probably the most reliable indication of driving ability (NRMA will do these)
1. When patient or family raise concerns about memory/cognition, do not dismiss as “old age”

2. Be alert to cognitive decline in older patients especially those aged 75+ - routinely ask about difficulties

3. Take history regarding cognition and function from informant
   a. Clinical history – onset, progression, medications, other illnesses, behavioural & psychological symptoms
   b. Interview informant, assess carer needs
   c. Activities of daily living (ADL), instrumental ADLs, mood, driving, safety

4. Assess cognition if any indication or suspicion of impairment
   a. MMSE\(^\text{†}\) and Clock Drawing Test, GPCOG\(^*\) or RUDAS\(^\text{‡}\) (for culturally and linguistically diverse groups)
   b. If uncertain, repeat over time

5. Conduct mental state and physical examination
   a. Look for specific conditions that mimic dementia (depression, delirium, drugs) or that can aggravate dementia e.g. cardiac failure, use of anti-cholinergic drugs
   b. Check nutrition, hygiene, visual or hearing impairment

6. Investigate for causes of cognitive decline
   a. Rule out rare, but reversible causes e.g. abnormal thyroid, calcium or Vit B12; tumour

7. Diagnose cause - exclude depression and delirium, diagnose type of dementia
   a. Type of dementia – 90% Alzheimer’s, vascular or mixed dementia; then Lewy body and frontotemporal dementia

8. Refer to specialist if ... unsure of diagnosis; patient is young or atypical; symptoms and signs are atypical; psychotic or severe behavioural disturbance occur; multiple, complex co-morbidities exist; or considering medication

9. Inform patient and family of diagnosis, management plan and prognosis

10. Discuss key issues with patient and family
    a. Legal issues – Enduring Power of Attorney, Enduring Guardianship, advance care planning, driving and work - particularly for licensed machinery operators
    b. Medication for Alzheimer’s if appropriate
    c. Lifestyle – regular exercise, mental stimulation, establish routine
    d. General health – blood pressure, other health conditions

11. Develop care plan (include legal/financial matters) and make follow-up appointments

12. Refer patient and family for further information and support to Alzheimer’s Australia (Phone 1800 100 500 National Dementia Help Line) and to community services

13. Manage physical and psychological co-morbidities and maintain optimal health – be alert to delirium

14. Regularly review care plan

\(^\text{†}\) Mini Mental State Examination  \(^*\) General Practitioner Assessment of Cognition  \(^\text{‡}\) Rowland Universal Dementia Assessment Scale
Effect of treatments on functional decline in dementia

<table>
<thead>
<tr>
<th>Intervention approach</th>
<th>Number of studies (participants)</th>
<th>SMD (95% CI)</th>
<th>SMD (95% CI)</th>
<th>Quality of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonpharmacological approach</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>6 (289)</td>
<td>0.68 (0.08 to 1.27)</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Dyadic intervention</td>
<td>8 (988)</td>
<td>0.37 (0.05 to 0.69)</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Psychological treatments</td>
<td>2 (313)</td>
<td>-0.13 (-0.35 to 0.09)</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Case management</td>
<td>3 (318)</td>
<td>-0.03 (-0.25 to 0.19)</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Music therapy</td>
<td>6 (195)</td>
<td>0.05 (-0.23 to 0.34)</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Cognitive stimulation therapy</td>
<td>4 (260)</td>
<td>0.21 (-0.05 to 0.47)</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Cognitive training</td>
<td>4 (107)</td>
<td>0 (-0.38 to 0.38)</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacological approach</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donepezil</td>
<td>3 (733)</td>
<td>0.18 (0.03 to 0.32)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Galantamine</td>
<td>3 (1422)</td>
<td>0.15 (0.04 to 0.25)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>1 (535)</td>
<td>0.19 (0.02 to 0.36)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Memantine</td>
<td>5 (1773)</td>
<td>0.11 (0.02 to 0.21)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Latrepirdine</td>
<td>3 (1243)</td>
<td>0.06 (-0.06 to 0.17)</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Melatonin</td>
<td>1 (86)</td>
<td>-0.15 (-0.58 to 0.27)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Selegiline</td>
<td>7 (810)</td>
<td>0.27 (0.13 to 0.41)</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Nimodipine</td>
<td>3 (1228)</td>
<td>0.12 (0.00 to 0.23)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td><strong>Alternative therapies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huperzine A</td>
<td>2 (70)</td>
<td>-1.48 (0.95 to 2.02)</td>
<td>Very low</td>
<td></td>
</tr>
<tr>
<td>Gingko Biloba</td>
<td>7 (2530)</td>
<td>0.36 (0.28 to 0.44)</td>
<td>Very low</td>
<td></td>
</tr>
<tr>
<td>Vitamin B sup</td>
<td>3 (481)</td>
<td>0.13 (-0.05 to 0.31)</td>
<td>Moderate</td>
<td></td>
</tr>
</tbody>
</table>

The effect of different treatment approaches on activities of daily living function in people with dementia. Laver 2016
Current treatment recommendations for Alzheimer’s disease

• Physical exercise – aerobic and resistance
• Mental exercise
• Vit E
• Support and education for carers
• Symptomatic treatment:
  – Cholinesterase inhibitors – donepezil, rivastigmine, galantamine for mild to moderate Alzheimer’s disease
  – Memantine for moderate to moderately severe Alzheimer’s disease
Current treatment recommendations for Alzheimer’s disease

• Behavioural and psychological symptoms of dementia (BPSD):
  – Non medication interventions should be used before medications are tried
  – Address environmental factors
  – Address unmet needs such as pain, hunger, boredom, constipation
  – If pain is suspected, consider use of analgesia using a stepped approach
    • Analgesics for agitation due to unrecognised/untreated pain eg regular paracetamol, oral morphine (ordine)
  – Consider use of music, massage, exercise (walking)
Current treatment recommendations for Alzheimer’s disease

• Behavioural and psychological symptoms of dementia (BPSD):
  – Citalopram for agitation
  – Antidepressants for depression eg citalopram, venlafaxine
  – Risperidone for psychotic symptoms (hallucinations and delusions) for up to 12 weeks, but increased risks of stroke and death
  – Avoid typical antipsychotics (haloperidol or droperidol) if any suggestion of Dementia with Lewy Bodies
  – Avoid anticholinergic drugs eg olanzapine
Common physical problems in dementia

• Conditions that are significantly more common in people with dementia:
  – Epilepsy – 7 times as common
  – Falls – 3 times as common
  – Delirium – 5 times as common
  – Malnutrition – 2 times as common
  – Dental disease – 2 times as common
  – Incontinence – 3 times as common
  – Visual problems – 3 times as common
  – Sleep problems – 2 times as common

Kurrle 2012
Caring for Cognitive Impairment - Commit to high quality care for people with cognitive impairment in hospital, including the prevention, recognition and treatment of delirium

Cognitive impairment including delirium or dementia are common among older people admitted to hospital but are frequently missed or misdiagnosed increasing their risk of harm. Delirium can be prevented with the right care and harm minimised if cognitive impairment is identified and acted on early. Commit to caring for cognitive impairment and also learn how to prepare for the new cognitive impairment actions in the draft version 2 of the National Safety and Quality Health Service Standards. We can all make a difference.

1,499 individuals have committed to Caring for Cognitive Impairment

160 hospitals on board
Useful websites

14 Essentials

Clinical Practice Guidelines for People with Dementia
Consumer Companion Guide to Guidelines
Thank you