Clinical Trials in Prodromal AD: An Industry Perspective

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Disclosure Statement

Ravi Anand consulted/consults for the following organisations

- Abbott
- Acadia
- Bioline
- Cephalon
- CliniRx
- Enkam
- Forest
- J&J
- Lundbeck
- Newron
- ONO
- Pfizer
- Roche
- Sigma Tau
- Schering Plough
- Takeda

R Hartman and M Ali have also consulted for some of these companies

Currently Approved Treatments for Alzheimer's Disease

- Tacrine (Cognex®)
  - Mild to Moderate AD (1993)
- Donepezil (Aricept®)
  - Mild to Moderate AD (1996)
  - Severe AD (2006)
- Rivastigmine (Exelon®)
  - Mild to Moderate AD (2000)
- Galantamine (Razadyne®)
  - Mild to Moderate AD (2001)
- Memantine HCl (Namenda®)
  - Moderate to Severe AD (2003)
- Assessment of usefulness of these drugs
  - Lack of long-lasting clinically significant benefits
  - Modest benefits on cognition, activities of daily living (ADLs) and behaviour
  - No/minimal improvement of Quality of Life (QoL)
  - Questionable cost effectiveness

Characterisation of Patients Entering AD Trials

- **Age:** mean = 73(52-92) yrs for mild/moderate; 84(59-99) yrs for severe
- **GDS:** 3-6 (mild to moderate); 5-6 (severe)
- **MMSE:** 12-24 (mild to mod. AD), 6-12 (severe AD) / 30
- **ADAS-Cog:** 23-27 / 70
- Deficits in ADL
- Minimal to moderate behavioural symptoms
- Time from diagnosis: 3-8 years
- Potential brain changes in these patients
  - Significant loss of cholinergic neurons, synapses
  - Decrease in neurotransmitters
  - 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

These data suggest that patients selected for these trials would have met criteria for Braak Stages III and higher, had the symptoms for 5-10 years, and suffered so much loss of function that significant improvement for more than transient periods, modifying disease progression, or reversal of disease, is virtually impossible.

Characterisation of Patients Entering Mild Cognitive Impairment (MCI) Trials

- Based on the limited effects noted in patients with AD, academia and industry embarked on studies evaluating the effects of treatment in patients with MCI.
- Numerous definitions exist for MCI, however all have fairly similar criteria:
  - 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 or recognition testing
  - No/very mild ADL impairment
  - Maximally 1 of 4 IADLs impaired (telephone, transportation, taking medication, finances)

Additional Criteria Proposed/Used for MCI Trials

- Minor Criteria (at least 1 required):
  - A. Presence of medial temporal lobe atrophy
    - Volume loss in hippocampus, entorhinal cortex, amygdale evidenced on MRI – qualitative ratings using visual scoring or quantitative volume
  - B. Abnormal CSF biomarkers
    - Low Aβ1-42, increased tau and/or phosphorylated-tau
    - Other well-validated markers, e.g. neural-thread protein
  - C. Specific pattern on functional neuro-imaging with PET
    - Reduced glucose metabolism – bilateral temporal / parietal
    - Other well-validated ligands, e.g., PiB, FDDNP
  - D. Proven AD autosomal dominant mutation within immediate family

Consistent Lack of Efficacy of Approved* AD Treatments in Major Government and Industry Supported 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
Rofecoxib (Rof)	Thal LJ et al..2005	48-month, n=1457	% of patients with clinical diagnosis of AD	Fewer patients on Pbo vs. Rof converted to AD (p=0.011)

***Rofecoxib not approved for AD**

Failure of Treatments was not a Function of the Rate of Conversion

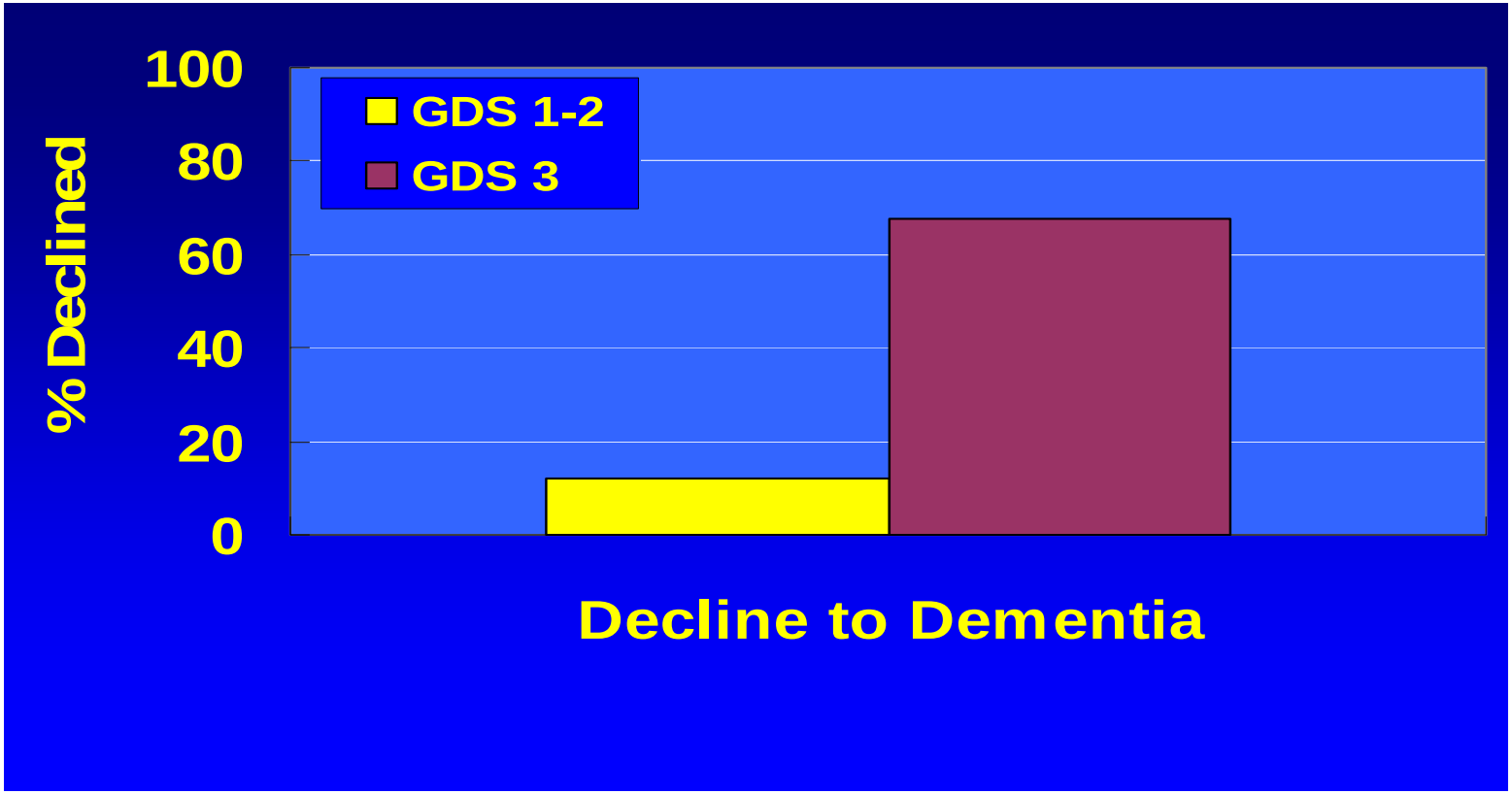
Drug	Study	Mean Age(SD) /Sex	Conversion Rate (MCI to AD) – Placebo
Donepezil	ADCS Study, Petersen R, et al. NEJM 2005; 352:2379-88	72 ± 7 46% F	14.7% / 1 yr 28.2% / 3 yr
Galantamine	Windblad B, et al. Neurol. 2008; 70:2024-35	Study 1:70 ± 9 53% F Study 2: 71 ± 9 57% F	Study 1: 22.6% / 2 yrs Study 2: 31.2% / 2 yrs
Rivastigmine	InDDEx Study, Feldman H, et al. Lancet Neurol. 2007; 6:501-12	70 ± 7 52% F	21.4% / 3-4 yrs
Rofecoxib	Thal LJ et al., Neuropsychopharm . 2005; 30:1204-15	75 ± 6 33% F	4.5% / yr 11.2% /4 yrs

Why Studies in MCI Did Not Show Benefits of Treatment?

- Treatments used were inappropriate for the symptoms
- Outcome measures used were inappropriate or insensitive to change
- Most likely reason: patients enrolled already had well established AD that was impossible to arrest for any length of time
  - When selected using “AD” inclusion/exclusion criteria, cases generally have prodromal AD (54% met pathological criteria for AD; medial temporal lobe involvement in most patients; hippocampal atrophy in over 70% at autopsy)

Ref: JA Schneider, et al 2009

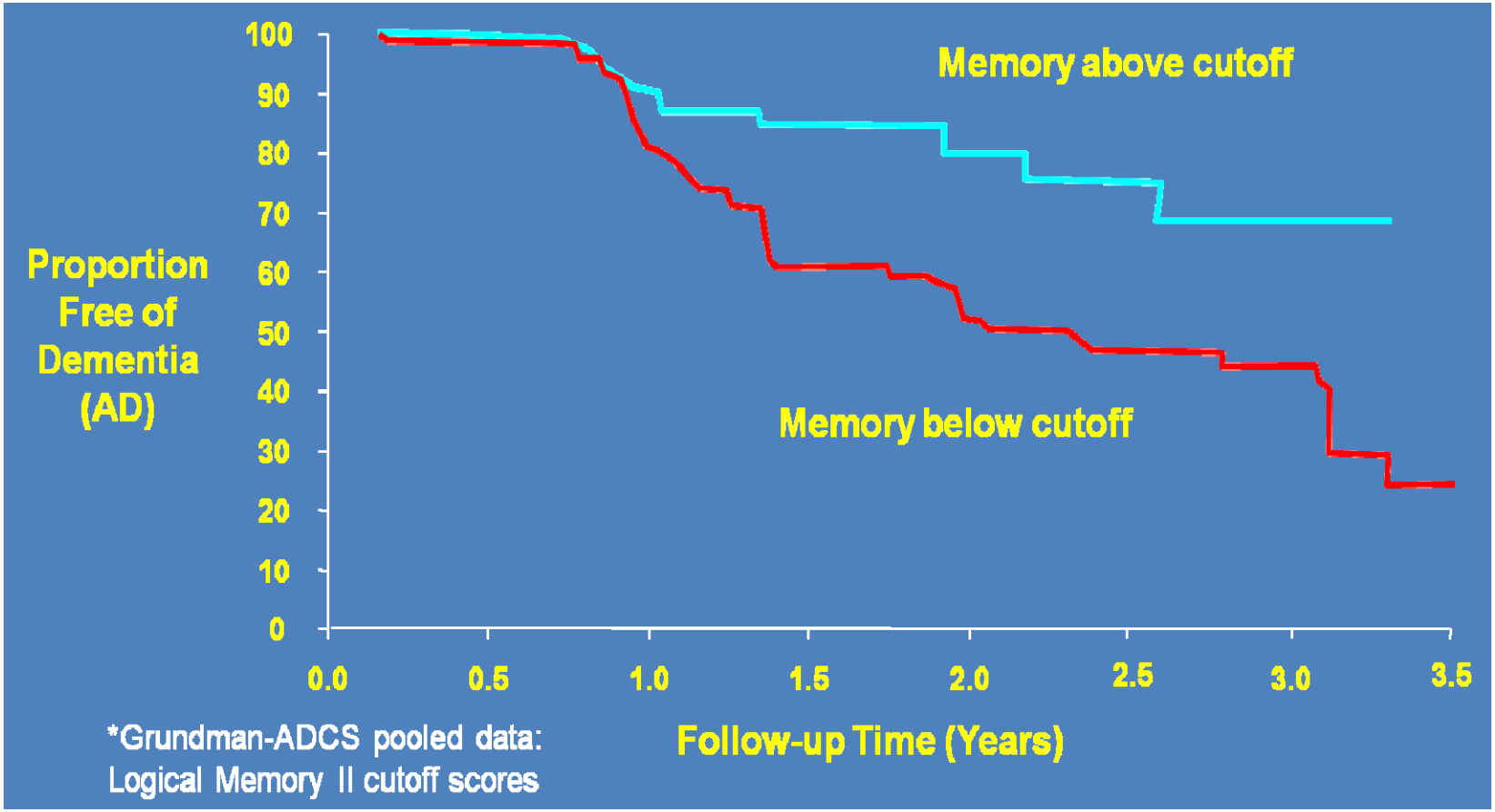
Decline To Dementia Among Non-demented Elderly (N=211)#



***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

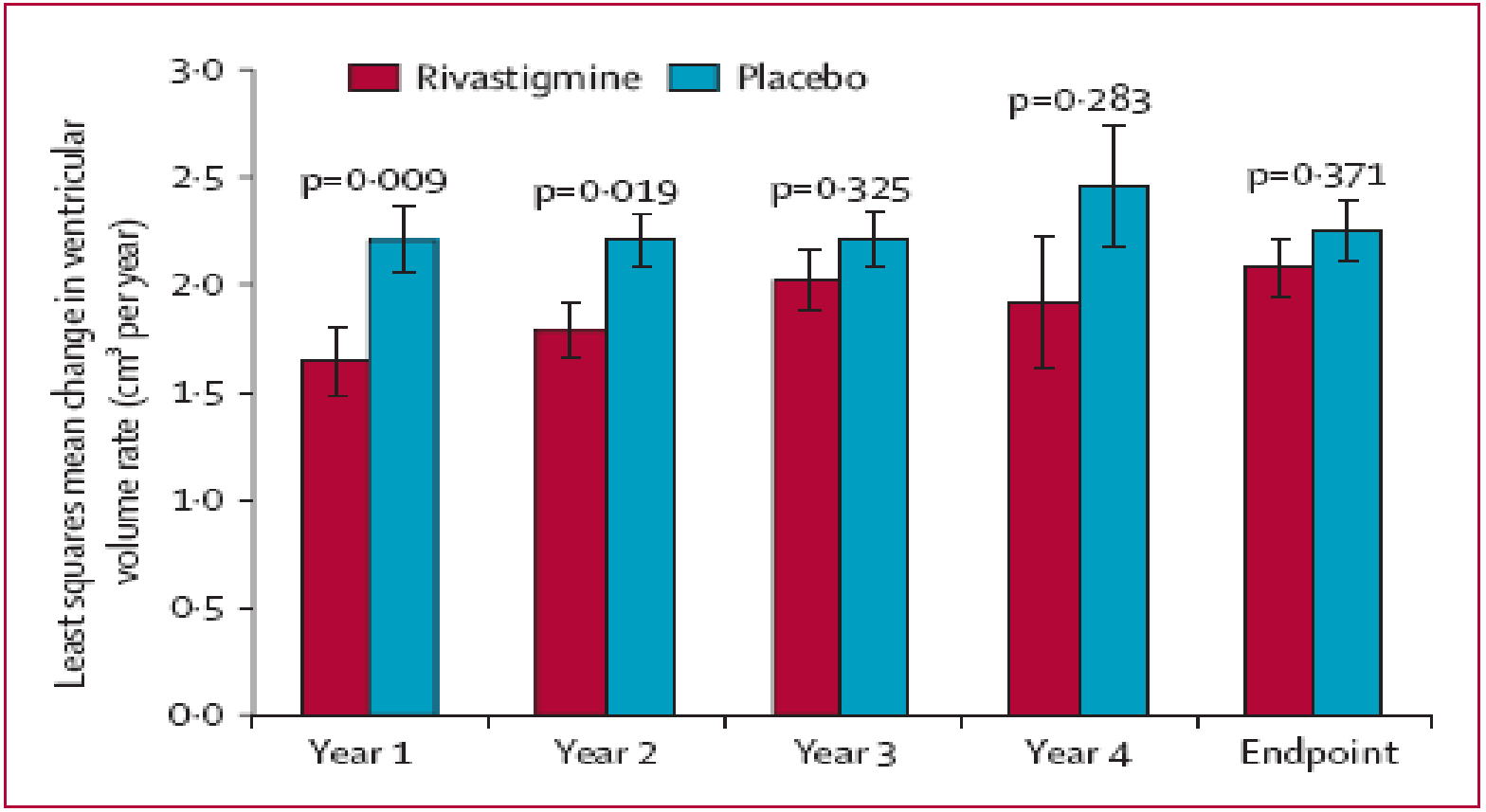
Increasing MCI to AD Conversion Rate with Memory Impairment Criteria*



*Grundman-ADCS pooled data:

Logical Memory II cutoff scores

InDDEx study: Absolute Change from Baseline per year in Ventricular Volume by Treatment Group (ITT analysis)



Ref: Feldman, et al 2007

Course of Prodromal AD

- Amieva H, et al. Ann Neurol, 2008; 64:492-498
  - 14-year follow-up of patients from PAQUID study
  - 350/3777 developed AD; matched with 350 elderly controls
  - Earliest decline in cognitive performance 12 yrs prior to AD diagnosis - semantic memory and conceptual formation (Isaacs Set Test)
  - 2 yrs later – deficits in Wechsler Similarities Test (verbal concept formation)
  - Global deficits appear with increasing memory complaints (Benton Visual Retention Test, MMSE) and depressive symptoms
  - 2 yrs later – slight dependence noted in ADLs
  - Last 3 yrs before AD diagnosis – impairment significantly worsened (all cognitive measures declined)

New Definition of “Prodromal AD”

- Although likely to be highly unpopular, we are proposing a redefinition of “prodromal AD”
  - This should not be what is currently called MCI, or very mild AD
- Conceptually this population should represent a transition stage between healthy aging and so called MCI
  - Patients should not have experienced the degree of neuropathological changes that are seen in patients with MCI and AD
- Performance deficits should be limited to a single cognitive domain, and the extent of the deficit should not overlap AD cases
- No functional deficits or treatable behavioural changes should be present
- Where possible, biomarkers, e.g., hippocampal atrophy, hypophosphorylated *tau*, should not be consistent with AD changes

Criteria for Prodromal AD

- We Propose the following General Criteria:
  - Patient and/or caregiver reported progressive deficit in cognition
  - Deficit on a cognitive measure (compared to normal, based on age and education) limited to one cognitive domain
  - No functional impairment, based on detailed examination
  - No manifest behavioral symptoms
  - MRI evidence excludes more than minimal atrophy
  - Changes in CSF markers (Aβ1-42, tau/ Aβ1-42 ratio not consistent with AD)

Challenges? – (i)

Difficulties in performing studies in "prodromal AD":

- Clinical definition

  Prodromal stage defined by cognitive impairment and current absence of changes indicative of AD (clinical , bio-marker, neuro-radiological),supported by presence of other risk factors

- Acceptance of indication/Regulatory considerations

  Risk state not disease; neuro-pathologic substrate uncertain (may not develop AD), insufficient data currently on time course of progression, benefit of treatment not visible till years later

  Would only one study meeting predefined efficacy criteria be accepted?

- Appropriate outcome measures

  Largely based on cognition (e.g., FCSRT); improvement, delay in worsening over time

  Worsening of ADLs, behaviour, increasing functional dependence could serve as valuable secondary measures

  During long-term treatment, delay in progression of GDS/CDR compared to placebo would be important

Challenges? – (ii)

Difficulties in performing studies in "prodromal AD":

- Trial duration

  Controlling attrition would be key

  Likely to be long-term, i.e. more than 5 years, likely to be 10 years

  MCI trials of upto 4 years did not show benefit despite more advanced pathology

  Would allow determination of conversion to dementia, revert to normalcy, or lack of progression

- Number of subjects

  Empirical data indicates sample size of approximately 500 patients per group if study were to be of 5-10 years with attrition not exceeding 25 %

  With all the uncertainties, the attendant costs, and the associated risk, is there any value to pursuing the indication as defined?

Analyses used in the Assessment of Treatment Benefits

1. Cost-Benefit Analysis

- The outcome of an intervention is in monetary units, taking into account the cost of the treatment and the financial benefit of shortening the period of disability, e.g. pain, hospitalization, need for nursing care, etc.

Analyses used in the Assessment of Treatment Benefits

2. Cost-Effectiveness Analysis

- The relationship between resources consumed and specified health-related benefits is expressed in health-oriented benefits, e.g. length or quality of life (QoL)
- Unlike cost-benefit analyses, these analyses allow inclusion of time spent in providing care in costs
- The analyses express the results in Quality Adjusted Life Years (QALYs), which allows incorporation of QoL and survival in a single outcome
- QALYs can be used as a benchmark to establish comparative values of different treatments for a condition; QALYs are used to define what represents “good value” and what society should pay for

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 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.

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

How Best to Target a Treatment that could Affect AD?

- 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