Scientific and Methodological Approaches to Developing Treatments to Arrest or Delay the Progression of Alzheimer's Disease: A Blueprint for the Future

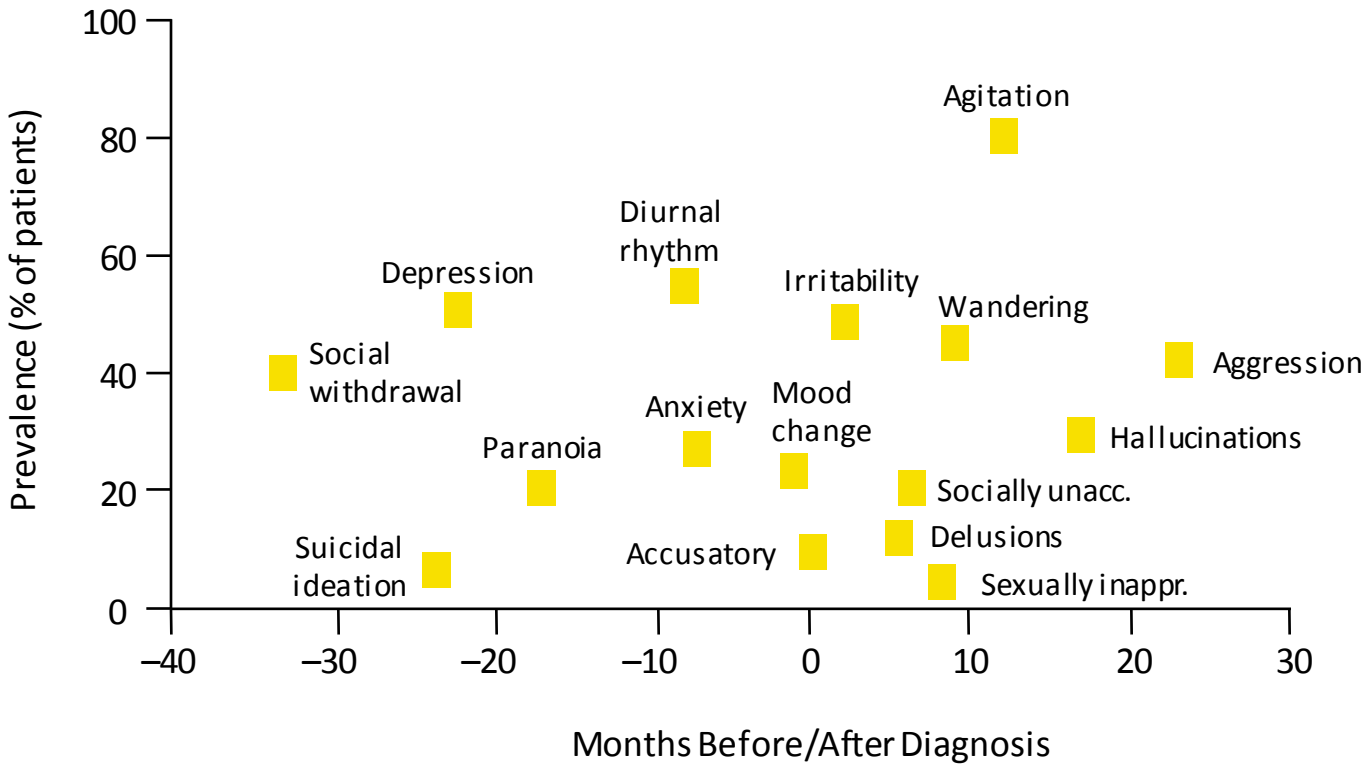
Ravi Anand, M.D.

Richard Hartman, Ph.D.

Disclosure

- Ravi Anand and/or Richard Hartman have consulted or are consulting for the following organizations:
  - Abbott, Acadia, Astra-Zeneca, Bioline, CliniRx, EryDel, Forest, J&J, Lundbeck, Newron, ONO, Pfizer, Roche, Sigma Tau, Schering Plough, and Takeda

Peak Frequency of Behavioral Symptoms as Alzheimer's Disease Progresses

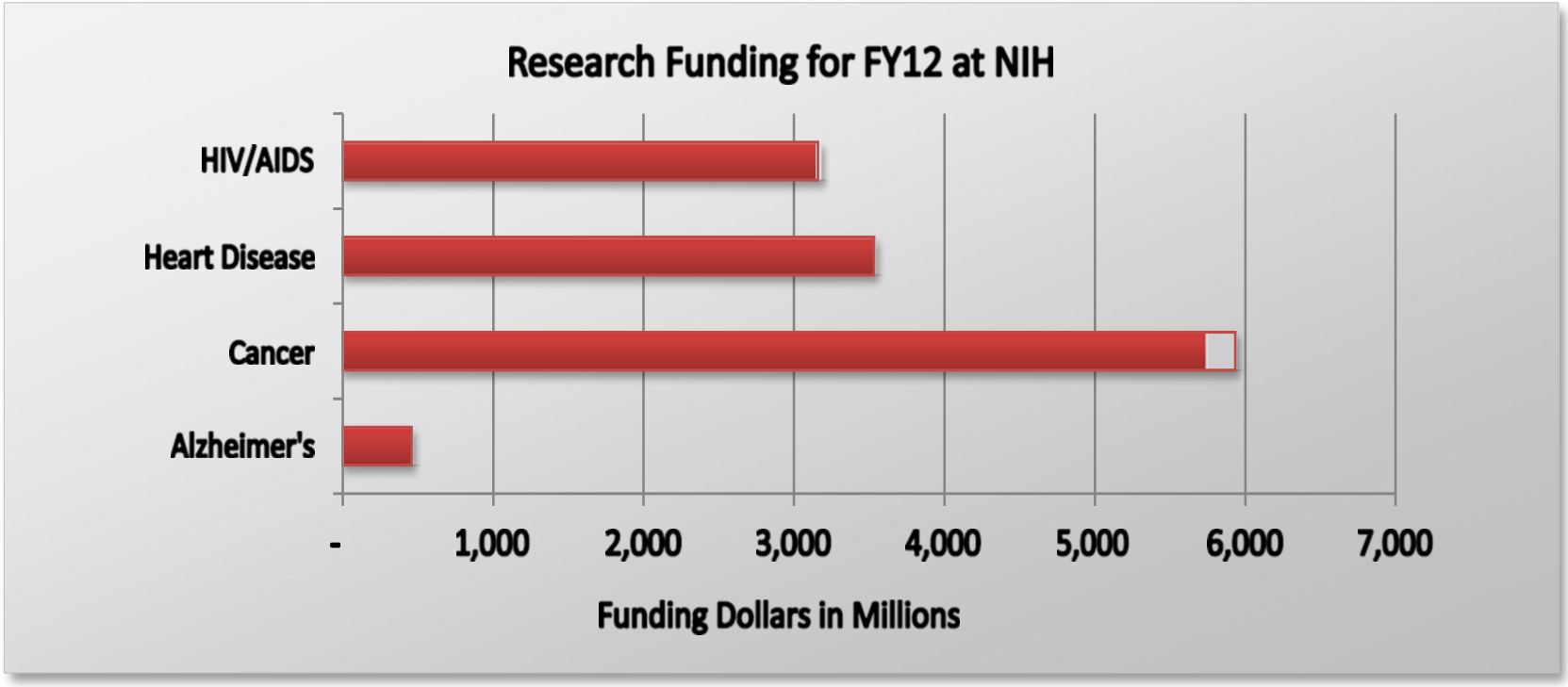


Jost BC, Grossberg GT. *J Am Geriatr Soc.* 1996;44:1078-1081.

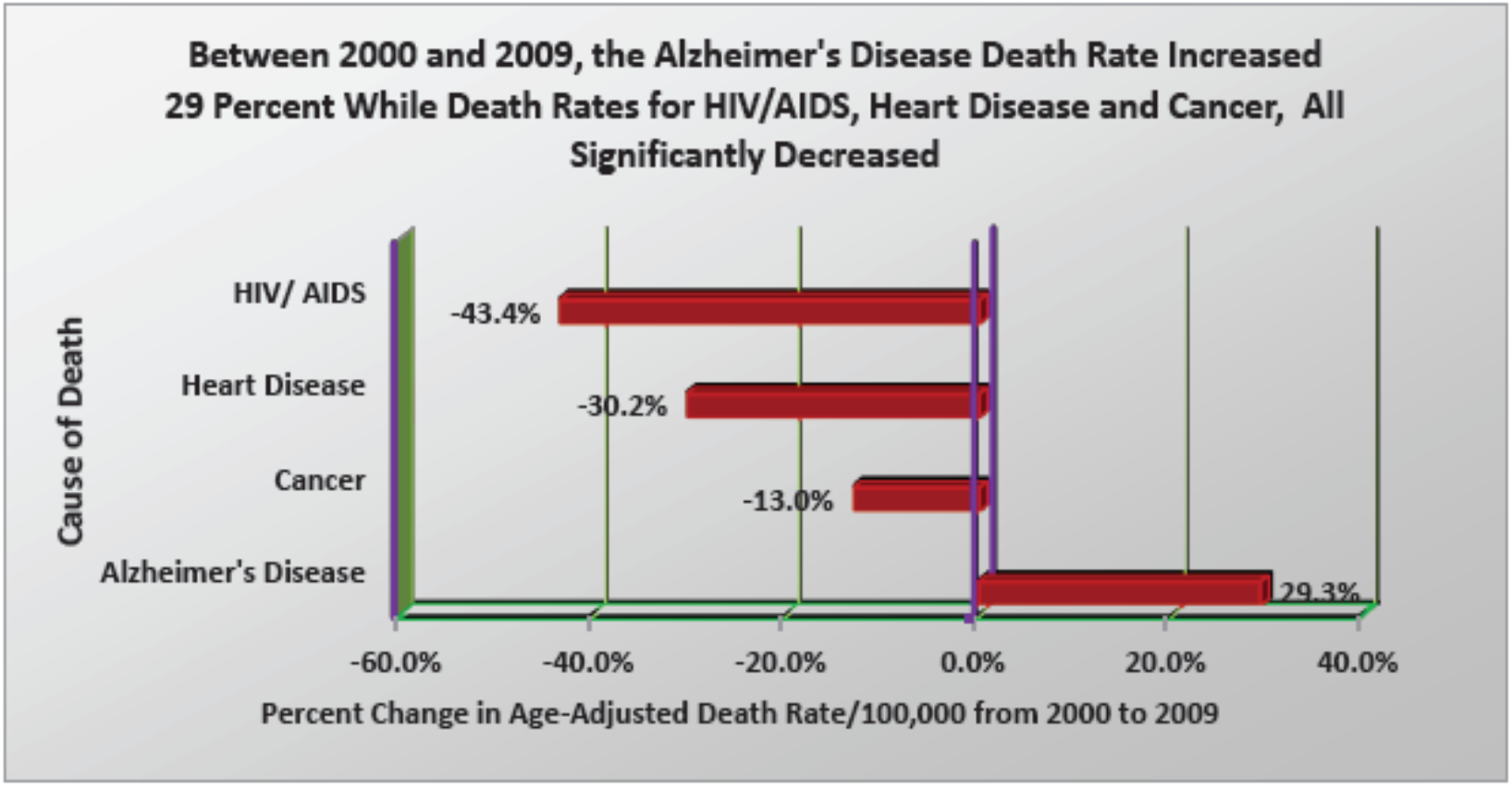
Impact of AD on Society

- Worldwide prevalence of dementia (~AD) is 25 million: doubling every 20 years to reach 80 million by 2040 (Ref: Ferri, et al 2005)
- Alzheimer's Disease Association 2007 study indicates
  - >5 million people in the US with AD - 4.9 million above 65 years; 200,000-500,000 below 65 years

    This represents a 10% increase from the previous nationwide prevalence estimate of 4.5 million
- Without a cure or effective treatment to delay the onset or progression of AD, the prevalence in the US will rise to 7.7 million by 2030, and 16 million by 2050
- Current cost of AD (direct and indirect) in US is $148 billion annually



Source: U.S Department of Health & Human Services, *Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC),* http://report.nih.gov/rcdc/categories (February 2011)
(*Note: Heart Disease includes funding for Heart Disease and Cardiovascular Disease)*



Source: National Vital Statistics Reports, Vol. 49, No. 4, March 16, 2011.
National Vital Statistics Reports, Vol. 50, No. 15, September 16, 2002.

Currently Approved Treatments for Alzheimer's Disease

- The 5 currently approved AD treatments (tacrine, donepezil, rivastigmine, galantamine, and memantine) show modest benefits on cognition, ADL and behavior, with no/minimal improvement of QOL, and a lack of long-lasting clinical benefits and cost-effectiveness
- Trials with these drugs were performed in patients with a mean age of 75 years, severity of dementia of moderate, and MMSE of 6-24, who were 3-8 years post-diagnosis
- Brain changes in these patients included significant atrophy in both amygdalae, both anterior hippocampal formations, and trans-entorhinal areas; right medial thalamus, posterior insula, and left middle temporal gyrus/temporal sulcus; right hippocampal body and tail
- Thus, these patients had lost so much function that modifying disease progression was virtually impossible.

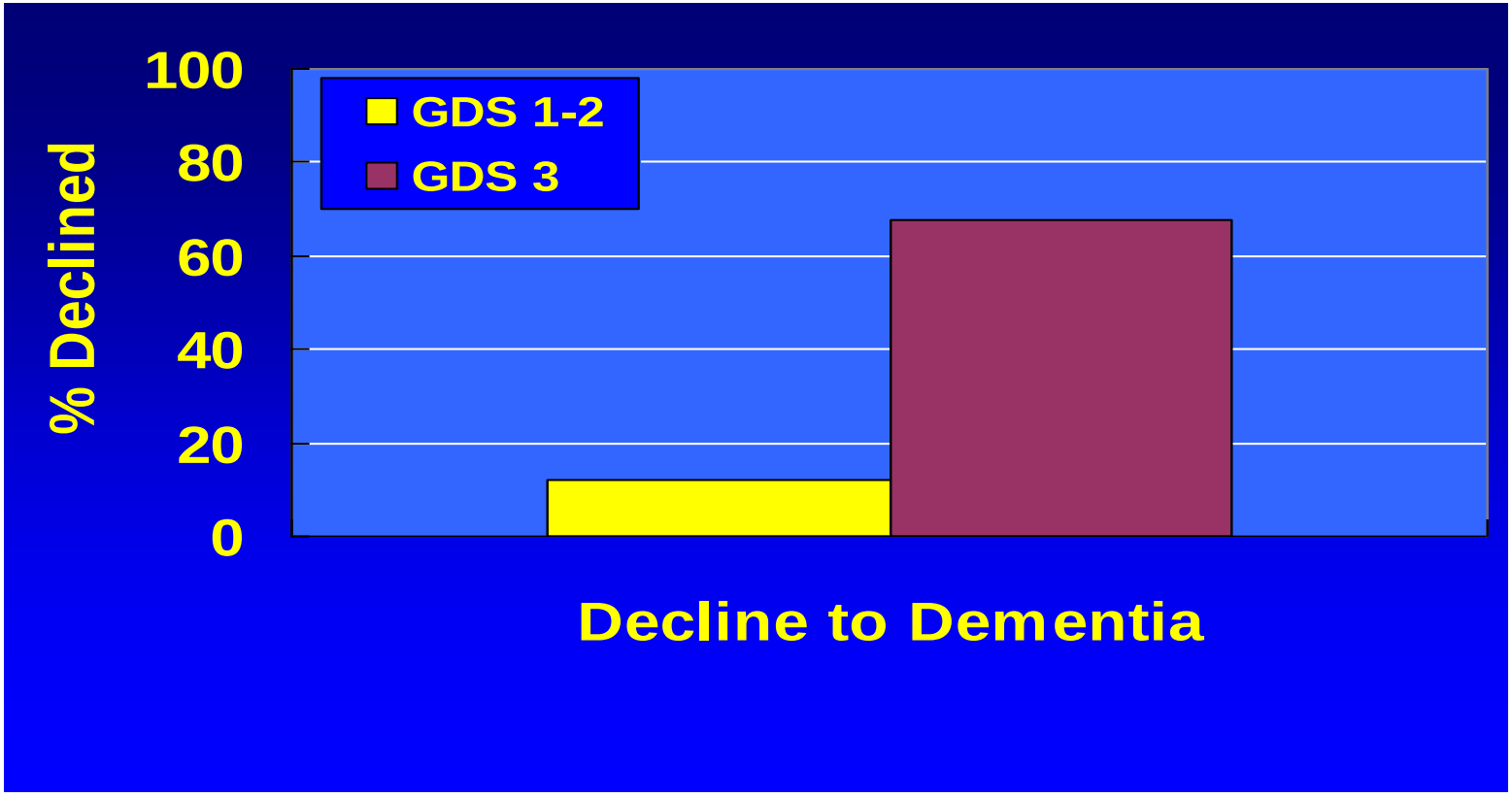
Characterisation of Patients Entering Mild Cognitive Impairment (MCI) Trials

- Numerous definitions exist for MCI:
  - MMSE ≥24, CDR 0.5, GDS 3 or 4
  - Cognitive complaint (informant and /or patient)
  - Episodic memory deficit (1.5 SD below norm)
  - Recall deficit that doesn't normalise with cuing
  - No/very mild ADL impairment
  - Maximally 1 of 4 IADLs impaired
- Minor Criteria (at least 1 required):
  - A. Presence of medial temporal lobe atrophy
  - B. Abnormal CSF biomarkers
  - C. Specific pattern on functional neuroimaging with PET
  - D. Proven AD autosomal dominant mutation within immediate family

Consistent Lack of Efficacy of Approved AD Treatments in MCI Trials

Drug	Study	Design	Primary Efficacy Measure(s)	Outcome
Donepezil (Don)	Salloway S, et al. 2004	24-week, n=270	- NYU Paragraph Recall - ADCS CGIC - MCI	No difference between groups
	ADCS Study, 2005	36-month, n=769, vs. Vit E	Time to AD (NINCDS-ADRDA criteria)	Don vs. Pbo - No difference except at 12 mo. (p=0.04); Vit E - no effect
	Doody R, et al. 2009	48-week, n=821	-Modified ADAS-Cog -CDR-SB	Mean change on mod. ADAS-Cog at endpoint favored Don (p=0.01); no difference between groups for CDR-SB
Galantamine (Gal)	Windblad B, et al. 2008	Study 1: 24-month, n=990	% conversion from MCI to dementia (CDR ≥ 1.0)	No difference between groups
		Study 2: 24-month, n=1058		No difference between groups
Rivastigmine (Riv)	InDDEx Study, Feldman HH, et al. 2007	48-month, n=1018	-Time to conversion from MCI to AD -Change on cognitive test battery	No significant difference vs. Pbo on either measure

Decline To Dementia Among Non-demented Elderly (N=211)#



***p < .001 (5.7- fold increase in risk for decline to dementia, x = 3.9 yrs.)

#Adapted from Kluger, Ferris, Golomb et al, J. of Geriatric Psychiatry and Neurology, 1999

Cost Effectiveness of Currently Available Treatments for AD

- Recent decisions by the National Institute of Clinical Excellence (NICE) to restrict use of AD drugs in most patients (except for most severely ill/advanced stages of disease) suggest the value of these treatments is <$50,000
  - $50,000/year is the value cut-off most cost effectiveness experts use for a single year of life in perfectly healthy, or a **Quality-Adjusted Life Year** (**QALY**; Vernon, et al, 2005)
- Above judgement appears to be based on available data that indicate that, although these changes have positive effects different from the effects of PBO, they have no impact on important outcomes, e.g., functional independence, time to hospitalisation, Quality of Life, etc.

How Best to Target a Treatment that could Affect AD Onset?

- Value of breakthrough will be greatest when age of subjects will be close to, but before the age of onset of the disease, i.e., more at age 50 than at 25 or 90 years old
- This suggests that the greatest benefits are likely to result from strategies that may delay the onset of AD (Vernon, et al 2005)
- QALY benefit by delaying onset of AD by 1, 3, and 5 years are estimated to be 0.52, 1.32, and 1.73, respectively (Vernon, et al 2005)
- NIMH/AD Association estimate 450,000 incident AD cases in 2010; this is estimated to increase to 959,000 by 2050

Present Value Benefit Gained from Delaying Onset of Alzheimer's Disease

AD Drug Effectiveness	Delay AD Onset by 1 Year	Delay AD Onset by 3 Year	Delay AD Onset by 5 Year
QALY Gains	6.86 million	17.29 million	22.66 million
Dollar Value ($100,000 per QALY)	$0.69 trillion	$1.73 trillion	$2.27 trillion
Dollar Value ($150,000 per QALY)	$1.03 trillion	$2.59 trillion	$3.40 trillion
Dollar Value ($175,000 per QALY)	$1.20 trillion	$3.03 trillion	$3.97 trillion

Ref: Vernon, et al 2005

Issues to Consider in Designing Long-term Treatment Trials in Prodromal AD

- Defining "at risk" populations:
  - Criteria of Dubois, Sperling, etc.
  - Use of prodromal markers, cognitive and/or behavioral symptoms
- Measures to assess long-term treatment effects?
- How long should patients be followed?
- What are the ethical issues involved in treating patients that are asymptomatic?
- Cost benefits of delaying/preventing AD vs. costs of early intervention and long-term treatment?