HOTCHKISS BRAIN INSTITUTE

UNIVERSITY OF CALGARY

Therapeutic Options

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Disclosures

- Speaking fees from Canadian Conference on Dementia.
- Grant funding related to VCI: Alberta Innovates – Health Solutions, CIHR, Canadian Stroke Network, Heart and Stroke Foundation of Canada, Alzheimer Society of Canada, NIH.

Outline

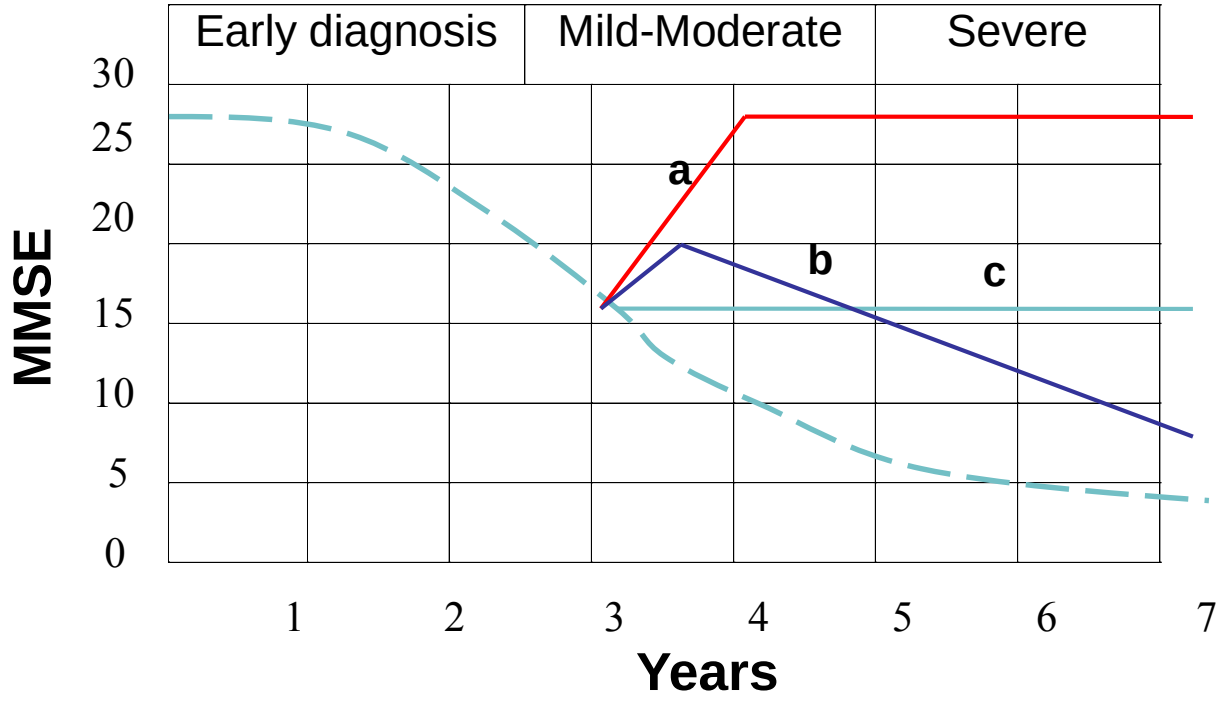
- Non-pharmacological management.
- Pharmaceutical options for AD.
  - Experimental therapeutics in AD.
- Management of VCI.
- Management of Lewy body disease.
- Management of frontotemporal dementia.

Non-pharmacological Management

- Home safety.
- Driving.
- Power of attorney, medical decision-maker, advance care planning.
- Day programs.
- Caregiver support.
- Management of neurobehavioural complications.
- Treatment of comorbid depression.

Management of AD

Figure 4. Hypothetical Treatment Responses in AD



a) ideal response - complete normalization

b) partial improvement, maintained on medication

c) stabilization

Gauthier et al., 1996

Acetycholinesterase Inhibitors

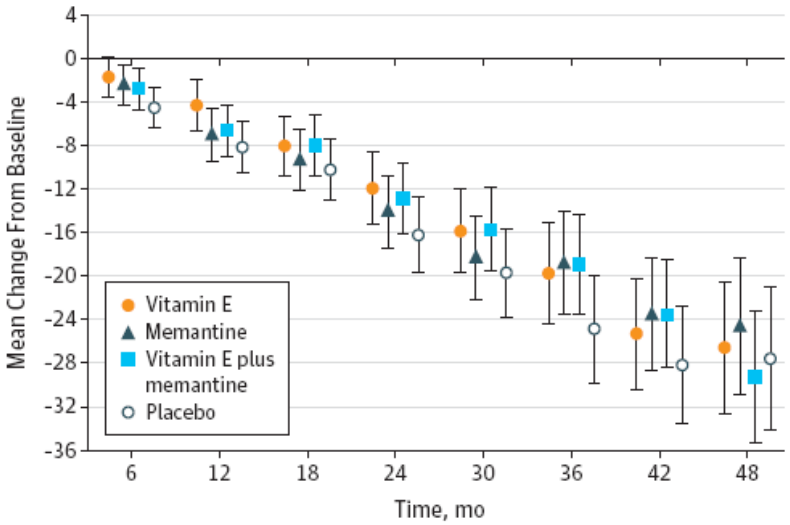
- Donepezil, galantamine, rivastigmine.
- Increase synaptic cholinergic activity.
- Addresses cholinergic deficit known to occur in AD, that affects memory networks.
- Symptomatic treatment, equivalent to delay in progression for 6-12 months. Not disease modifying.
- Indicated in mild to moderate AD.
- Potential adverse effects: diarrhea (10%), syncope (<1%).

Memantine

- NMDA receptor antagonist.
- Also thought to be symptomatic treatment, not disease modifying.
- Consider for moderate to severe AD.
- Less strong data than for acetycholinesterase inhibitors.
  - Not covered by Alberta Blue Cross.
- Can be used in combination with acetycholinesterase inhibitors.
- Potential adverse effects: uncommon, but can include confusion, dizziness, drowsiness.

Vitamin E

Figure 2. Changes in Primary Outcome (ADCS-ADL Inventory Score) During the 4-Year Study Period, Compared With Baseline



No. of patients

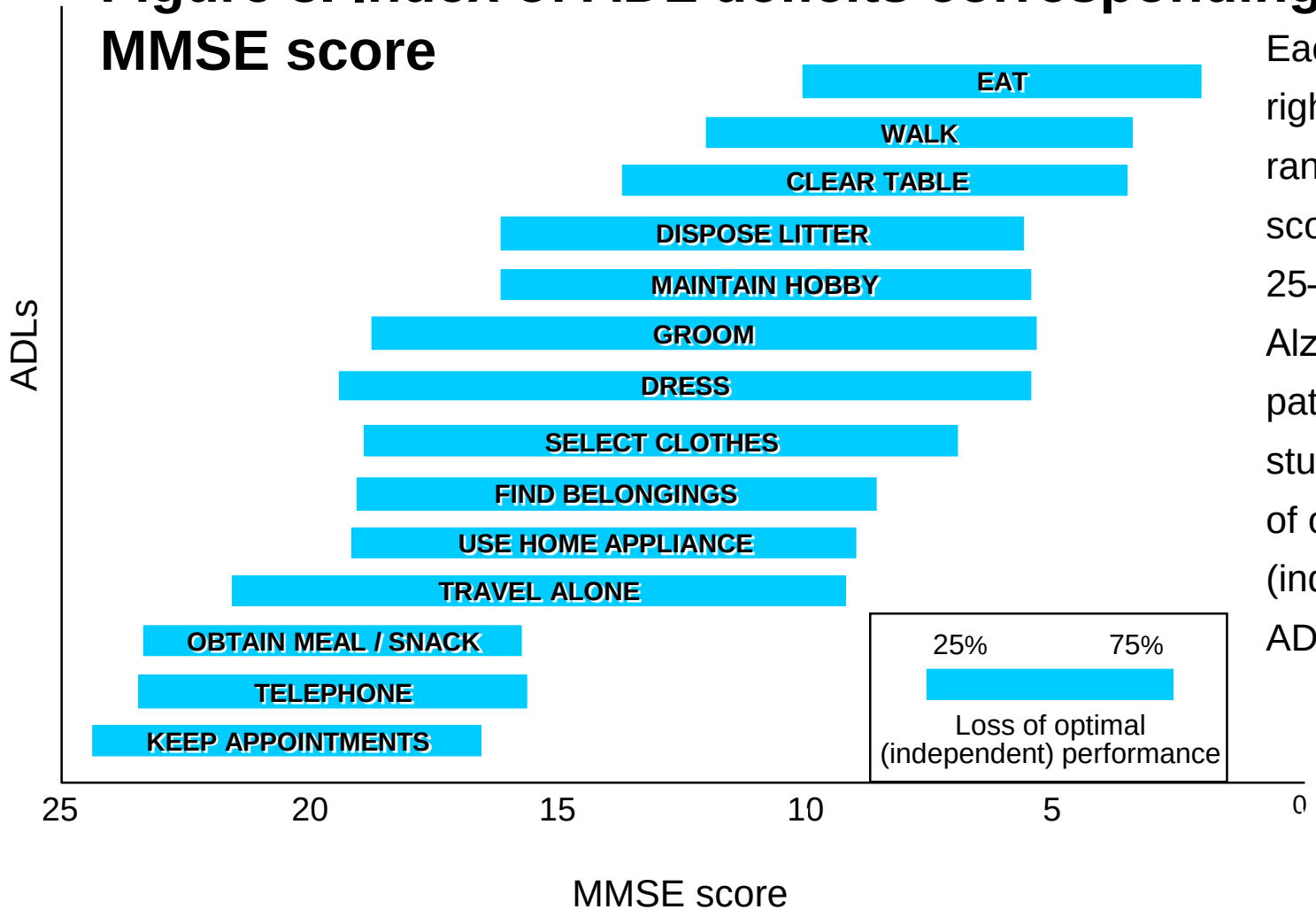
Vitamin E	134	122	103	88	66	51	39	31
Memantine	139	119	95	80	64	45	38	30
Vitamin E plus memantine	131	120	102	84	64	55	46	32
Placebo	135	112	96	77	54	41	33	25

- Trial of 613 mild-mod AD randomized 2x2 factorial to vitamin E vs placebo and memantine vs placebo.
- Vitamin E had less functional decline but no difference on cognition.
- Vitamin E associated with increased mortality in meta-analysis, but no discernable increased mortality in this study.
- I do not recommend vitamin E in my practice.

Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. Jama. 2014 Jan 1;311(1):33-44.

Correlation between Cognition and Activities of Daily Living

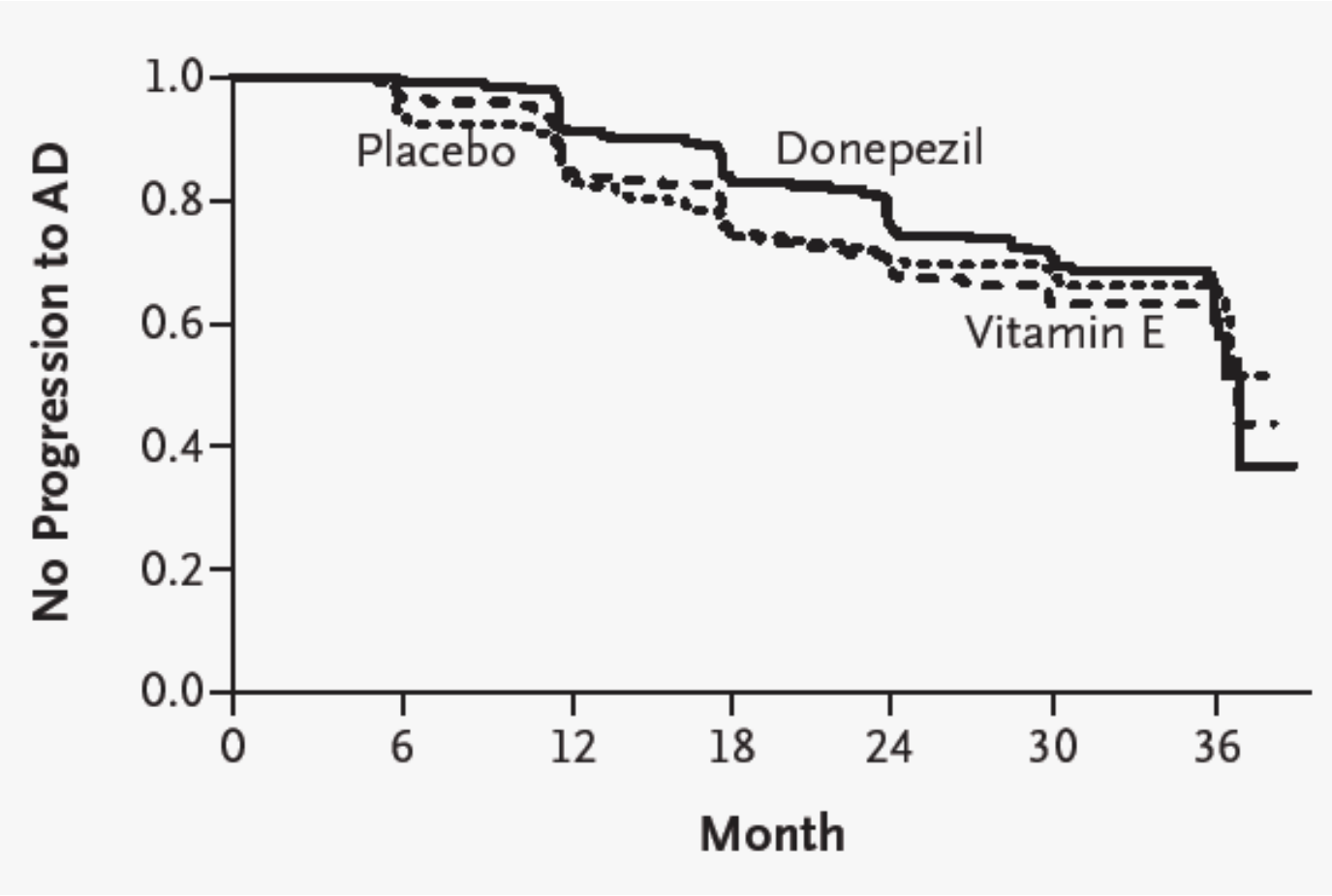
Figure 3. Index of ADL deficits corresponding to MMSE score



Each bar from left to right represents the range of MMSE scores over which 25–75% of Alzheimer's patients in one study† showed loss of optimal (independent) ADL performance

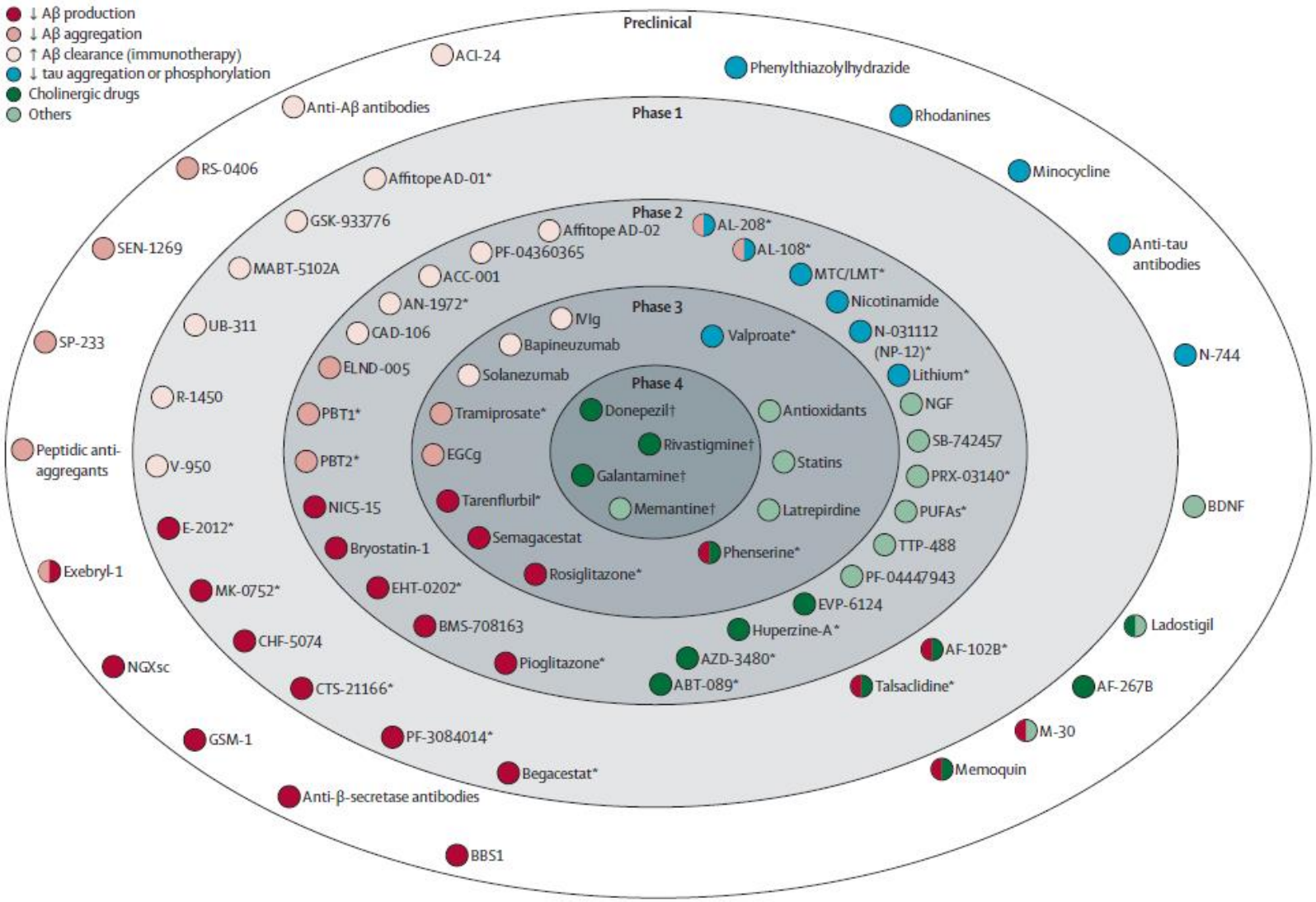
Galasko *et al.*,1997

Donepezil Does Not Prevent Progression from MCI to Dementia



Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med. 2005 Jun 9;352(23):2379-88.

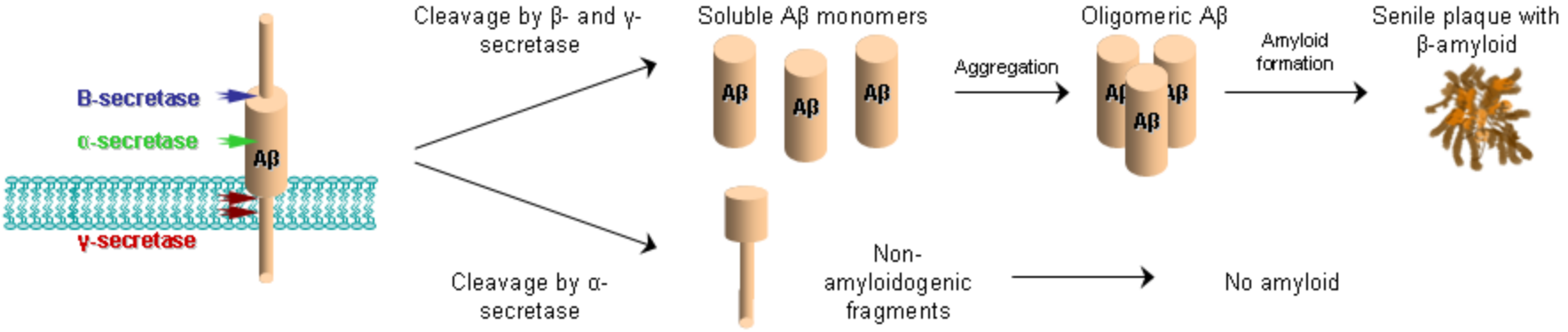
AD Research Pipeline 2010



Mangialasche F, Solomon A, Winblad B et al. Alzheimer's disease: clinical trials and drug development. Lancet Neurol. 2010;9:702-716.

Amyloid Hypothesis

- Production of abeta, with aggregation into beta-amyloid and deposition as senile plaques, initiates neurodegeneration in AD.
- Supported by observation that all genetic forms of AD (1-2% of all AD) are caused by mutations in amyloid precursor protein or cleavage enzymes.



Abeta Immunotherapy

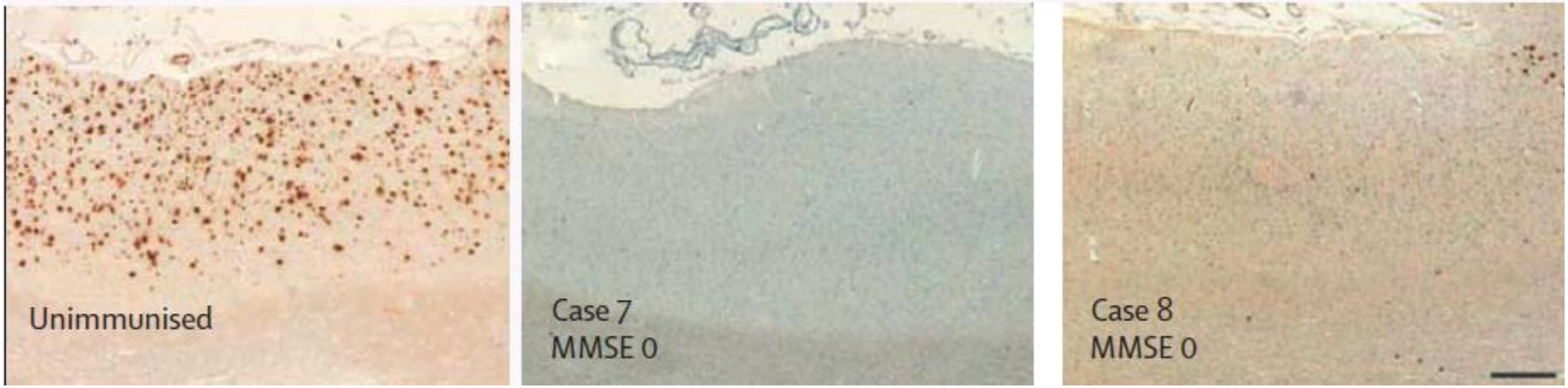
- Passive or active immunization clears brain neuritic plaques in animal models.
- Phase 2 study in humans with mild dementia suggests biological effect but no detectable effect on cognitive decline (AN1792).
  - Trial stopped early because of meningoencephalitis in 6%.
- Phase 3 trials of anti-abeta monoclonal antibody immunotherapy reported negative in 2014.

Holmes, C., D. Boche, et al. (2008). "Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial." Lancet 372(9634): 216-23.

Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med. 2014 Jan 23;370(4):311-21.

Salloway S, Sperling R, Fox NC, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med. 2014 Jan 23;370(4):322-33.

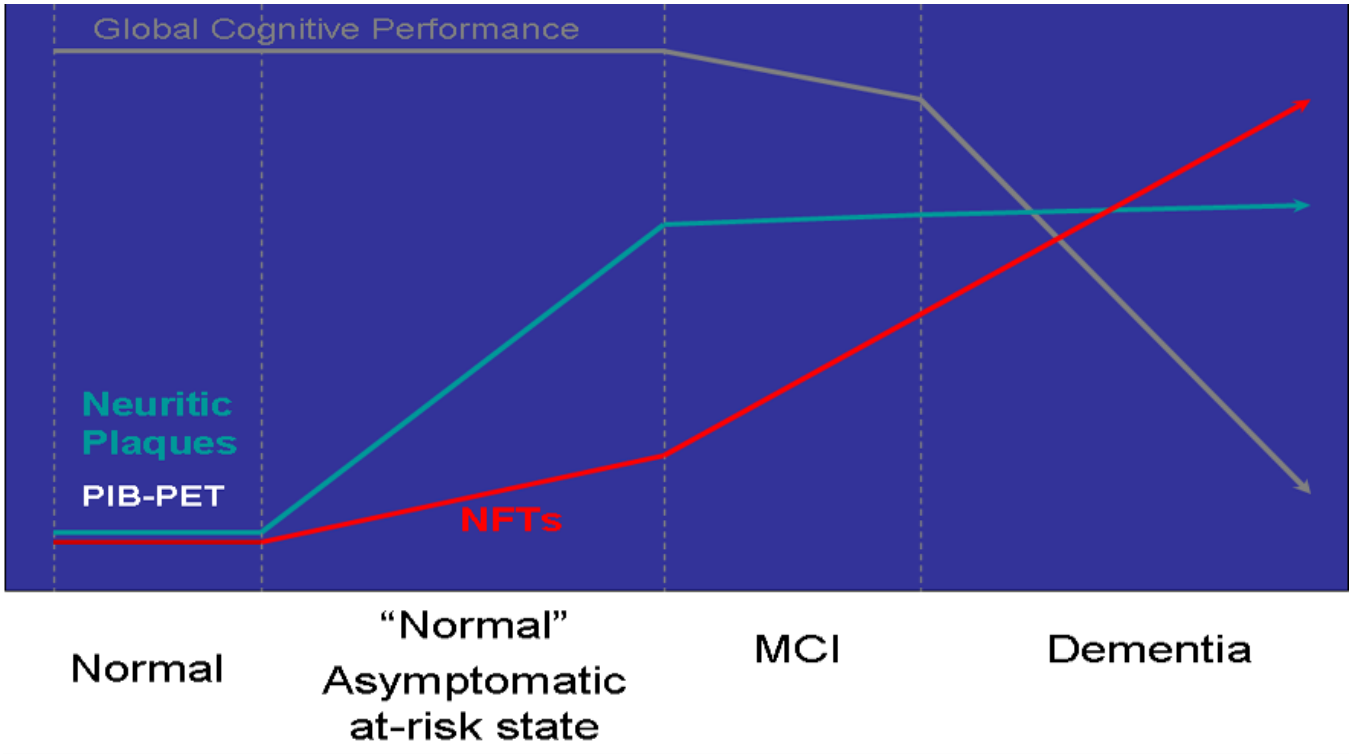
Long Term Effect of Immunotherapy



7/8 immunized cases died of end-stage dementia despite mean amyloid reduction of 60% vs. age-matched AD controls.

Reasons for Lack of Effect

- End-stage.
- Soluble oligomeric forms of abeta.
- Inadequate sample size.
- Beta-amyloid hypothesis is wrong.



Ongoing Immunotherapy Trials

- Trials in presymptomatic persons.
  - A4 trial: PET biomarker evidence of amyloid (florbetapir) without impaired cognition.
  - Trials in presymptomatic AD mutation carriers: DIAN study, Columbia.
- Solaneuzumab in mild AD (MMSE 20-26) with biomarker evidence of amyloid (PET or CSF).

Holmes, C., D. Boche, et al. (2008). "Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial." Lancet 372(9634): 216-23.

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Other Disease Modifying Approaches

- Gamma secretase inhibitors: phase 3 trial of semagacestat negative.
- Beta-secretase (BACE1) inhibitors: liver toxicity problems.
- Intranasal insulin: NIH-sponsored SNIFF trial.
- Tau-directed therapies: dimebon unsuccessful.

Management of VCI

Secondary Prevention of New Strokes

- Vascular risk factors (e.g., hypertension, atrial fibrillation) should be managed aggressively to achieve optimal control of the pathology underlying cognitive impairment following a stroke or TIA [Evidence Level A].

www.strokebestpractices.ca, section 7.2 Mood and Cognition.

Canadian Best Practice Recommendations for Stroke Care

Cognitive Rehabilitation

- Compensatory strategy training, and direct remediation/cognitive skill training show promise [Evidence level B]…but more research is required.
- http://www.ebrsr.com/reviews_list.php for detailed review.

Pharmacology

- Cholinesterase inhibitors should be considered:
  - There is fair evidence of small magnitude benefits for donepezil in cognitive and functional outcomes, with less robust benefits on global measures [Evidence Level B].[1]
  - There is fair evidence of small magnitude benefits for galantamine on cognition function and behaviour in mixed Alzheimer and cerebrovascular disease [Evidence Level B].[2]

[1]Malouf R, Birks J. Donepezil for vascular cognitive impairment. Cochrane Database of Systematic Reviews 2004:CD004395.

[2]Birks J, Craig D. Galantamine for vascular cognitive impairment. Cochrane Database of Systematic Reviews 2013;4:CD004746.

Management of Lewy Body Dementia

- Galantamine or other acetycholinesterase inhibitor.
- Levodopa can be tried for Parkinson's symptoms but is generally ineffective and can cause hallucinations.
- Sensitive to antidopaminergics; avoid them.

Management of Behavioural Variant Frontotemporal dementia

- SSRI for agitation or aggression.
  - Neuroleptics can also be used.
- Usually do not respond to acetylcholinesterase inhibitors, which may even cause agitation.
- Memantine ineffective in an RCT.

Declining Dementia Prevalence in 2011 vs. 1989-1994

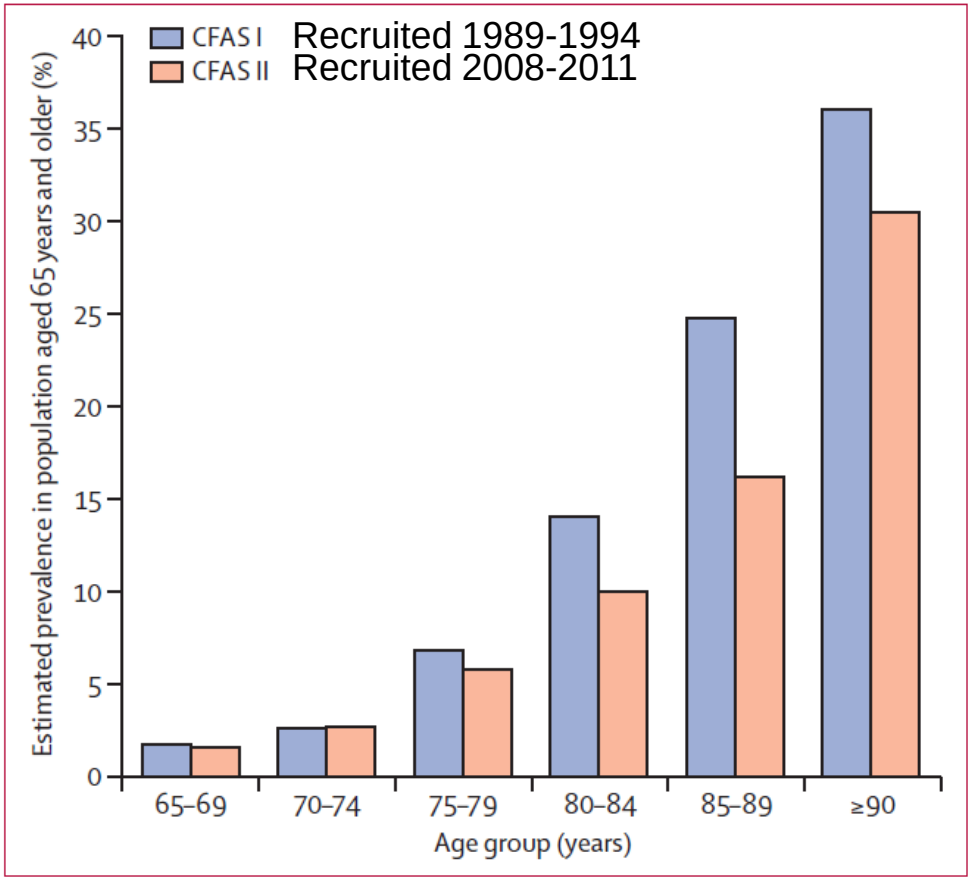

Figure 1: CFAS I and CFAS II age-specific dementia prevalence
CFAS=Cognitive Function and Ageing Study.

- Overall dementia prevalence 1.5% lower among >65 year olds in 2008-2011 vs. 1989-1994.
- Suggests primary prevention of dementia is possible (in this case, unintentional).
- Best candidates: better early life education, improved risk factor control with decreased burden of silent cerebrovascular disease.

Matthews FE, Arthur A, Barnes LE, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. Lancet. 2013 Jul 17.

Summary

- Support for community living and caregiver.
- Modestly effective symptomatic treatments for AD, VCI and Lewy Body.
- Active research programs in AD with no recent positive results.
- Primary prevention is possible.
- Still, we need better symptomatic and disease-modifying treatments.

Role of Imaging in Therapeutics

- Ensure appropriate treatment strategy:
  - AD: acetylcholinesterase inhibitor.
  - VCI: vascular risk reduction.
  - bvFTD: avoid acetylcholinesterase inhibitor.
- Prognosis
  - VCI may be stabilized with risk factor control.
- Diagnosis may provide access to services.
- Research: determine eligibility, identify biological treatment effects, surrogate outcome marker.
- Rapid growth in neuroimaging/molecular imaging will ultimately depend on whether diagnosis is accompanied by a disease modifying treatment strategy.

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Thank You