Treatment of Alzheimer's disease: where we are and prospects for the future

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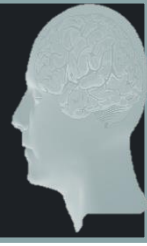
DISCLOSURES



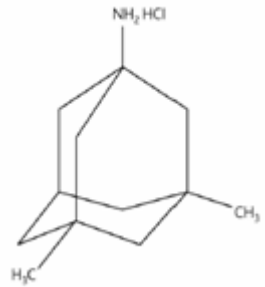
- Clinical trial support from Lilly, Roche, TauRx, Lundbeck
- DSMB member for ADCS, ATRI, API, Eisai
- Scientific advisor to Alzheon, Boehringer-Ingelheim, Kalgene, Lilly, Lundbeck, Schwabe, TauRx

OUTLINE

- Current symptomatic drugs
- Targeting pathophysiological factors
- Having a second look at old drugs
- Prevention strategies are essential
- Conclusions

Therapy in AD: The first hundred years and looking forward…….

Memantine
NMDA
Uncompetitive
Receptor
Antagonist

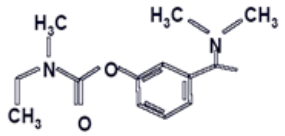


1906 1910 1974 1982 1997 2004 2010 2020

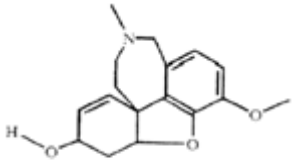
The cholinergic hypothesis

Acetylcholinesterase inhibitors

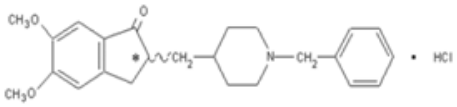
First Disease Modifying Rx?
Amyloid and tau lowering?
Next generation targets?



rivastigmine

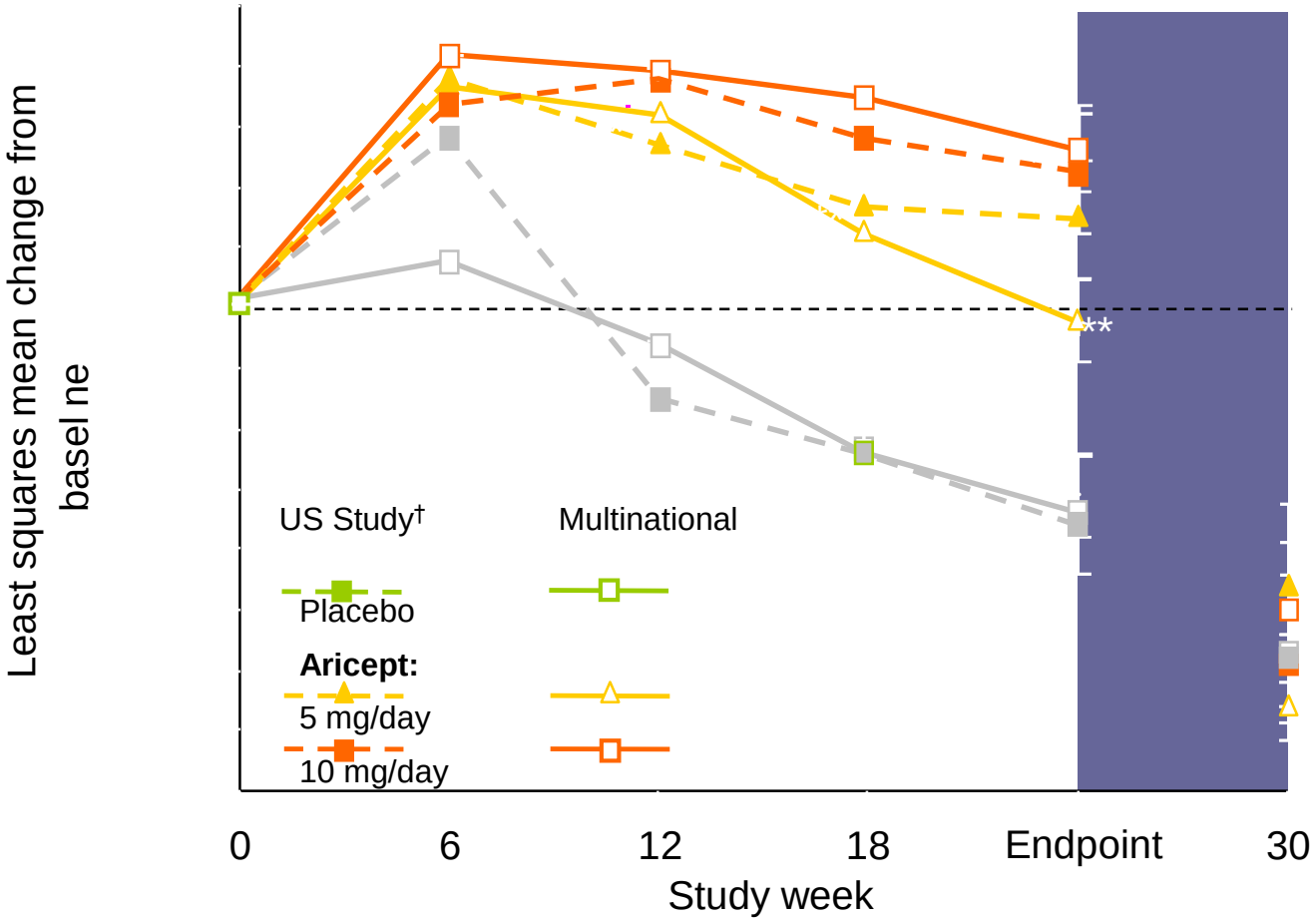


galantamine



donepezil

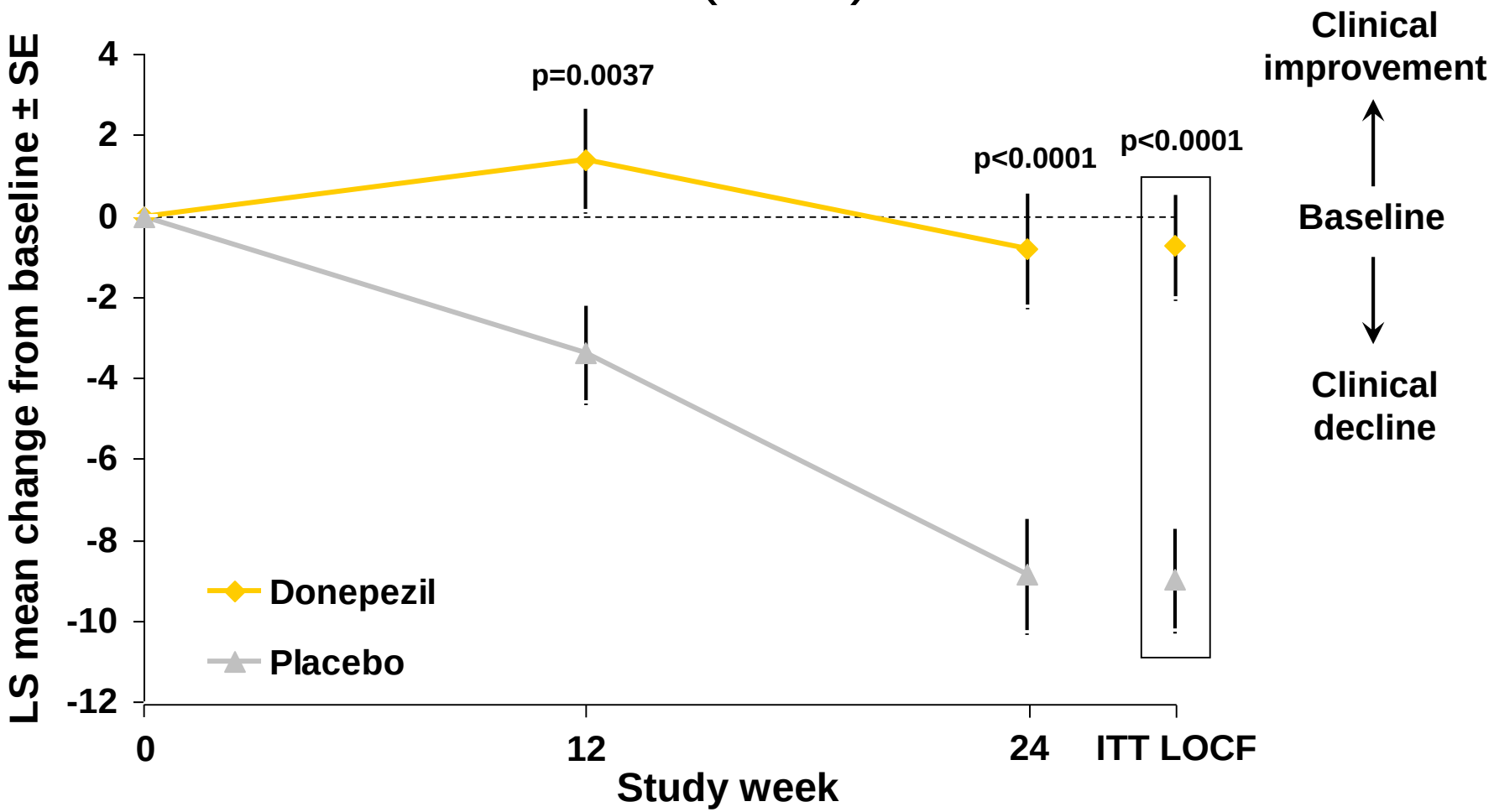
DONEPEZIL VS PLACEBO
COGNITION (ADAS-cog)



ITT-LOCF analysis; **p≤0.001 for Aricept versus placebo

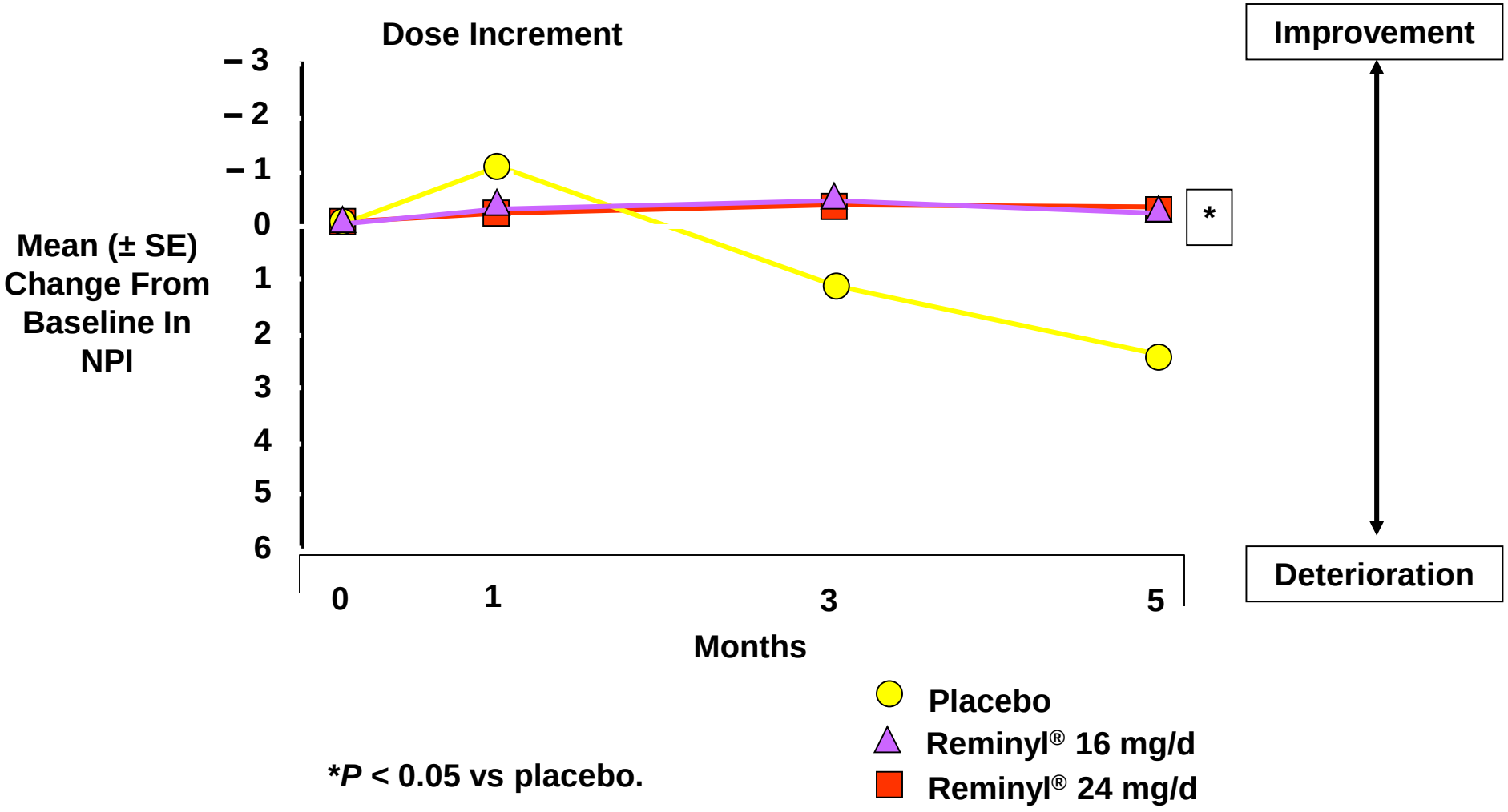
†Rogers *et al*. *Neurology* 1998;**50**:136–145; ‡Burns *et al*. *Dement Geriatr Cogn Disord* 1999;**10**:237–244

DONEPEZIL VS PLACEBO
ADL (DAD)



Donepezil *n*=134	125	121	(134)
Placebo *n*=140	129	126	(140)

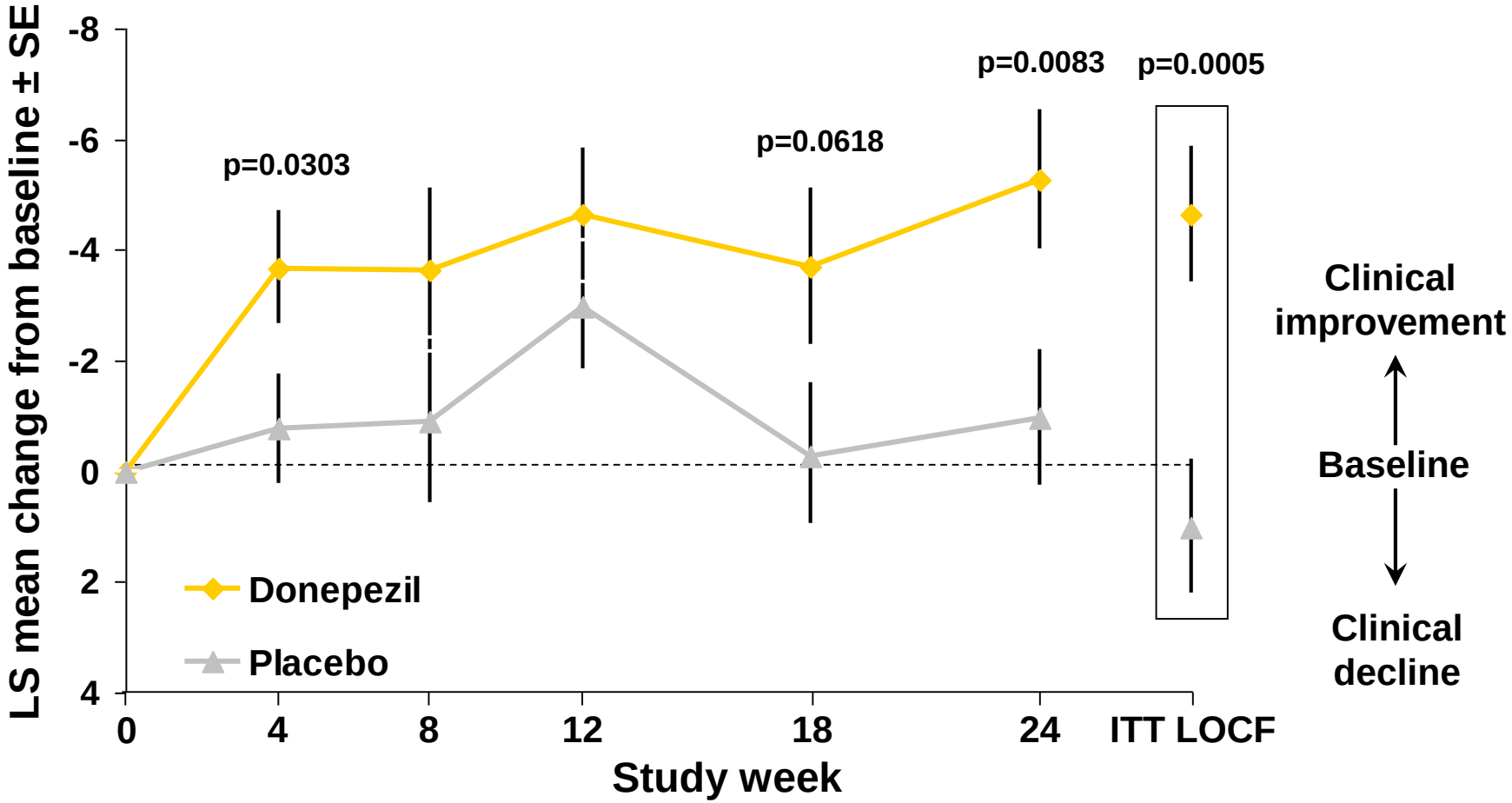
GALANTAMINE VS PLACEBO BEHAVIOR (NPI)



****P* < 0.05 vs placebo.**

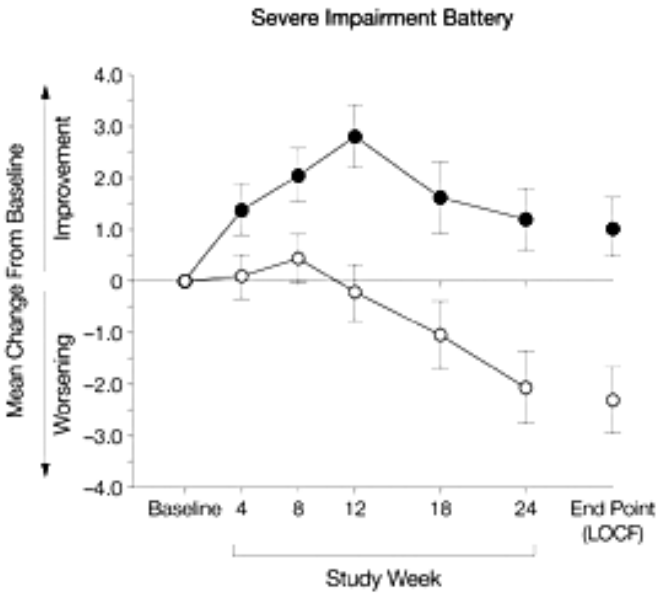
Reference: Tariot, et al. *Neurology* 2000

DONEPEZIL VS PLACEBO BEHAVIOR (NPI)

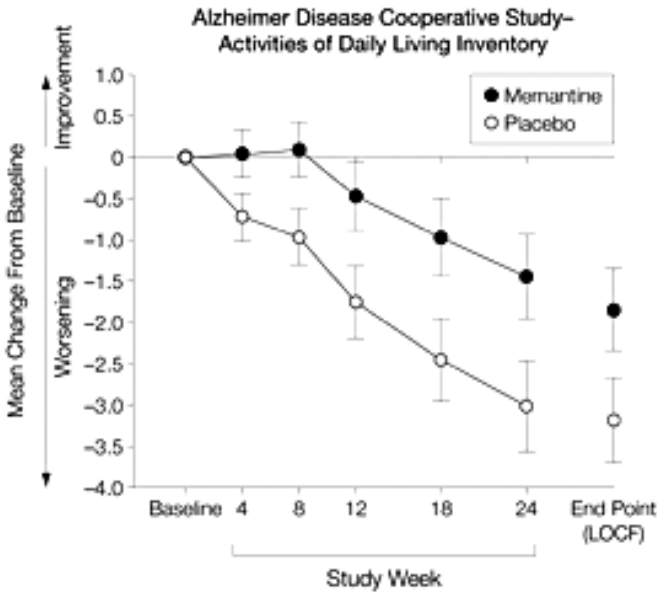


Donepezil *n*=138	130	114	124	118	119	(138)
Placebo *n*=144	138	116	128	128	125	(144)

Memantine Treatment in Patients With Moderate to Severe Alzheimer Disease Already Receiving Donepezil

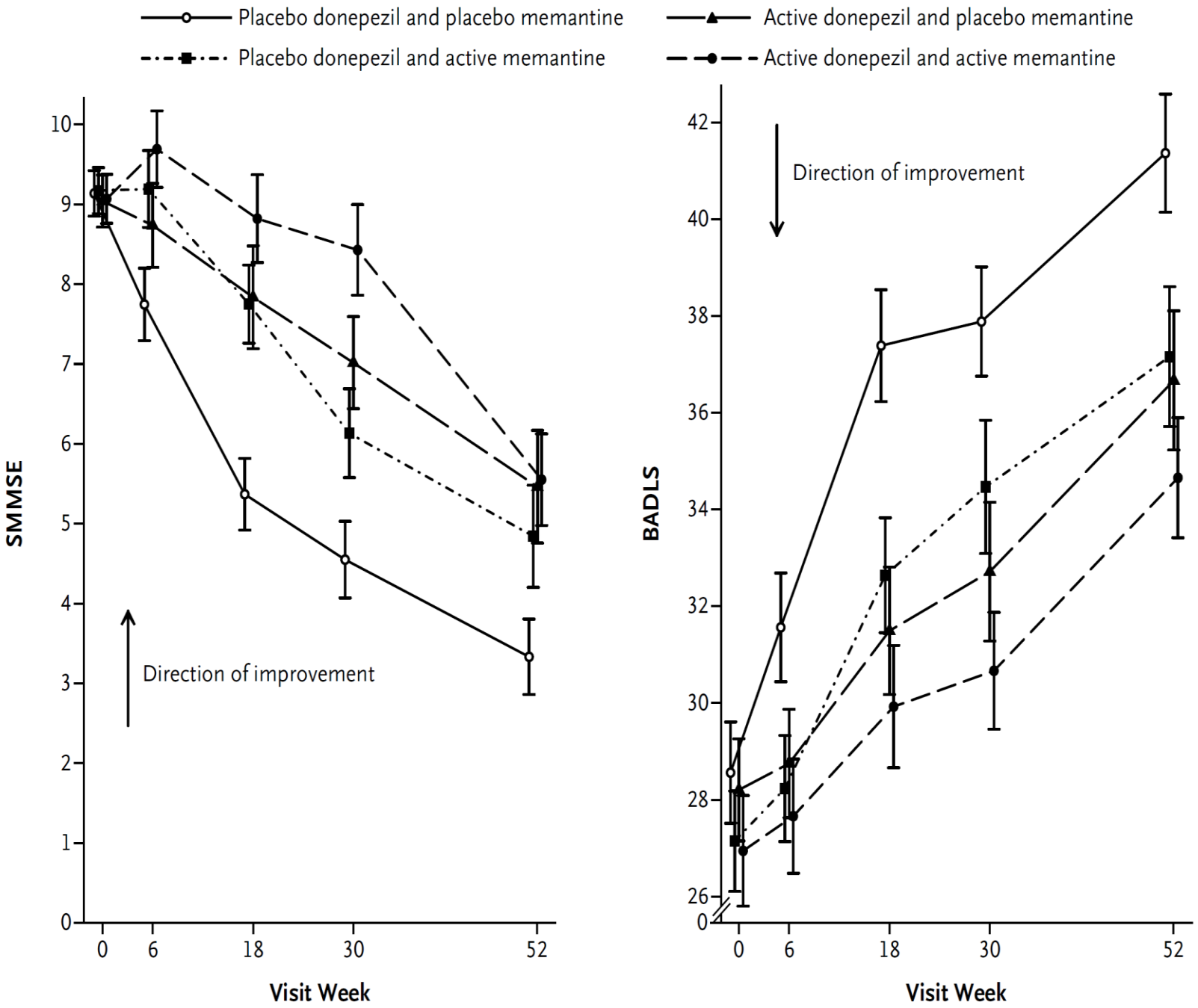


No. of Patients							
Memantine	198	197	190	185	181	171	198
Placebo	197	194	180	169	164	153	196
LS Mean Difference		−1.2	−1.5	−3.1	−2.7	−3.4	−3.4
P Value		.06	.03	<.001	.006	<.001	<.001



No. of Patients							
Memantine	198	198	190	185	181	172	198
Placebo	197	195	182	170	163	152	197
LS Mean Difference		−0.8	−1.1	−1.3	−1.4	−1.6	−1.4
P Value		.03	.01	.02	.03	.02	.03

Tariot et al., JAMA 2004


Placebo donepezil and placebo memantine
Active donepezil and placebo memantine
Placebo donepezil and active memantine
Active donepezil and active memantine
SMMSE
Direction of improvement
Visit Week
BADLS
Direction of improvement
Visit Week

RECENT FAILURES

- 5HT6 receptors as a target to increase acetylcholine levels
- Study drugs added to donepezil
- *Idalopirdine* and *intepirdine* both failed in Phase III

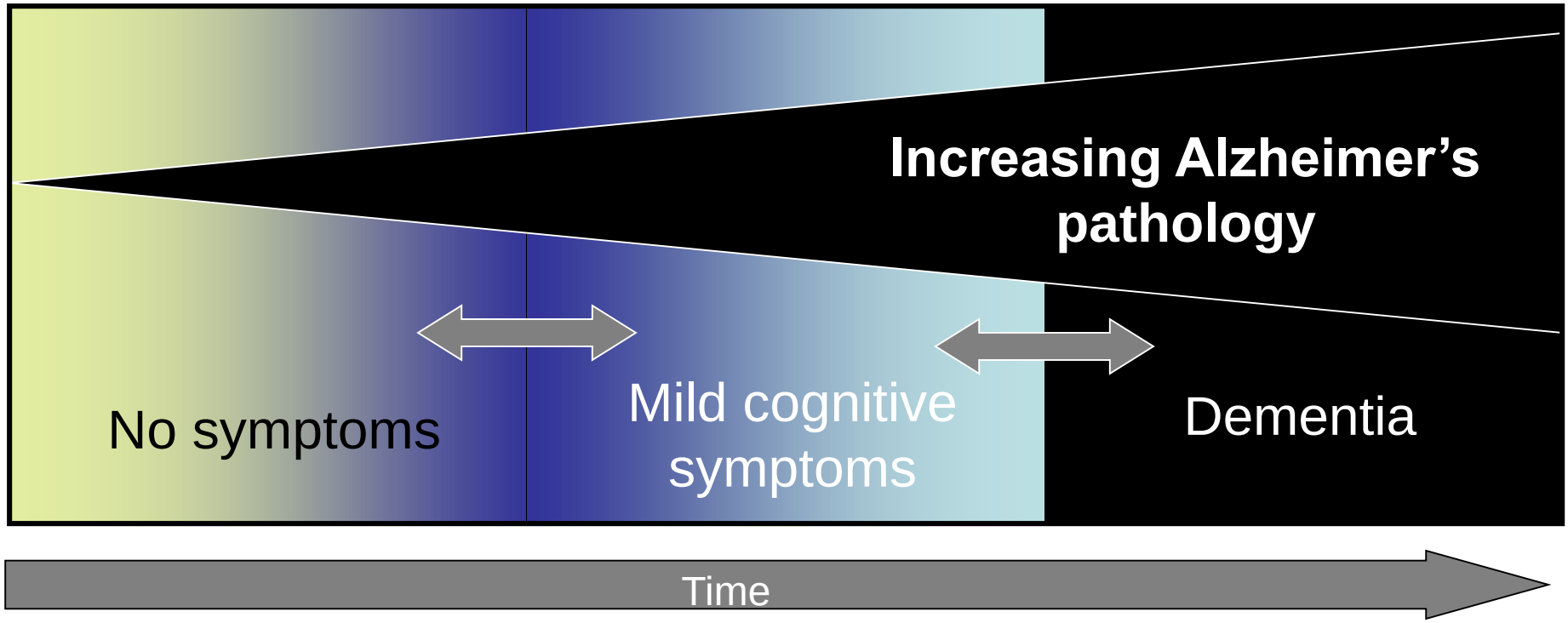
STUDY DESIGNS AND OUTCOMES FOR SYMPTOMATIC DRUGS IN AD

- 3 to 6 months
- Placebo control group
- Single-blind wash-out, rarely done
- Add-on to ‘standard of care’, usually donepezil
- Only one study with a ‘factorial’ design
- Cognition as primary outcome

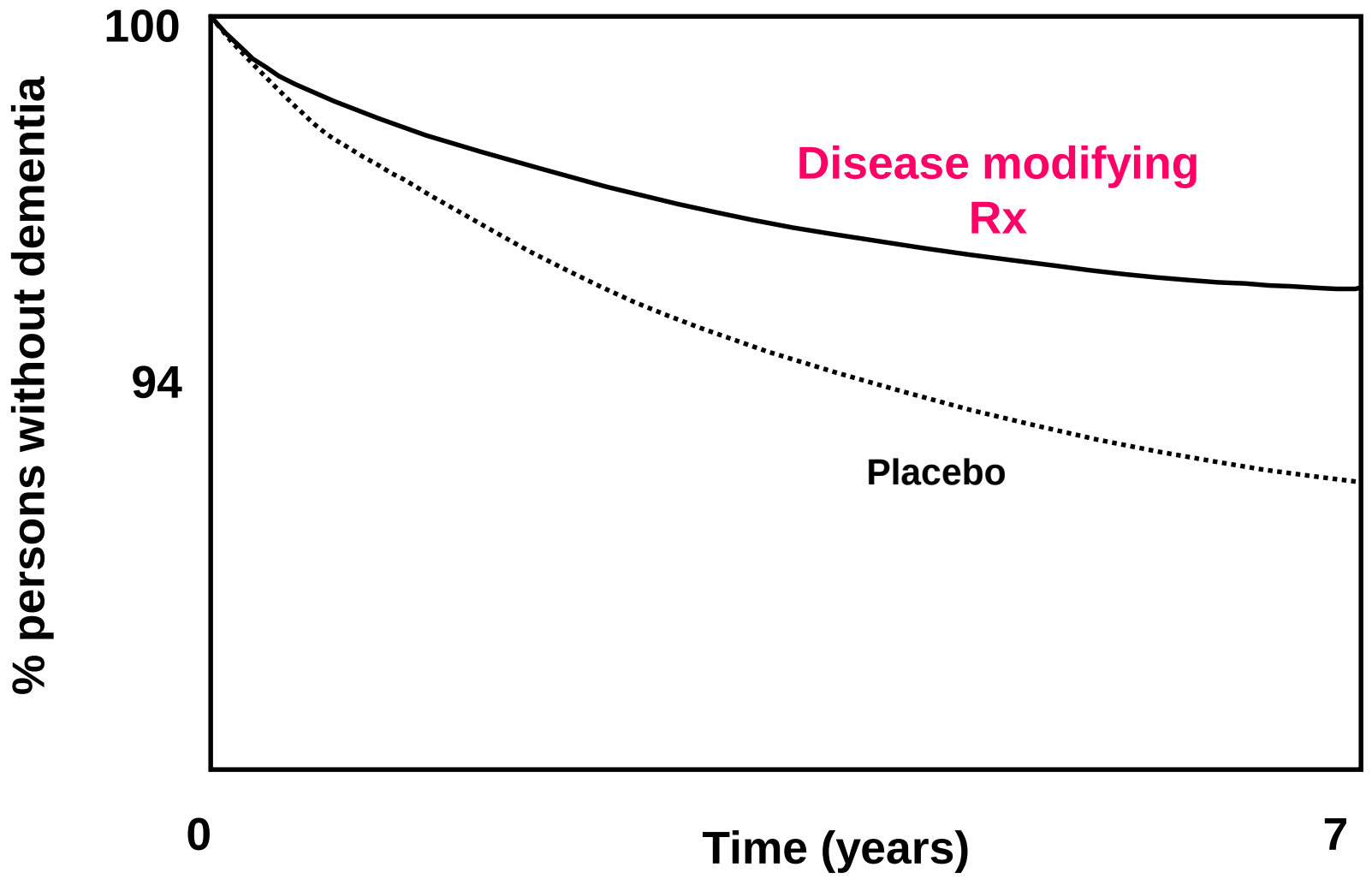
OUTLINE

- Current symptomatic drugs
- **Targeting pathophysiological factors**
- Having a second look at old drugs
- Prevention strategies are essential
- Conclusions

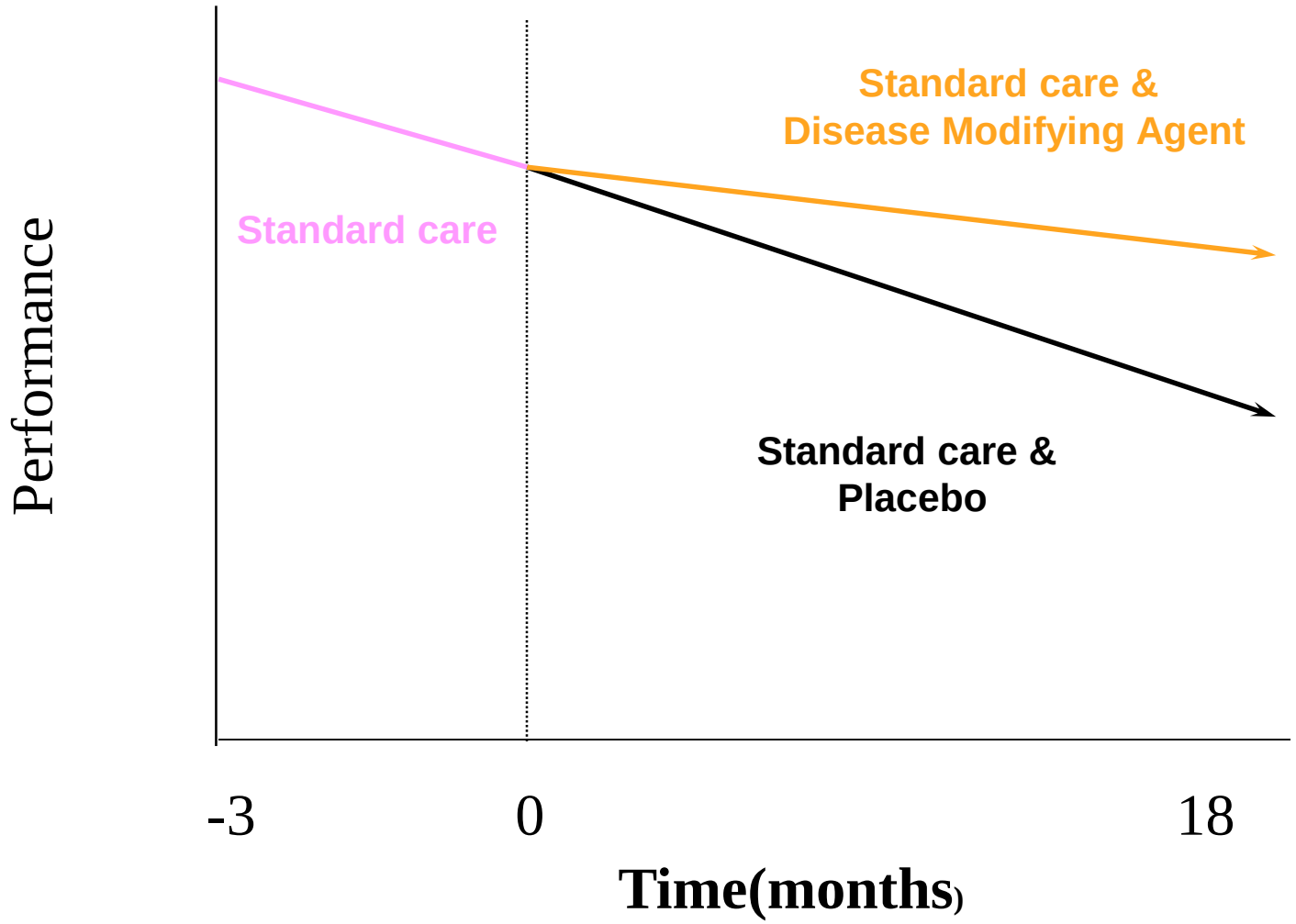
STAGES OF ALZHEIMER'S DISEASE



Survival design from CN to MCI or to dementia



Add On Design in persons with dementia due to AD

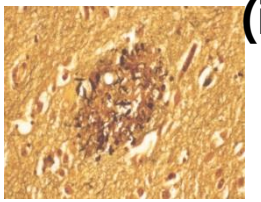


PATHOLOGIES ASSOCIATED WITH AD

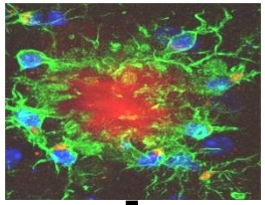
AGE

30
40
50
60
70
80
90
100

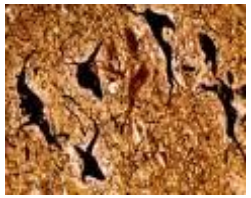
β-amyloid Deposition (plaques)



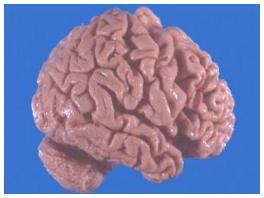
Microglial Activation (inflammation)



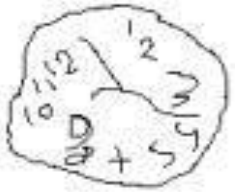
NFTs (tangles)



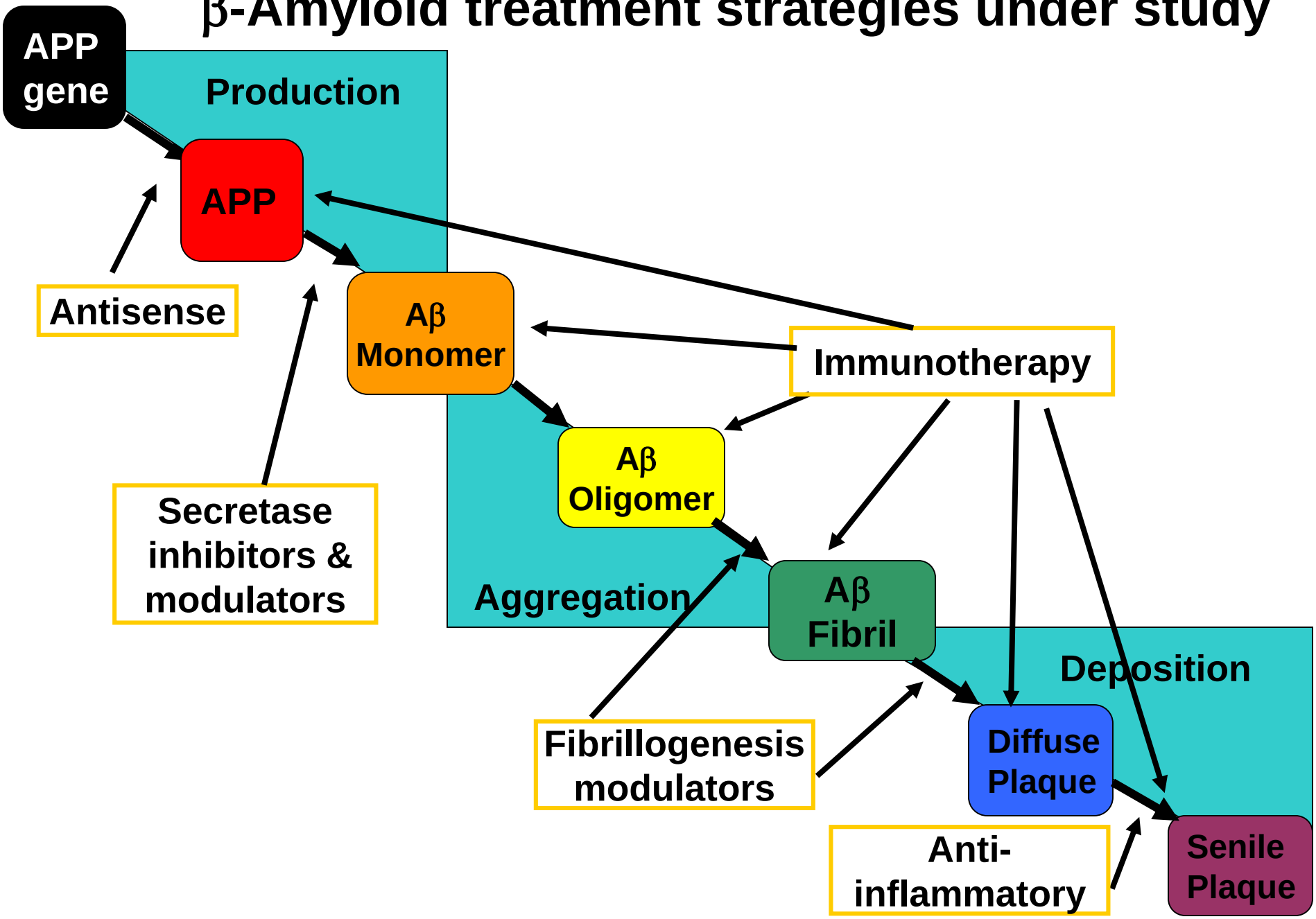
Neuronal Loss (atrophy)



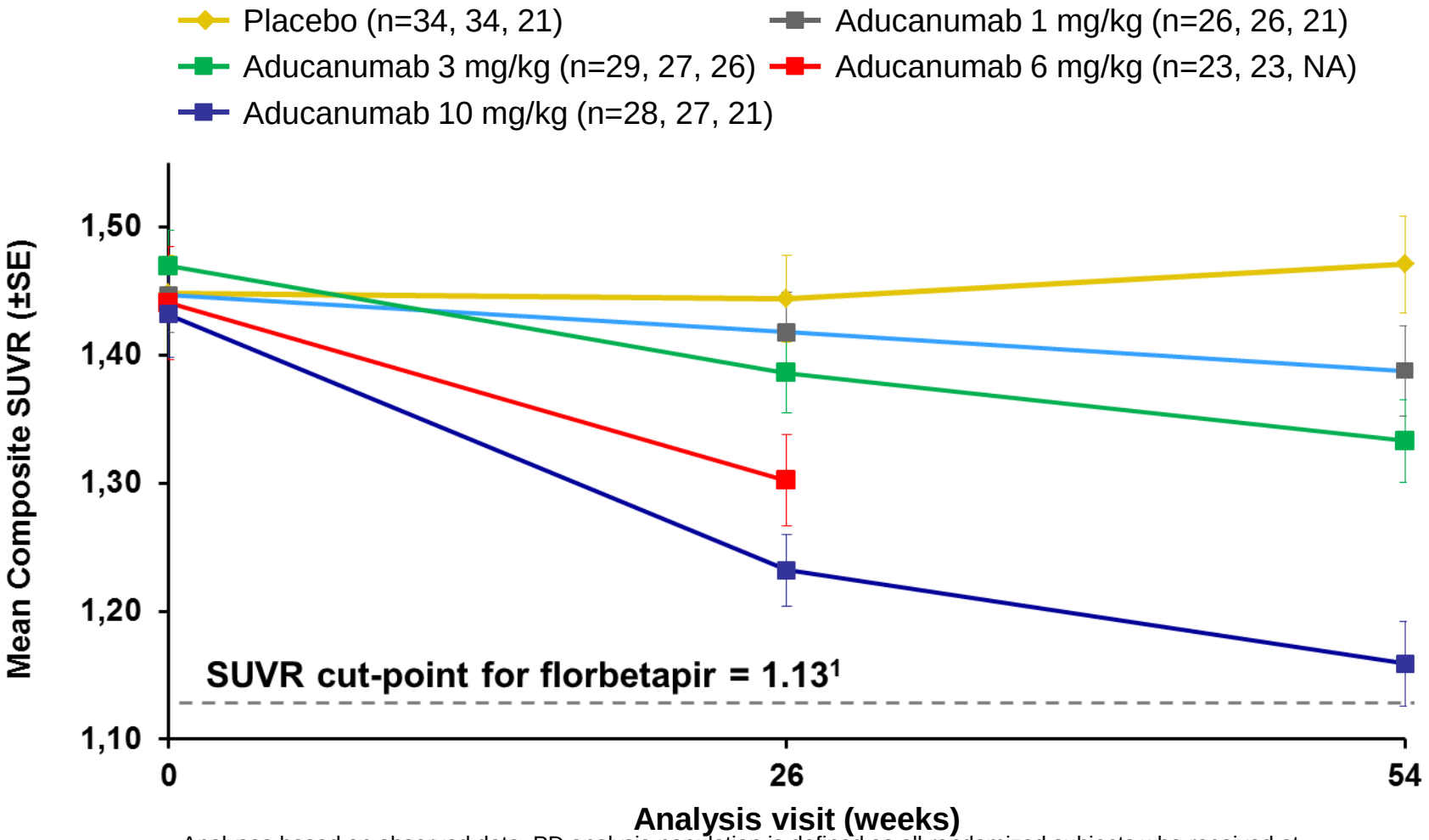
Symptoms



β-Amyloid treatment strategies under study



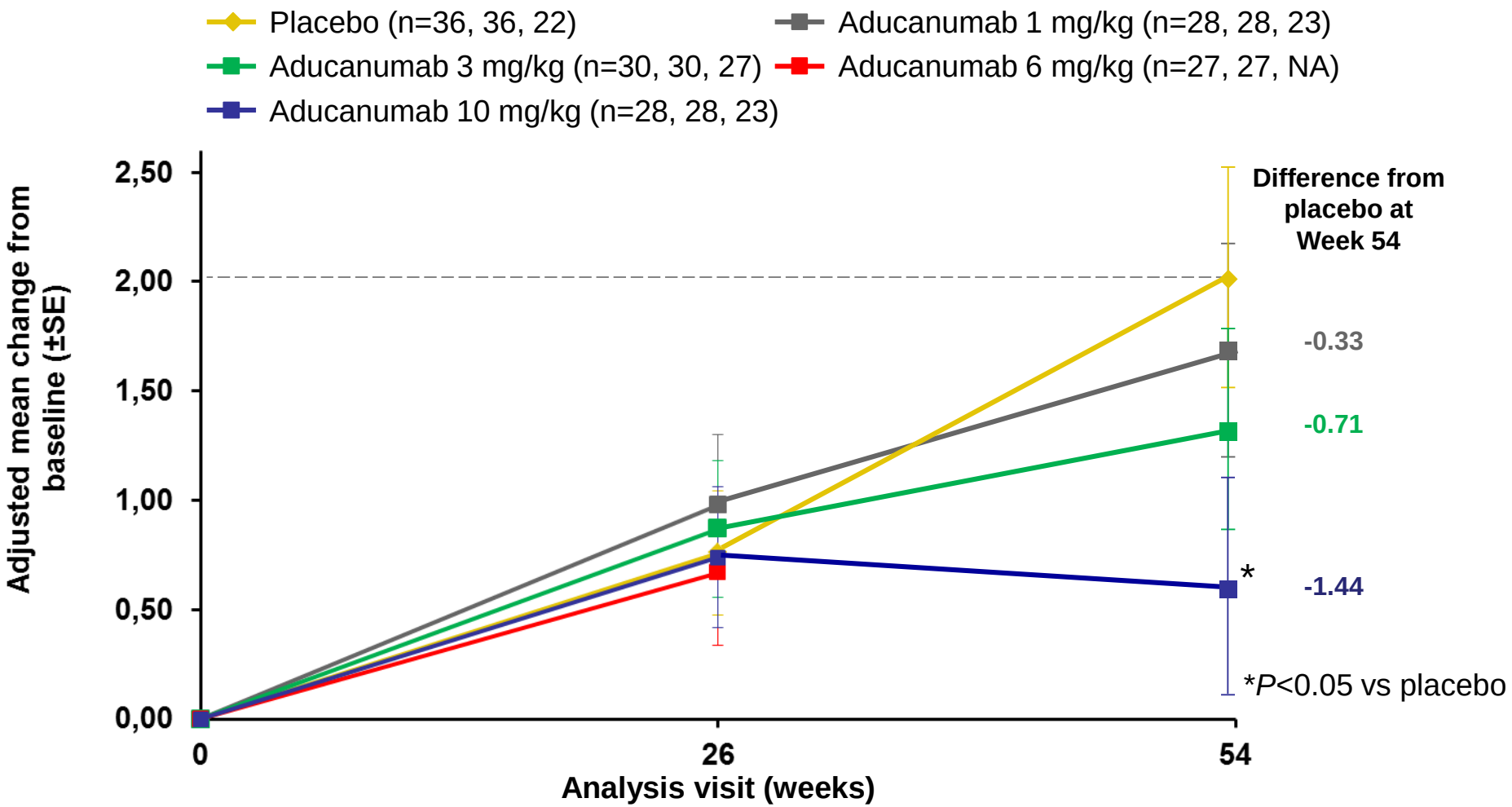
Amyloid Plaque Reduction with Aducanumab



Analyses based on observed data. PD analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.

1. Landau et al. J Nucl Med 2013

Aducanumab Effect on CDR-SB



CDR-sb is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-sb. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment.

Original Article

Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

Randall J. Bateman, M.D., Chengjie Xiong, Ph.D., Tammie L.S. Benzinger, M.D., Ph.D., Anne M. Fagan, Ph.D., Alison Goate, Ph.D., Nick C. Fox, M.D., Daniel S. Marcus, Ph.D., Nigel J. Cairns, Ph.D., Xianyun Xie, M.S., Tyler M. Blazey, B.S., David M. Holtzman, M.D., Anna Santacruz, B.S., Virginia Buckles, Ph.D., Angela Oliver, R.N., Krista Moulder, Ph.D., Paul S. Aisen, M.D., Bernardino Ghetti, M.D., William E. Klunk, M.D., Eric McDade, M.D., Ralph N. Martins, Ph.D., Colin L. Masters, M.D., Richard Mayeux, M.D., John M. Ringman, M.D., Martin N. Rossor, M.D., Peter R. Schofield, Ph.D., D.Sc., Reisa A. Sperling, M.D., Stephen Salloway, M.D., John C. Morris, M.D., for the Dominantly Inherited Alzheimer Network

N Engl J Med
Volume 367(9):795-804
August 30, 2012

The NEW ENGLAND JOURNAL of MEDICINE

DRUGS SELECTED BY DIAN-TU

- Gantenerumab, antibody against aggregated amyloid
- Solanezumab, monoclonal antibody against soluble amyloid

AMYLOID AS TARGET FOR DISEASE-MODIFICATION

- Amyloid as single target
- No effect demonstrated beyond mild dementia
- Special groups of interest such as Autosomal Dominant Familial AD and ApoE4/4

STUDY DESIGNS FOR DISEASE-MODIFYING DRUGS IN AD

- 18 months to 7 years
- Placebo control group in CN and MCI outside the US
- Add-on to ‘standard of care’ at the dementia stage, usually donepezil
- Cognition as primary outcome, biomarkers in some

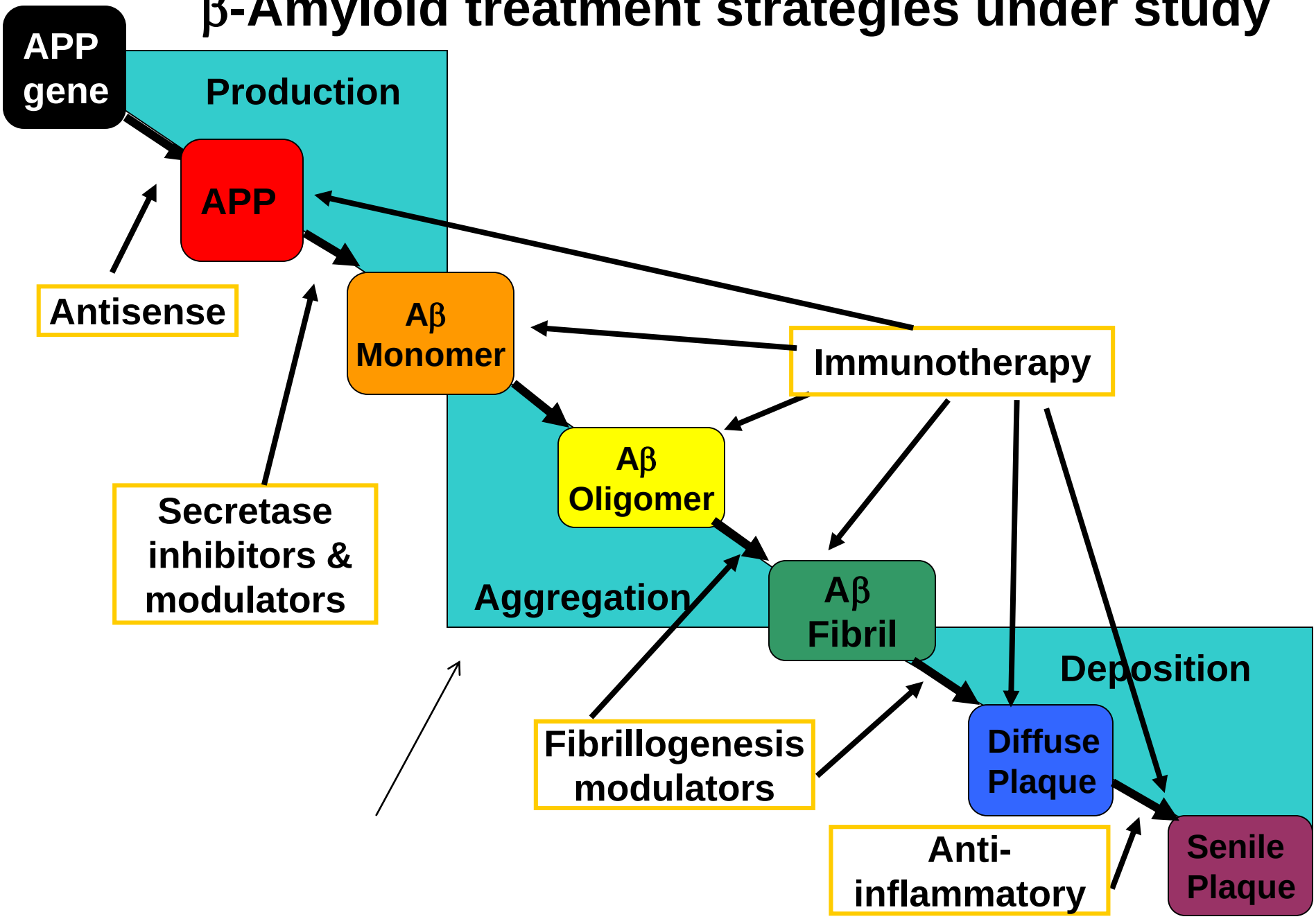
OUTLINE

- Current symptomatic drugs
- Targeting pathophysiological factors
- **Having a second look at old drugs**
- Prevention strategies are essential
- Conclusions

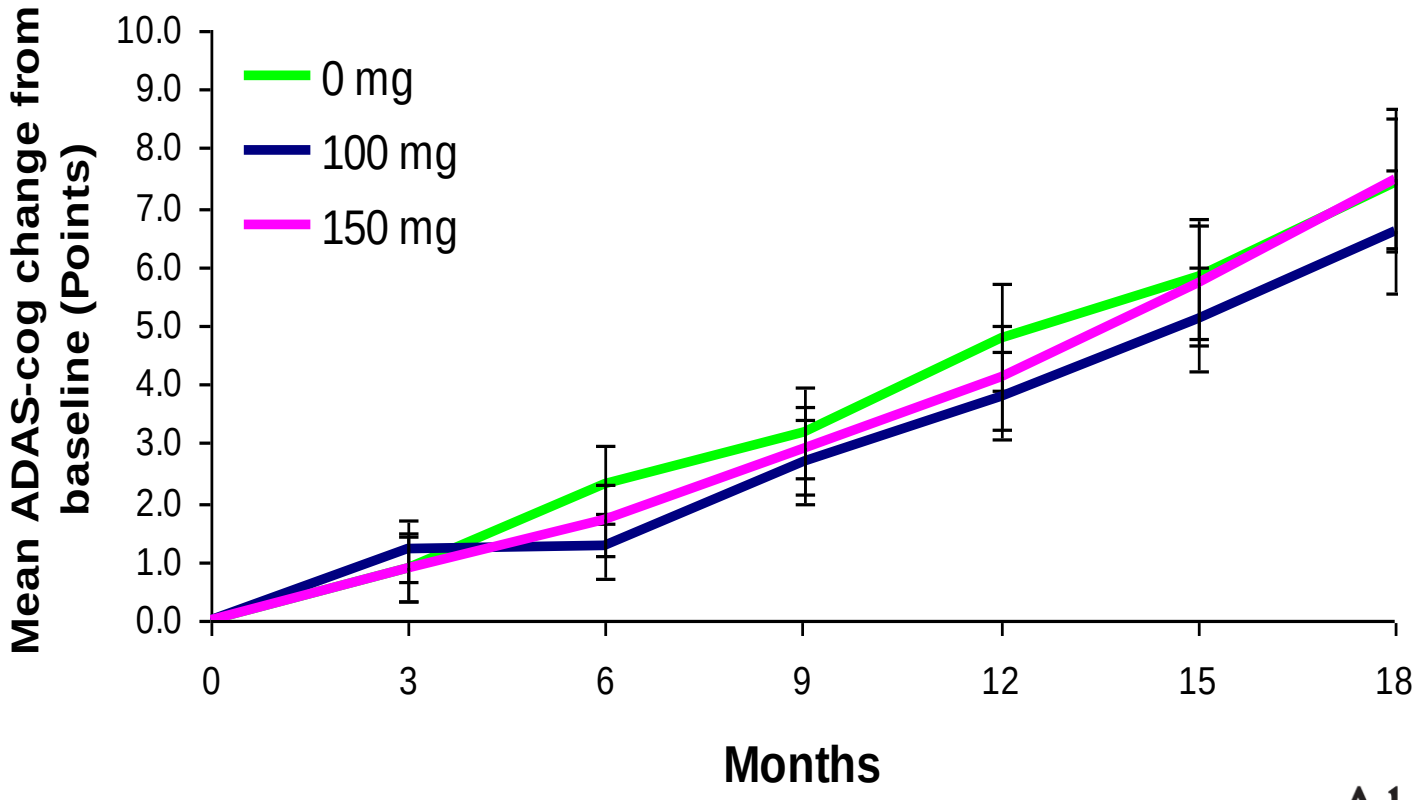
New look at old drugs - 1

- *Tramiprosate* as an anti-aggregation of amyloid fibrils drug was tested in mild to moderate ‘probable AD’
- Negative Phase III studies in the primary analysis
- Reanalysis showed an effect in participants with the ApoE4/4 genotype

β-Amyloid treatment strategies under study



Tramiprosate vs placebo, 18 months, cognition (ADAS-cog)

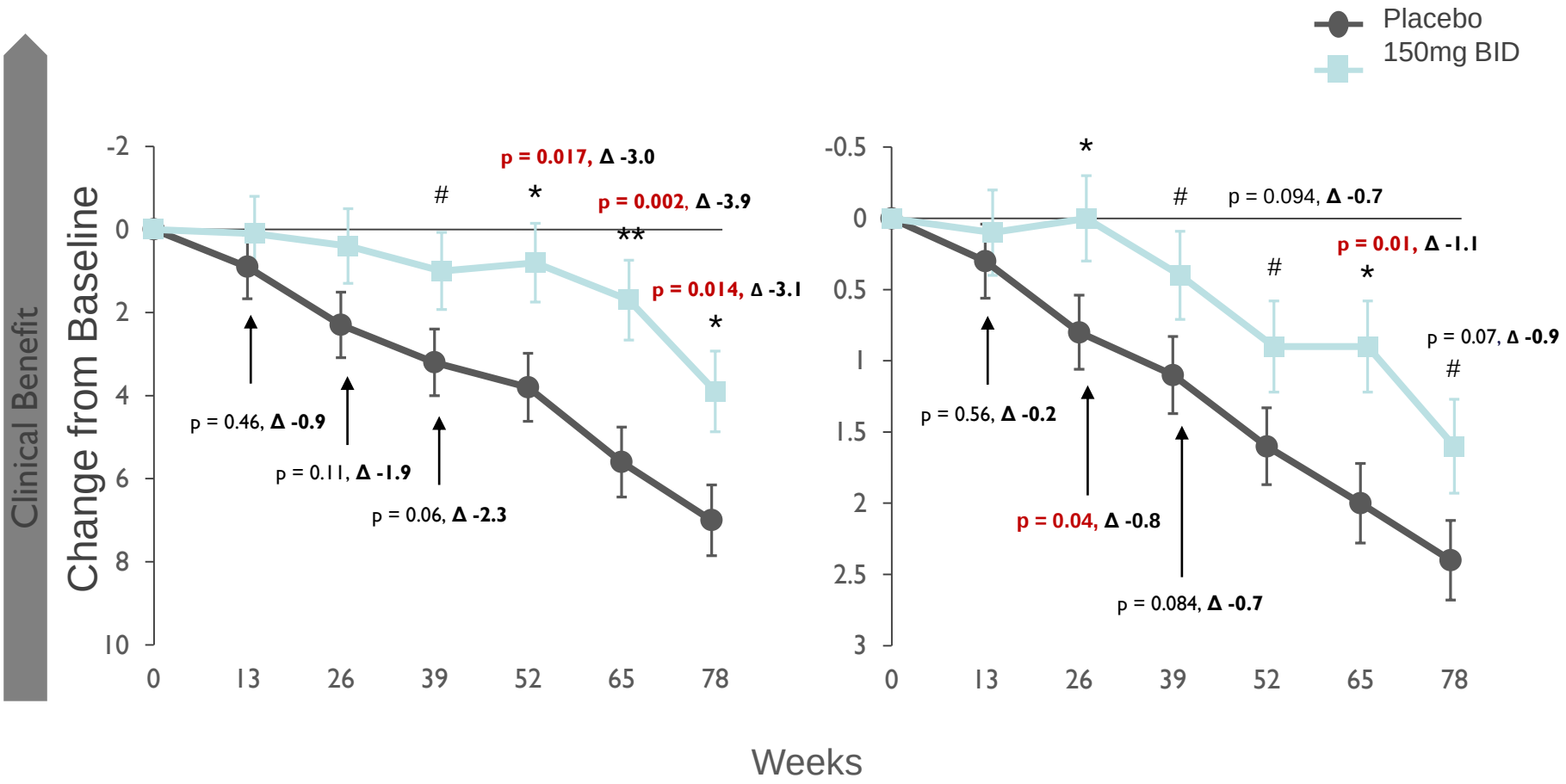


*Arithmetic mean +/- 95% CI

Alphase III Study

Effects in Mild to Moderate AD E4/4

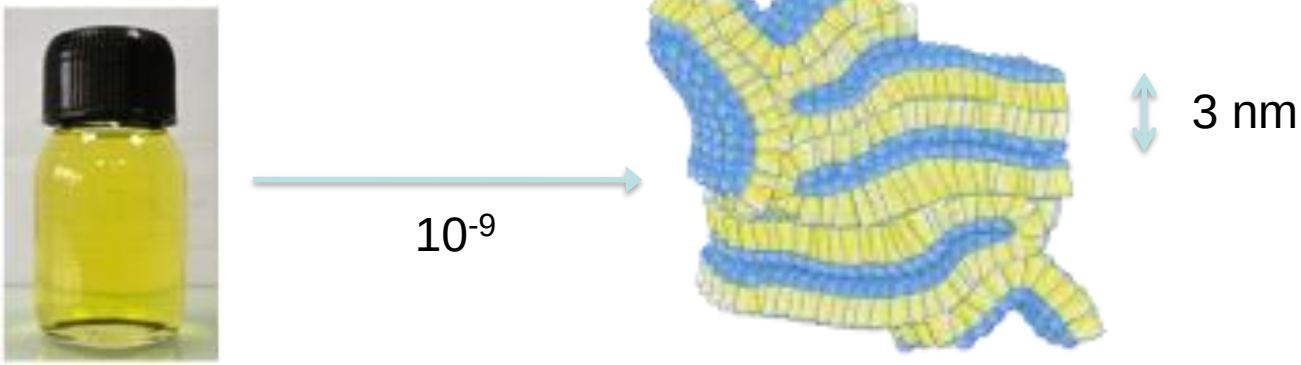
North American Study: APOE4/4, Age ≤85 Years, MMSE 16-26



* p < 0.05
** p < 0.01
\# p = 0.05 - 0.1 (trend)

New look at old drugs - 2

- *Lithium* may have symptomatic and disease stabilization effects, but needs better tolerated doses: possible with new “NanoLithium” NP03 formulation



Aonys® is a unique nanotechnology shared by all products under development
Aonys® is protected by 8 **international patents**
A pharmaceutical microemulsion composed of water and specific lipids
The active pharmaceutical ingredient is dissolved in the water phase
Administration is via buccal mucosa, transported by HDL lipoproteins and delivered directly in cells in all tissue types, including the brain

New look at old drugs - 3

- Working group led by Robert Howard looking at all available data on

  (1) angiotensin receptor blockers

  (2) angiotensin convesting enzyme inhibitors

  (3) liraglutide/exenatide

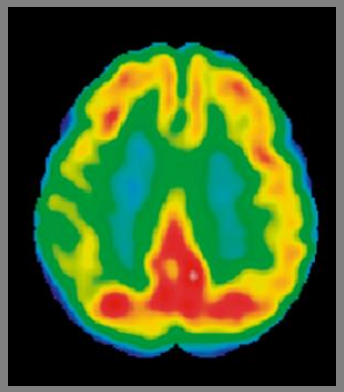
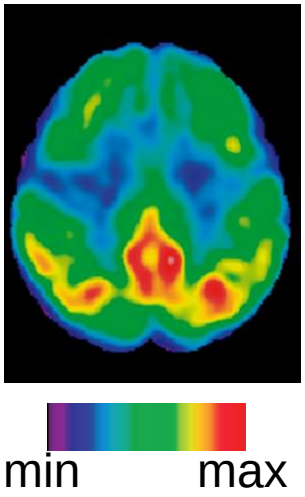
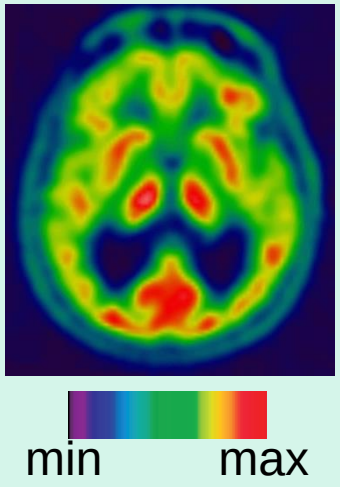
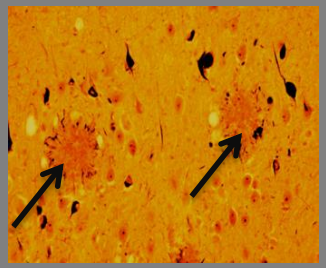
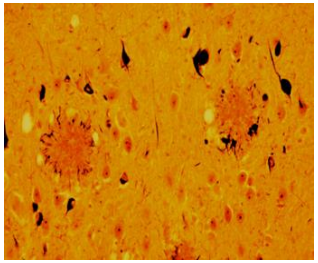
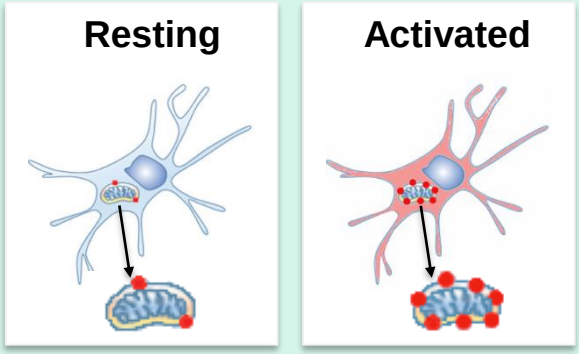
  (4) lithium (5) infliximab/etanercept

  (6) fasudil (7) metformin

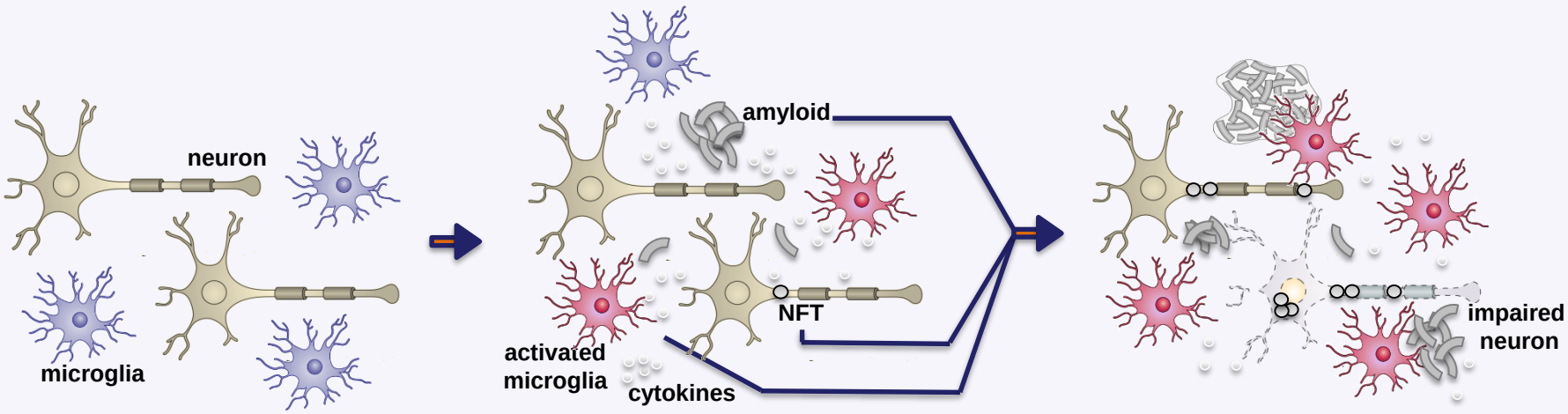
New look at old drugs - 4

- Neuroinflammation is an important pathophysiological factor at some stage of AD
- It may be possible to visualize the microglial activation using novel PET ligands such as [^{11}C]PBR28
- May lead to new trials using *NSAIDS*

CURRENT RESEARCH PET IMAGING AT MCGILL CENTER ON AGING

tracer	**Amyloid imaging** [^{11}C]PIB SUVR	**Tau imaging** [^{18}F]THK5351 SUVR	**TSPO imaging** [^{11}C]PBR28 SUVR
Image			
Interpretation	**Amyloid plaques**  Tissue availability of Fibrillary amyloid	**Neurofibrillary tangles**  Tissue availability of Paired Helical Filaments	**Microglia**  Tissue availability of TSPO expression • TSPO =Translocator protein (18kDa) -

Interactions between pathological processes drive disease progression in preclinical AD



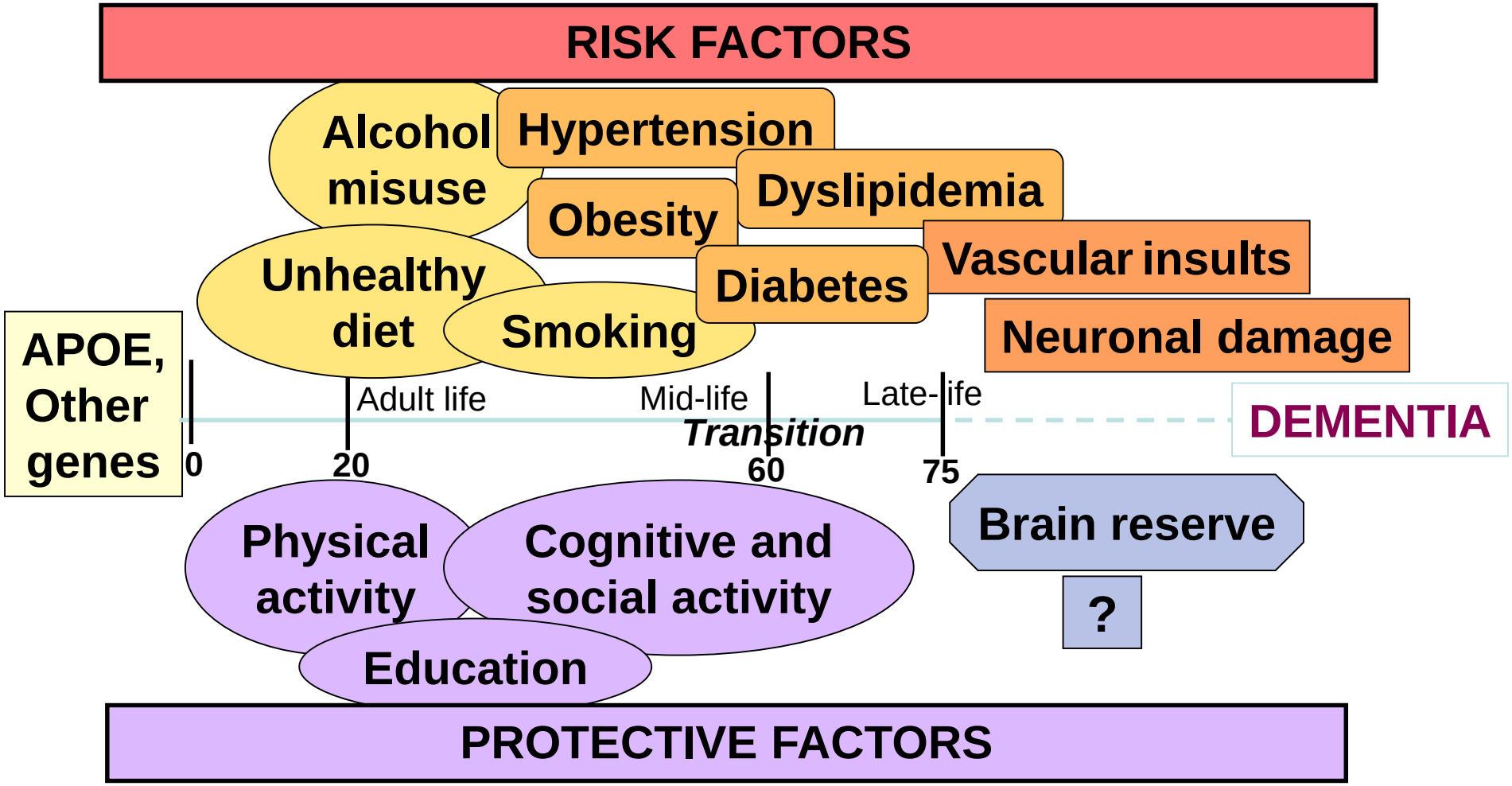
Increased tissue concentrations of amyloid in preclinical Alzheimer's disease will activate microglia.

We hypothesize that the interaction between regional amyloid, local NFT and levels of microglial activation will drive propagation of NFT and cognitive decline (see statistical methods).

OUTLINE

- Current symptomatic drugs
- Targeting pathophysiological factors
- Having a second look at old drugs
- **Prevention strategies are essential**
- Conclusions

WHAT IS ALZHEIMER'S DISEASE? RISK AND PROTECTIVE FACTORS

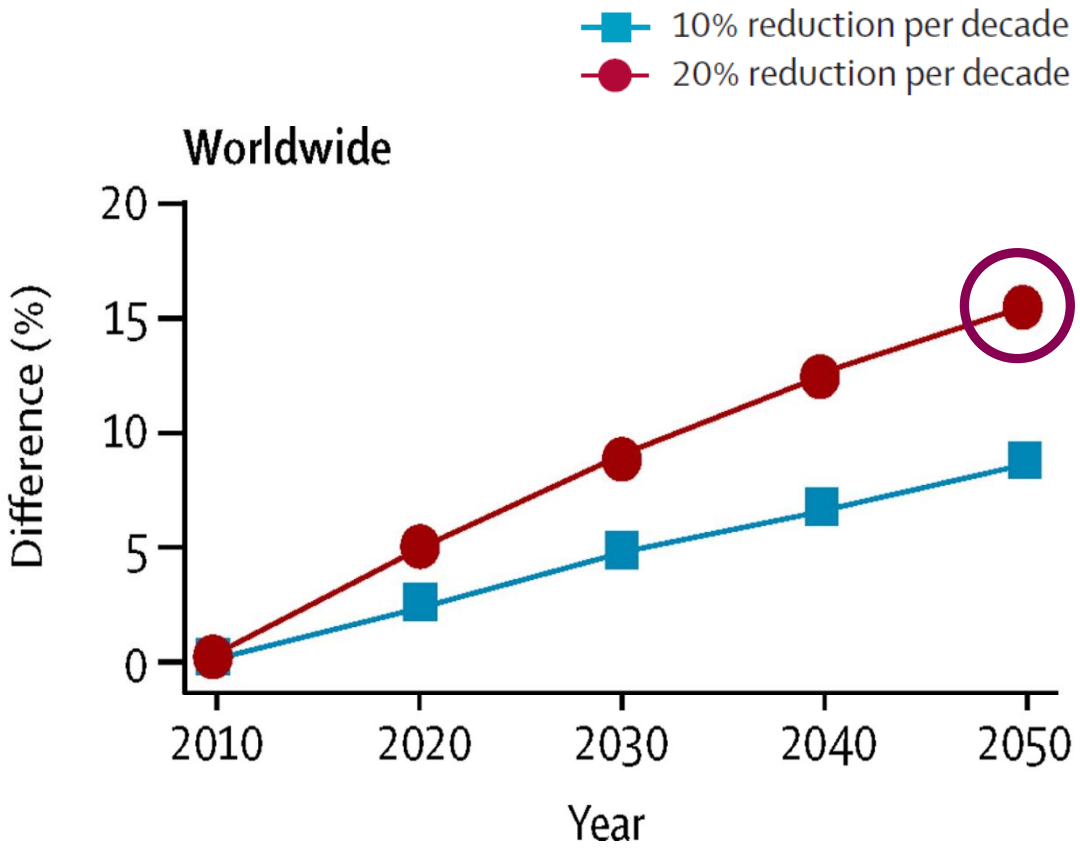


Mangialasche, Kivipelto et al., 2012

To what extent can Alzheimer dementia be prevented?

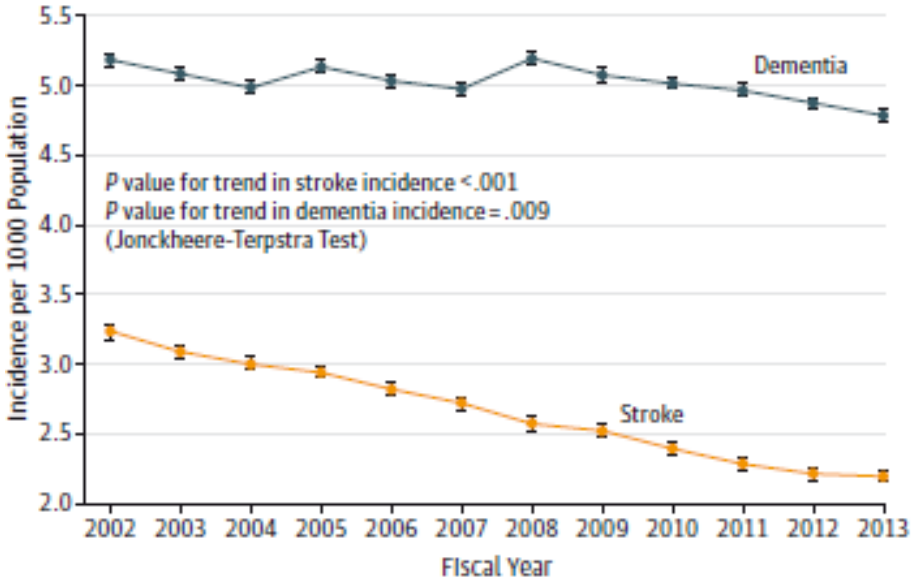
Risk factor	PAR
Diabetes mellitus	2.9%
Midlife hypertension	5.1%
Midlife obesity	2.0%
Physical inactivity	12.7%
Depression	7.9%
Smoking	13.9%
Low education	19.1%
Combined PAR*	28.2%

PAR=population-attributable risk.
*Adjusting for non-independence of the risk factors.



Norton et al., Lancet Neurol, 2014; Kivipelto and Mangialasche, Nature Neurol Rev, 2014

Figure. Trends in Stroke and Dementia Incidence Rates, Ontario 2002-2013



The error bars represent 95% CIs.

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

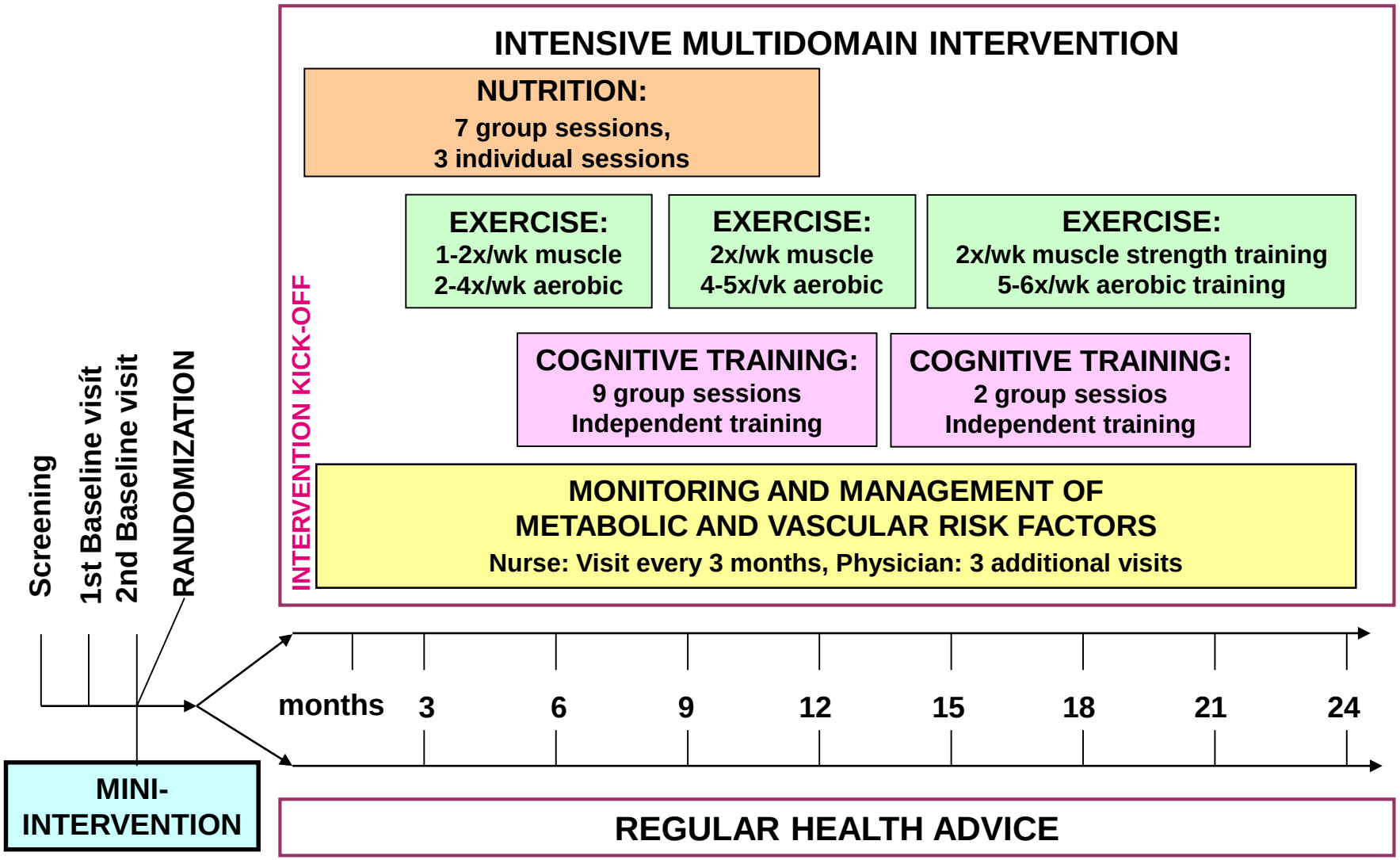
Tiia Ngandu, Jenni Lehtisalo, Alina Solomon, Esko Levälahti, Satu Ahtiluoto, Riitta Antikainen, Lars Bäckman, Tuomo Hänninen, Antti Jula, Tiina Laatikainen, Jaana Lindström, Francesca Mangialasche, Teemu Paajanen, Satu Pajala, Markku Peltonen, Rainer Rauramaa, Anna Stigsdotter-Neely, Timo Strandberg, Jaakko Tuomilehto, Hilkka Soininen, Miia Kivipelto

The Lancet, 2015

(Published online March 12 2015)

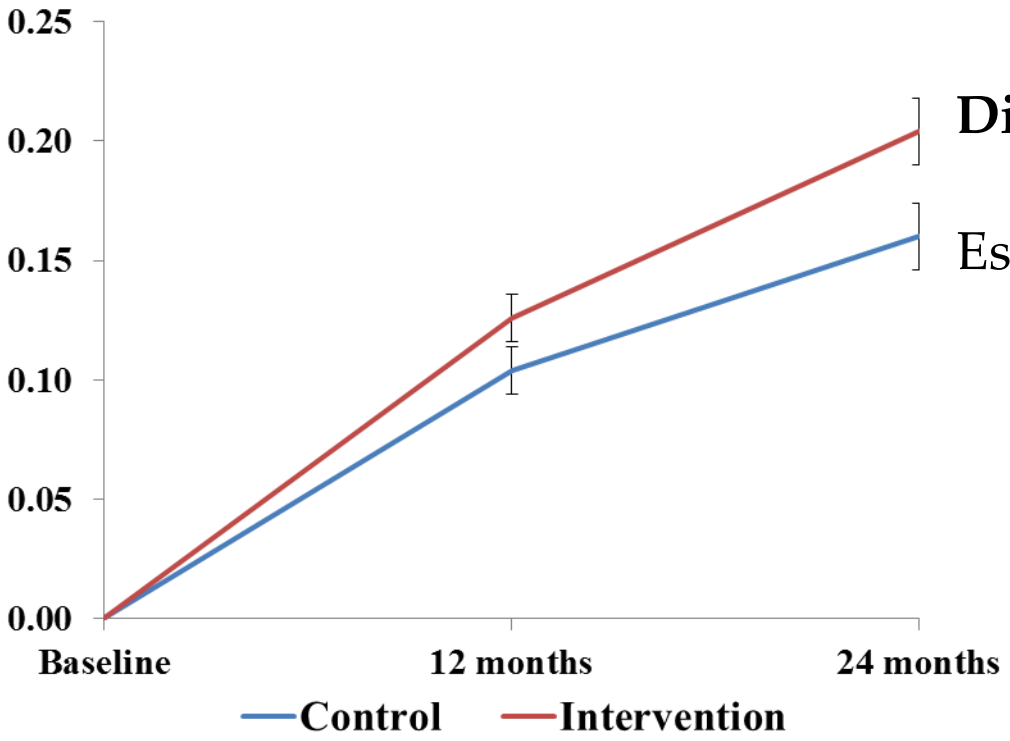
FINGER

INTERVENTION SCHEDULE



Kivipelto et al., Alzheimer & Dementia 2013

Primary efficacy outcome: overall cognition (NTB composite Z score)



Difference between intervention and control groups per year:

Estimate (95% CI) = 0.022 (0.002-0.042)

p=0.03

Kivipelto et al, Lancet 2015

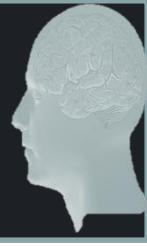
Lines = estimates for cognitive change from baseline to 12 and 24 months

Higher scores = better performance

Error bars = standard errors.

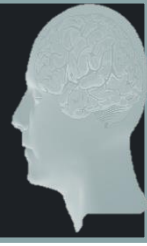
P-values = difference in trajectories over time between groups

CONCLUSIONS - GENERAL



- Earlier and more accurate diagnosis of AD is possible but ethical isssues about it
- Drug treatments should be targeting amyloid, tau, inflammation, at the right stage of disease for the right patient
- Prevention strategies are to be encouraged at the population level, through national plans

CONCLUSIONS - SPECIFIC



- Consider using a factorial design in Phase II to rule out negative interactions in combination therapies
- Target the most promising phenotypically and biologically defined group of patients
- Plan for optimal use of the new drugs: start rules and stop rules