

Presentation, Diagnosis and Management of Alzheimer's Disease



Madhav Thambisetty, MD, PhD

Staff Clinician (Neurology)

Section of Brain Physiology and Metabolism

&

Laboratory of Personality and Cognition

National Institute on Aging

National Institutes of Health

A vertical, faded portrait of a man with a mustache, wearing a suit and tie, is positioned on the left side of the slide. The man is looking slightly to the right of the camera.

Outline

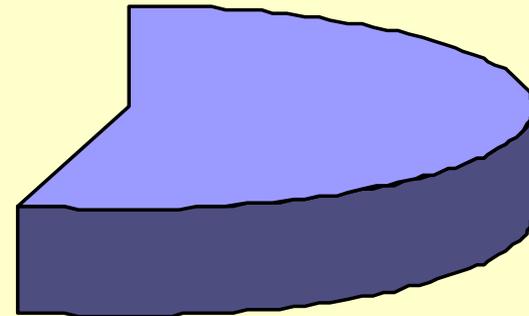
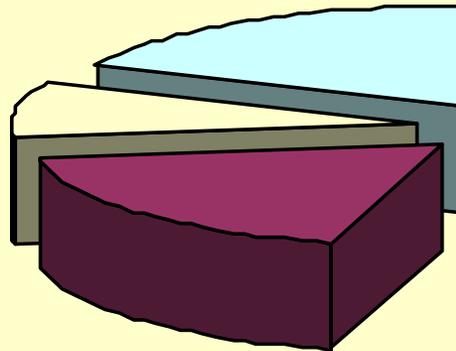
- I. CLINICAL FEATURES AND NATURAL HISTORY OF ALZHEIMER'S DISEASE
- II. DIAGNOSTIC CRITERIA FOR AD
- III. NON-COGNITIVE SYMPTOMS OF AD
- DIAGNOSTIC TOOLS IN ALZHEIMER'S DISEASE
- IV. EXISTING AND EMERGING THERAPIES FOR AD

Disorders causing dementia

**other
dementias
< 10 %**

**Vascular
dementia
< 20%**

**Alzheimer's
disease
> 60%**



**Dementia with
Lewy bodies
< 20 %**



Scope of the Problem

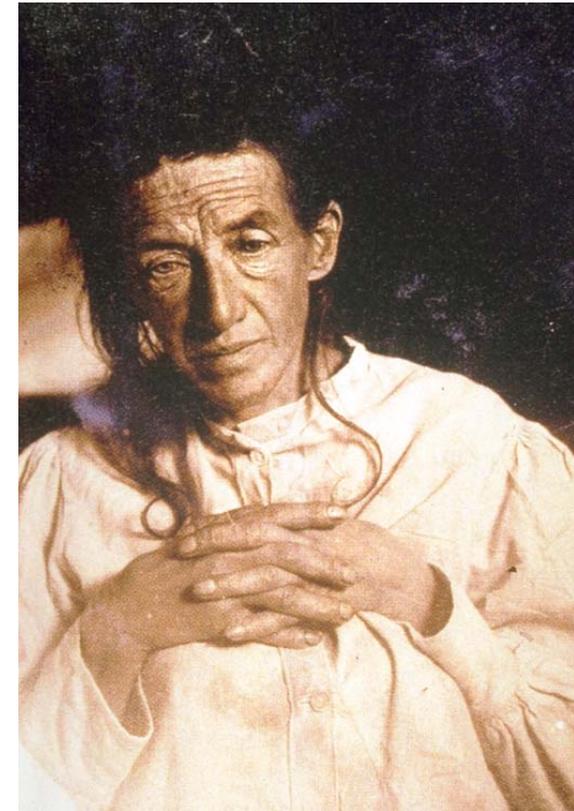
- AD affects 4.5 million Americans
- Expected to increase to 11-16 million over the next 50 years
- Accounts for \$24.6 billion in direct costs annually
- \$36.5 billion indirect costs annually due to lost productivity/caregiver absenteeism



Clinical features of Alzheimer's disease



“The first noticeable symptom of illness shown by this 51-year-old woman was suspiciousness of her husband. [At times] believing that people were out to murder her, [she] started to scream loudly. At times she.....seems to have auditory hallucinations.”



Alzheimer A 1907

(trans Jarvik & Greenson Alz.dis.Ass.Disord (1987) 1 7-8

November 26, 1901

Städt. Irren-Anstalt Frankfurt a. M.

No. _____

Aerztliche Acten

über
Auguste D. geb. D.
Alter: 51 Jahre. Religion: katholisch

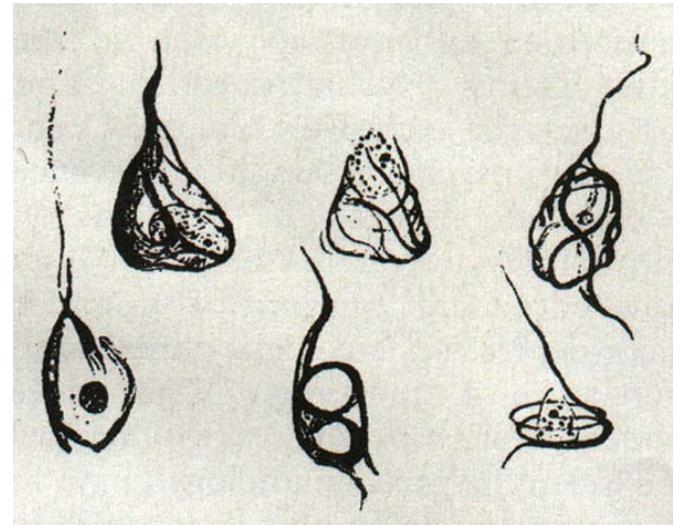
Lat. No.	Aufgenommen	Entlassen
1.	am 26. November 1901	am _____
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.		
12.		

gestorben am 6. April 1906.

- She sits on the bed with a helpless expression. What is your name?
- *Auguste*
- What is your husband's name?
- *Auguste, I think*
- Your husband?
- *Ah, my husband*
- Are you married?
- *To Auguste*
- Mrs D?
- *Yes, yes. Auguste D*

“A characteristic serious disease of the cerebral cortex” 1906

- In the centre of an otherwise normal cell there stands out one or several fibrils due to their characteristic thickness and peculiar impregnability





Natural history of Alzheimer's disease

- Onset
 - gradual, probably imperceptible
- Progression
 - slow and gradual but not linear
- Duration
 - less than 10 years, on average, from diagnosis to death

A faint, grayscale portrait of a man with a mustache, wearing a suit and tie, is visible on the left side of the slide. The man is looking slightly to the right of the camera.

Clinical Presentation of AD Amnesia

- Loss of Memory is the commonest presenting symptom
- Initially affects ability to recall new information
- Remote memory declines as the disease progresses
- Disorientation to time and place is closely related to memory impairment



Aphasia

- Reduced conversational output
- Word-finding difficulties
- Reduced vocabulary
- Increasingly non-fluent with disease progression
- Global aphasia

A black and white portrait of a man with a mustache, wearing a suit and tie, positioned on the left side of the slide.

Apraxia

- Inability to carry out learned purposeful movements despite normal strength and coordination
- Difficulties with:
 - Utensils
 - Appliances
 - Dressing

Agnosia

- Impaired recognition of sensory stimuli not attributed to sensory loss or language disturbance
- Prosopagnosia: Inability to recognize familiar faces
- Object agnosia
- Auditory agnosia: pure word deafness or non-speech sounds



A black and white portrait of a man with a mustache, wearing a suit and tie, standing with his hands in his pockets. The portrait is positioned on the left side of the slide.

Executive dysfunction

- Problem solving
- Abstraction
- Reasoning
- Decision-making
- Judgment

Visuospatial dysfunction

- Impaired driving
- Getting lost
- Copying figures





The non-cognitive symptomatology of Alzheimer's disease

Behavioural and
Psychological Symptoms of
Dementia (BPSD)

A faint, grayscale portrait of a man with a mustache, wearing a suit and tie, is visible on the left side of the slide. The man is looking slightly to the right of the camera.

BPSD in AD

- Symptoms of disturbed perception, thought content, mood, behavior
- Occurs in up to 50% of patients with AD



Psychological symptoms

- Depression
- Anxiety
- Persecutory ideas
- Visual hallucinations

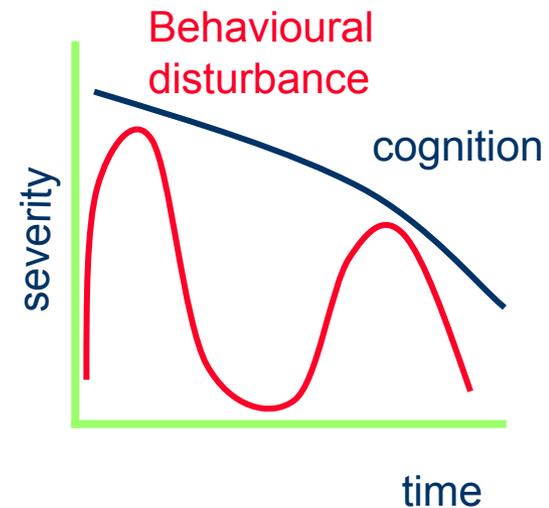
A faint, grayscale portrait of a man with a mustache, wearing a suit and tie, is visible on the left side of the slide. He is looking slightly to the right of the camera.

Behavioural disturbance

- Symptoms assessed by behavioural observation
 - Wandering
 - Aggression
 - Screaming
 - Restlessness

The importance of BPSD in AD

- Carer distress
- Hospitalisation
- Morbidity and mortality
- Cost



Causes of BPSD

Personality
Psychiatric

Neuroanatomy
Neurochemistry
Genetics

Psychological

Biological

Social

Carer factors
Patient factors
Environmental factors



A faint, grayscale portrait of a man with a mustache, wearing a suit and tie, is visible on the left side of the slide. The man is looking slightly to the right of the camera.

Diagnosis of AD

- Identify elements ***suggestive*** of the disease from the History and Physical examination
- Exclude other causes of dementia by laboratory tests and Neuro-imaging if necessary
- Most widely used clinical criteria for AD are:
 - National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)
 - Diagnostic and statistical manual of mental disorders IVth edition (DSM-IV)



NINCDS-ADRDA criteria for Probable AD

- I The criteria for clinical diagnosis of AD include
 - Dementia by clinical exam and supported by neuropsychological testing
 - Deficits in two or more areas of cognition
 - Progressive worsening
 - No disturbance of consciousness
 - Onset ages 40-90
 - Absence of other systemic or brain disease that could account for the condition



NINCDS-ADRDA criteria for AD

- **Diagnosis of Probable AD is supported by:**
 - Progressive deterioration in specific cognitive areas (e.g aphasia or apraxia)
 - Impaired function and altered behaviour
 - Family history
 - Normal EEG, Neuroimaging and CSF



NINCDS-ADRDA

Probable AD

- III other clinical features compatible with probable AD
 - Plateau in progression
 - Other neurological features such as gait disorder, myoclonus or abnormal primitive reflexes, especially late in the disorder
 - Seizures
 - Atrophy on CT



NINCDS-ADRDA

Probable AD

- IV features making the diagnosis of probable AD unlikely
 - Sudden apoplectic onset
 - Focal neurological features
 - Seizures or gait disturbance early in the disease



NINCDS-ADRDA

Possible AD

- Atypical onset and/or course of cognitive decline
- Focal neurological findings
- Co-existing disorders that may themselves produce dementia

A faint, grayscale portrait of a man with a mustache, wearing a suit and tie, is visible on the left side of the slide. The man is looking slightly to the right of the camera.

NINCDS-ADRDA

Definite AD

Definite AD=Probable AD + Neuropathology

- May only be made in the presence of a clinical diagnosis of probable AD together with neuropathological evidence of AD

A faint, grayscale portrait of a man with a mustache, wearing a suit and tie, is visible on the left side of the slide. He is looking slightly to the right of the camera.

DSM-IV Criteria

- Insidious onset and progressive decline in cognition with impairment in social/occupational functioning
- Impairment in recent memory, and one of:
 - Aphasia
 - Apraxia
 - Agnosia
 - Executive functioning
- Absence of other neurological, psychiatric, metabolic, systemic disease causing cognitive decline
- No delirium



Clinical Approach to AD

- History obtained from patient ***and*** reliable informant/caregiver
 - Changes from prior levels of cognitive performance
 - Decline in functional abilities
 - Personality changes
 - Confirm insidious onset and slow progression
- Cognitive testing:
 - Memory
 - Language
 - Attention
 - Orientation
 - Executive function

A faint, grayscale portrait of a man with a mustache, wearing a suit and tie, is visible on the left side of the slide. The man is looking slightly to the right of the camera.

Clinical Approach to AD

- Neurological examination:
 - Primarily to rule out other conditions
 - Focal deficits and suggest VaD
 - Prominent rigidity, tremor, bradykinesia suggest PD, LBD
 - Myoclonus
 - Primitive reflexes
- Rule out polypharmacy

A faint, grayscale portrait of a man with a mustache, wearing a suit and tie, is visible on the left side of the slide. The man is looking slightly to the right of the camera.

Laboratory evaluation

- Mainly to exclude other causes and/or treatable conditions:
 - **Complete blood count**
 - **Chemistry panel**
 - **Thyroid function**
 - **Vitamin B12 level**
 - ESR
 - Syphilis serology
 - Heavy metals
 - Chest X-ray
 - HIV test
 - EEG

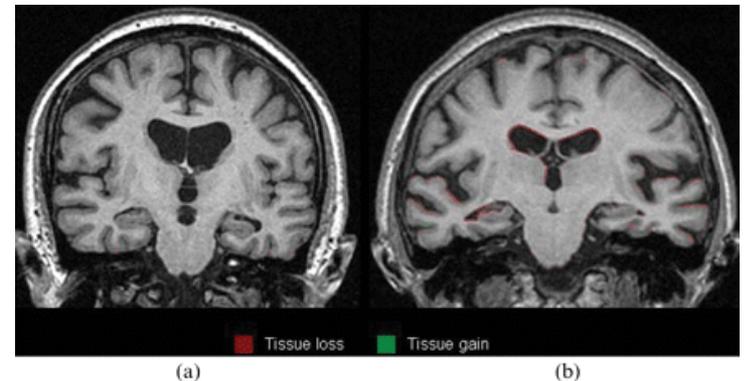
A black and white portrait of a man with a mustache, wearing a suit and tie, standing with his hands in his pockets. The portrait is positioned on the left side of the slide.

Role of Neuroimaging in AD

- American Academy of Neurology recommends structural neuroimaging to rule out:
 - Strokes
 - NPH
 - Space occupying lesions
 - Subdural hematoma
 - Non contrast CT or MRI

Structural neuroimaging in AD

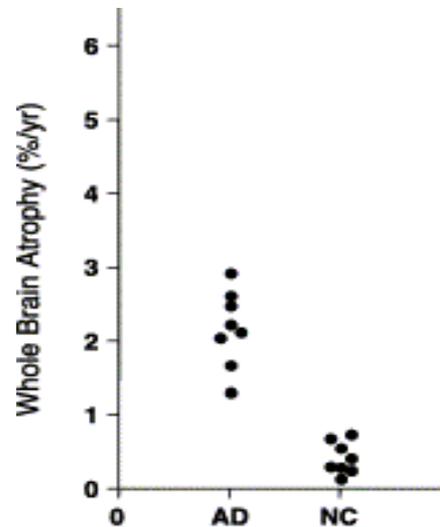
- Hippocampal atrophy predicts cognitive decline
 - Rate of hippocampal atrophy in healthy subjects 0.1-0.2% a year at 30-50 years
 - 0.8% in mid-70s
 - 1.5-2% between 80-90 years
 - Hippocampal atrophy rates are 4-8% a year in early AD
 - Hippocampal atrophy accelerates several years before diagnostic criteria for AD are met



Scahill RI and Fox NC
British Journal of Radiology
(2007) 80, S92-S98

Whole Brain Atrophy in AD

- Early event in AD
- Excellent discriminator between AD and control
- Correlates well with cognitive decline
- Longitudinal measures used in a clinical trial setting (AN 1792)

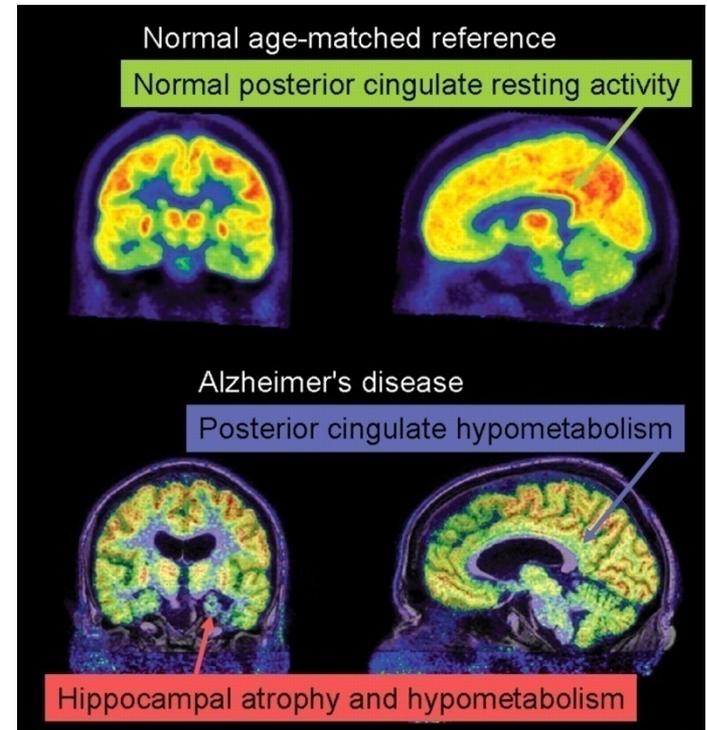


Chen et al.
Neuroimage
(2004) 22, 134-143

Functional Neuroimaging in AD

FDG-PET

- Reduced metabolism in the posterior cingulate cortex, precuneus and temporo-parietal cortices is an early event
- Good discriminant between AD and control as well as other dementias (FTD)

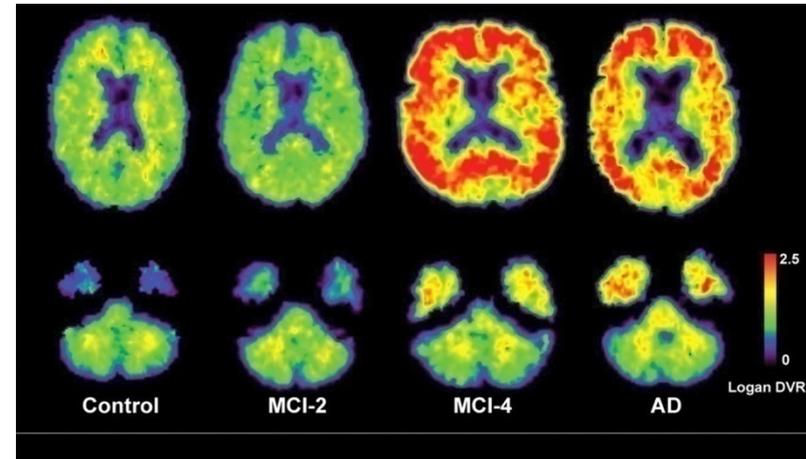


Herholz et al.
Br J Radiology
(2007) 80, S160-S167

Functional Neuroimaging in AD

^{11}C -PIB

- Binds fibrillar $\text{A}\beta$
- High sensitivity for $\text{A}\beta$ in plaques and vascular amyloid *in vivo*
- In AD, specific binding observed in frontal, temporal and parietal association cortices
- Bimodal distribution of increased PIB retention in MCI and control subjects



Herholz et al.
Br J Radiology
(2007) 80, S160-S167



Other A β tracers for PET

- (3'-[¹⁸F]F-PIB): ¹⁸F analog of PIB
- ([¹¹C]SB-13): Stilbene compound with a high affinity for A β
- Fluorinated stilbenes
- [¹⁸F]FDDNP: Binds to A β and tau



Diagnostic biomarkers in CSF

	Sensitivity	Specificity
■ Increase in total tau	90%	81%
■ Increase in phospho-tau	80%	90%
■ Decrease in $A\beta_{1-42}$	86%	90%
■ Predict progression to both MCI and AD		



Treatments for AD

Disease specific treatment for Alzheimer's disease



The cholinergic hypothesis

Cholinergic neurons are essential for memory

- Inhibition of cholinergic function results in cognitive loss
- Lesioning of cholinergic tracts also results in cognitive loss
- Cholinergic rich grafts restore memory functioning

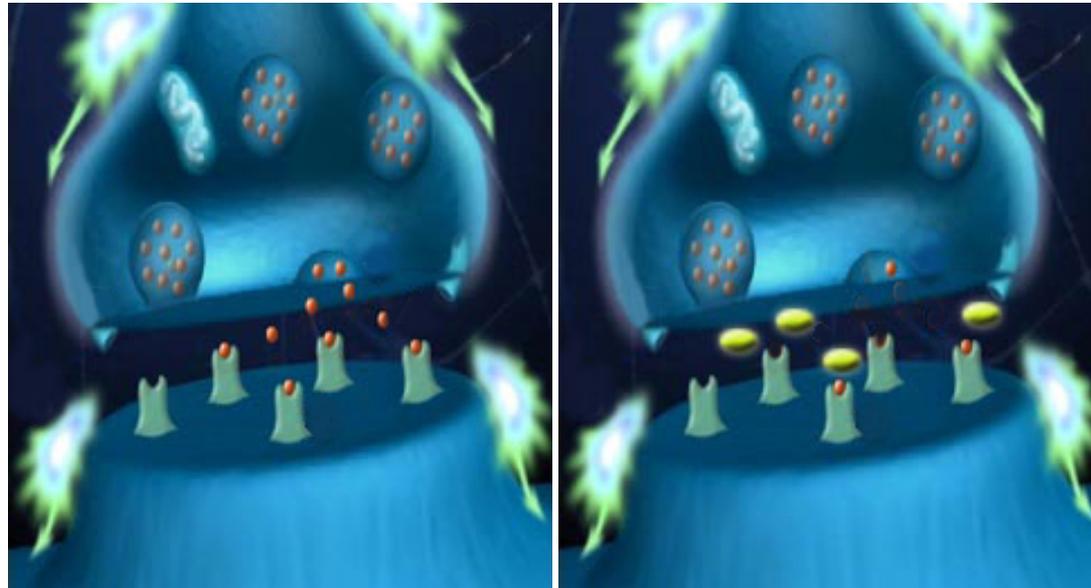
Cholinergic neurons are lost first and most in AD

- Choline acetyl transferase (ChAT) markers lost in AD
- Reduced choline uptake and ACh release in AD
- Neuronal loss in cholinergic nuclei in AD



**ACh formed from
phosphatidylcholine
(lecithin) and
Acetyl-CoA**

Cholinergic system

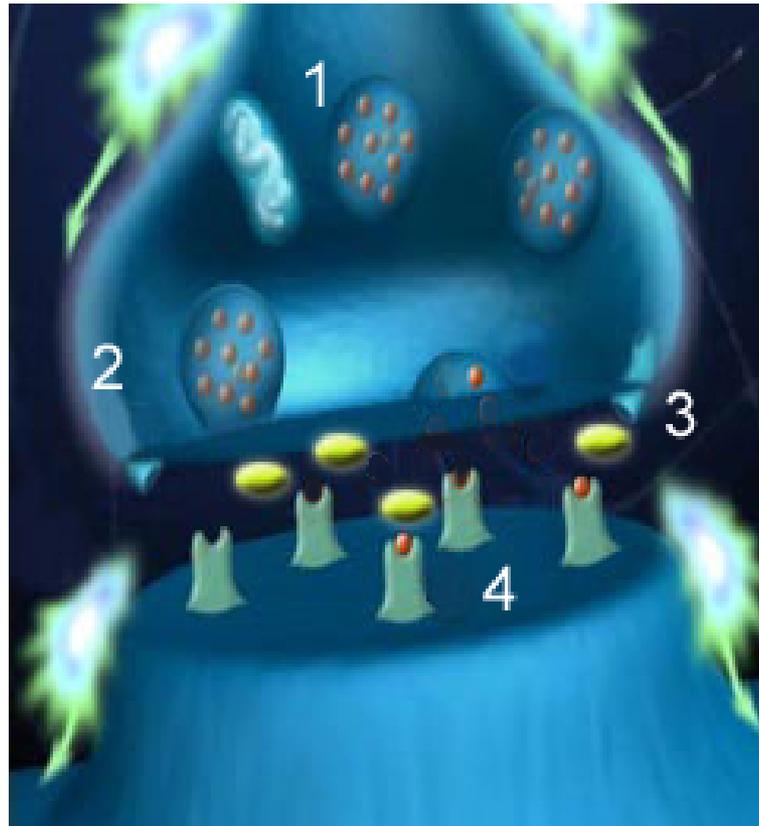


**ACh broken
down by
cholinesterase**

Options to enhance cholinergic function

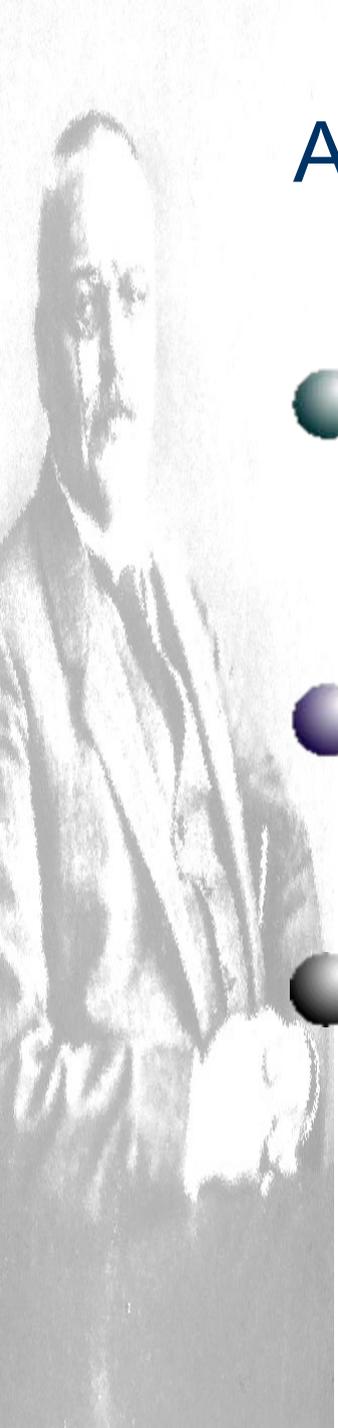
1. Drive synthesis

2. Enhance release



3. Prevent
breakdown

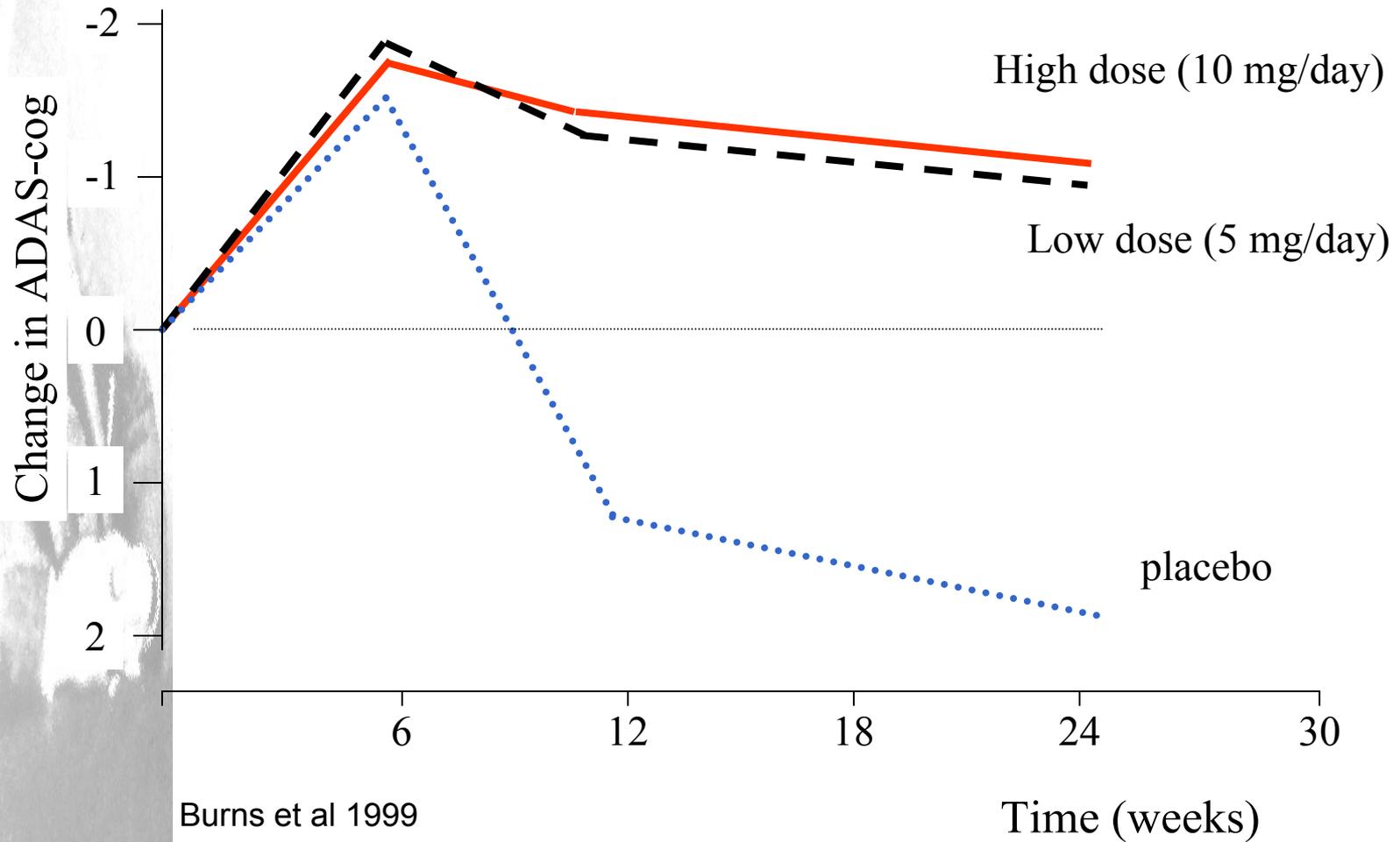
4. Post-synaptic
stimulation



Acetylcholinesterase inhibitors (ACHEIs)

- Approved in US and Europe 1995 onwards
- Modestly efficacious
- Effects on cognition, global change, function and behavior

Donepezil





ACHEIs in AD

- Donepezil, Galantamine, Rivastigmine
- Most common side effects are GI, sleep disturbances
- Comparable safety and efficacy profiles
- First choice as monotherapy in mild AD
- Which ACHEI to use is upto the treating clinician and is governed by tolerability and efficacy



Memantine in AD

- Non-competitive NMDA antagonist
- Blocks Glutamate-induced excitotoxicity
- Approved for moderate-severe AD
- May be used in combination with the AChE-inhibitors

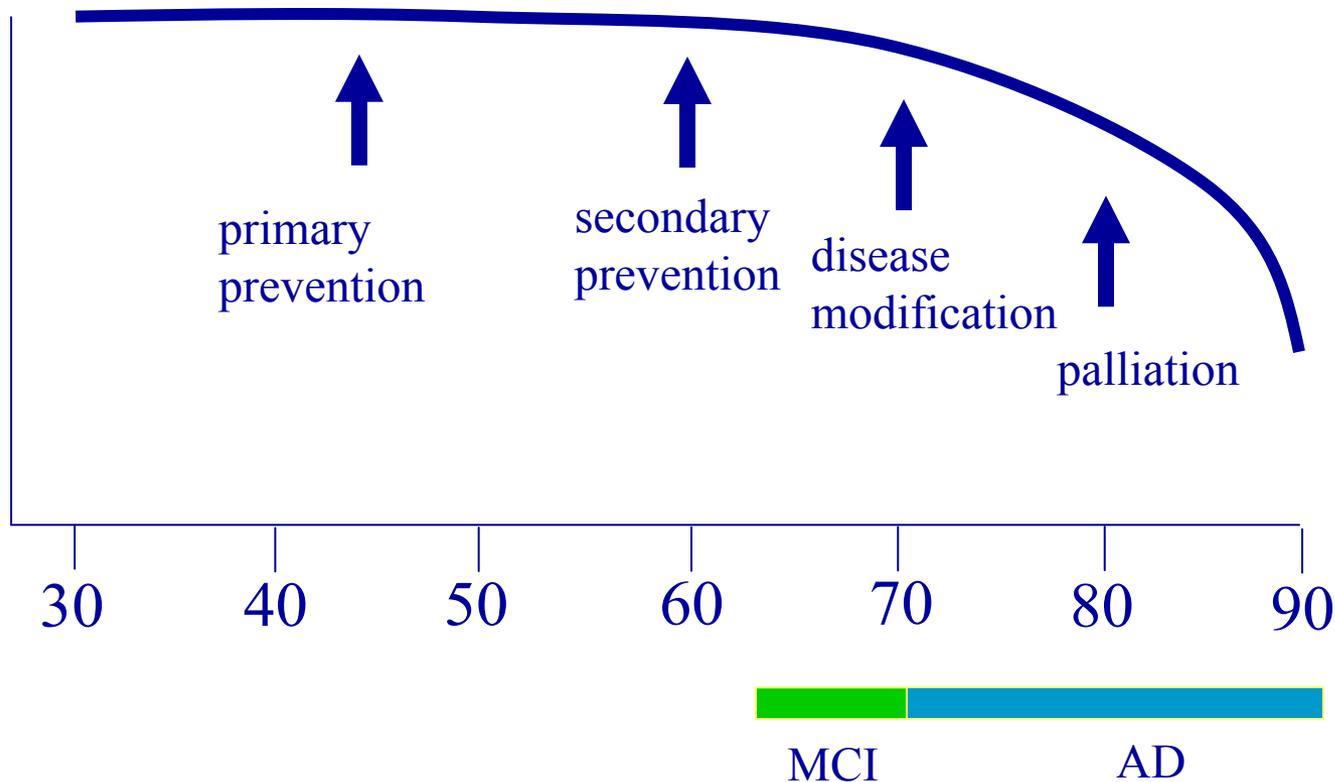
Amyloid is a good target for therapy ?



Plaques



Tangles



The promise of emerging treatments

