Advances in diagnosis and treatment of Alzheimer disease

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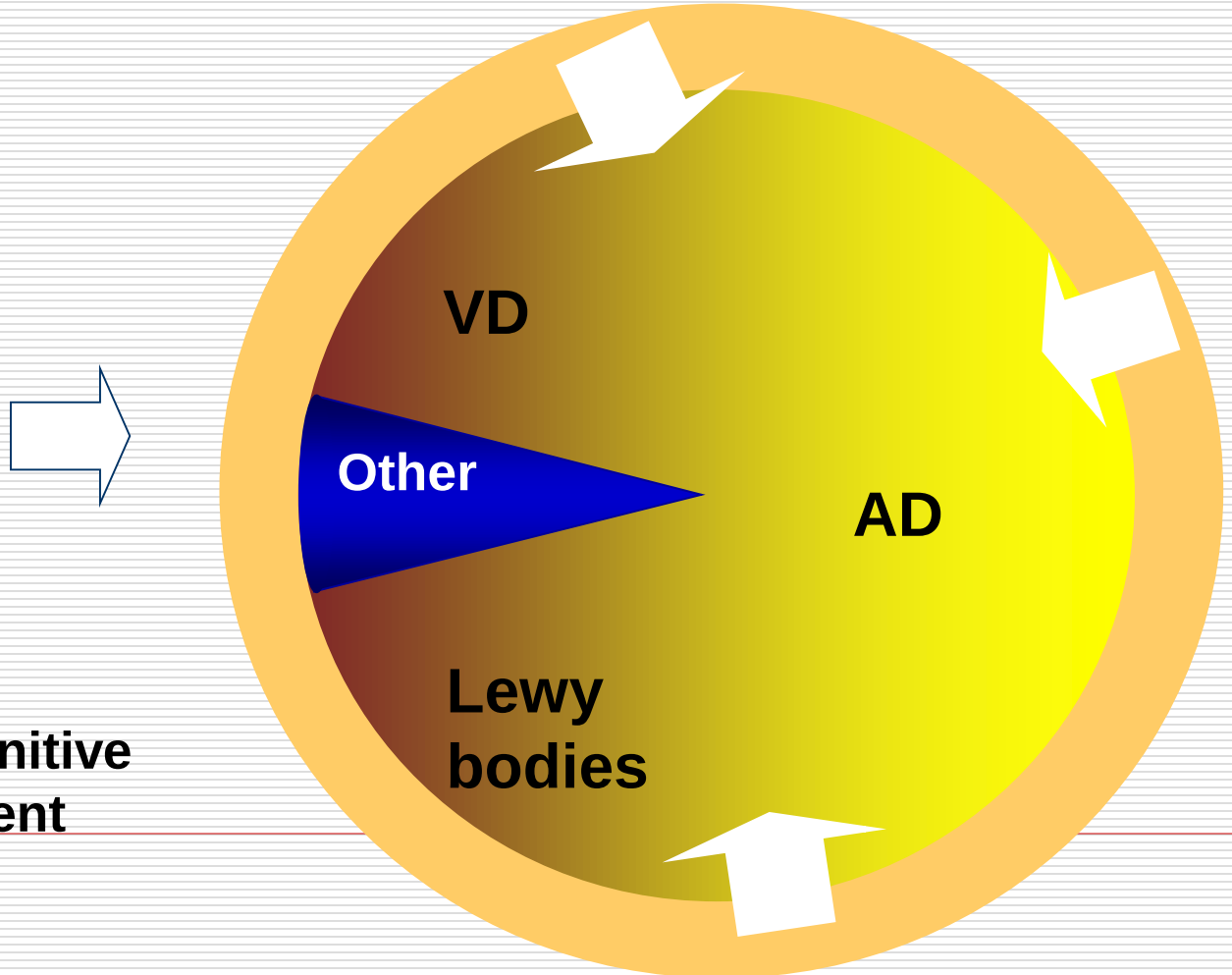
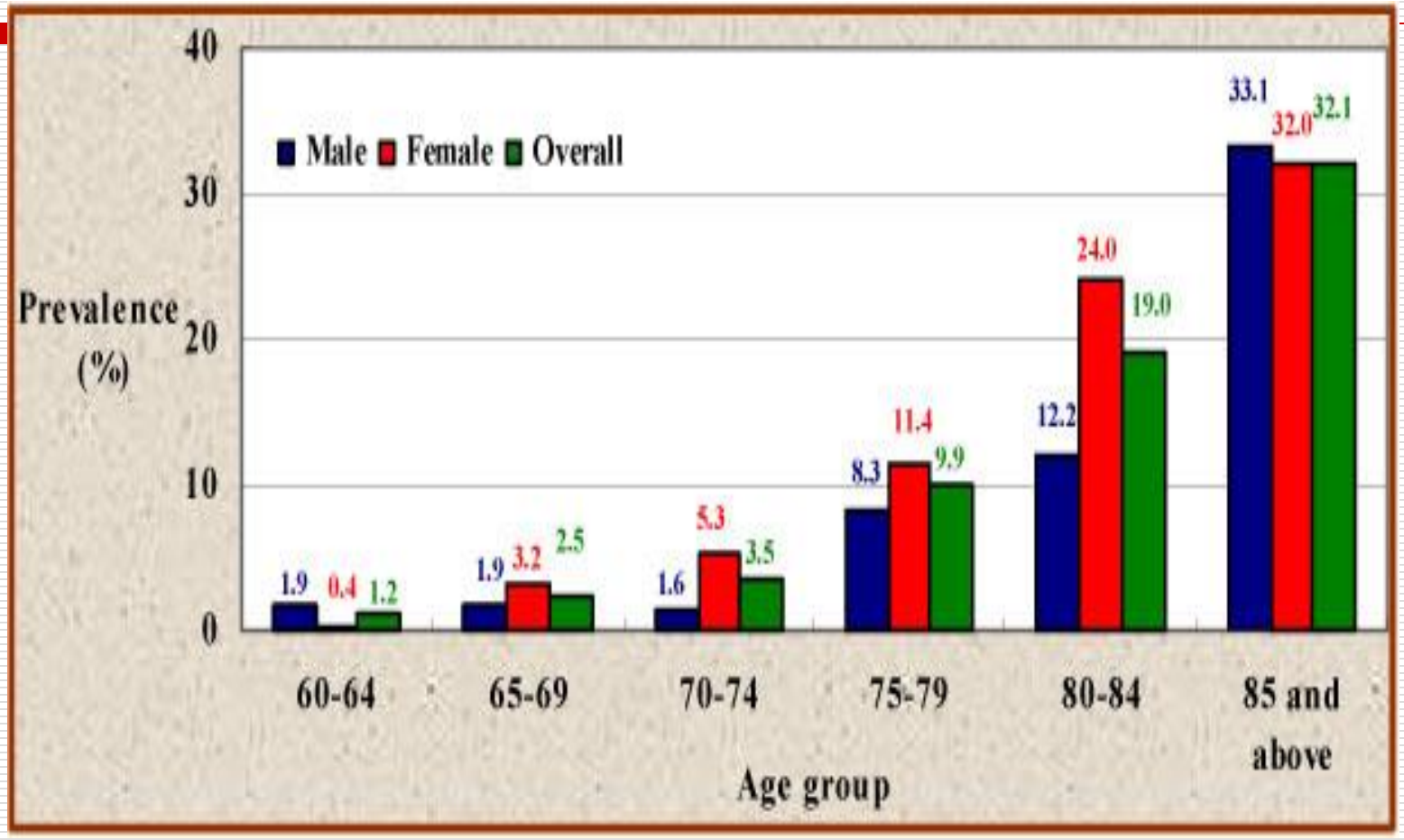
Emerging Spectrum of Dementia

The emerging consensus



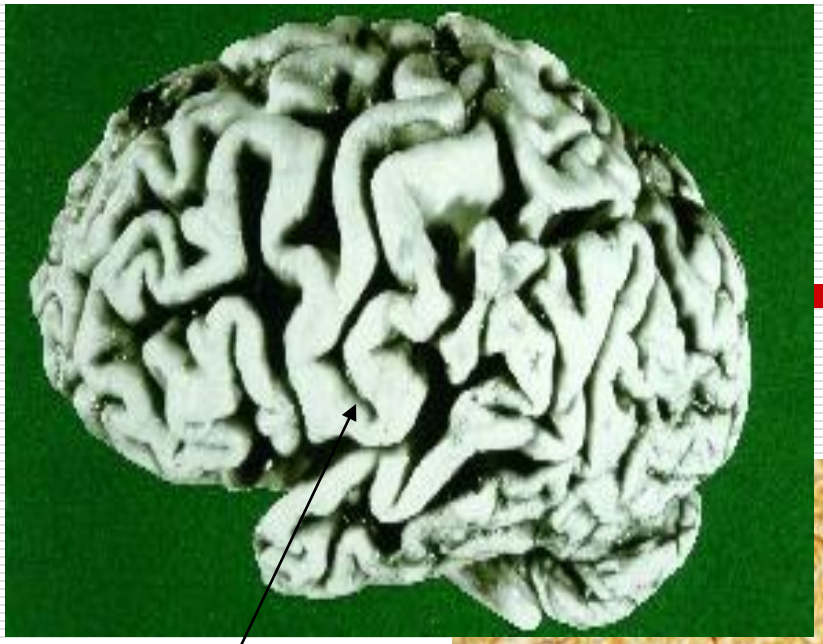
Mild cognitive impairment

Prevalence of dementia in community



Centre for Health Protection (2006). Aware (Newsletter). Volume 3, Issue 12

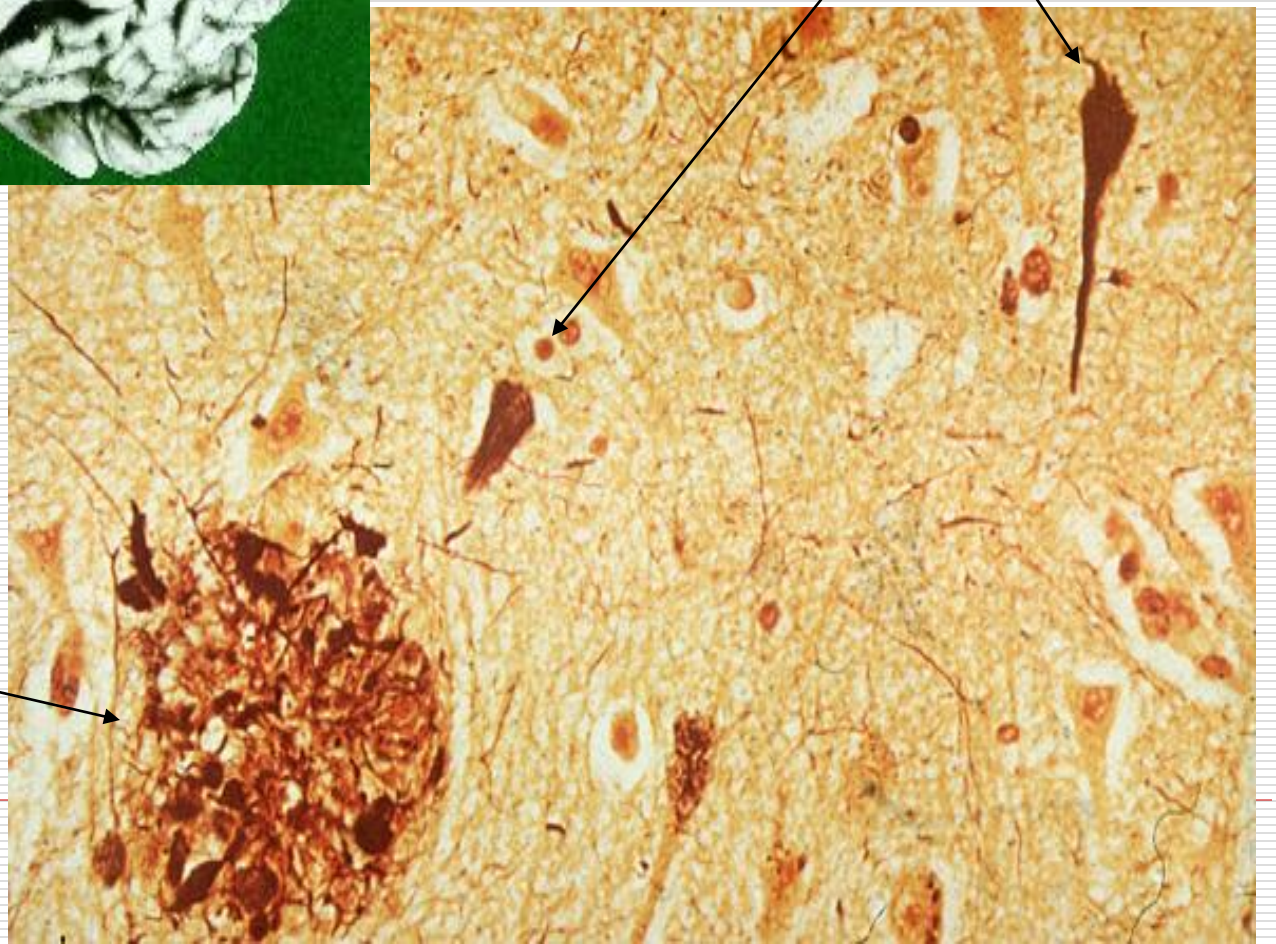
Alzheimer's Disease



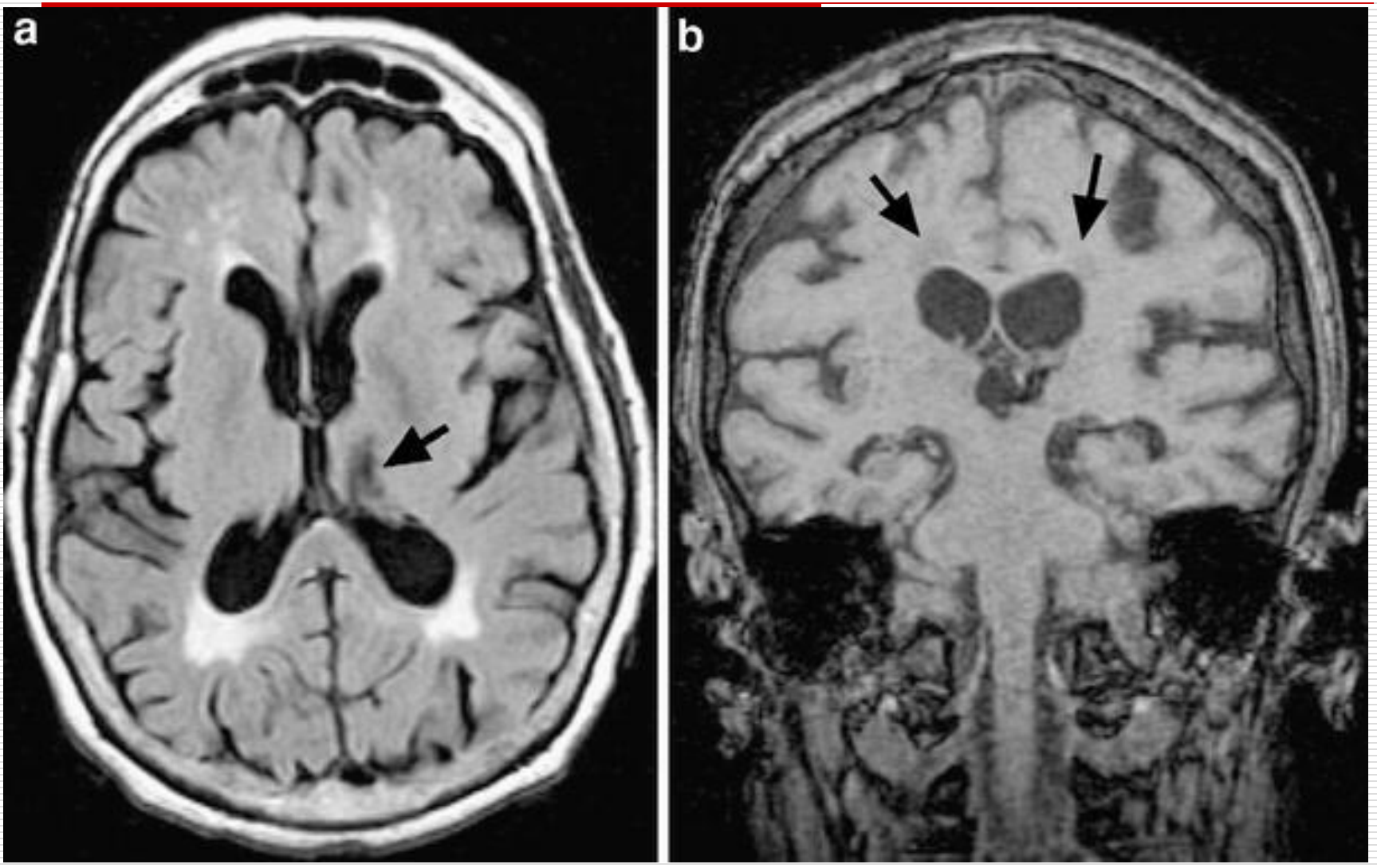
Atrophy

Tangles

Plague



MRI changes in Mixed dementia

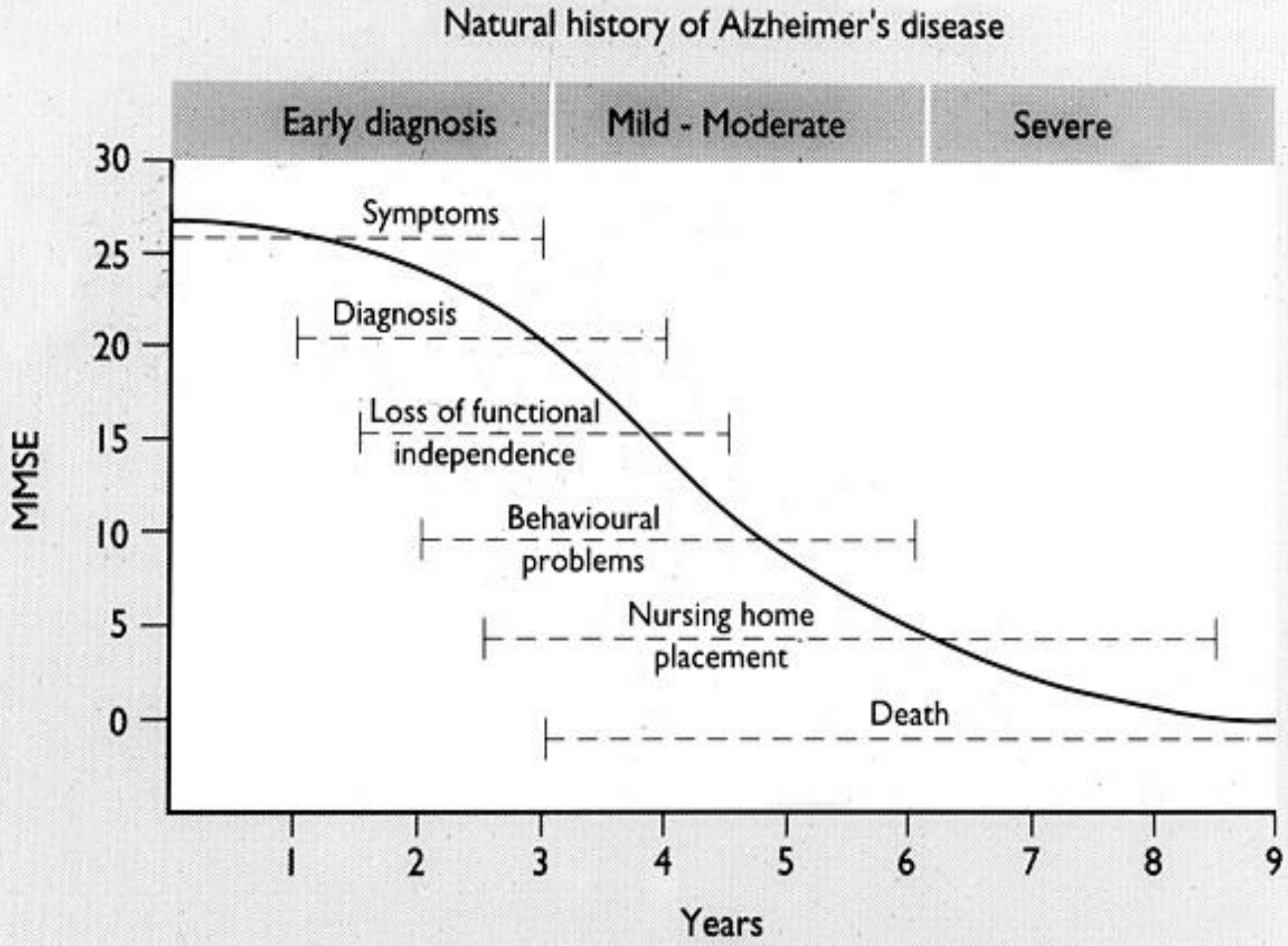


Diagnosis of Dementia

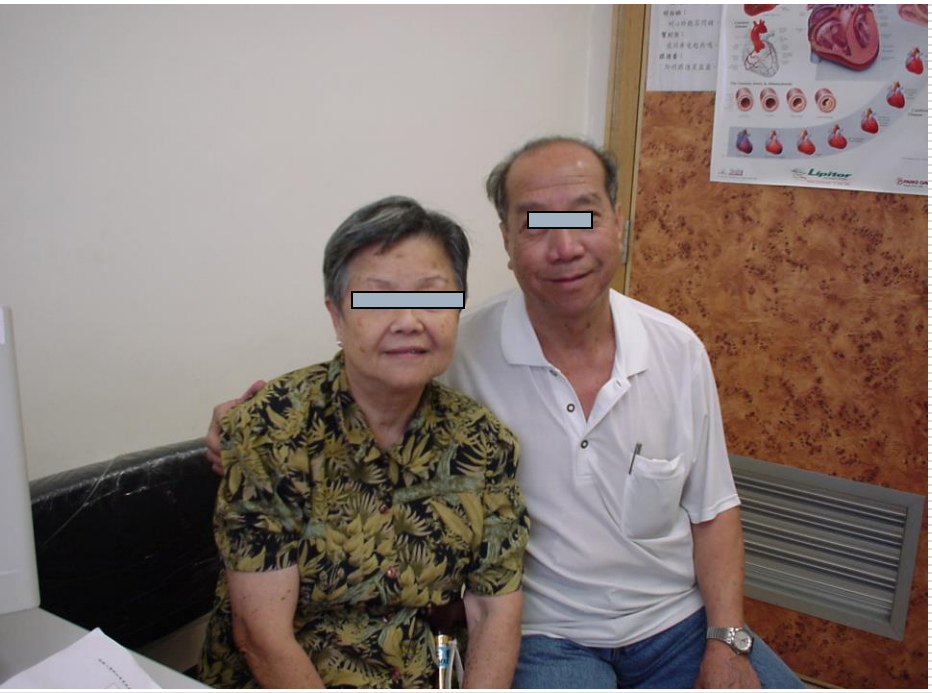
- Cognitive impairment affecting daily living – short term memory, orientation, ADL function, mood
- Corroborated by caregivers
- Objective evidence of cognitive impairment

Symptoms of Dementia

- Forgetfulness
- Getting lost in familiar settings
- Lose interest in family
- Deterioration of work performance
- Disorientation (time and place)
- Behavioral changes
- Slower walking/ falls

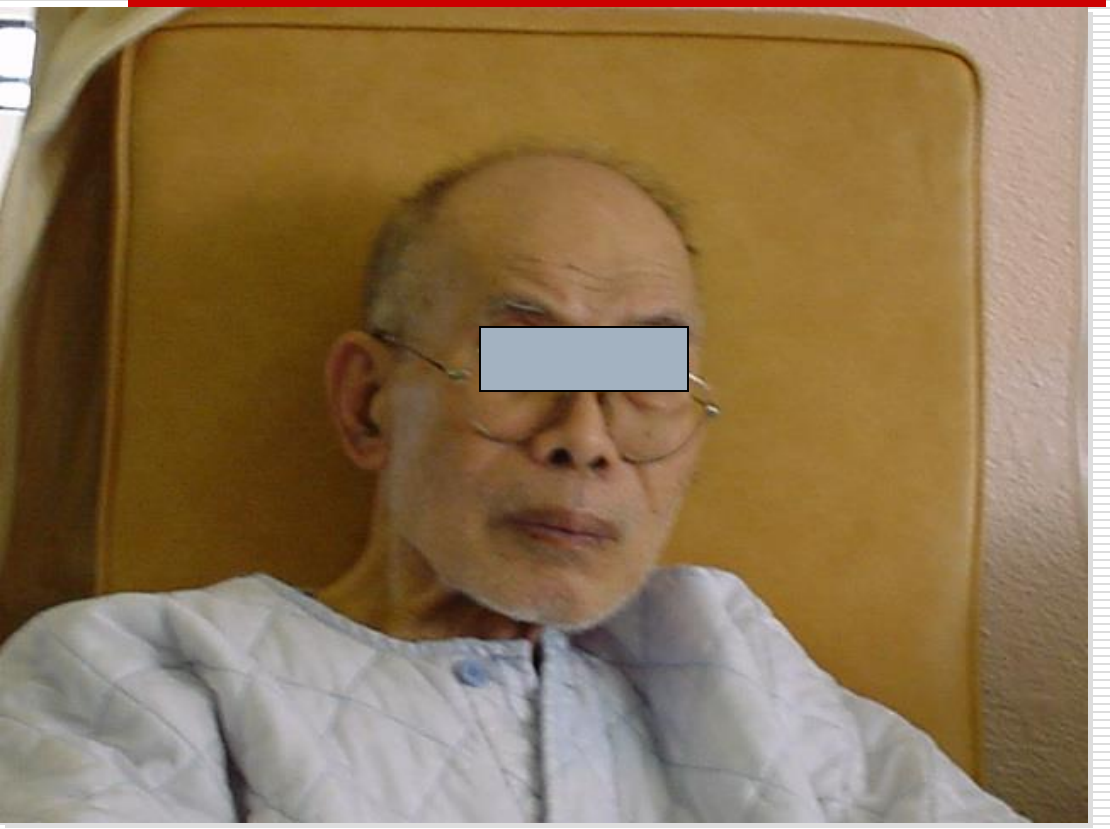

Natural history of Alzheimer's disease
Early diagnosis
Mild - Moderate
Severe
MMSE
30
25
20
15
10
5
0
Symptoms
Diagnosis
Loss of functional independence
Behavioural problems
Nursing home placement
Death
1
2
3
4
5
6
7
8
9
Years

Early Stage



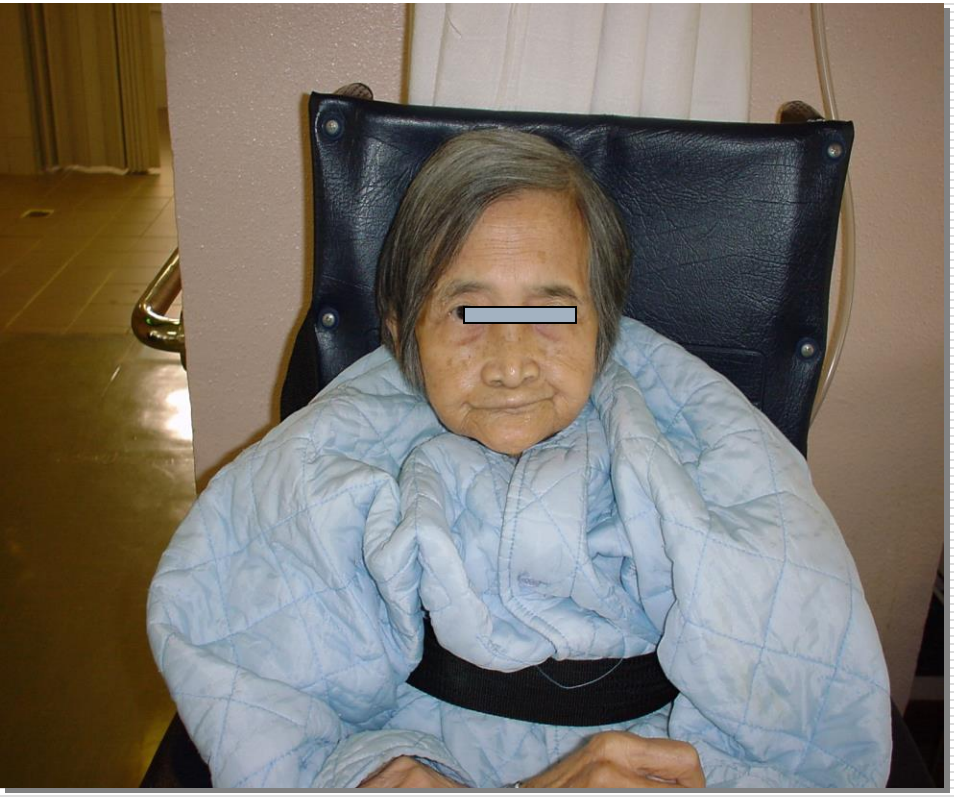
- Loss of advanced ADL
- Insight
- Anxiety, Depression
- Social relationship problems
- Drug/ lifestyle non-adherence
- Nutritional problems
- Financial management
- Home safety

Moderate Stage



- Loss of Basic ADL
- Home safety
- Caregiver support
- Behavioral problems
- Depression
- Psychosis
- Loss of insight

Late Stage



- Instability
- Physical dependency
- Somnolence
- Feeding problems
- Psychiatric problems
- End of life issues

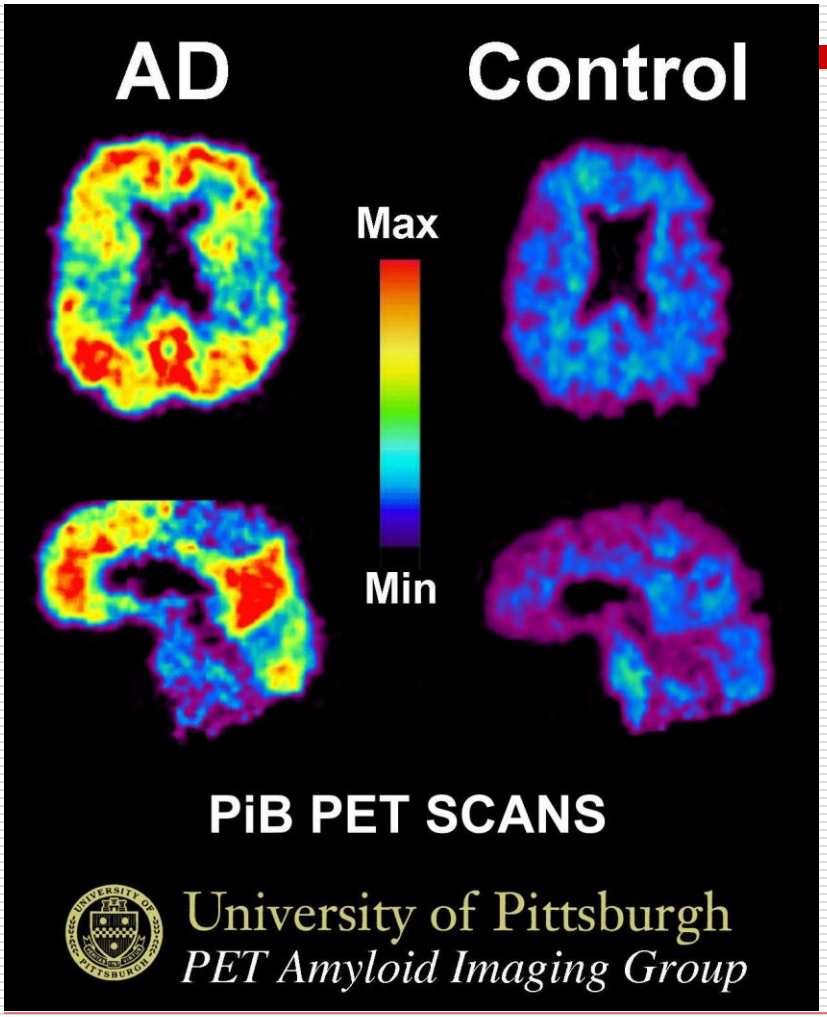
Behavioural Problems

- Emotional outburst
- Accusation of theft/ infidelity
- Wandering
- Refusal to bath
- Urinate outside toilet
- Sexual harassment
- Delusion/Hallucination
- Day night reversal

Diagnosis of Alzheimer disease

- Slow progressive decline in cognitive function
  - Short term memory
  - Executive function
  - Attention
- Degeneration of temporal, parietal → frontal lobes
  - Amyloid PET
  - PET (glucose)
  - Single-photon emission computed tomography (SPECT)
  - MRI

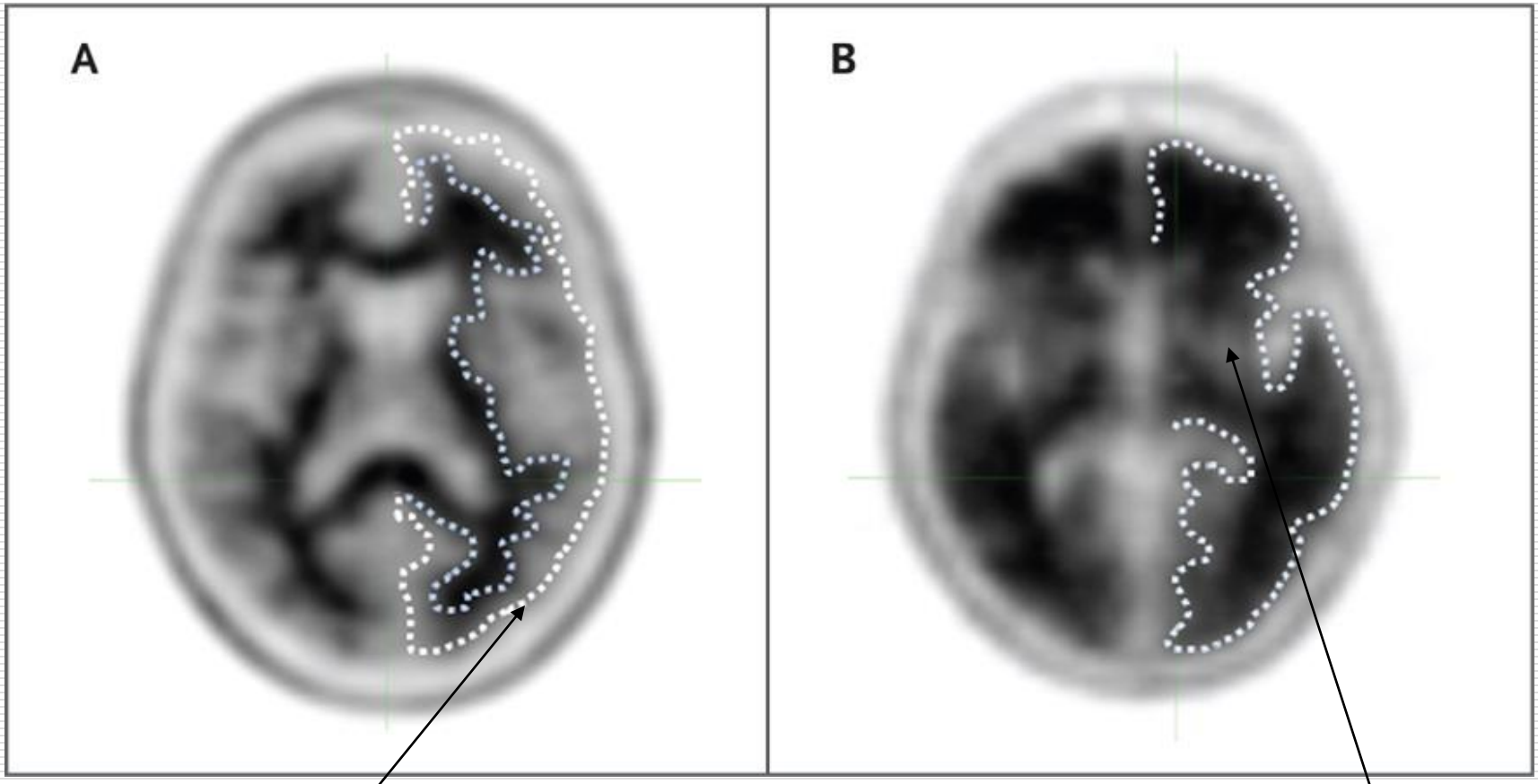
PiB PET scan (Positron emission tomography)



- ^{11}C-labeled PET tracer of fibrillar beta amyloid
- Predict cognitive decline in mild cognitive impairment, but not in dementia
- Half life 20 minutes (unlikely to be commercially viable)

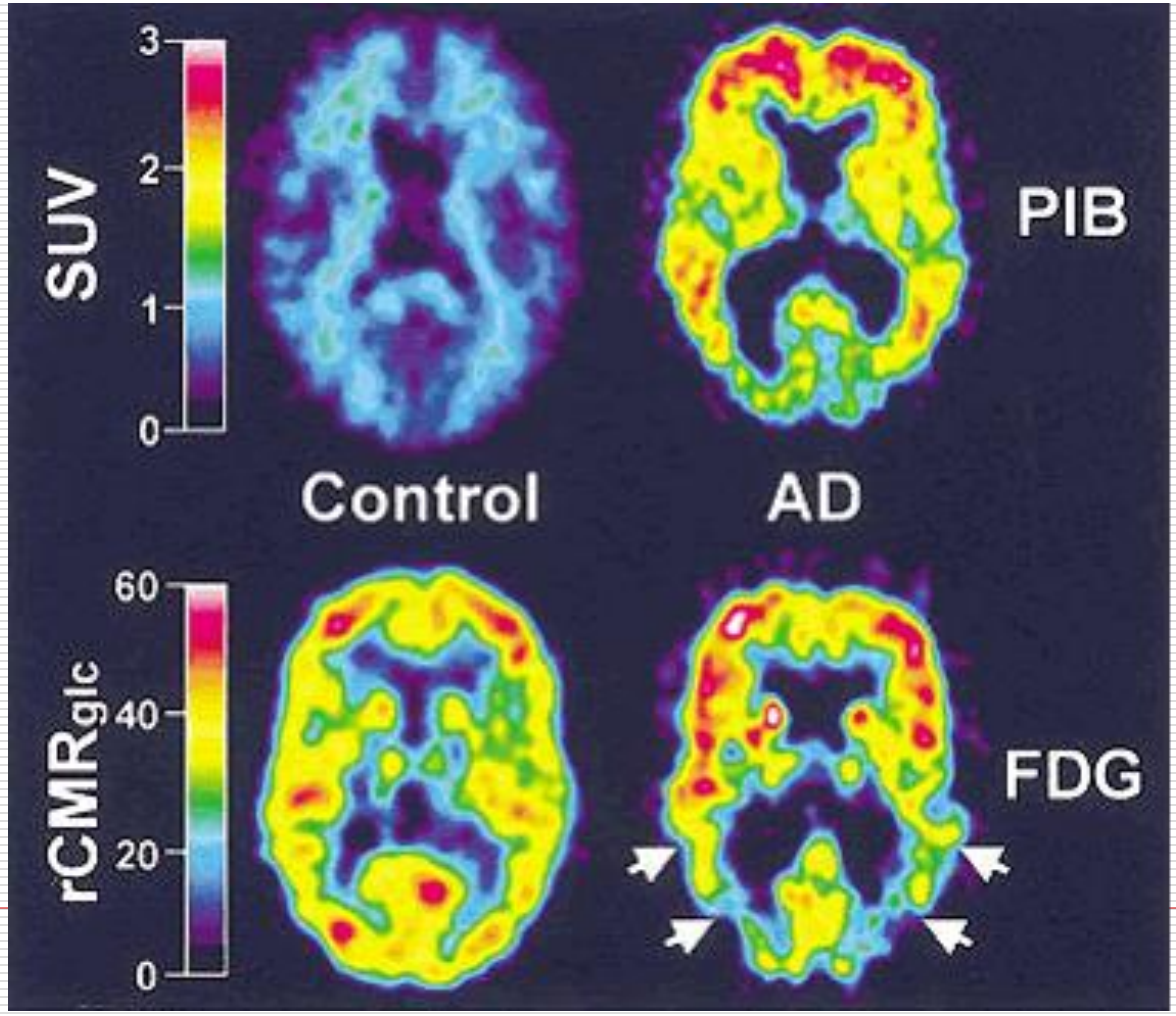
Klunk W.E. Annals of Neurology, 2004

Typical Negative and Positive Florbetapir Scans (18F-labeled Abeta ligand)



Yang L et al. N Engl J Med 2012;367:885-887.

Discrepancy between amyloid deposit and brain hypoactivity



CSF biomarkers

- AD
  - CSF amyloid -β_{42} decreased
  - Tau and phosphorylated Tau increased
- Prospective change in AD
  - amyloid -β_{42} decreased
  - phosphorylated Tau decreased
- Use limited by lack of standardized method and patient's intolerance of LP

CSF Aß42 and pTau in normal, cognitively impaired (CI) and AD patients

	Normal	CI-CI	CI-AD	AD-AD
MMSE	26	26	26	20
$Aß_{42}$	709	674	464	379
chge/yr	-20.6	3.4	0.8	-11.9
pTau	57	55	76	90
chge/yr	0.84	1.24	-0.21	-2.20
Aß:pTau	14.7	12.8	5.3	4.0
Chge/yr	-0.3	-0.2	-0.1	0.2

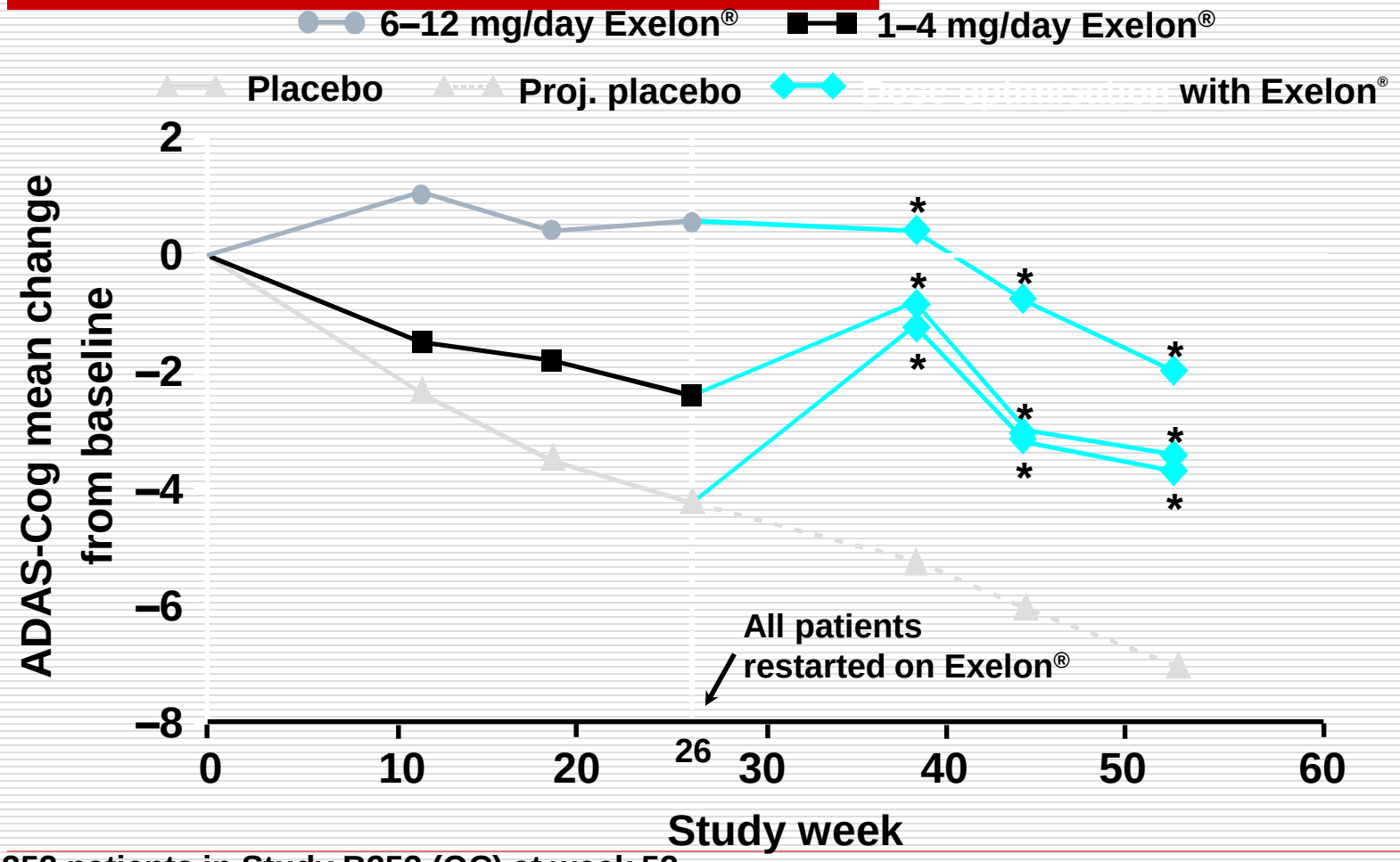
Seppala TT J Alzheimer disease 2011

Use of imaging and CSF

- To diagnose AD and predict cognitive decline in patients with mild cognitive impairment (prodromal stage of dementia)
- To exclude AD in atypical cases of dementia
- Clinical trial

Drug therapy for AD

Exelon® on cognition: greater benefits with earlier therapy



B352 patients in Study B353 (OC) at week 52
*p<0.05 vs projected placebo

Messina et al., 2000

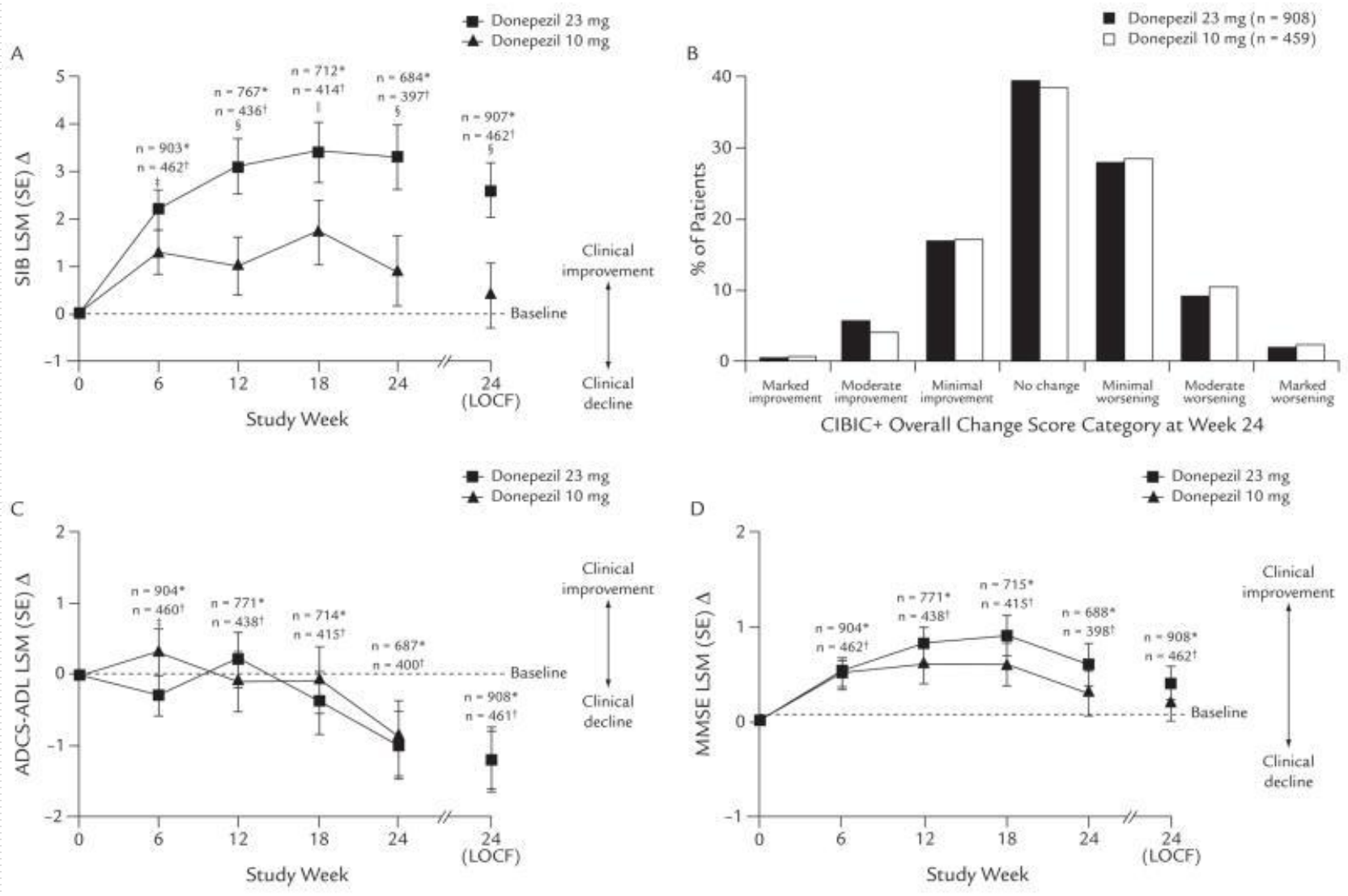
Adverse effects of chlolinesterase inhibitors

- Nausea (11%)
- Anorexia (10%)
- Vomiting (5%)
- Insomnia (9%)
- Dizziness (8%)
- Muscle cramps (5%)
- Nightmares (up to 10%)

Adverse effects of Chlolinesterase inhibitors

- Most patients do not have adverse effects
- Side effects are dose dependent
- less frequent if dose is titrated up
- Usually remit over time or if dose reduced
- Exelon patch may have less GI upset

High versus standard doses of Donepezil (Farlow MR Clin Ther 2010)



Side effects of high versus standard dose of Donepezil

Table IV

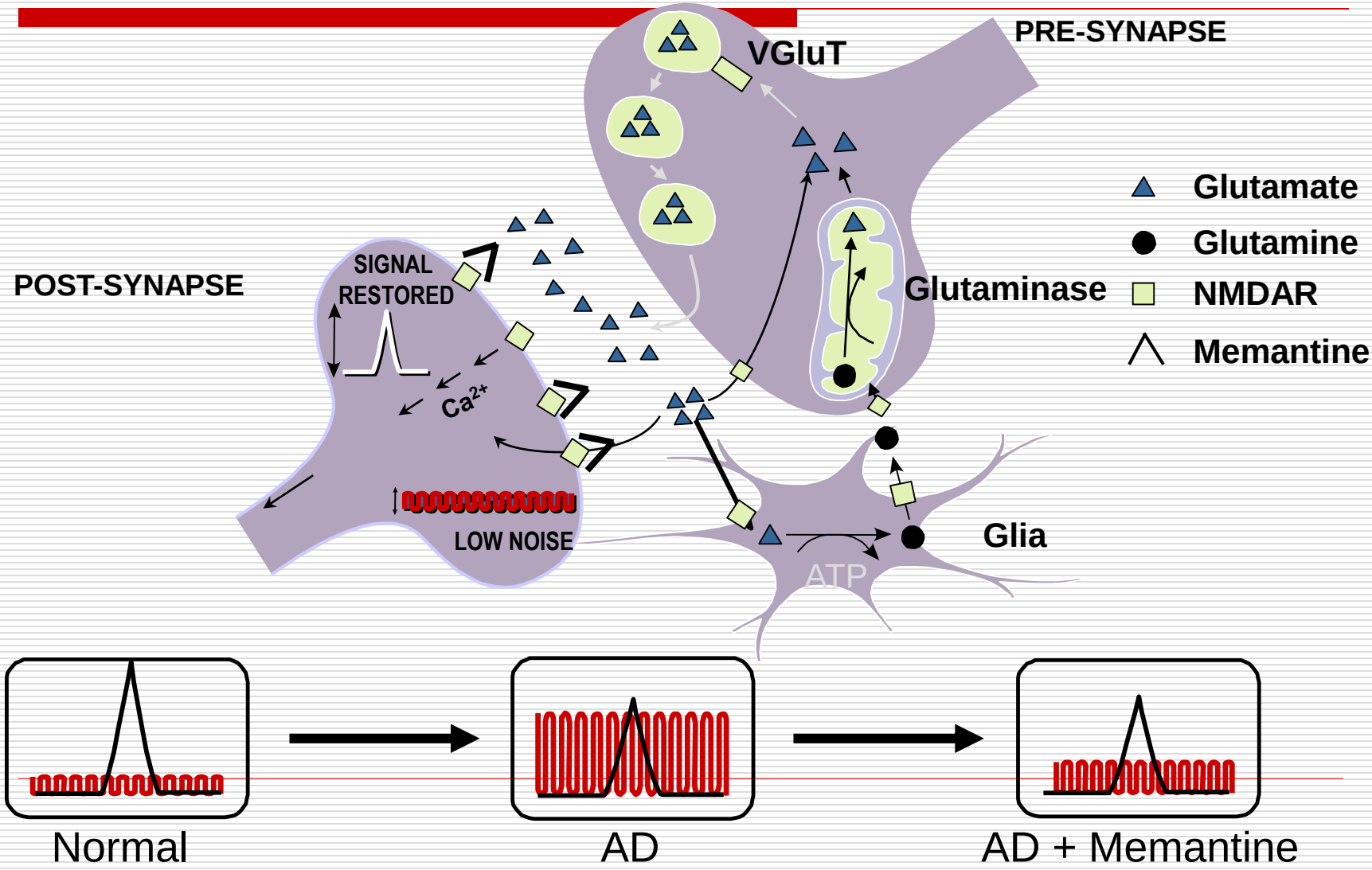
Treatment-emergent adverse events* (TEAEs) in patients with moderate to severe Alzheimer's disease who received ≥1 dose of treatment with donepezil 23 or 10 mg/d. Data are number (%) of patients.

Parameter	Donepezil 23 mg/d (n = 963)	Donepezil 10 mg/d (n = 471)
Patients with ≥1 TEAE	710 (73.7)	300 (63.7)
TEAE		
Nausea	114 (11.8)	16 (3.4)
Vomiting	89 (9.2)	12 (2.5)
Diarrhea	80 (8.3)	25 (5.3)
Anorexia	51 (5.3)	8 (1.7)
Dizziness	47 (4.9)	16 (3.4)
Weight decrease	45 (4.7)	12 (2.5)
Urinary tract infection	42 (4.4)	19 (4.0)
Headache	41 (4.3)	15 (3.2)

Ebixa (memantine)

- An uncompetitive NMDA antagonist
- Effective for AD and VaD
- Well tolerated
- Proven efficacy and safety by FDA & EMEA (moderate/severe AD)
- Available in tablets (10mg b.d.)

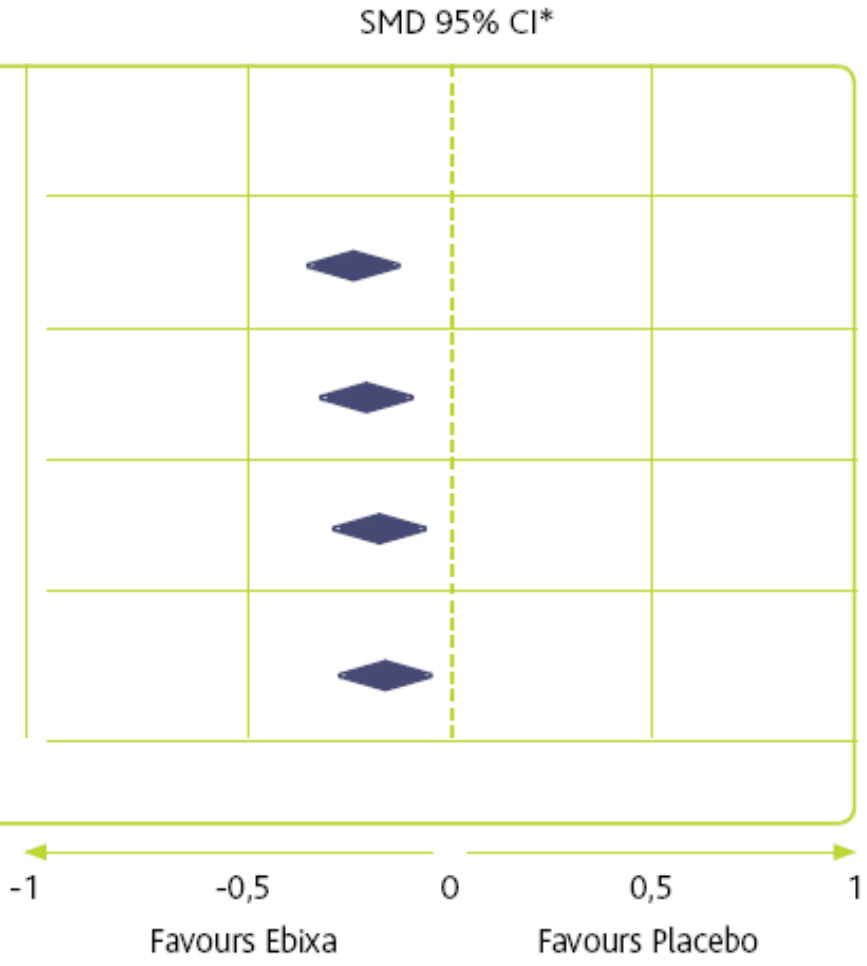
Glutamate–glutamine cycle in AD



Significant benefits of Ebixa across domains in moderate to severe Alzheimer's disease

Domain: scale	n Ebixa®	n Placebo	P-value
Cognitive: ADAS-Cog/SIB	778	664	<0.00001
Global: CIBIC-Plus	789	669	<0.0001
Functional: ADCS-ADL$_{23/19}$	791	670	0.0007
Behavioural: NPI	790	670	0.03

CI = confidence interval

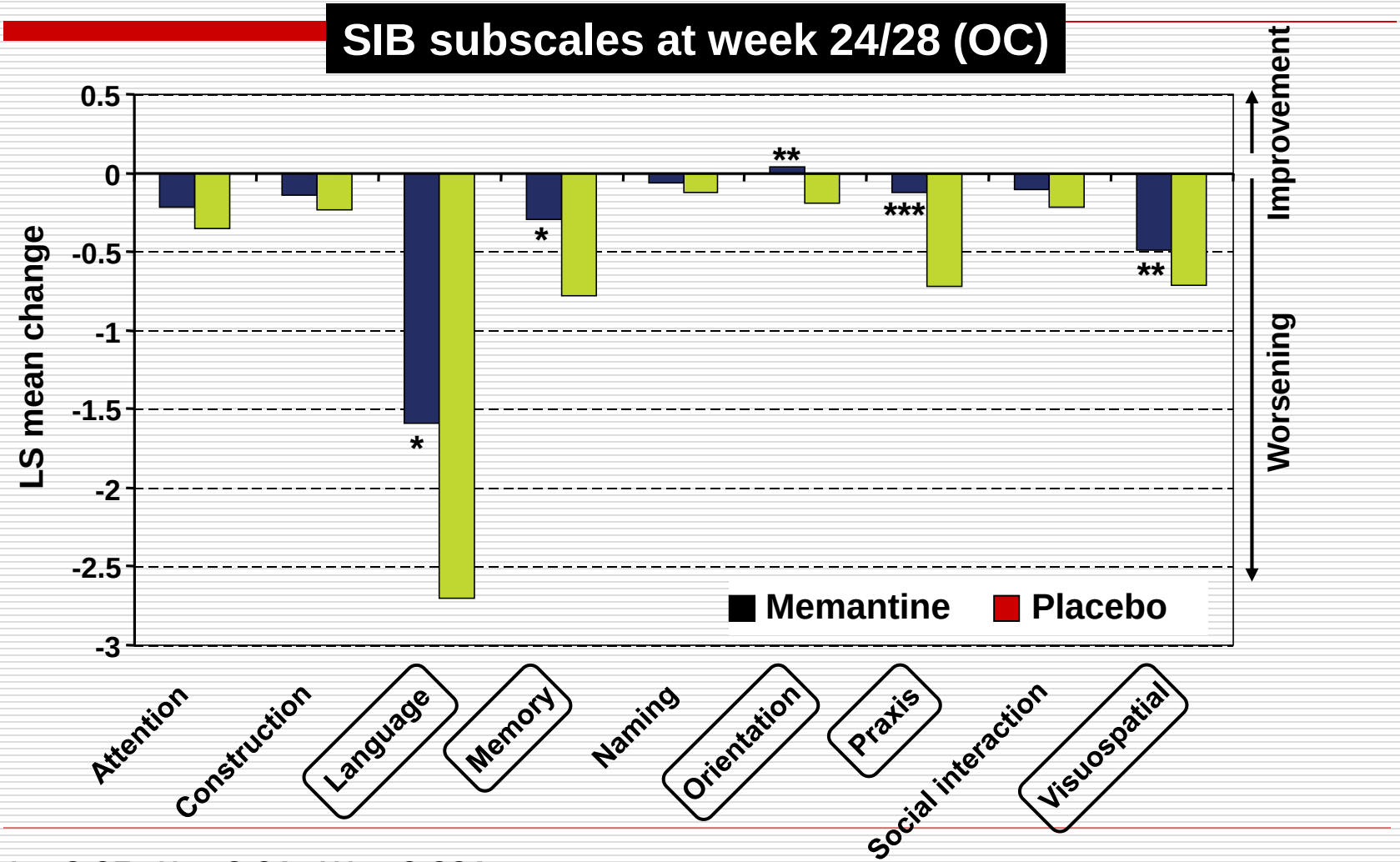


* SMD: Standardized Mean Difference

Winblad et al. Dement Geriatr Cogn Disord 2007;24:20-27

Effects of memantine on cognition

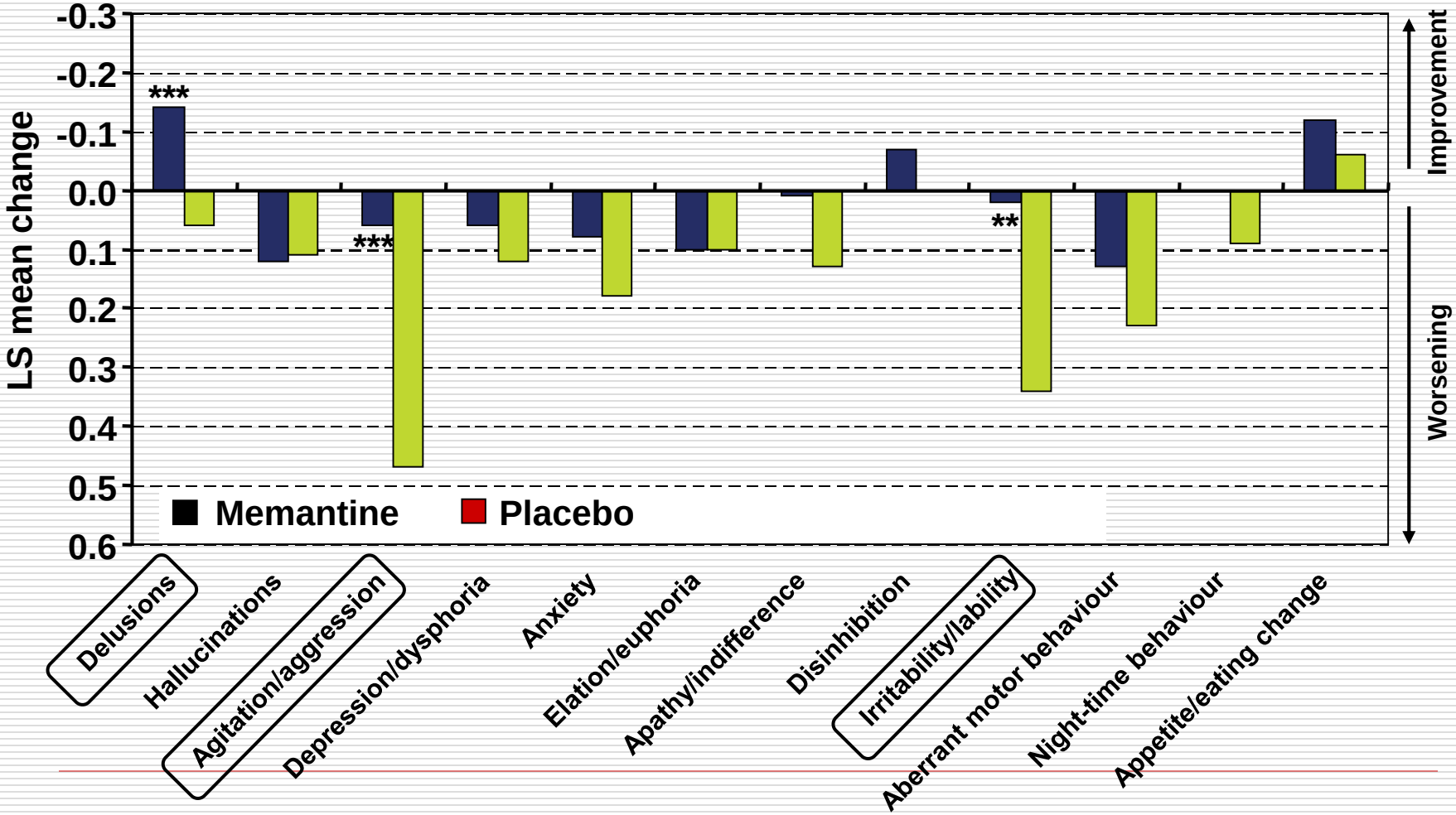
Pooled analysis of moderate to severe studies



*p<0.05; **p<0.01; ***p<0.001

Mecocci et al. Poster at EFNS 2005

Effects of memantine on behaviour
Pooled data from six Phase III, placebo-controlled studies (MMSE <20)



**p<0.01; ***p=0.001

Gauthier et al. Poster at ICAD 2006

Baseline Characteristics of the Participants, According to Treatment Group.

Table 1. Baseline Characteristics of the Participants, According to Treatment Group.*

Characteristic	Donepezil Tapered and Discontinued		Donepezil Continued		Total (N=295)
	Placebo Memantine Added (N=73)	Active Memantine Added (N=76)	Placebo Memantine Added (N=73)	Active Memantine Added (N=73)	
Age — yr	77.7±8.0	76.2±8.9	77.2±7.5	77.5±9.0	77.1±8.4
Sex — no. (%)					
Male	26 (36)	30 (39)	22 (30)	24 (33)	102 (35)
Female	47 (64)	46 (61)	51 (70)	49 (67)	193 (65)
Race — no. (%)†					
White	71 (97)	73 (96)	69 (95)	67 (92)	280 (95)
Black	2 (3)	2 (3)	1 (1)	4 (5)	9 (3)
Other	0	1 (1)	3 (4)	2 (3)	6 (2)
Previous duration of donepezil therapy — no. (%)					
3 to <6 mo	3 (4)	4 (5)	3 (4)	4 (5)	14 (5)
6 to <12 mo	8 (11)	4 (5)	9 (12)	3 (4)	24 (8)
12 to <24 mo	15 (21)	17 (22)	14 (19)	16 (22)	62 (21)
24 to <36 mo	19 (26)	17 (22)	18 (25)	8 (11)	62 (21)
36 to <60 mo	19 (26)	20 (26)	21 (29)	31 (42)	91 (31)
≥60 mo	9 (12)	14 (18)	8 (11)	11 (15)	42 (14)
SMMSE score‡					
Mean	9.1±2.4	9.2±2.5	9.0±2.8	9.1±2.6	9.1±2.6
Distribution — no. (%)					
5–9, indicating severe Alzheimer's disease	39 (53)	39 (51)	38 (52)	38 (52)	154 (52)
10–13, indicating moderate Alzheimer's disease	34 (47)	37 (49)	35 (48)	35 (48)	141 (48)
BADLS score§	28.6±8.9	27.1±9.0	28.2±9.0	26.9±9.8	27.7±9.2
NPI score¶	22.9±17.0	23.1±16.2	22.3±16.7	20.3±14.4	22.2±16.1
DEMQOL-Proxy score‖	101.4±11.7	96.5±15.3	98.3±13.5	100.9±12.9	99.3±13.5
GHQ-12 score**	2.8±3.1	3.1±3.1	2.3±2.3	1.8±2.3	2.5±2.8

* Plus–minus values are means ±SD. Apart from two missing General Health Questionnaire 12 (GHQ-12) scores (one for a caregiver of a patient who discontinued donepezil and received placebo memantine and one for a caregiver of a patient who discontinued donepezil and received active memantine), scores were available for all 295 enrolled patients at baseline. There were no significant differences among the groups for any of the baseline characteristics, with the exception of the total GHQ-12 score (P=0.03).

† Race was determined by the investigator.

‡ Scores on the Standardized Mini–Mental State Examination (SMMSE) range from 0 to 30, with higher scores indicating better cognitive function. Because of eligibility criteria, the scores for patients in this trial were between 5 and 13.

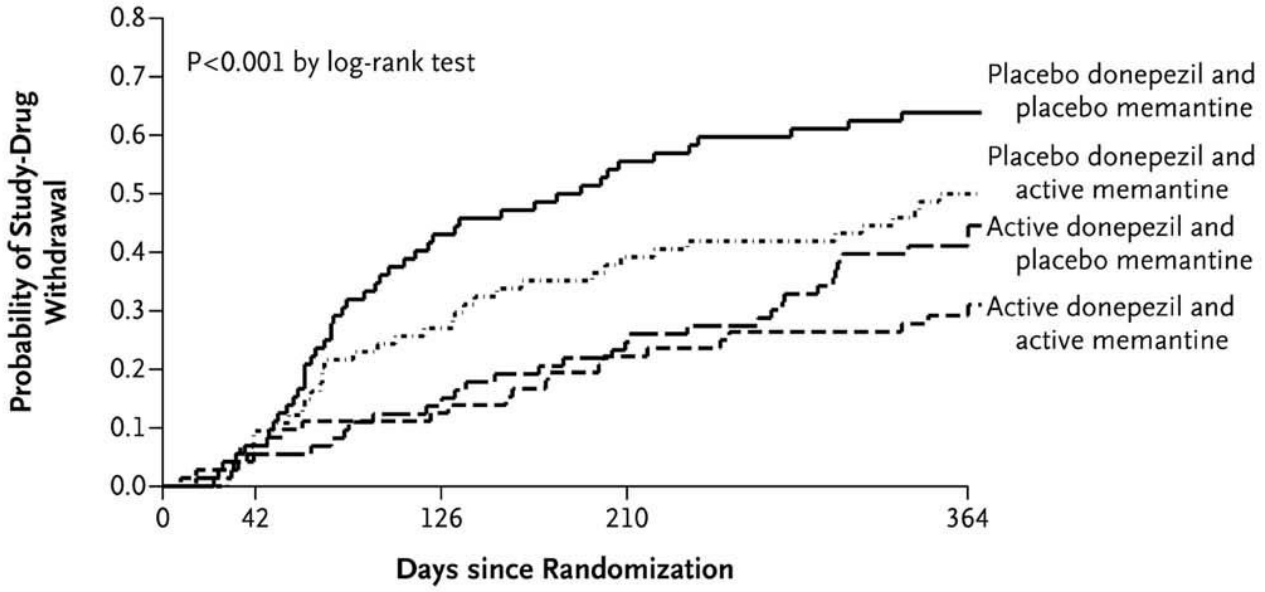
§ Scores on the Bristol Activities of Daily Living Scale (BADLS) range from 0 to 60, with higher scores indicating greater functional impairment.

¶ Scores on the Neuropsychiatric Inventory (NPI) range from 0 to 144, with higher scores indicating increased behavioral and psychological symptoms.

‖ Scores on the DEMQOL-Proxy range from 31 to 134, with higher scores indicating better patient health-related quality of life.

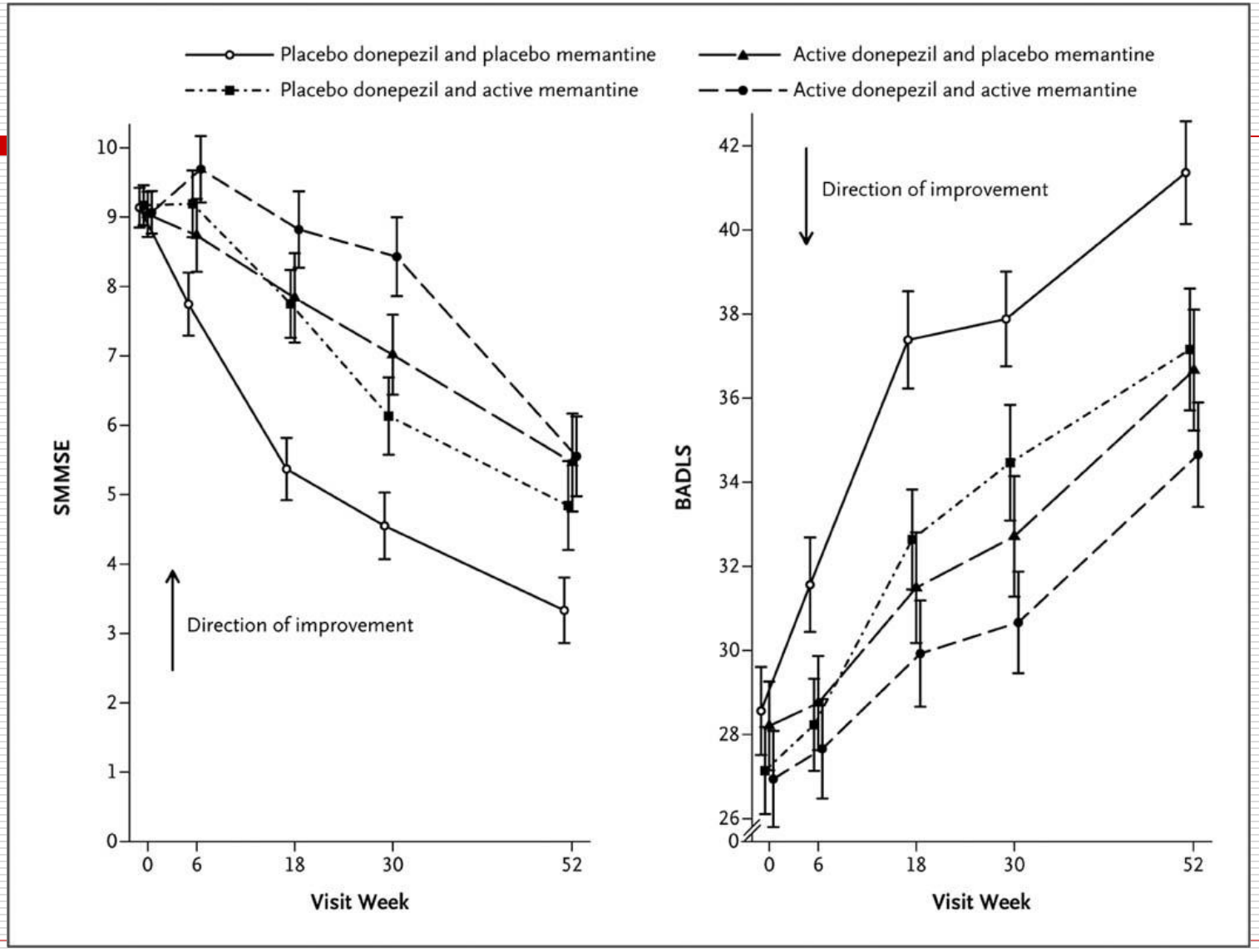
** Scores on the GHQ-12, which measures caregiver health status, range from 0 to 12, with higher scores indicating increased psychological symptoms in informal caregivers.

Kaplan–Meier Actuarial Plot of the Cumulative Probability of Withdrawal from the Assigned Study Drug.



No. of Patients Still Receiving Study Drug					
Placebo donepezil and placebo memantine	72	67	41	32	20
Placebo donepezil and active memantine	74	67	54	45	27
Active donepezil and placebo memantine	73	69	63	55	34
Active donepezil and active memantine	72	68	63	56	38

Mean Scores on the Standardized Mini–Mental State Examination (SMMSE) and the Bristol Activities of Daily Living Scale (BADLS), According to Visit Week and Treatment Group



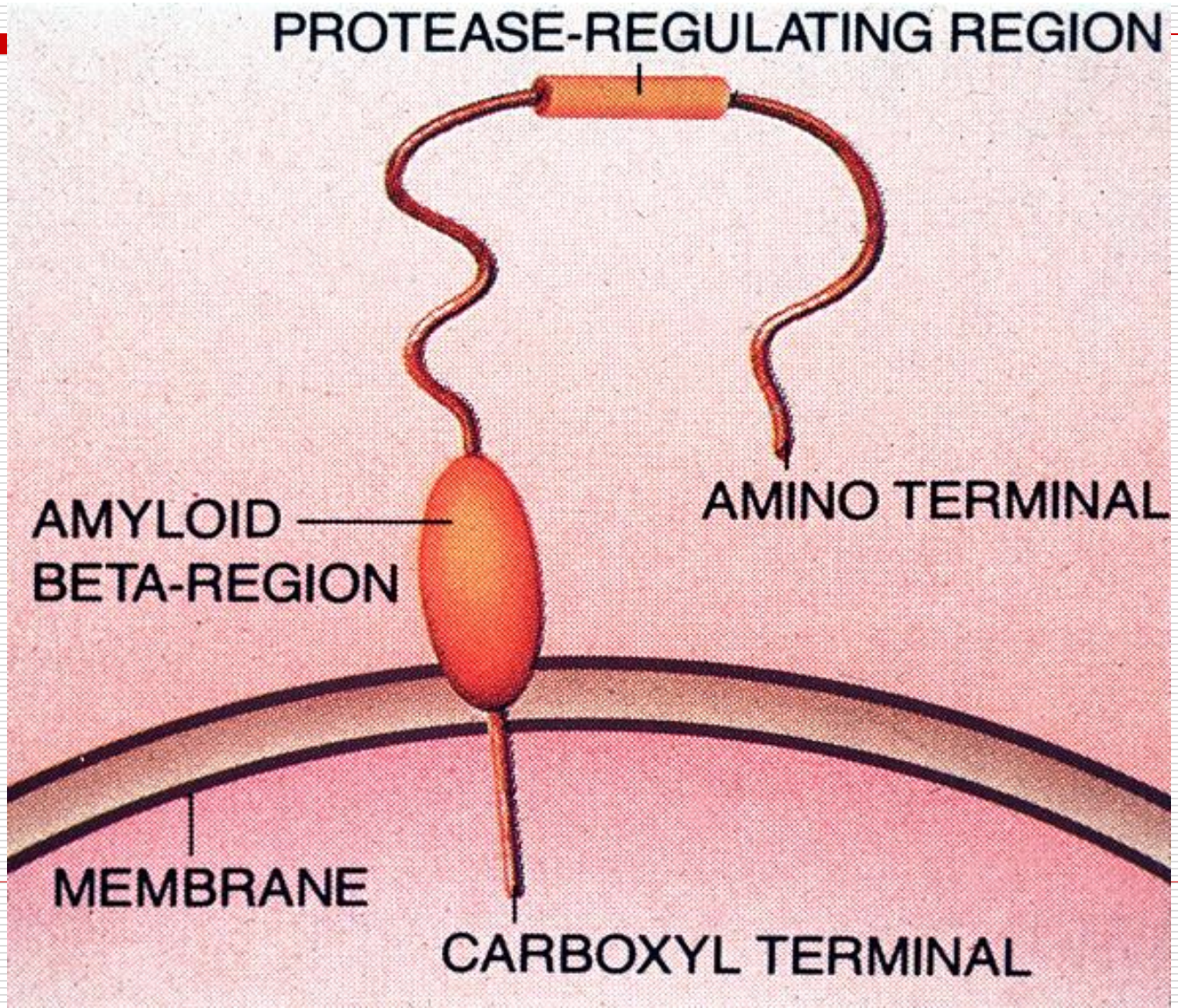
Summary

- In patients with moderate or severe Alzheimer's disease receiving donepezil, those assigned to continue donepezil had less cognitive decline than did those assigned to discontinue donepezil.
- The combination of donepezil and memantine did not confer benefits over donepezil alone.

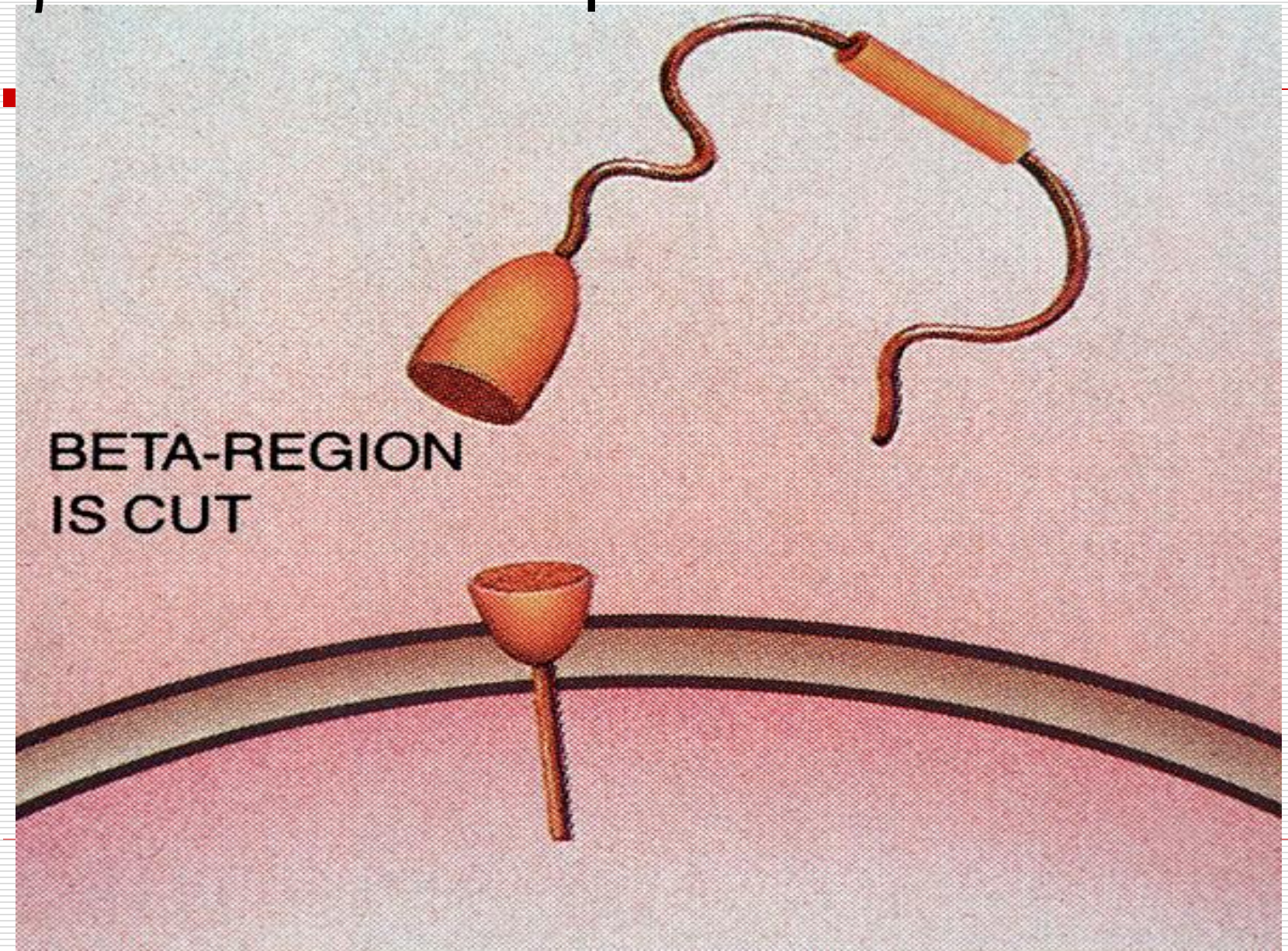
Disease drug development

- Amyloid hypothesis
- Aß oligomer → Neurofibrillary tangles →Synapse failure → neuronal death
- So far focused on Aß protein
  - Reduce production
  - Increase removal

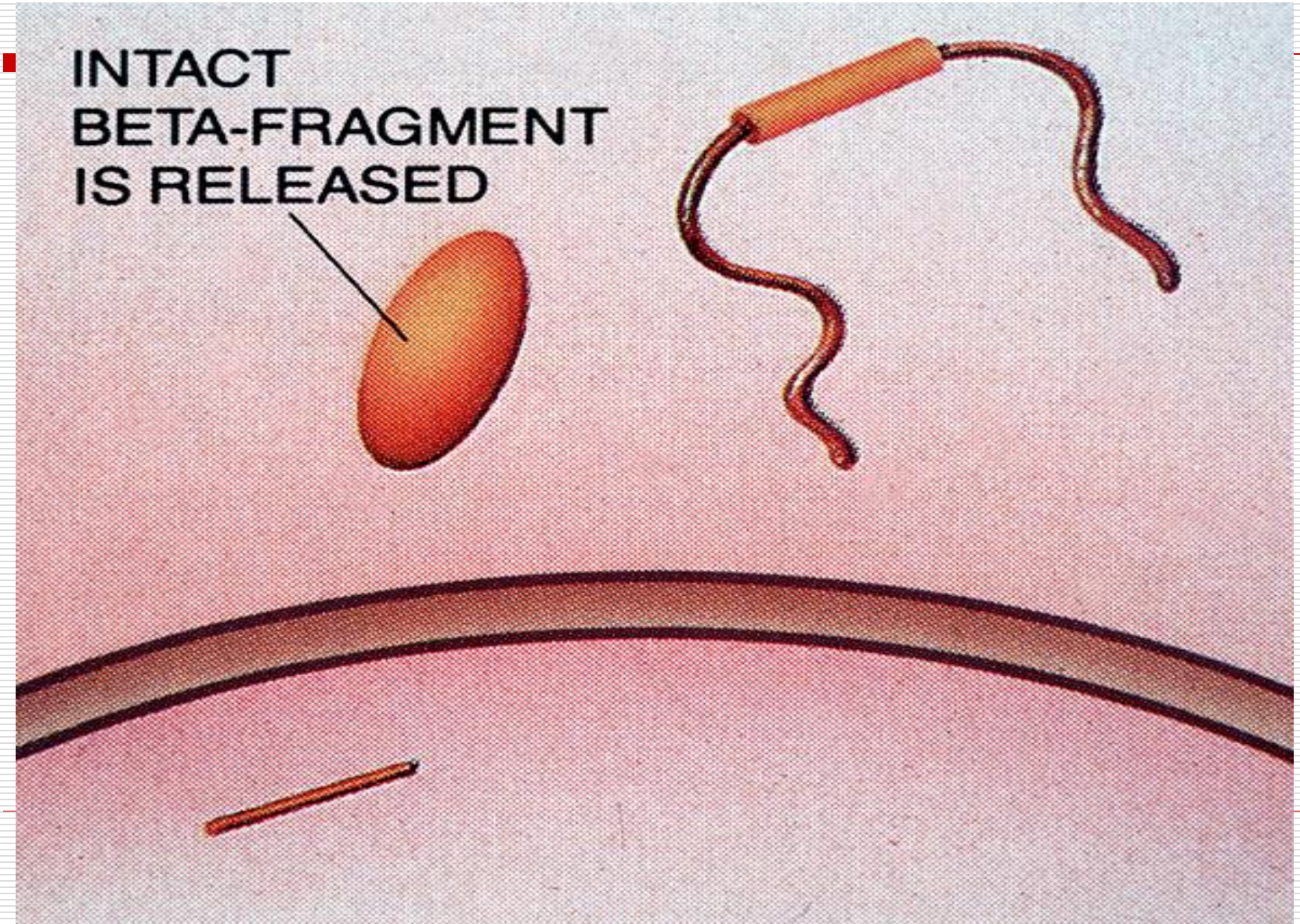
Amyloid precursor protein (APP)



β -secretase splits APP



β- and δ- secretase split APP releasing βA4 fragment



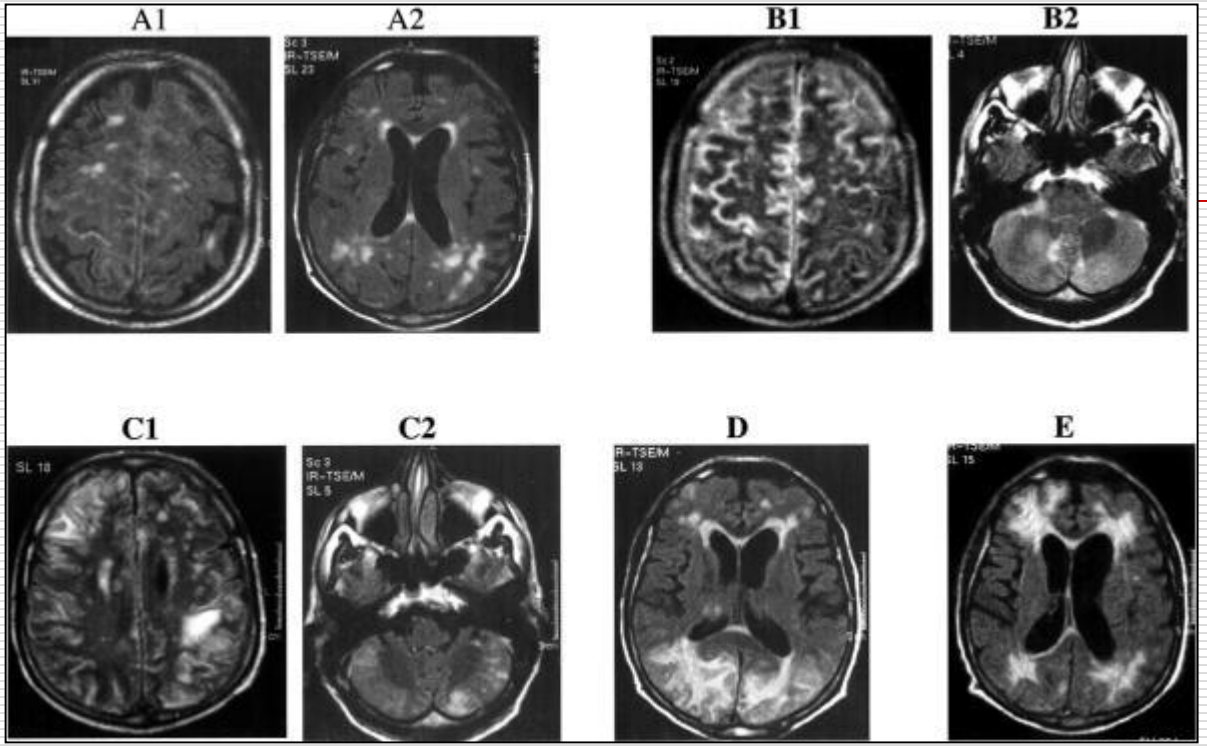
Secretase inhibitors

- β secretase inhibitor difficult to design
- α secretase inhibitor
  - Limited by other system actions of α secretase e.g. Notch signaling protein
  - Toxicity in GI, lymphatic, skin and immunity systems
  - Semagacestat entered phase three trial which was terminated because of adverse effect on cognition
    - Accumulation of neurotoxic peptide

Immunological approach

- A ß amyloid
  - Active vaccination
    - 6% Meningoencephalitis
  - Monoclonal antibody
    - bapineuzumab, solanezumab
- Tau

Figure 2



Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization.
Orgogozo JM; Gilman S; Dartigues JF; Laurent B; Puel M; Kirby LC; Jouanny P; Dubois B; Eisner L; Flitman S; Michel BF; Boada M; Frank A; Hock C

Neurology. 61(1):46-54, 2003 Jul 8.

Figure 2 . Serial brain MRI scans of Patient 2. A set of fast fluid-attenuated inversion recovery (FLAIR; repetition time = 11,000 milliseconds, echo time = 140 milliseconds, inversion time = 2,500 milliseconds) T2-weighted images performed 22 days (A1 and A2), 41 days (B1 and B2), 64 days (C1 and C2), 87 days (D), and 170 days (E) after immunization. (A) Presence of high signal intensities in the subcortical white matter and in the central sulcus (A1); numerous high signal intensities in the deep white matter (A2). (B) All sulci present an increased signal intensity that is related to the presence of protein in the CSF (B1); new lesions in the white matter of the right cerebellar peduncle (B2). (C) Worsening in the number and location of the lesions, now affecting the white matter and the gray matter of the cerebral (C1) and the cerebellar cortex (C2), while the lesions in the cerebellar peduncle have disappeared. (D) Extensive new lesions in the deep posterior white matter also affecting the adjacent cortex. (E) New lesions in the deep frontal white matter, while some lesions in the posterior white matter disappeared. (Courtesy of Prof. Vincent Dousset, trial neuroradiologist).

Phase two trial of bapineuzumab

- 234 mild to moderate AD
- IV x 6 times 13 weeks apart
- 78 weeks follow-up

Salloway S; Neurology 2009

Phase two trial of bapineuzumab

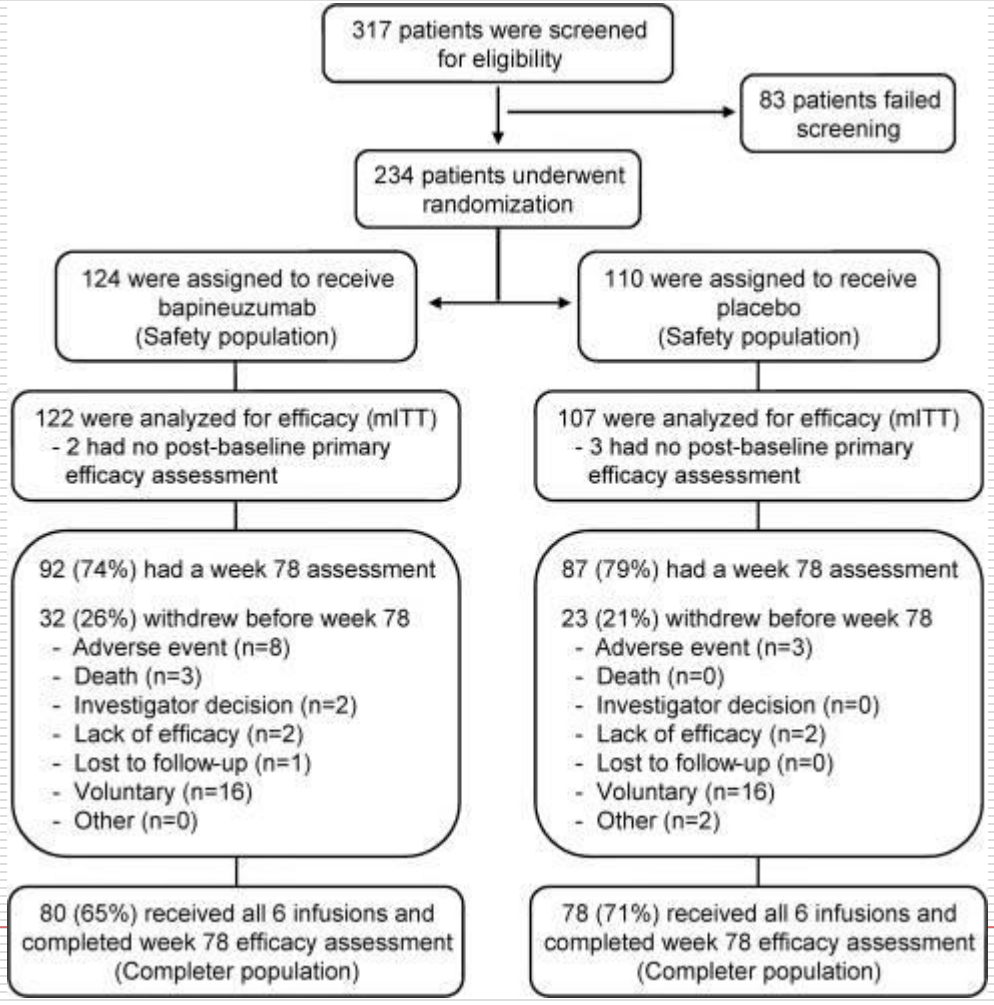
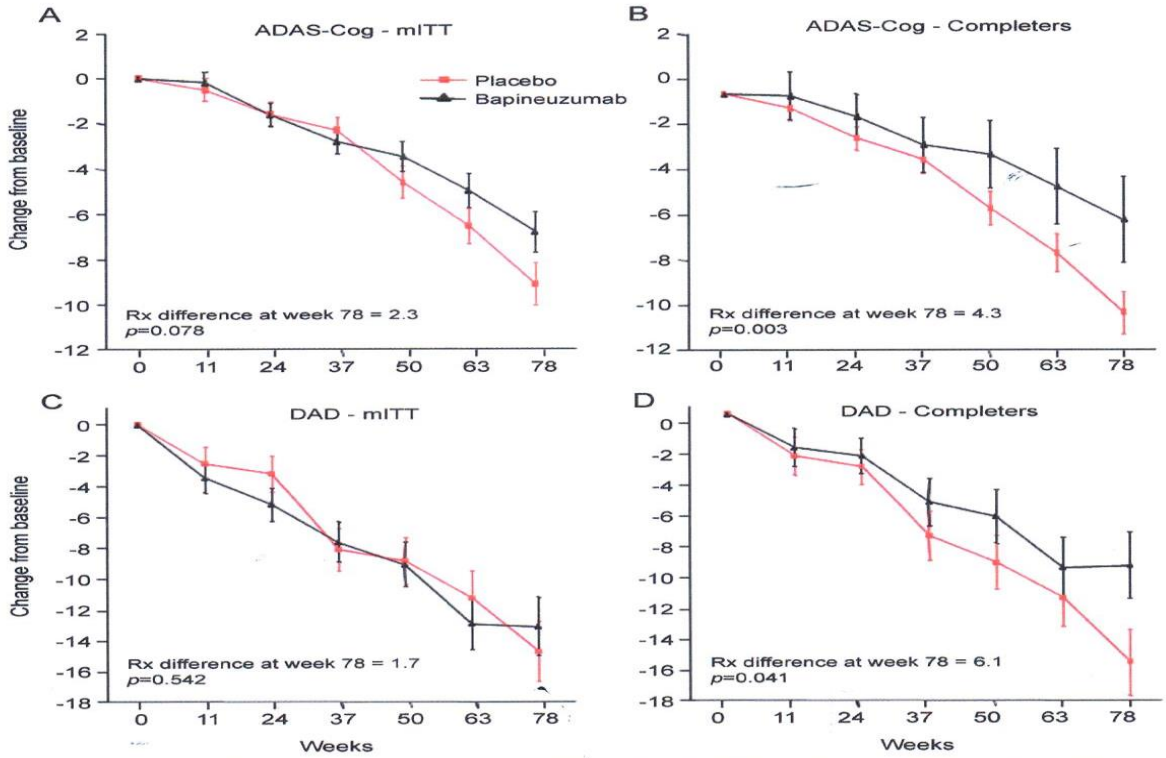
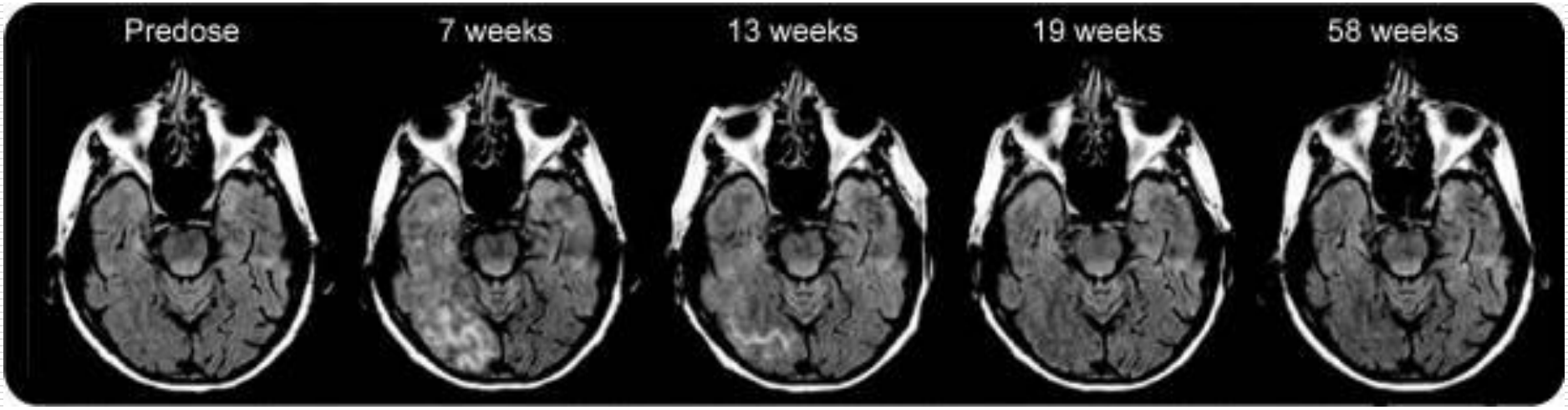


Figure 2 Estimated mean change from baseline over time on Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog) and Disability Assessment for Dementia (DAD) for the 4 combined dose cohorts in the modified intent-to-treat (mITT) and completer populations



Error bars represent one standard error. A positive change from baseline represents improvement. The *p* values are not adjusted for multiple comparisons. (A) ADAS-Cog, mITT; (B) ADAS-Cog, completers; (C) DAD, mITT; (D) DAD, completers.

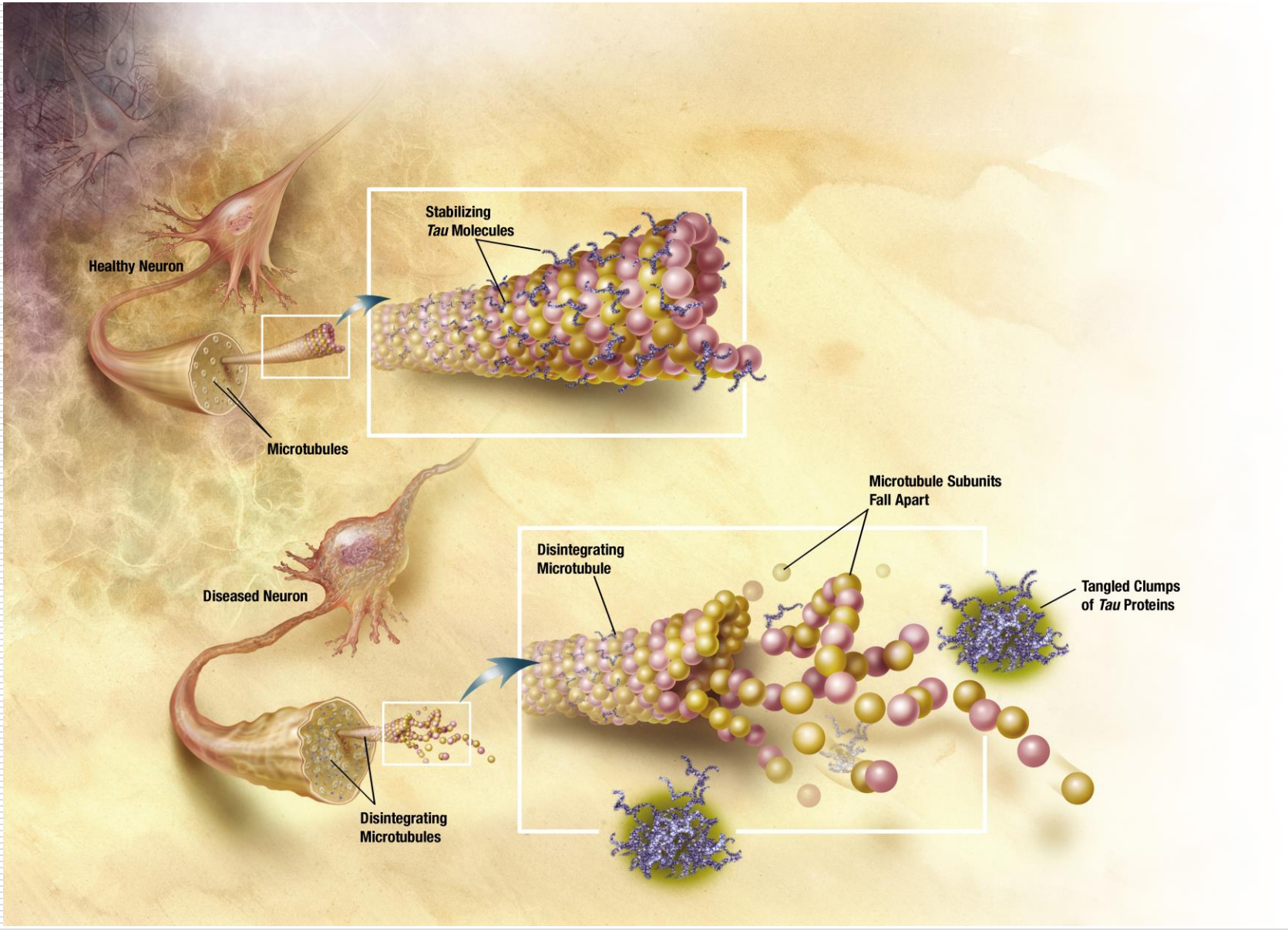
Vasogenic oedema with bapineuzumab



Results

- No significant effect on ADAS Cog and DAD
- Treatment effect in completers and APOE e4 noncarriers
- Reversible vasogenic oedema in 9.7% (more frequent in APOE e4 carriers and high dose)
- Phase three trial terminated because of lack of efficacy

Functional and dysfunctional Tau protein



Advantages of targeting hyperphosphorylated Tau protein

- pTau is more closely related to brain dysfunction
- PTau is involved in other dementia's e.g. progressive supranuclear palsy
- Target
  - Tau – potentially harmful
  - Tau aggregation – methylene blue
  - Tau hyperphosphorylation –lithium, valproate

Nasal Insulin

- Insulin in brain
  - Glucose utilization e.g. hippocampus
  - Synaptogenesis
  - Synaptic remodeling
  - Modulates Aβ and protect against Aβ oligomers
- Insulin level and activity reduced in AD
- Nasal insulin can be safely administered without causing hypoglycemia

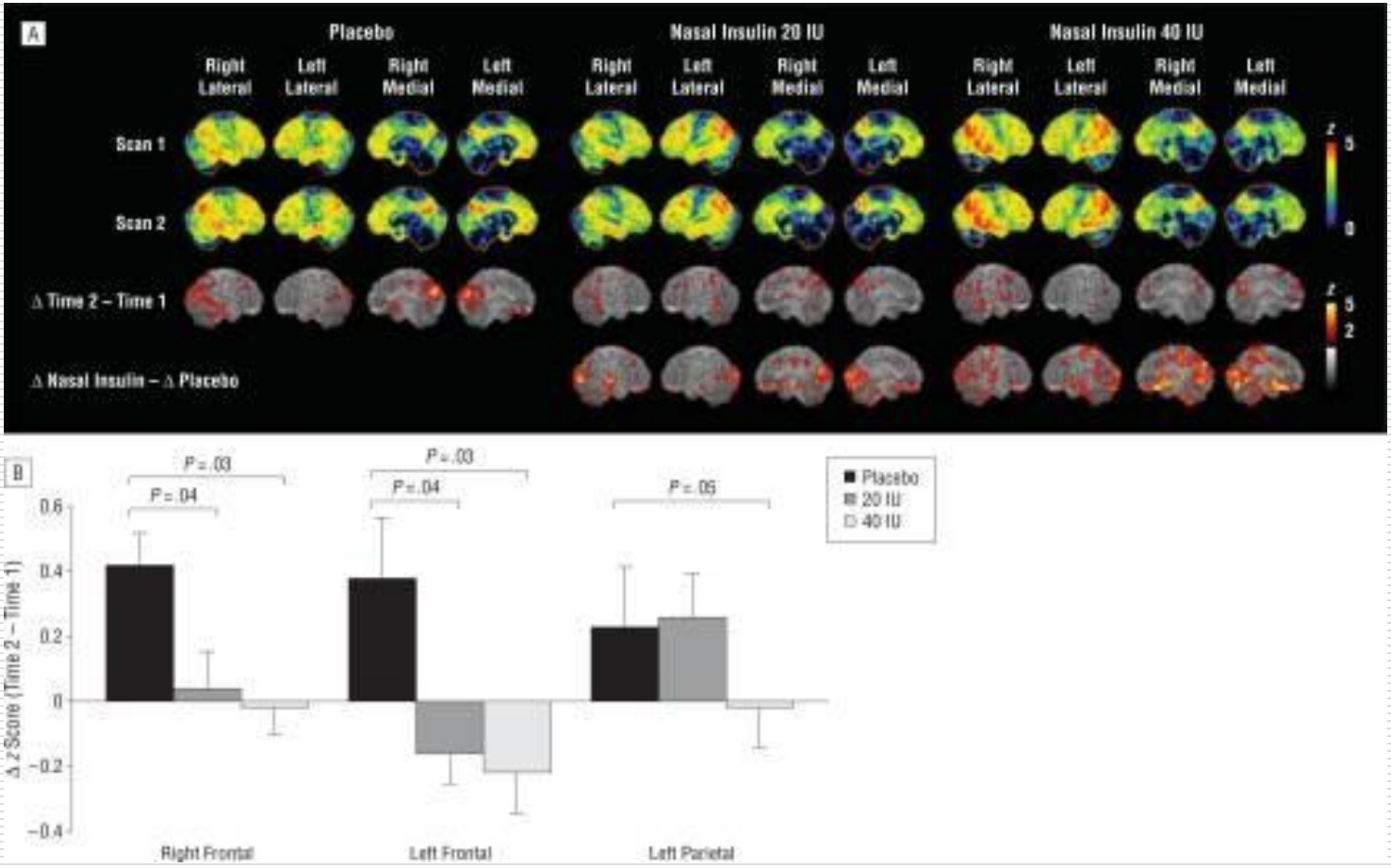
Subject and Method

- 64 MCI 40 mild to moderate AD randomized to take placebo, 20iu or 40 iu insulin per day for four months

Results

- Low dose improved delayed memory
- Both doses of insulin preserved functional ability
- CSF markers did not change
- Preserved glucose uptake in parietotemporal, frontal lobes

Improved cognition and brain activity with nasal insulin



Neuroleptic drugs

- Commonly used to "control" behavioral problems in AD
- No evidence that it works in dementia
- There is evidence that they lead to dependency and increased mortality
- Side effects include Parkinsonism, over-sedation, falls

Alternative drugs for mood swing and aggression

- Memantine
- SSRI
- Trazodone
- Sodium valproate

Trial of prazosin (6mg/day) in AD with agitations and aggression

Table 1

Baseline Characteristics

Characteristic	Prazosin n=11	Placebo n=11	All n=22
Age (years)[a]	83.2 ± 11.5	78.1 ± 10.8	80.6 ± 11.2
MMSE (score)[a,b]	9.3 ± 6.6	14.0 ± 12.0	11.4 ± 9.3
Female/male	4/7	5/6	9/13
Nursing home/community dwelling	6/5	6/5	12/10

[a]mean ± standard deviation

[b]Six participants were unable to cooperate with testing: 2 Prazosin, 4 Placebo

Wang LY; Am J Geri Psychiatr 2009

Outcome of BPDS with prazosin

Table 2

Behavioral Responses to Prazosin versus Placebo: Behavior Scores Presented as M... Deviation

	Baseline (n=22)	Change from baseline for participants remaining at each time point					Mean group change[a]	T... st...
		Week 1 (n=22)	Week 2 (n=19)	Week 4 (n=15)	Week 6 (n=13)	Week 8 (n=13)		
N								
Prazosin	11	11	10	8	7	7		
Placebo	11	9[c]	9	7	6	6		
NPI								
Prazosin	49 ± 16	-20 ± 19	-16 ± 23	-16 ± 25	-15 ± 24	-13 ± 23	-19 ± 21	X...
Placebo	43 ± 18	-5 ± 17	-2 ± 21	4 ± 17	-1 ± 14	5 ± 21	-2 ± 15	
BPRS								
P...zosin	45 ± 8	-9 ± 8	-8 ± 10	-7 ± 13	-7 ± 9	-9 ± 8	-9 ± 9	X...

Conclusions

- Neuroimaging shows promise in early diagnosis of AD
- Combination of Cholinesterase inhibitor and memantine is not justified for cognitive benefit
- New therapies directed at Aß amyloid have shown disappointing results
- Worldwide search for drugs for AD is on-going

Challenges of AD drug developement

- No animal model of AD
- Amyloid pathology precedes clinical AD by 20 years
- Older AD patients have slower cognitive decline
- Older AD patients have comorbidities
- Clinical AD may not have AD

Future trends in AD drug development

- Prodromal drug treatment
- Targeted drug use in patients with specific pattern of biomarkers
- Multiple therapy
- Targets outside amyloid cascade

Day Care

- Group & Individualized activities

賽馬會耆智園
Jockey Club Centre for Positive Ageing

Web-site for family caregivers of dementia (ADCARER.COM)

Funded by Kao's walkathon 2010, Knowledge transfer grant (CUHK)

短片：「小小花」

讓我們了解多一點腦退化症患者的世界

Short Film: “The Little Flower”

“Understanding dementia: A different reality”