Dementia: great expectations
Hope and realism

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UNSW

Never Stand Still | Medicine

DCRC
Dementia Collaborative Research Centres

CHeBA
Healthy Brains Positive Ageing

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NHMRC National Institute for Dementia Research (NNIDR)

Today's topics

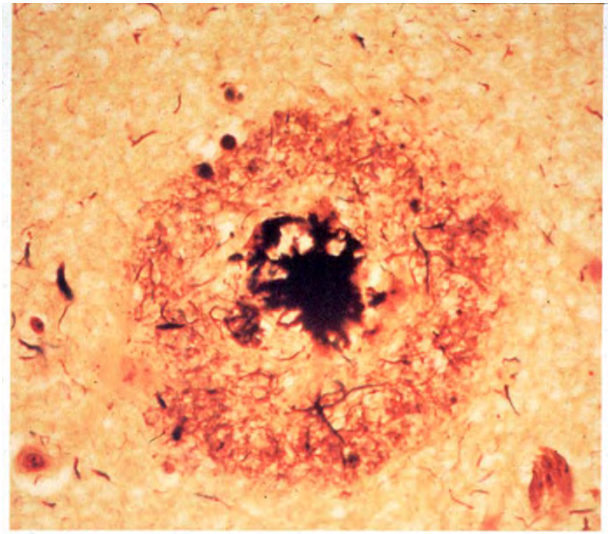
- Terminology
- Cause of AD
- Why this is important
- Diagnosis
- Prevention
- Drug treatment of AD – the silver bullet
- Behavioural and Psychological Symptoms
- Conclusions

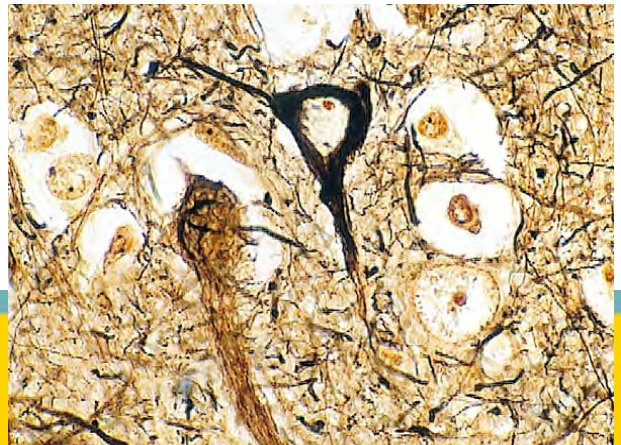
Let's get our terms straight

- 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 Aβ protein → clumps → toxic to brain → plaques
- Phosphorylated tau → paired helical filaments → NFTs
- Chemicals in brain ↓ esp ACh





The cause of AD??

- Make excess Aβ protein
  - Familial AD, mutations in APP, PSEN1 or 2
  - Onset in 40s, 50s.
- Decreased clearance of β- 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

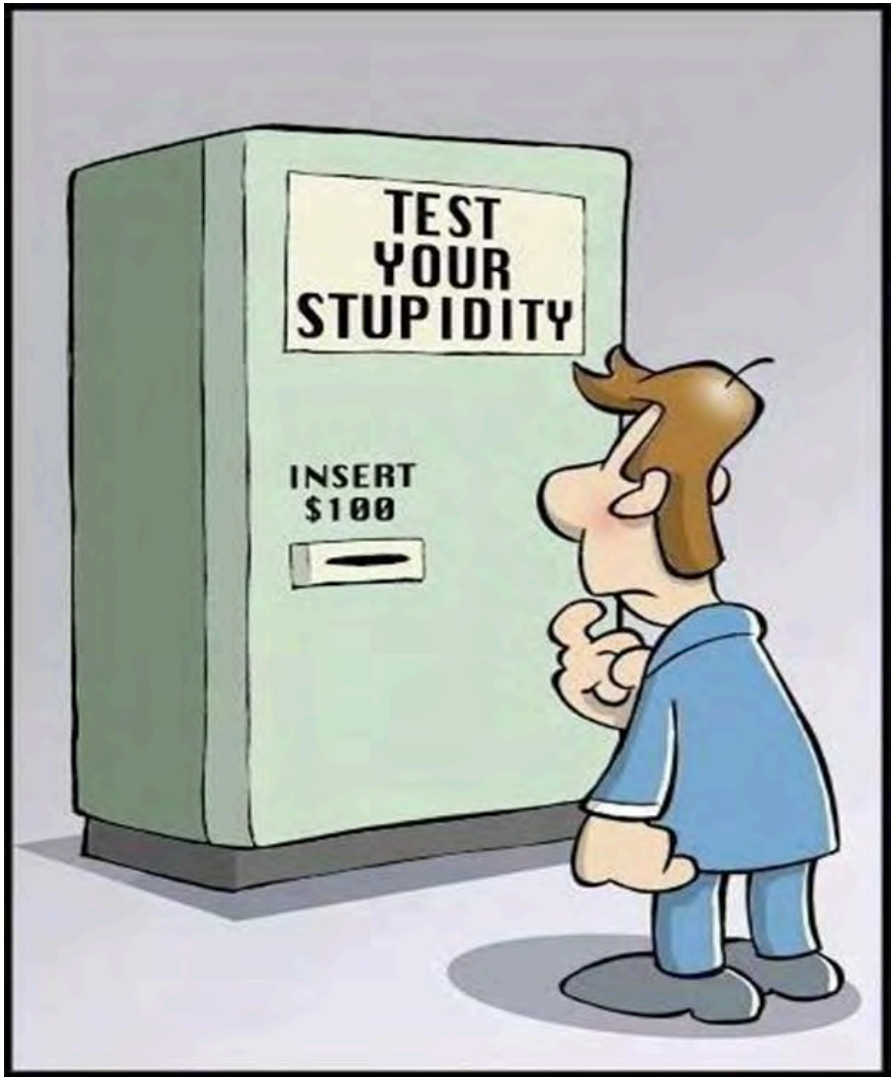
Why dementia is important in Australia?

- 413,000 in 2017 → 1.1 million by 2056 [1]
- 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% ↓ nº of people ≥ 65 developing dementia → save $5.7b from 2016-25 & $120.4b by 2056
- 28,000 under 65 years of age [2]
- 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

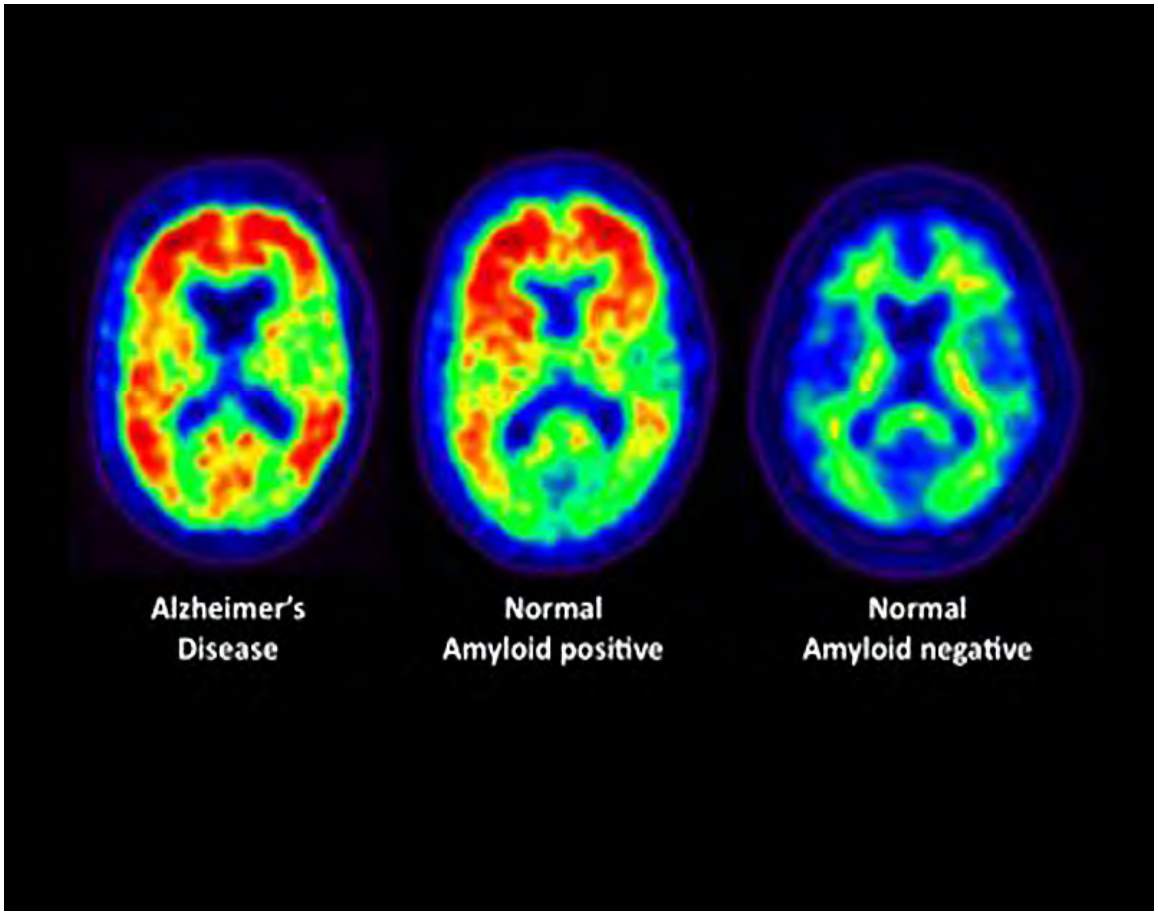
- 2-3 year gap from Sx to Dx
- 50% of (mild) dementia undiagnosed in GP
- DTA, AA, LaTrobe and DCRC ‘Timely Diagnosis’
  - Aim to reach 5000 GPs
  - Face-face or online

Diagnosis: the revolution

Tradition: History + Examination + Tests → 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[1]: delay AD onset by…
  - 2 years, ↓ prevalence by 20%
  - 5 years, ↓ prevalence by 50%

[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

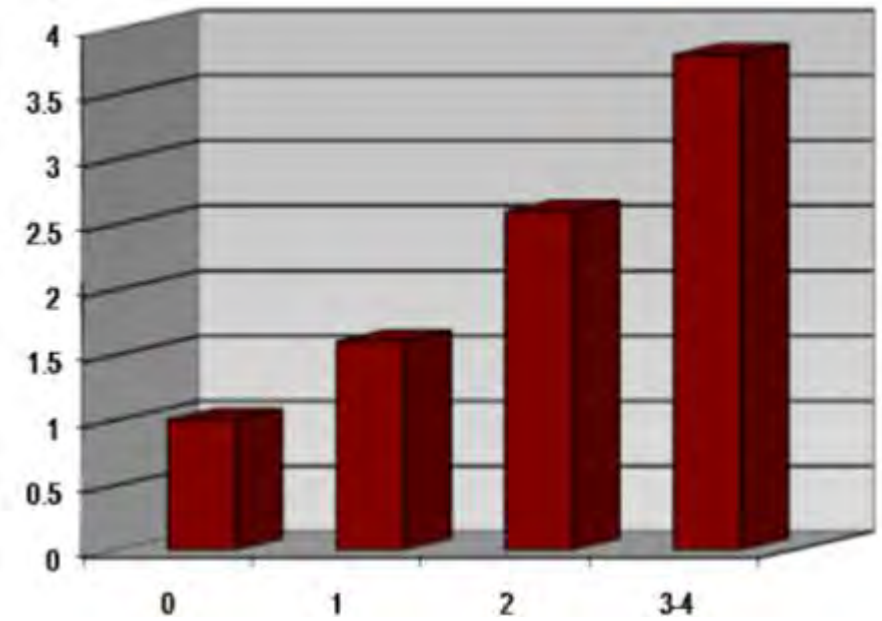
- Look after your heart
- Be physically active
- Mentally challenge your brain
- Follow a healthy diet
- Enjoy social activity

yourbrainmatters.org.au

Dosage effect

As cardiovascular risk factors accumulate, AD dementia risk increases

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



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[1]**
- **Statins linked to reduced AD risk – differences by sex, race & statin [2]**

[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**
- **≥ 3x per week; >150 min/wk, e.g. Perth Study[3]**
- **Combine with social and mental activity better?**

Denkinger et al. *Z Gerontol Geriat 2012*; 45:11–16 DOI 10.1007/s00391-011-0262-6
Fiatarone Singh MA et al *JAMDA* 2014;15:873-80; Lautenschlager N, JAMA 2008

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 evident[1]
- Results suggest complex patterns of mental activity in the early, mid- and late-life stages are associated with ↓ dementia incidence[1]
- Results held when covariates in source studies were controlled for[2]

[1]Valenzuela MJ. Sachdev P. (2006). Psychol Med. 36(4): 441-454;
[2]Valenzuela MJ. Sachdev P. (2006) Psychol Med. 36(8): 1065-1073

Cognitive training

- **Systematic review of RCTs with longitudinal follow-up (>3mths) in healthy elderly[1]**
  - **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 dementia[2]**
  - **11 RCTs, no benefit**

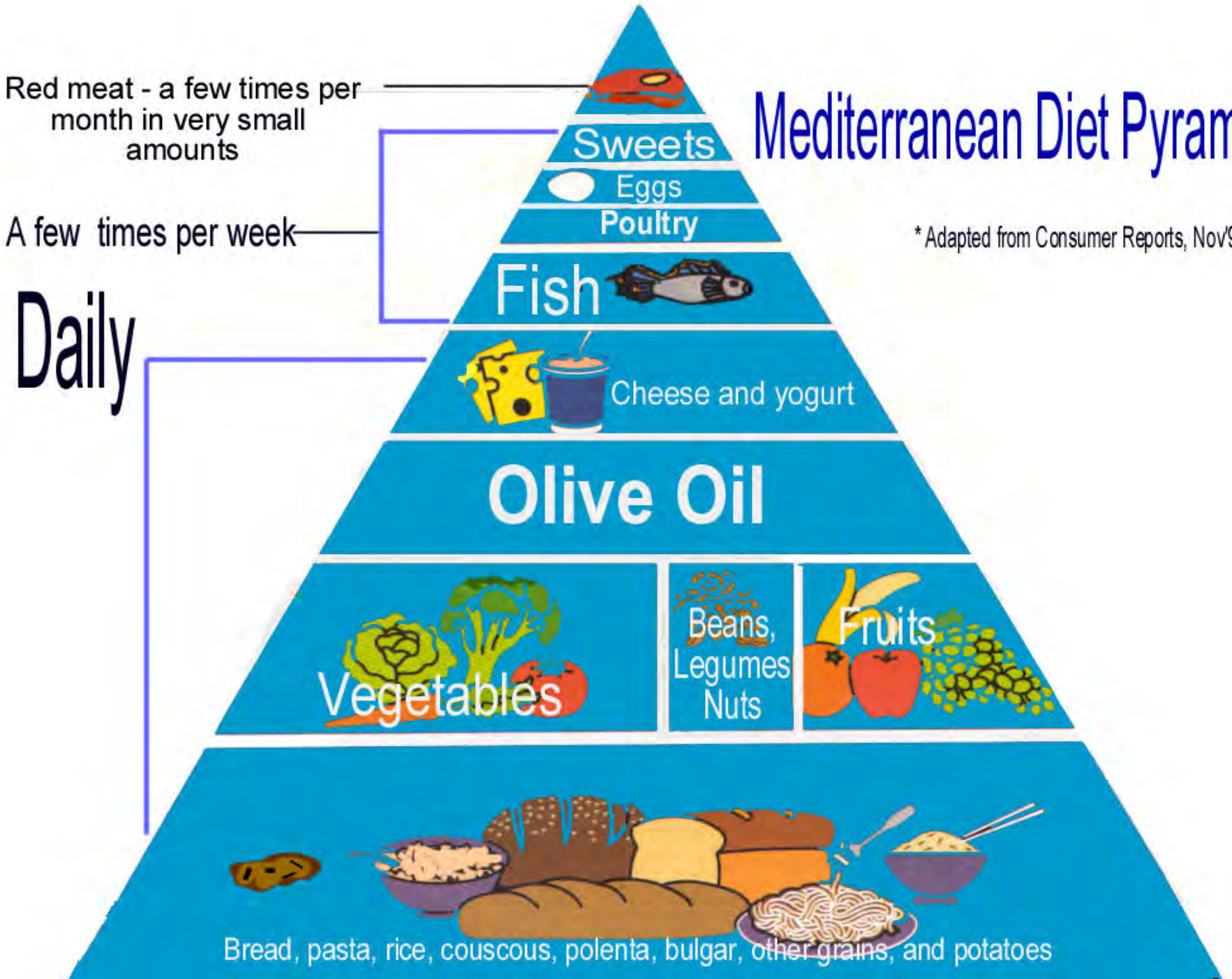
Valenzuela & Sachdev (2009) Am J Geriatr Psychiatry 17(3)
Bahar-Fuchs, Clare, Woods – Cochrane Database Syst Rev. 2013 Jun 5;6:CD003260. doi: 10.1002/14651858.CD003260.pub2.

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*



* 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

Ginkgo leaves

Member of ginger family

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

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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^{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)

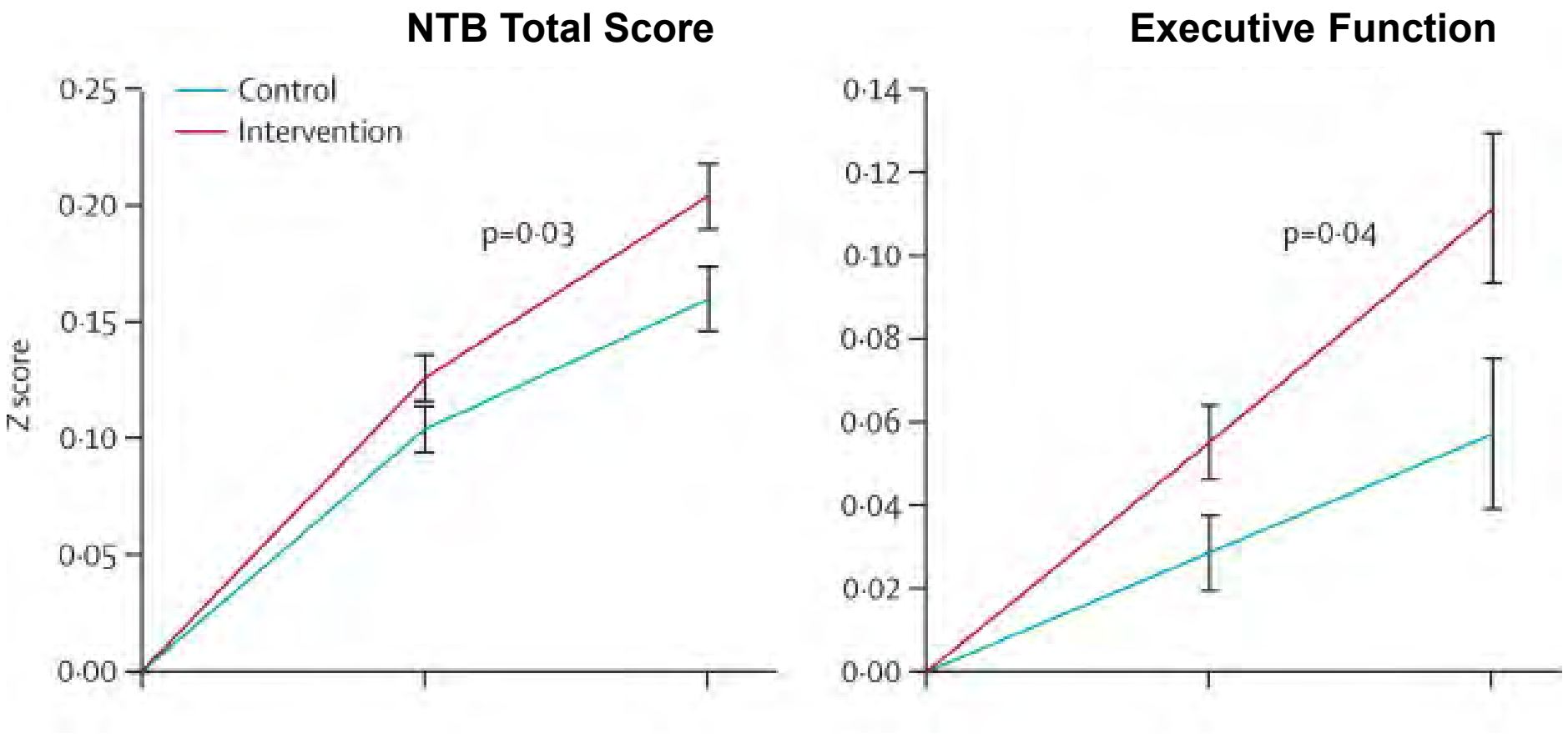
Barnes & Yaffe, 2011; Norton et al, 2014


CLINICAL
TRIAL

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



Ngandu et al. *The Lancet. 2015;*
http://dx.doi.org/10.1016/S0140-6736(15)60461-5

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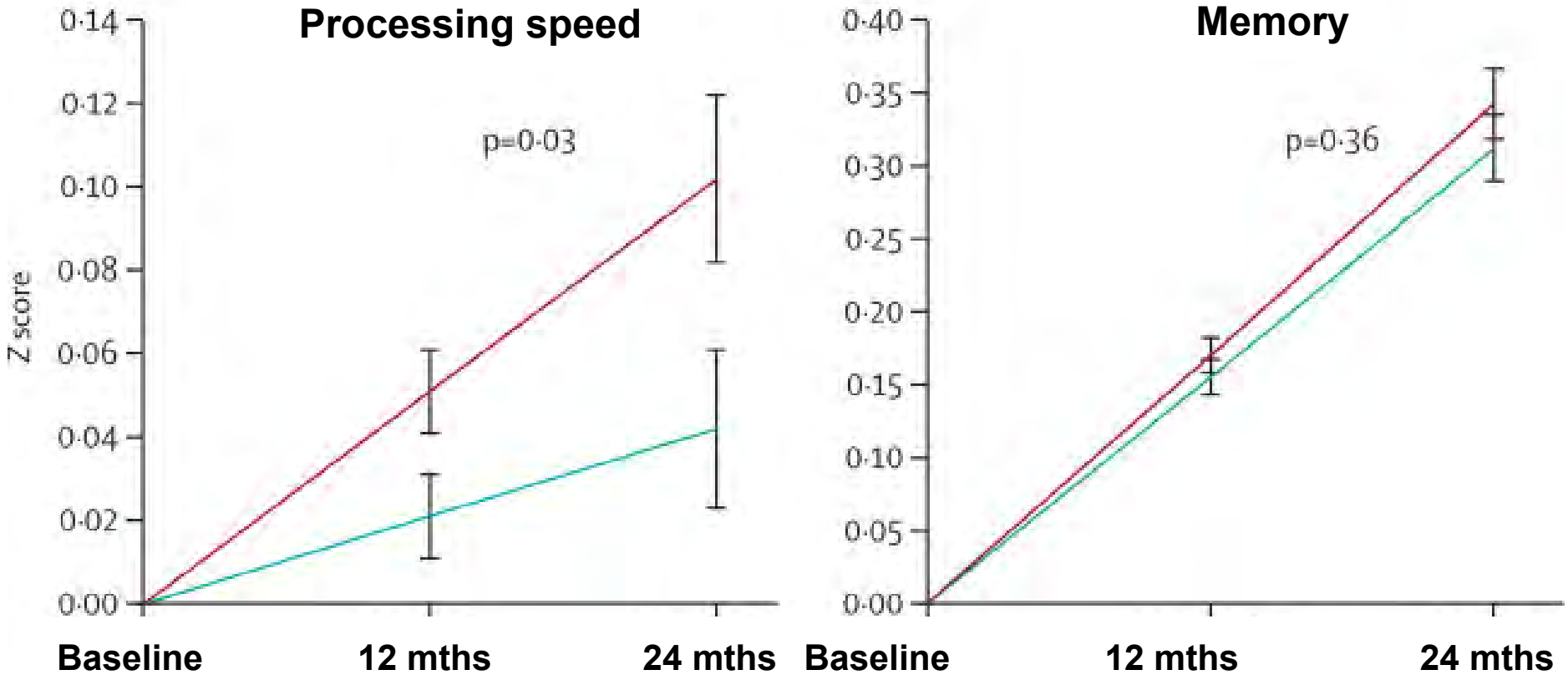
Mean change in cognition over 2 years



Ngandu et al. *The Lancet. 2015;*
http://dx.doi.org/10.1016/S0140-6736(15)60461-5

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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/**
- ***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

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)
    - Aducanumab – Phase 1b positive
  - IV immunisation with immunoglobulin - failed

Anti-amyloid therapies - 3

- **Prevent Aβ aggregation**
  - **Tramiprosate (3APS) – ceased**
  - **PBT1 (clioquinol) – ? 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

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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 (γ-secretase inhibitor)
- Bapineuzemab
- Verubecestat (β-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[1]

'The mainstay of treatments for AD is supportive care from family .." [2]

[1] Cummings J et al, 2016 Alz Research & Therapy
[2] Scheltens P et al, Lancet, 2016:388:505-17

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-effective [2]**

[1]Brodaty H & Arasaratnam C, Am J Psychiatry, 2012

[2] Chenoweth L et al, Lancet Neurology, 2009

Psychological

- Humour therapy ↓agitation, ↓depress^{n}, ↑QoL[1,2]
- Tailored Activity Program[3,4] – OT led
- Others – Volunteers, music, singing, dance therapy, Integrating kindergarten/ babies

[1]Low LF et al BMJ Open 2013; [2] Brodaty et al Am J Ger Psych 2014

[3] Gitlin L et al, Am J Ger Psych 2008 & [4]Gerontologist, 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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