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How can we tell which treatment works?



Professor Henry Brodaty
Collaborative partnerships • Translating evidence • Research partnerships




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Prevention



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How do you know if X (diet, vitamin, exercise, etc) prevents dementia 1

- Compare people with dementia and those without as regards their experience with X (Case Control Study)
 - Women who had AD were less likely to have been on HRT
 - Women with AD may have had other exposures


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How do you know if X (diet, vitamin, exercise, etc) prevents dementia 2

- Compare people who are exposed to X and those not and see how many develop dementia (Cohort Study)
 - Women on HRT less likely to develop AD than those not on HRT
 - But women who take HRT may differ
 - eg education


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How do you know if X (diet, vitamin, exercise, etc) prevents dementia 3

- Do a Randomised Controlled Trial
 - Randomise group of women to receive HRT or placebo, WHIMS
 - Need large numbers of people and many years to → results

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Women's Health Initiative Memory Study

- Double blind RCT of 4532 women
- 0.625mg estrogen + 2.5mg progestin compared to placebo
- Mean f/u = 4.2 years
- Significantly greater % in estrogen + progestin group ↓ on modified MMSE by ≥ 2SD (6.7%) compared to placebo (4.8%)
- Risk of dementia 45/10,000 v 22/10,000

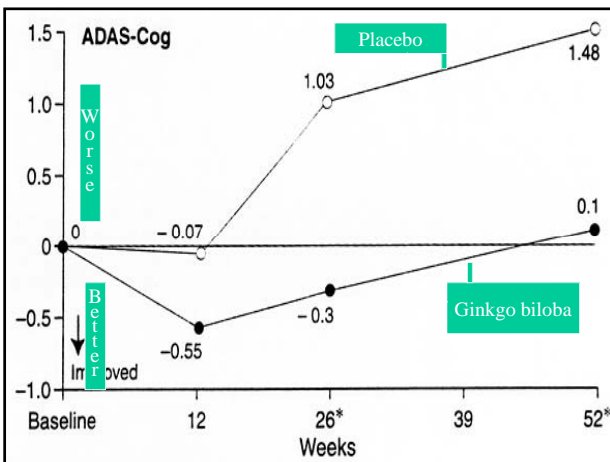
¹Shumaker S et al JAMA 2003;289:2651-2662

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Drugs to prevent AD

- More suited to RCT
 - Eg Ginkgo biloba

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Can Ginkgo 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

The Kaplan-Meier plot shows cumulative dementia rates (Y-axis, 0 to 0.25) over time to dementia in years (X-axis, 0 to 7). The Placebo group (grey line) shows a higher cumulative rate of dementia compared to the Ginkgo biloba group (black line). The Hazard Ratio (HR) is 1.12 (95% CI: 0.94-1.33), with a P-value of .21.

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How to assess claims for prevention

- Where was it published?
- Who did research?
- How significant were findings:
 - Statistically
 - Meaningfully
- Does it make sense? Plausible mechanism?
- Has research been replicated?

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Conflict of interest

- I have received financial support, sponsorship and/or participated in research from/with many pharmaceutical companies
- I am on Novartis Advisory Board for Australia and for Asia-Pacific
- Novartis sponsored my attendance at ADI conference

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Treatment



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Drug trials

- Preclinical - laboratory, animals
- Phase 1 – safety, volunteers
- Phase 2 – dose finding
- Phase 3 – DB RCT
- Phase 4 – post marketing surveillance

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How do you know if a treatment works? 1

- Open label study (all know who is on Rx)
 - May provide clue but not definitive
- Double blind randomised controlled trial
 - Gold standard
 - Must be replicated
 - There are traps

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Memantine in Moderate to Severe AD: Reisberg B et al NEJM 348:1333-41, 2003 (MMSE 3-14)

A

No. at Risk	
Memantine	126 119 107 96 124
Placebo	126 117 106 83 123
P value	0.002 <0.001

Severe Impairment Battery

B

No. at Risk	
Memantine	126 119 107 97 124
Placebo	126 117 106 84 123
P value	0.003 0.02

ADCS ADL

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Trap = drop outs

- Patients drop out of trials →
- Lost to follow-up = longitudinal data problem
- Solution: Last Observation Carried Forward (LOCF)
- LOCF = missing values are replaced by last observed value

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Last observation carried forward (LOCF)

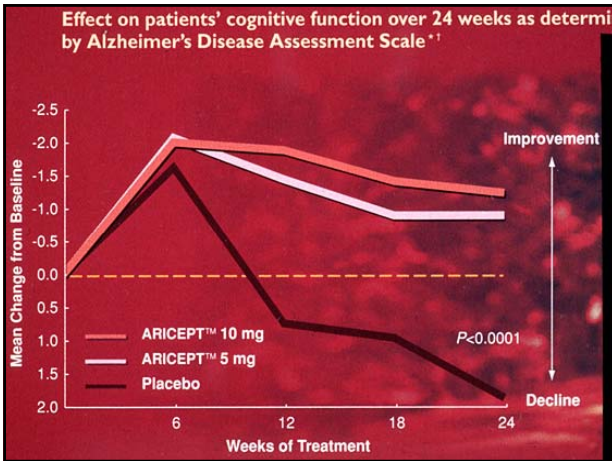
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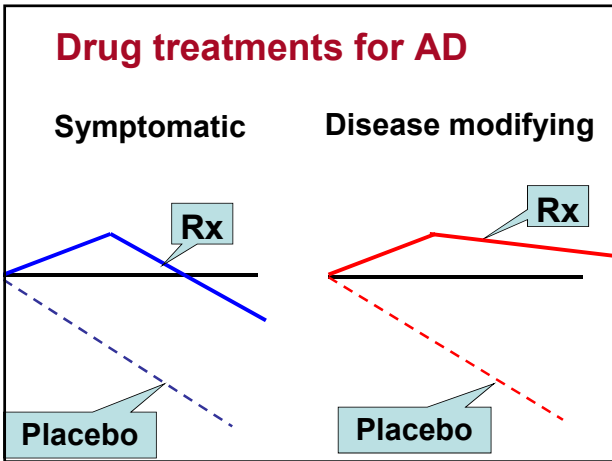
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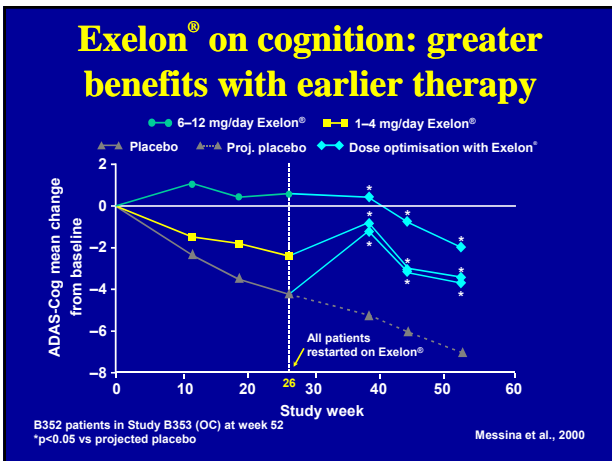
Is Rx symptomatic or disease modifying?


- Most trials ≤ 6 months duration
 - Ethics of longer placebo
- Current trials now longer and add-on
 - New drug or placebo + ChEI
- Slope of decline may differentiate

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Which outcome is important?

- Cognition – ADAS-cog
- Function – ADL/IADL
- Global – CIBIC
- Behaviours – NPI
- Quality of life – ADQOL, DEMQOL


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Dimebon



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Dimebon (Phase II)

- Long used in Russia as antihistamine
- Inhibitor of cholinesterase and NMDA receptors
- Inhibits neuronal death, potentially by mitochondrial-mediated inhibition of apoptosis
- RCT 183 AD patients; improvement in ADAS-Cog, CIBIC-plus, MMSE, NPI & ADLs at 26 wks compared to placebo; strong effects
- Russian trial, well supervised; need replication

Doody et al. (2008) *Lancet*; 372:207-215

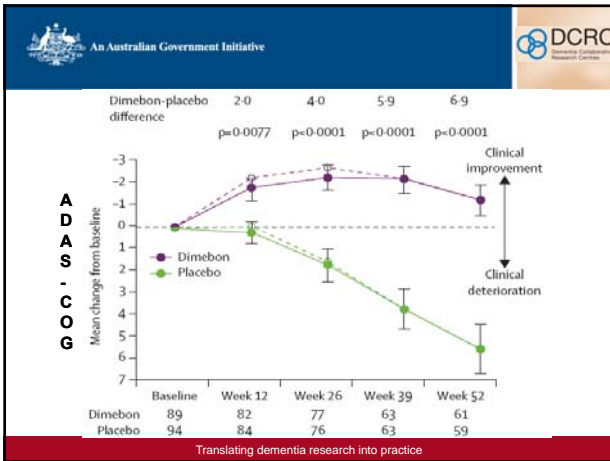
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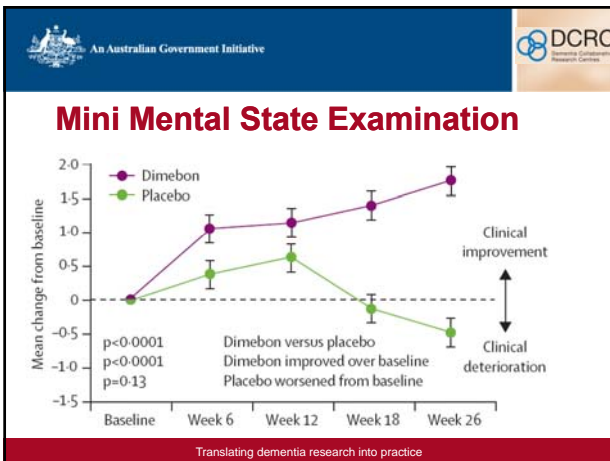
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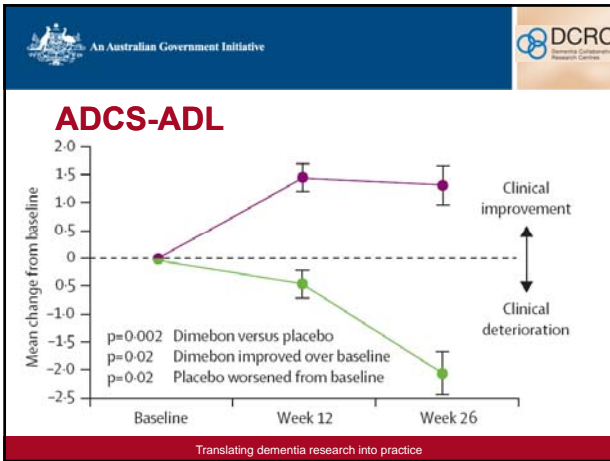
First Pivotal Dimebon Study

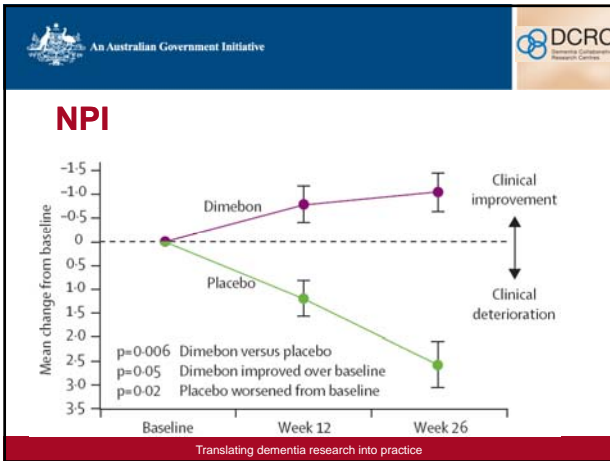
- A DB RCT, placebo-controlled study
- Dimebon, 20 mg po TID versus placebo
- Duration: 6 months plus 6 month extension
- 183 patients with mild-to-moderate AD (MMSE 10-24)
- Endpoints: ADAS-cog (11-item), CIBIC-plus (ADCS-CGIC), MMSE, ADCS-ADL, NPI, Safety

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Conclusions re Dimebon

- Significant benefits vs placebo on all five outcomes: cognition, global function, activities of daily living and behavior.
- Benefits stable or increased over one year
- Global signs and symptoms of AD improved or stabilised in 70% of pts who remained on Dimebon at one year
- Dimebon well-tolerated over study duration

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Levels versus rates?

- Which is more important
 - average improvement? or
 - number of people who achieve significant improvement?

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CIBIC-plus at One Year

p = 0.0058; Observed Case
p = 0.0014; LOCF

Category	Dimebon (%)	Placebo (%)
Improvement	30	15
No Change	40	30
Worsening	30	50

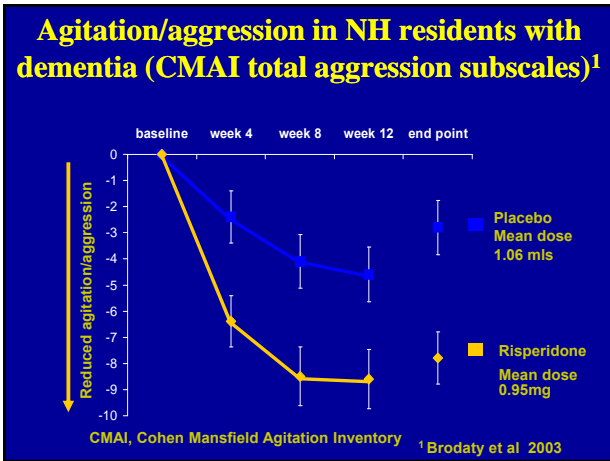
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Other considerations in Rx trials

- How long should follow-up be?
- How meaningful is
 - 4 point improvement on ADAS-cog?
 - 2 point less functional decline?
- Post-hoc analyses
- Adverse effects (Side effects)

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Adverse effects of antipsychotics

- Higher rate of stroke
- Higher mortality rate
- Faster cognitive decline

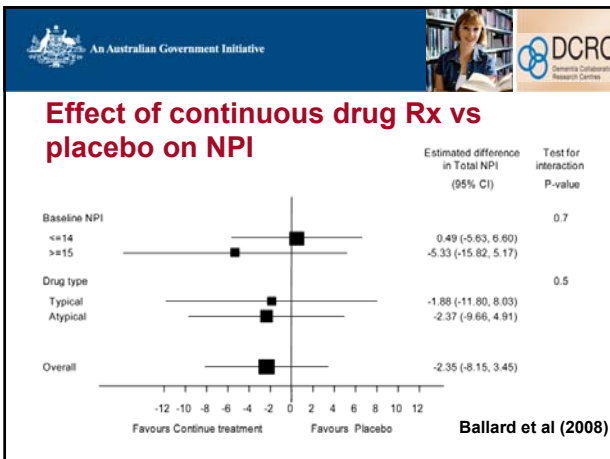
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Continuing vs stopping neuroleptics in dementia patients?


- 12 months RCT
- Continuous use of neuroleptics vs placebo
- For most AD pts withdrawal had no overall detrimental effect
- Subgroup of pts with more severe symptoms (NPI ≥ 15) might benefit from continuous Rx

Ballard et al (2008) PLOS Medicine. 5(4).587-599







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Active AD Immunisation¹

- Trial stopped in phase II: 6% of subjects → meningo-encephalitis; some died
- *Head shrinkers*: Brains of those with antibody response → *smaller*
- Some improvement in neuropsychological tests – post hoc analysis

¹Solomon B, *Expert Opinion on Biological Therapy*, 2002

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Treatment of BPSD

- Drug treatments
- Psychosocial treatments

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Psychosocial Interventions

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Caregiver interventions

- Cannot be blind
- Two “subjects” = PWD and CG
 - Improve CG but PWD worse?
- Intervention more difficult to standardise

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The Prince Henry Hospital Caregiver intervention

Months to death	Immediate & Wait-List (n=63)	Memory Retraining (n=30)
0	1.0	1.0
12	0.95	0.85
24	0.9	0.75
36	0.85	0.65
48	0.8	0.55
60	0.75	0.45
72	0.65	0.4
84	0.55	0.35
90	0.45	0.3

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Cost-benefit

- Intensive caregiver intervention delayed nursing home admission
- Saved US\$6000 per couple
 - Cost of training vs cost of institutional care


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Cognitive-behavioural family intervention¹

- RCT, 3 mths follow-up, N=42 dyads
- Only included if carer GHQ > 4 (= psychiatric cases)
- Carer educatⁿ, stress management, coping
- Post Rx and after 3 months intervention sig better than both control groups
- Number of psychiatric cases reduced


¹ Marriott et al (2000). British Journal of Psychiatry.

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Effect of day care use on caregiver stress¹

- 121 day care users vs 203 non-users
- Main outcome measures
 - Role captivity
 - Overload* * Sig difference after 3 mths.
 - Worry and strain*
 - Depression (CES-D)*
 - Anger*
 - Positive affect

¹ Zarit et al (1998). Journal of Gerontology Social Sciences; 53B(5): S267-S273

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Floor effect

- = If caregivers are not depressed they can't show any improvement with any given intervention

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Re-Analysis of data

- Study of Day Centre attendance no benefit (Zarit)
- Reanalysis → benefit (Whitlach)

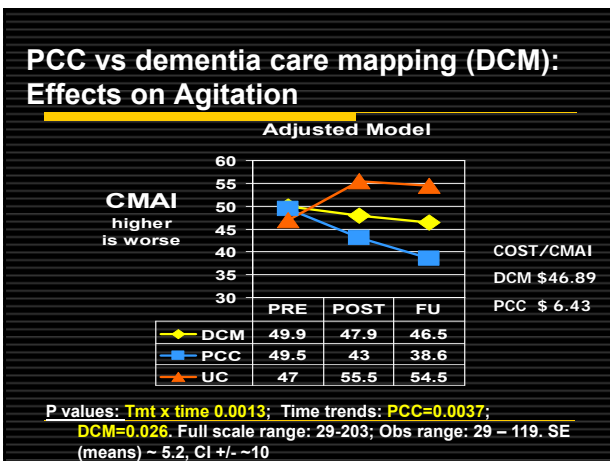
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Person Centred Care vs Dementia Care Mapping vs Usual Care

- Chenoweth L et al,
- Lancet Neurology, 2009

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Conclusions

- Need research to determine what works
- Critically analyse reports
 - multiple motivations to publish
- Interventions that show cost benefit more likely to influence government

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www.dementia.unsw.edu.au



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