DEMENZE, DISTRETTO E TERRITORIO
Costruiamo le alleanze

Taranto, Cittadella della Carità
26 Febbraio 2016

Update sul trattamento farmacologico e nutraceutico

Francesco Panza

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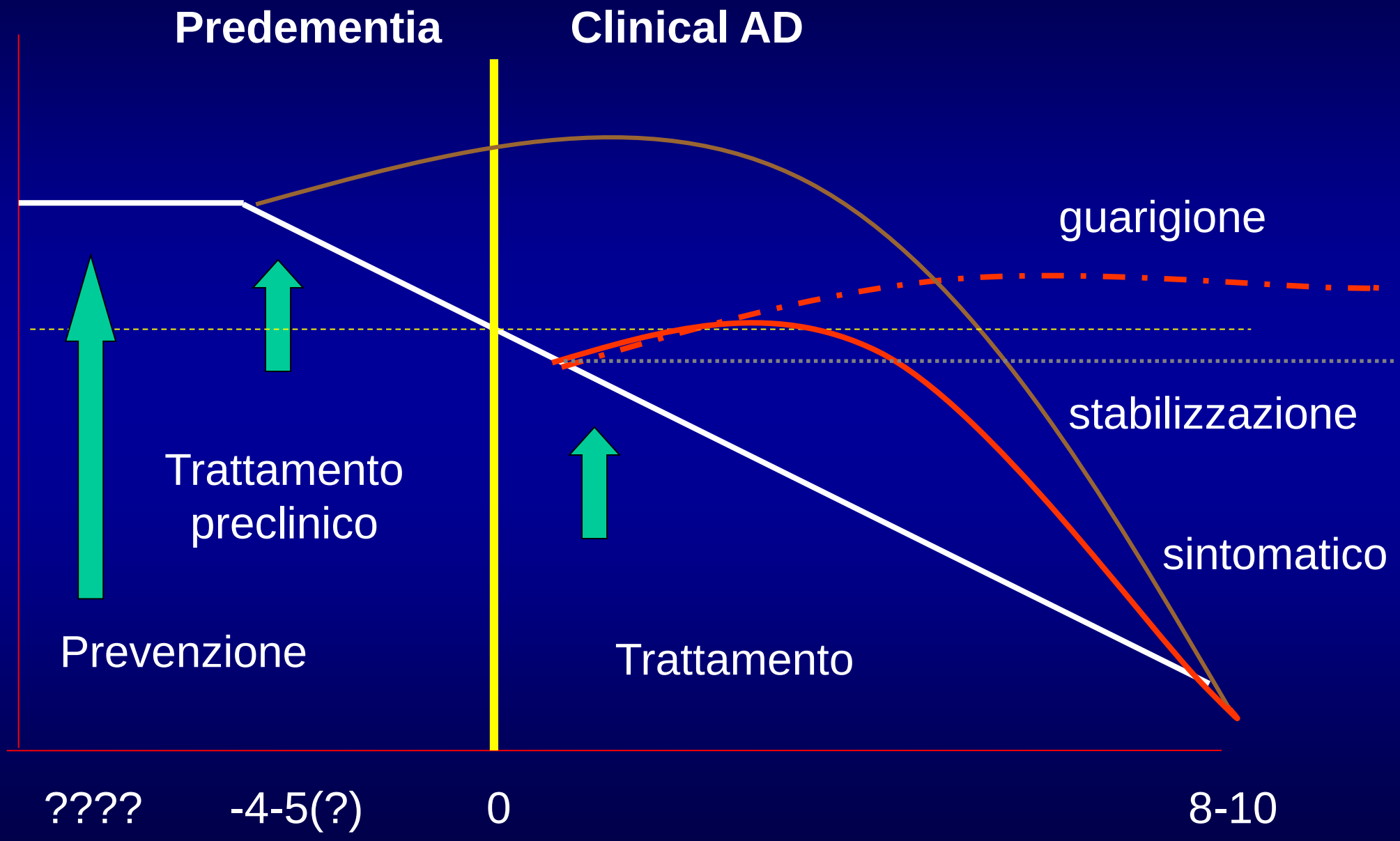
Strategie di intervento per la malattia di Alzheimer



Aging Clinical and Experimental Research

REVIEW ARTICLES

Beyond the neurotransmitter-focused approach in treating Alzheimer's Disease: drugs targeting

β-amyloid

Tau protein

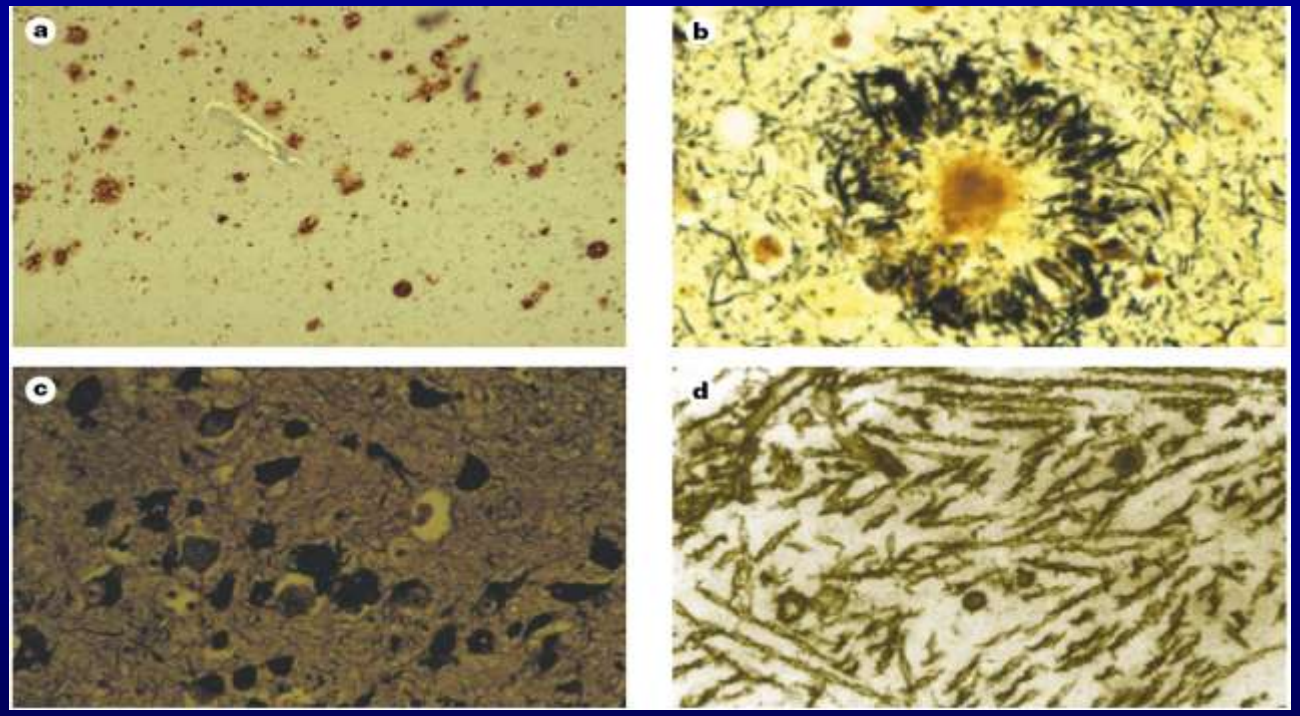
imbo[2], Cristiano Capurso[3],
emiale[3,4], Antonio Capurso[1]

f Bari, Bari, [2]Research and Development Department, Chiesi Farmaceutici, Parma, [3]Department of Geriatrics, University of Foggia, Foggia, [4]Internal Medicine Unit, IRCCS Casa Sollievo dalla Sofferenza, San Giovanni Rotondo, Foggia, [5]Geriatric Unit and Gerontology-Geriatric Research Laboratory, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

Panza et al. Aging Clin Exp Res 2009;21:386-406

Conoscere la patogenesi molecolare

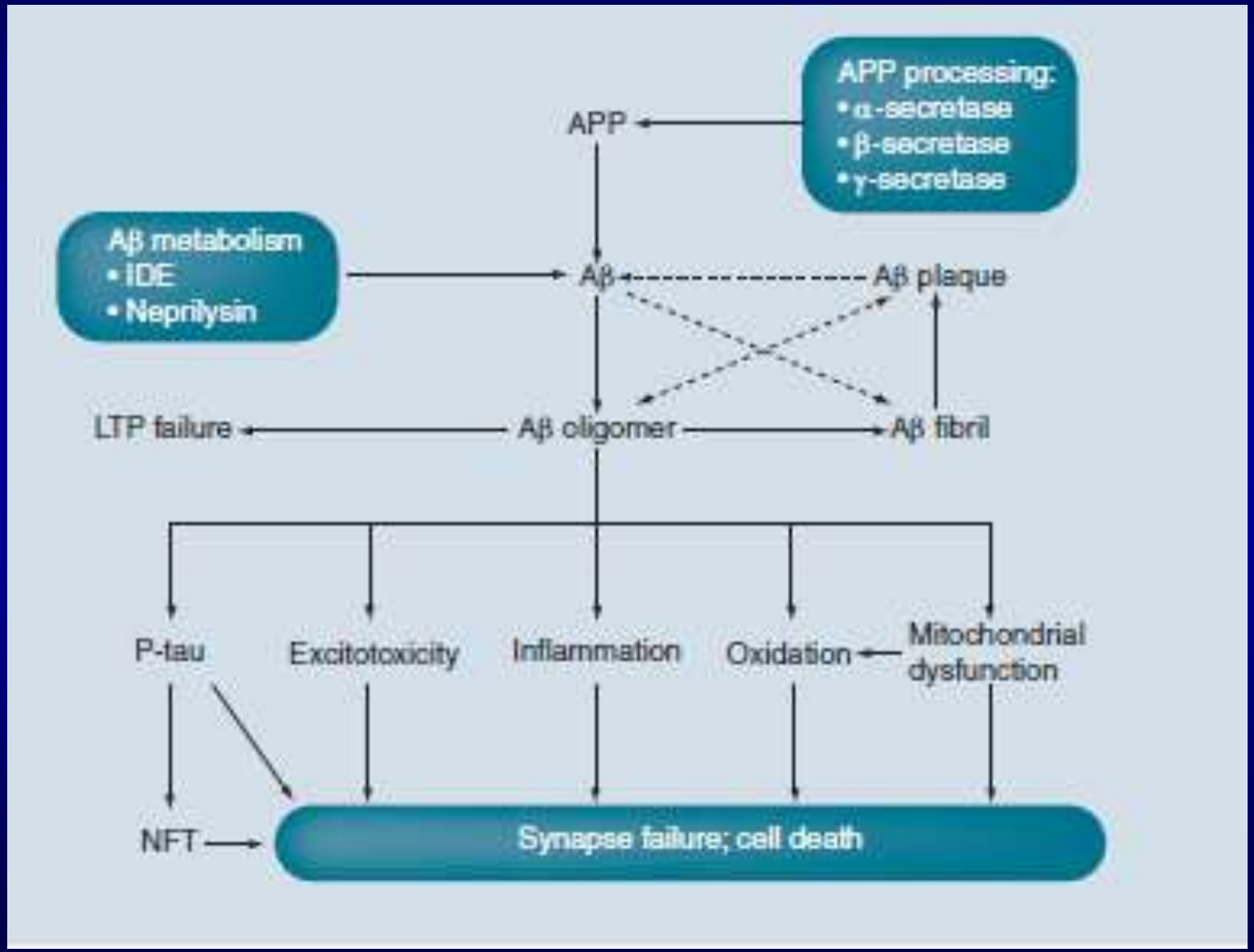
- **La comprensione dei meccanismi molecolari di patogenesi e' strumentale per comprendere le basi molecolari della terapia**



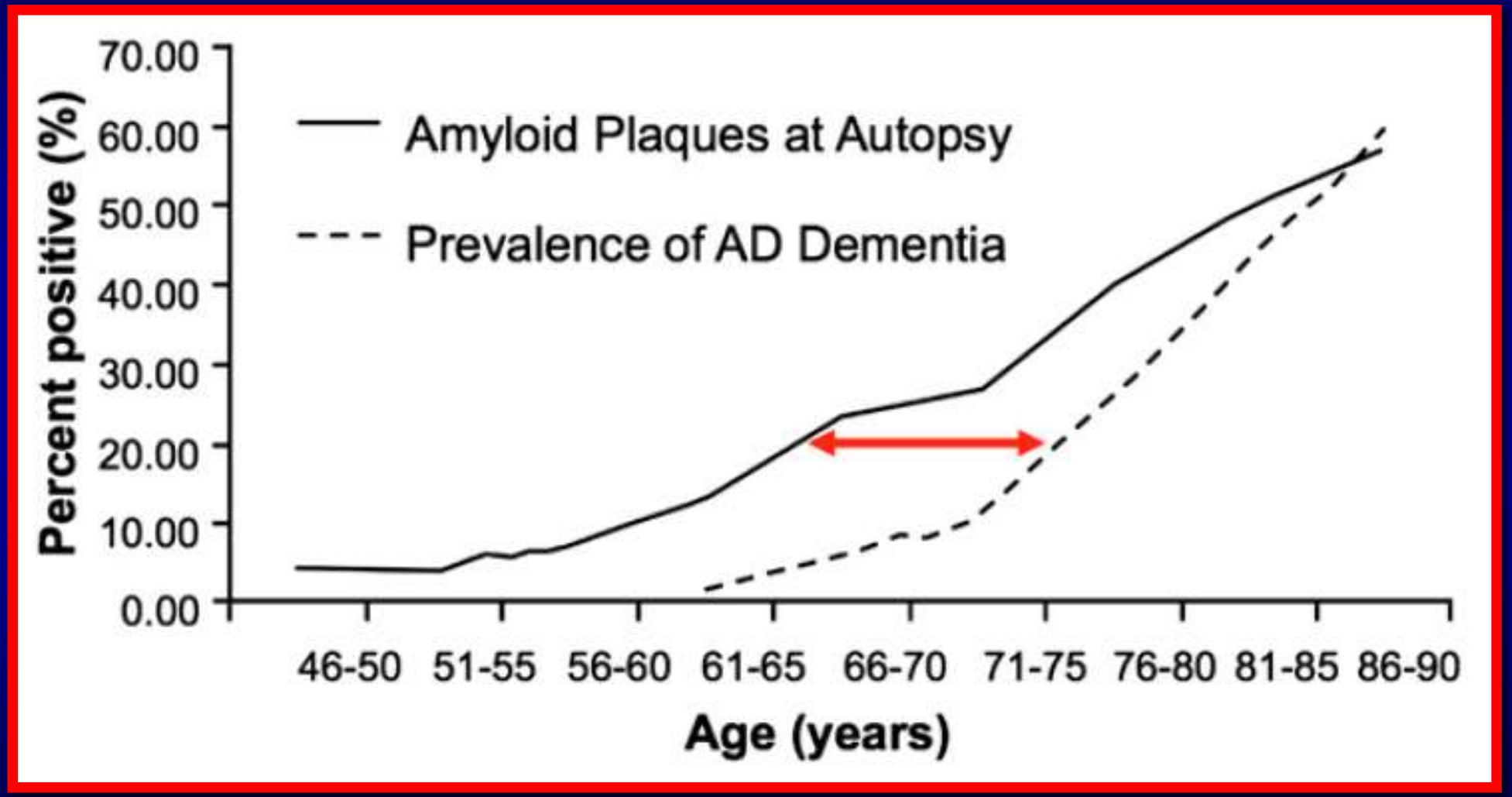
Placche senili: Aβ

Grovigli neurofibrillari: τ

Pathological cascade of Alzheimer's disease



APPEARANCES OF PLAQUES vs DEMENTIA



R.A. Sperling et al. / Alzheimer's & Dementia- (2011) 1–13

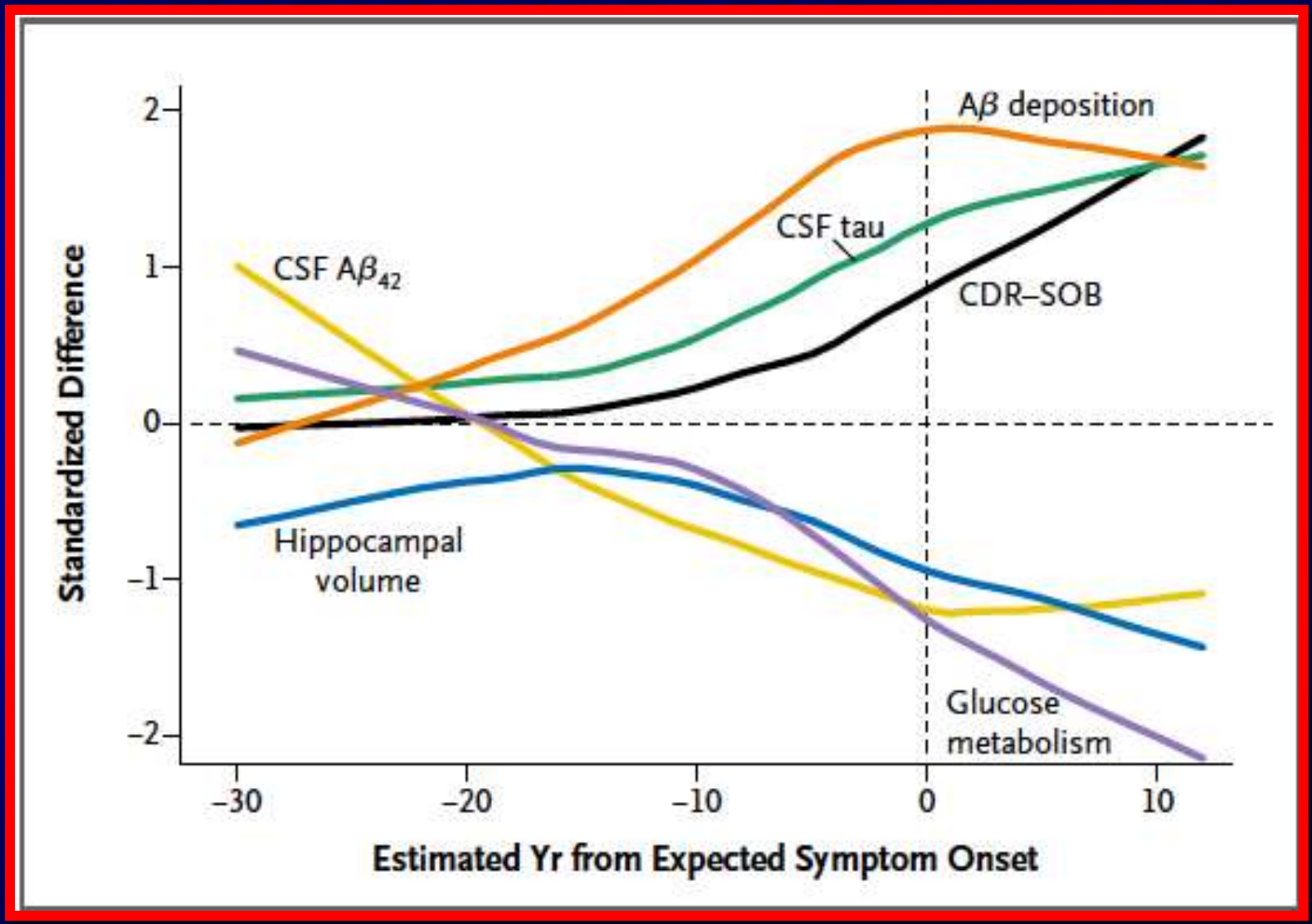
Current most-validated AD biomarkers

	Pathophysiological markers	Topographical markers
Cerebrospinal fluid		
Amyloid β_{42}	Yes	No
Total tau, phospho-tau	Yes	No
PET		
Amyloid tracer uptake	Yes	No
Fluorodeoxyglucose	No	Yes
Structural MRI		
Medial temporal atrophy	No	Yes

AD=Alzheimer's disease.

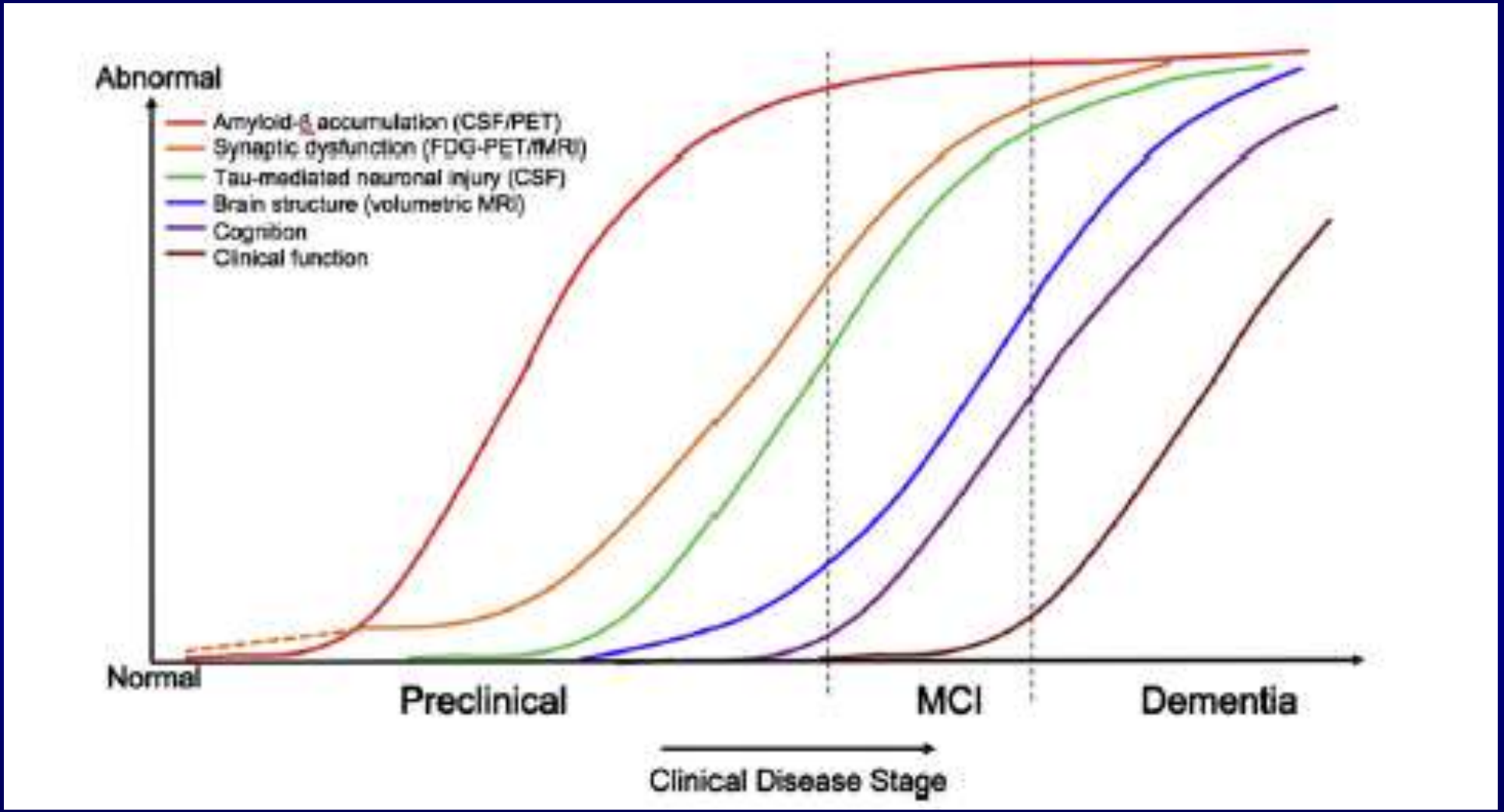
Dubois et al. Lancet Neurol 2010; 9: 1118–27

COMPARISON OF CLINICAL, COGNITIVE, STRUCTURAL, METABOLIC, AND BIOCHEMICAL CHANGES AS A FUNCTION OF ESTIMATED YEARS FROM EXPECTED SYMPTOM ONSET



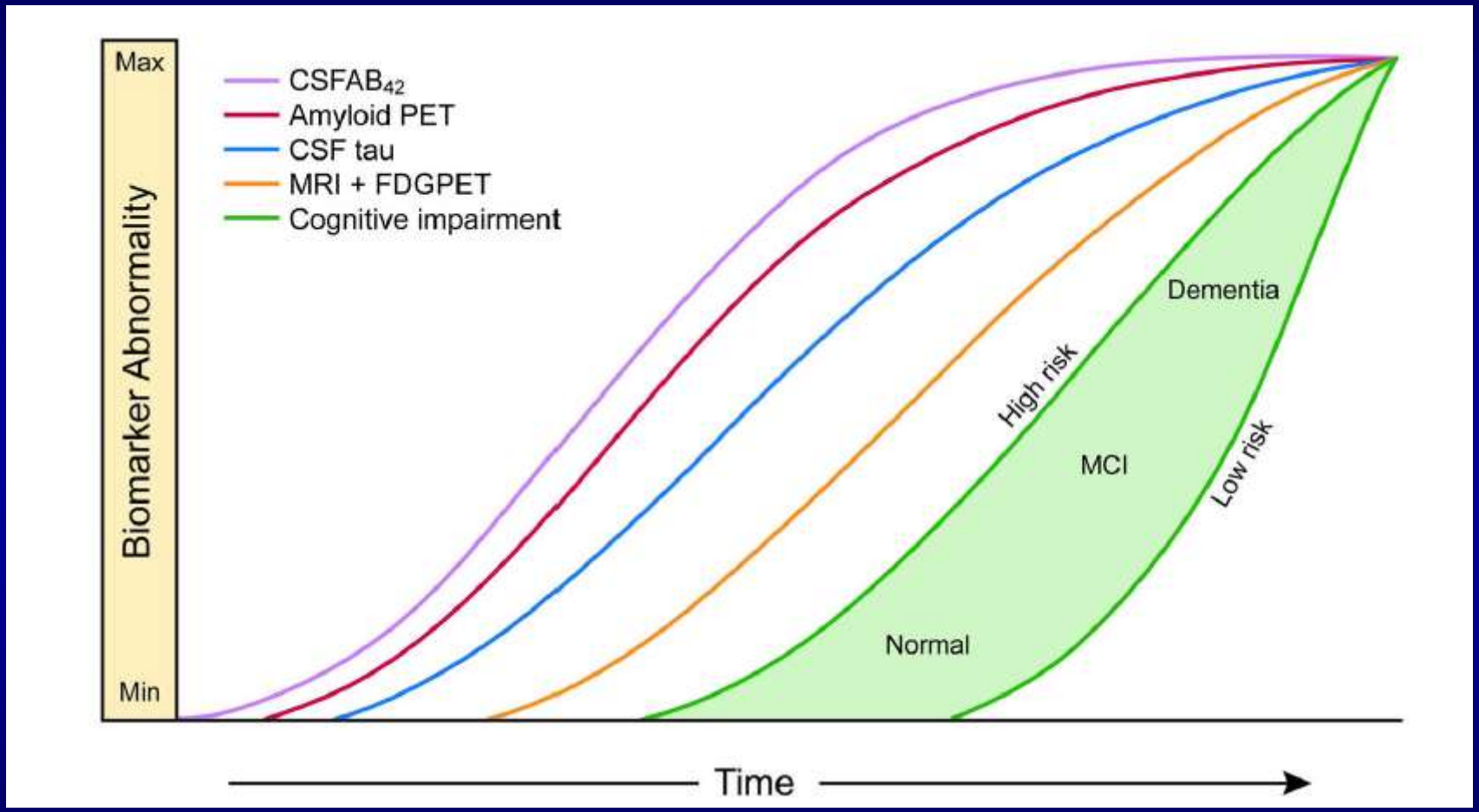
Bateman RJ et al NEJM 2012;367;9

Model of dynamic biomarkers of AD



Alzheimers Dement 2011;7:280-92

Revised model of dynamic biomarkers of AD



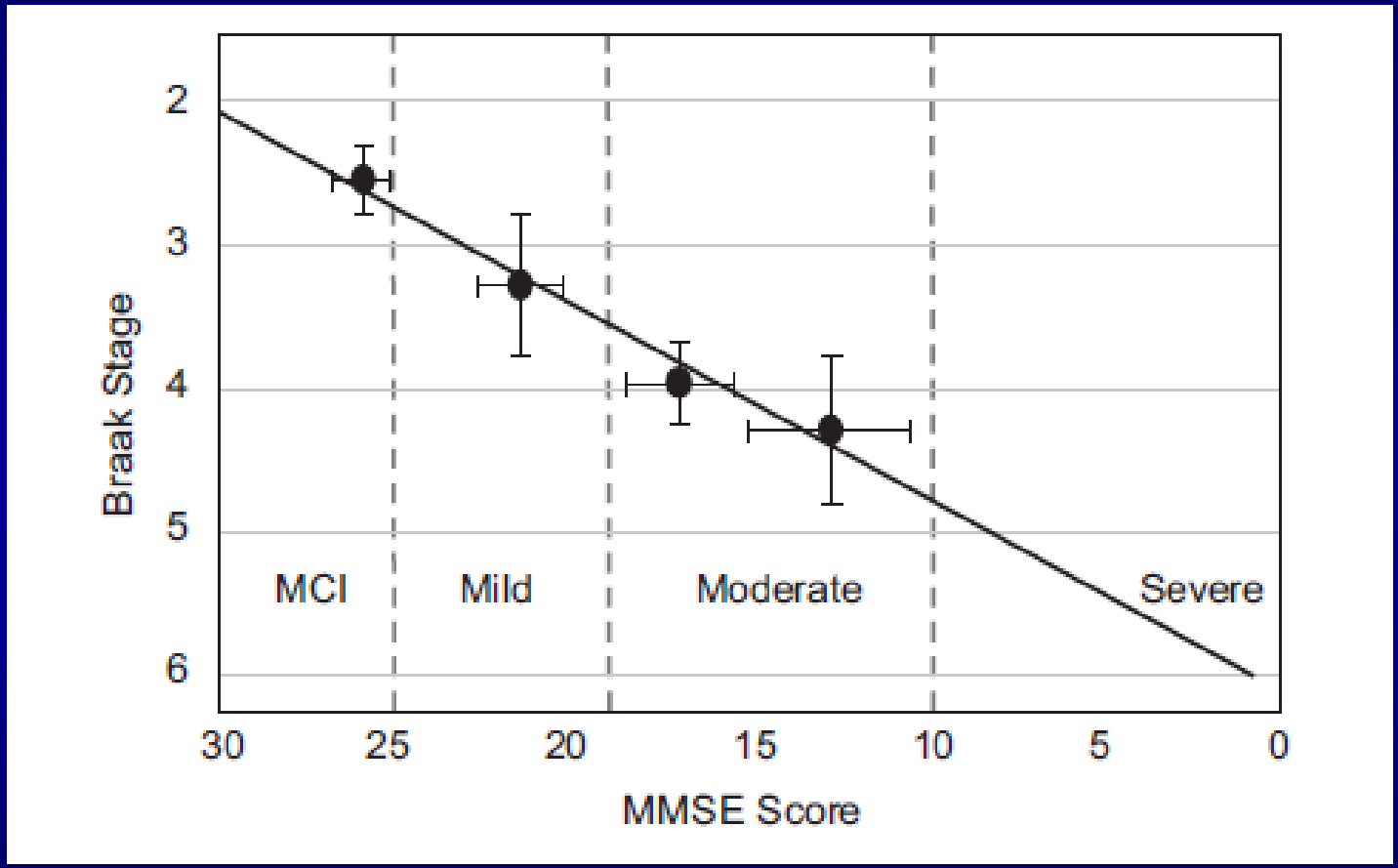
Lancet Neurol 2013;12:207-216

Braak staging correlation with cognitive decline

NFTs and NTs entorhinal cortex (stages I and II)

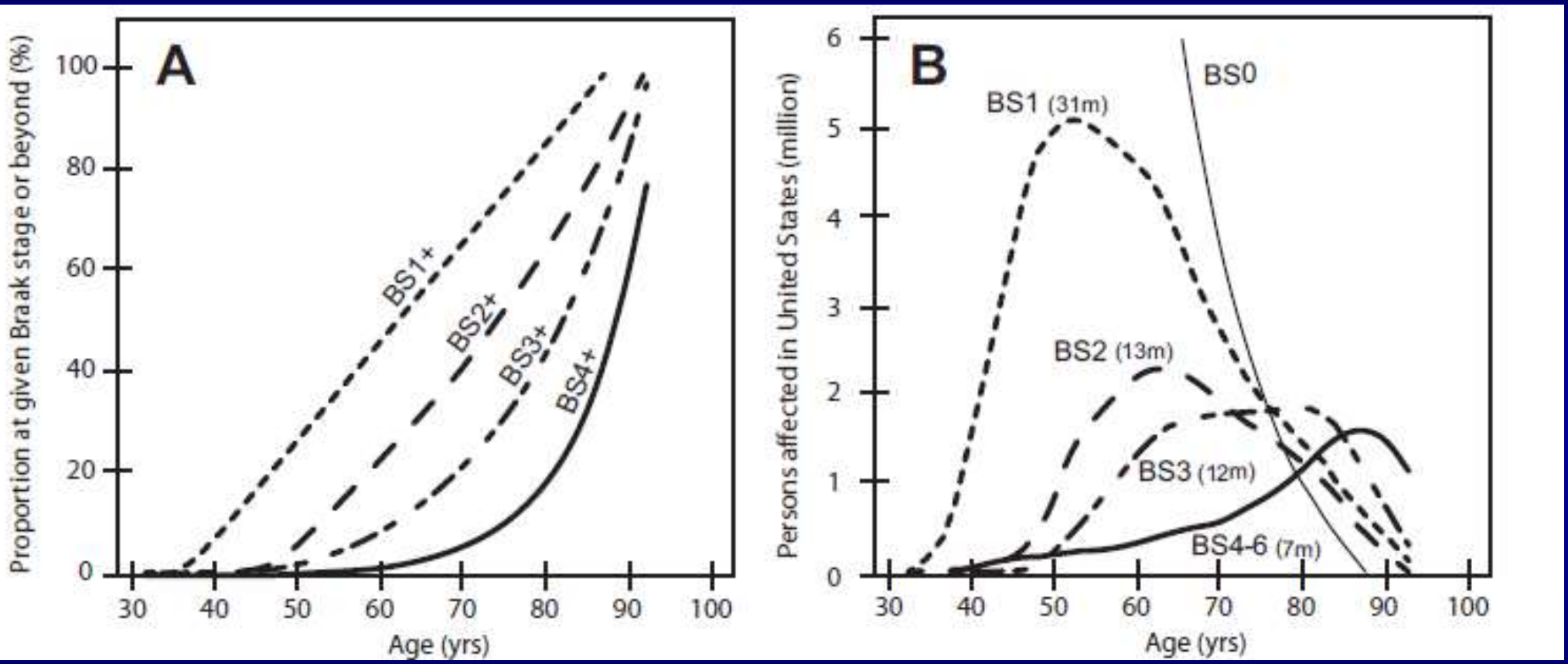
NFTs and NTs hippocampal areas (stages III and IV)

NFTs and NTs neocortical areas (stages V and VI)



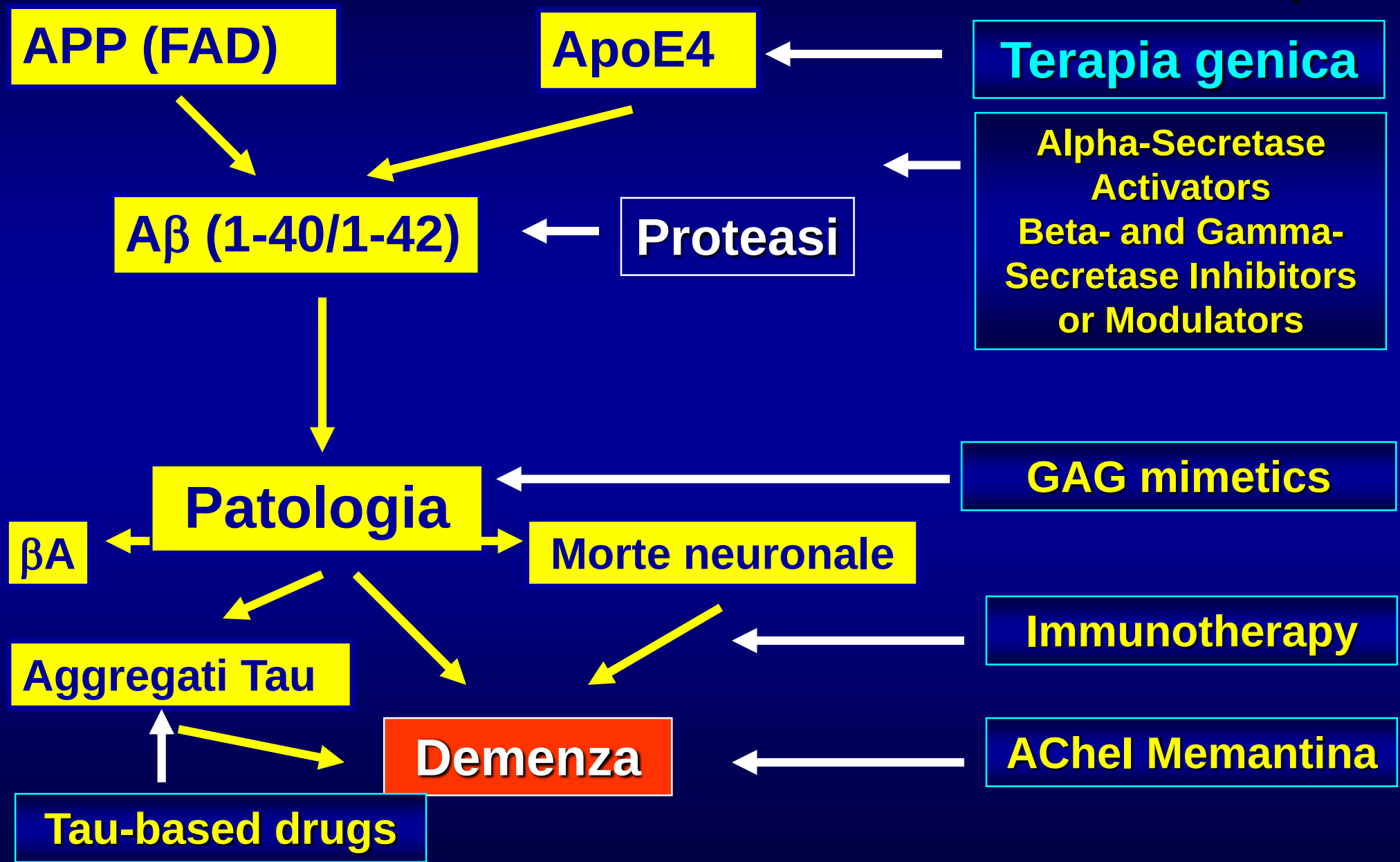
Braak H, Braak E. Acta Neuropathol 1991;82:239–259

Age-specific probability of Braak stage (BS) transitions



Wischik et al. Biochem Pharmacol 2014;88:529–539

RIDUZIONE DELLA CONCENTRAZIONE E DEPOSITO EXTRACELLULARE DELLA Aβ



Tau-based targets in AD

1) Inhibition of tau aggregation

2) Inhibition of tau phosphorylation (inhibiting tau kinases or activating tau phosphatases)

3) Increase of microtubule stabilization

4) Increase of tau clearance (immunotherapy)

Ongoing Phase I RCTs of tau-directed drugs in clinical development for AD treatment

Compound (Company) ClinicalTrials.gov Identifier	Mechanism of action	Estimated enrollment	Characteristics	Status
TPI-287 (University of California, San Francisco) NCT01966666	Microtubule-stabilizing agent	Thirty-three patients with mild to moderate AD (2013–2015)	The purpose of the study is to determine the highest dose of TPI-287 that is safe and tolerable when administered as an intravenous infusion	Phase I trial (currently recruiting)
AADvac1 (Axon Neuroscience SE) NCT01850238	Active tau-based immunotherapy	30 patients with mild to moderate AD (2013–2015)	Patients will receive 1 dose of AADvac1 per month over 3 months, for a total of three administrations	Phase I trial (completed)
AADvac1 (Axon Neuroscience SE) NCT02031198	Active tau-based immunotherapy	This follow-up study continues to observe patients who have completed the Phase I trial of AADvac1, for another 18 months (2014–2017)	Patients who have received six doses in the previous trial will be administered 1–2 booster doses of AADvac1 (two if their antibody titers decline below those achieved in the previous trial) Patients who have received three doses in the previous trial will be administered another three doses, and then vaccinated with booster doses as above	18-month follow-up Phase I trial (active, not recruiting)
ACI-35 (AC Immune AG)	Active tau-based immunotherapy	Patients with mild to moderate AD (2013–2014)	This Phase I trial compared two doses of ACI-35 to investigate its safety, tolerability, and immunogenicity	Phase I trial
RG7345 (RO6926496, MAb86) (Hoffmann-La Roche) NCT02281786	Passive tau-based immunotherapy	Forty-eight healthy subjects (January 2015–October 2015)	Single, ascending dose, intravenous administration	Phase I trial (active, not recruiting)

Seripa et al. Expert Rev Neurother 2016 [Epub ahead of print]

EXPERT OPINION ON PHARMACOTHERAPY, 2016
http://dx.doi.org/10.1517/14656566.2016.1146686

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EDITORIAL

Tau aggregation inhibitors: the future of Alzheimer's pharmacotherapy?

Panza et al. Expert Opin Pharmacother 2016 [Epub ahead of print]

EXPERT REVIEW OF NEUROTHERAPEUTICS, 2016
http://dx.doi.org/10.1586/14737175.2016.1140039

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REVIEW

Tau-directed approaches for the treatment of Alzheimer's disease: focus on leuco-methylthioninium

Davide Seripa[a*], Vincenzo Solfrizzi[b], Bruno P. Imbimbo[c], Antonio Daniele[d], Andrea Santamato[e], Madia Lozupone[f], Giovanni Zuliani[g], Antonio Greco[a], Giancarlo Logroscino[f,h] and Francesco Panza[a,f,h*]

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Seripa et al. Expert Rev Neurother 2016 [Epub ahead of print]

Journal of Alzheimer's Disease 44 (2015) 705–720
DOI 10.3233/JAD-142874
IOS Press

Short Communication

Tau Aggregation Inhibitor Therapy: An Exploratory Phase 2 Study in Mild or Moderate Alzheimer's Disease

Claude M. Wischik[a,*], Roger T. Staff[b], Damon J. Wischik[c], Peter Bentham[d], Alison D. Murray[e], John M.D. Storey[f], Karin A. Kook[g] and Charles R. Harrington[a]
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[b]Aberdeen Royal Infirmary, NHS Grampian, Aberdeen, UK
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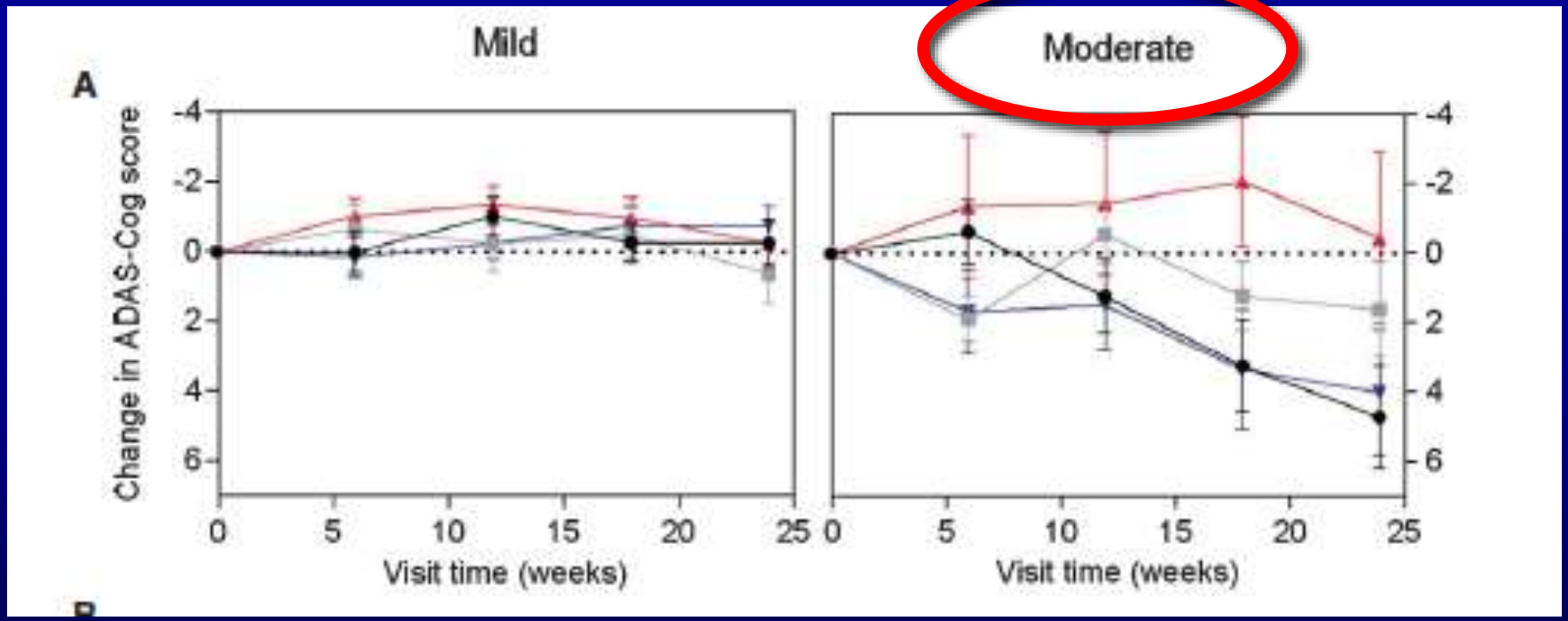
[f]Department of Chemistry, University of Aberdeen, Aberdeen, UK
[g]Salamandra LLC, Bethesda, Maryland, USA



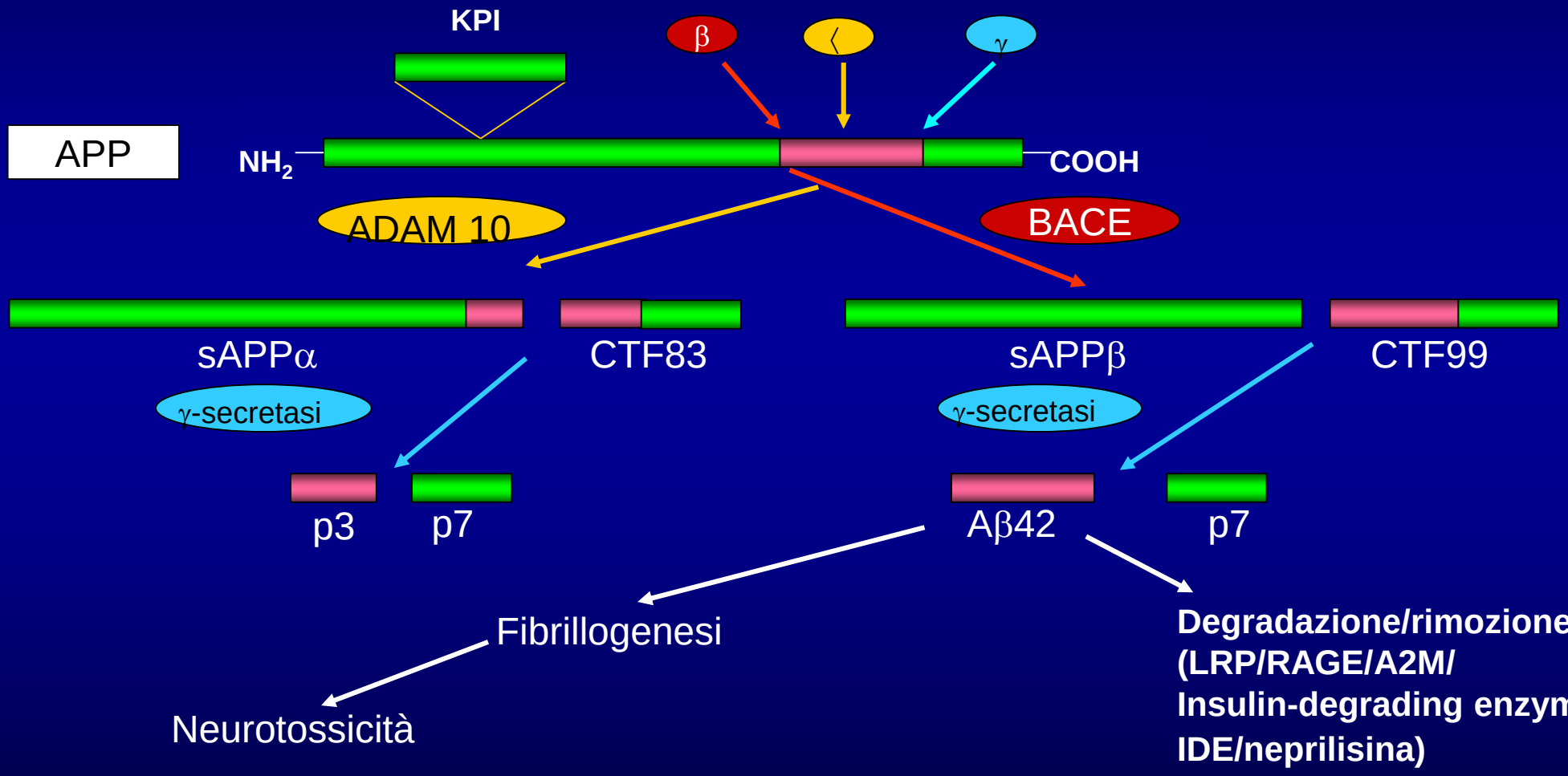
Wischick et al. J Alzheimers Dis 2015;44:705-20

Phase II and III randomized controlled trials of TRx0237 (LMTX™) for the treatment of AD and frontotemporal dementia (FTD)

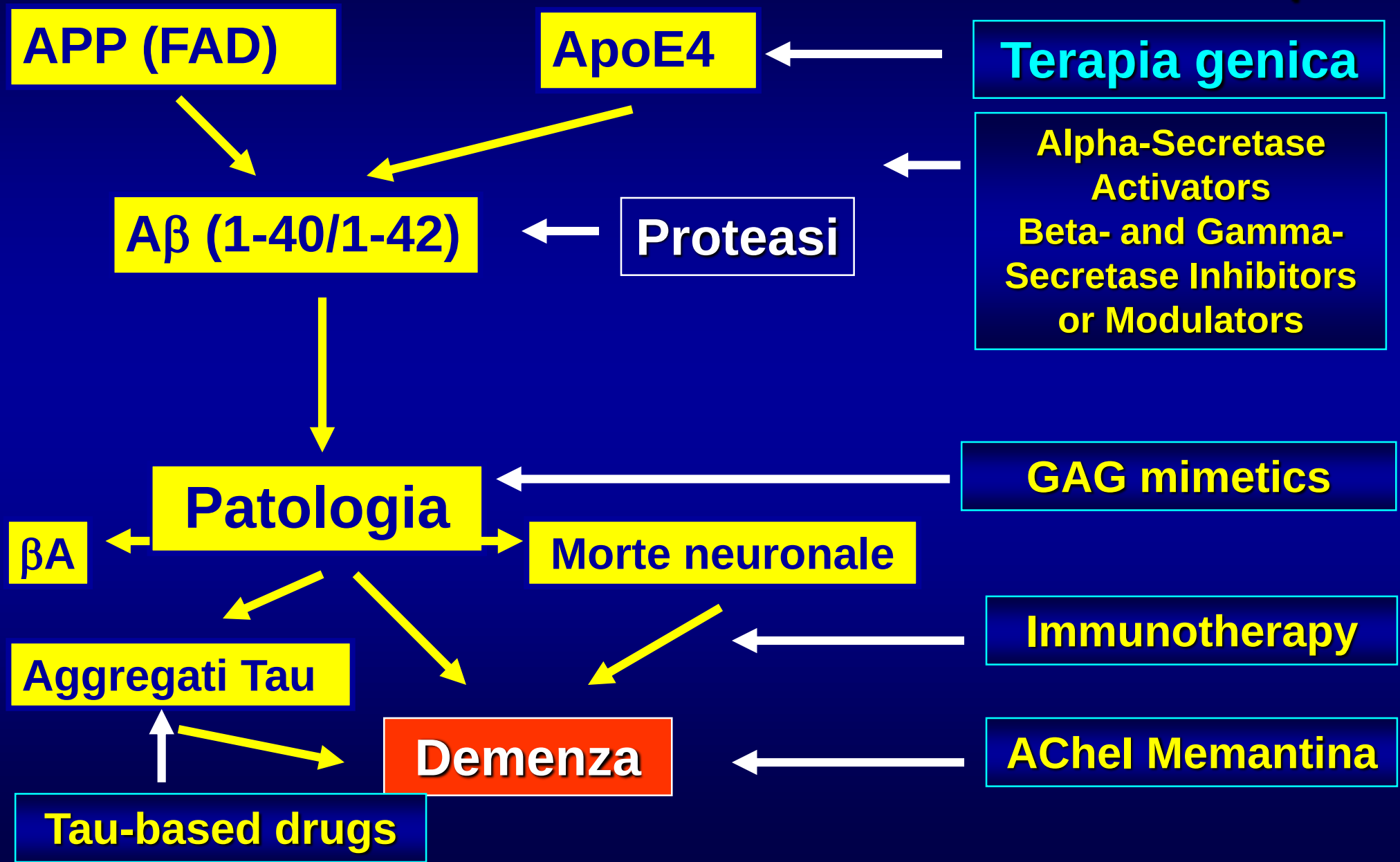
Compound (Company) ClinicalTrials.gov Identifier	Mechanism of action	Estimated enrollment	Characteristics	Status
TRx0237 (LMTX™) (TauRx Therapeutics Ltd) NCT01626391	Tau aggregation inhibitor	Nine patients already taking medications for probable mild to moderate AD (2012–2013)	TRx0237 125 mg tablets administered twice daily for 4 weeks	Phase II trial (terminated)
TRx0237 (LMTX™) (TauRx Therapeutics Ltd) NCT01689233	Tau aggregation inhibitor	700 patients with probable mild AD (2012–2015)	TRx0237 100 mg tablets administered twice daily	Phase III trial (active not recruiting)
TRx0237 (LMTX™) (TauRx Therapeutics Ltd) NCT01689246	Tau aggregation inhibitor	A total of 833 patients with probable mild to moderate AD (2013–2016)	TRx0237 75 and 125 mg tablets administered twice daily	Phase III trial (active not recruiting)
TRx0237 (LMTX™) (TauRx Therapeutics Ltd) NCT01626378	Tau aggregation inhibitor	A total of 220 patients with the behavioral variant of FTD (2013–2016)	TRx0237 100 mg tablet administered twice daily	Phase III trial (active not recruiting)
TRx0237 (LMTX™) (TauRx Therapeutics Ltd) NCT02245568	Tau aggregation inhibitor	Subjects who have completed participation in a Phase II or Phase III trial with TRx0237 continued access to therapy to evaluate the long-term safety of TRx0237 (2014–2017)	All subjects will initially be given TRx0237 100 mg tablets administered twice daily. Thereafter, dosing is flexible (100 mg tablets administered twice or thrice daily)	Open-label Phase III trial (currently recruiting)

Seripa et al. Expert Rev Neurother 2016 [Epub ahead of print]

Aspetti fisiopatologici del metabolismo della APP



RIDUZIONE DELLA CONCENTRAZIONE E DEPOSITO EXTRACELLULARE DELLA Aβ



AD treatment: recent therapeutic approaches in Phase II or III

Main mechanism of action	RCTs completed (examples)	RCTs ongoing (examples)
Anti-amyloid: ↓Aβ production		
β-secretase inhibitors	Development limited by difficulties in identifying molecules able to cross the BBB and safety issues. Thiazolidinediones: *rosiglitazone*, tested in three phase 3 RCTs in mild–moderate AD (up to 1 year, ≈ 3800 participants); and *pioglitazone*, phase 2 RCT in mild–moderate AD, no benefits [136]	*Pioglitazone*: phase 2 RCT in MCI (6 months, ≈ 300 participants) New compounds with increased ability to pass the BBB tested: *MK-8931*: Phase 2/3 RCT in mild-moderate AD (18 months, ≈ 1500 participants)
γ-secretase modulators (GSMs)	*Tarenflurbil*: negative phase 3 RCT (≈1684 participants, 18 months; another RCT in 900 subjects interrupted) in mild AD [86]. New compounds (e.g. *CHF 5074*, *EVP-0962*) are under development	*EVP-0962*: phase 2 RCT in healthy subjects, MCI and early AD cases (14 days, ≈ 50 participants)
γ-secretase inhibitors (GSIs)	GSI: development hampered by safety issues (i.e. interference with Notch signalling). Notch-sparing GSI under development *Semagacestat*: failures of phase 3 RCTs in 2600 participants with mild–moderate AD, halted because of lack of efficacy and adverse events, including ↑ skin cancer risk and infections [88]	
	Avagacestat: a 6-month, phase 2 RCT in 209 patients with mild–moderate AD: ↑ adverse events for high dosages, pharmacodynamics poorly characterized, no significant effects on CSF/MRI markers [89]	*Avagacestat*: phase 2 in prodromal AD, 2 years, 270 participants; arms with higher doses already discontinued due to [illegible]
α-secretase activators	*Etazolate*: ↑ α-secretase activity and modulates GABA-A receptors, 3 months, phase 2 RCT in 159 cases of mild–moderate AD, reported acceptable safety and tolerability [137]	*Epigallocatechin gallate*: ↑ α-secretase activity and ↓ Aβ aggregation, Phase 2/3 RCT in early AD, 18 months, ≈ 50 participants

Verubecestat

Scheineder et al. J Intern Med 2014;275:251-283

AD treatment: recent therapeutic approaches in Phase II or III

Main mechanism of action	RCTs completed (examples)	RCTs ongoing (examples)
Anti-amyloid: ↓Aβ aggregation or oligomerization	*Tramiprosate*: negative phase RCT in 1052 cases of mild–moderate AD, 18 months [138]. Another phase 3 RCT, 930 subjects, interrupted based on the latter results *PBT2*: negative 12-week phase 2 RCT, 78 participants with mild AD with positive secondary outcome [139] *Scyllo-inositol*: 18 months, phase 2 RCT in 353 cases of mild–moderate AD, showed no evidence of clinical benefits, and with high doses stopped because of unexpected death and infections [87]	*PBT2*: phase 2 trial in 40 patients with prodromal or mild AD and PiB-PET positive treated for 12 months, PiB-PET as primary outcome (ACTRN12611001008910)
Anti-amyloid: ↑Aβ clearance, active immunotherapy	*Vaccines*: contain different Aβ-derived epitopes with various adjuvants and mechanisms of delivery (e.g. adenovirus, DNA vaccine, single-chain antibody fragments) *AN1792*: first anti-Aβ vaccine tested in a 12-month, phase 2 trial of 372 patients with mild–moderate AD, stopped because of meningoencephalitis due to cytotoxic T cells and/or autoimmune reactions [22] *CAD-106* (Novartis and Cytos): phase 2, 12-month RCT (plus 16-month open-label extension), 120 subjects with mild AD, showed good safety, tolerability and antibody response [140]	ACI-24: a phase 1/2 12-month RCT to evaluate safety and efficacy in ≈ 186 patients with mild–moderate AD
	Affitopes: short peptides mimicking native Aβ. AD02 and AD03 in phase 1 in mild–moderate AD, ≈76 individuals, 12 months [141] *ACC-001:* two phase 2 RCTs in ≈520 subjects with early or mild–moderate and prodromal AD over 24 months (results unpublished)	*AD02* (Affiris/GSK): Phase 2 RCT in 300 individuals with early AD (18 months); additionally, extended follow-up of subjects who participated in the phase I RCT is ongoing (total follow-up of 2 years) *AD03* (Affiris): an RCT is ongoing to follow-up subjects who participated in the phase I RCT

Scheineder et al. J Intern Med 2014;275:251-283

Table 1. Phase II–III clinical trials of passive immunization targeting β-amyloid for the treatment of Alzheimer's disease.

Compound Company/institution ClinicalTrials.gov Identifier	Binding characteristics	Estimated or completed enrollment	Characteristics	Status	Ref.
Monoclonal antibodies					
Solanezumab (LY2062430)	Humanized monoclonal IgG1 anti-$A\beta_{1-42}$ antibody ($A\beta_{13-28}$), binding soluble Aβ				
Eli Lilly NCT01127633 (EXPEDITION EXT)		1275 patients (2010–2016)	400 mg administered once every 4 weeks by intravenous infusion for 100 weeks	Phase III trial (ongoing, but not recruiting)	[101]
Eli Lilly NCT01900665 (EXPEDITION3)		2100 patients (2013–2016)	400 mg administered once every 4 weeks by intravenous infusion for 18 months	Phase III trial (currently recruiting)	[103]
Gantenerumab (RO4909832)	Fully human monodonal IgG1 antibody against $A\beta_{1-42}$ ($A\beta_{3-}$ and [illegible] not binding soluble Aβ				
Hoffmann-La Roche NCT01224106 (SCarlet RoAD trial)		770 patients with prodromal AD (2010–2016)	Subcutaneous multiple doses	Phase III trial (currently recruiting)	[115]
Solanezumab (LY2062430) Gantenerumab (RO4909832) Washington University School of Medicine Eli Lilly Hoffmann-La Roche Alzheimer's Association National Institute on Aging (NIA) Avid Radiopharmaceuticals NCT01760005 (DIAN TU)		210 patients (2012–2016)	Solanezumab: 400 mg intravenous infusion every 4 weeks Gantenerumab: 225 mg subcutaneously every 4 weeks	Phase II/III trial (currently recruiting)	[102]
[illegible]zumab (MABT5102A) Genentech NCT01723826	Humanized monodonal IgG4 antibody against $A\beta_{1-42}$ ($A\beta_{12-23}$)	400 patients (2012–2016)	Patients who completed the Phase II study ABE4869g or ABE4955g	Phase II trial (currently recruiting)	[126]

Aβ: β-amyloid; AD: Alzheimer's disease.

Panza et al. Expert Rev Clin Immunol 2014;10:405-19

EXPERT REVIEWS

Efficacy and safety studies of gantenerumab in patients with Alzheimer's disease

Expert Rev. Neurother. Early online, 1–14 (2014)

Francesco Panza*[1–3], Vincenzo Solfrizzi[4], Bruno P Imbimbo[5], Michele Giannini[4], Andrea Santamato[6], Davide Seripa[3] and Giancarlo Logroscino[1,2]

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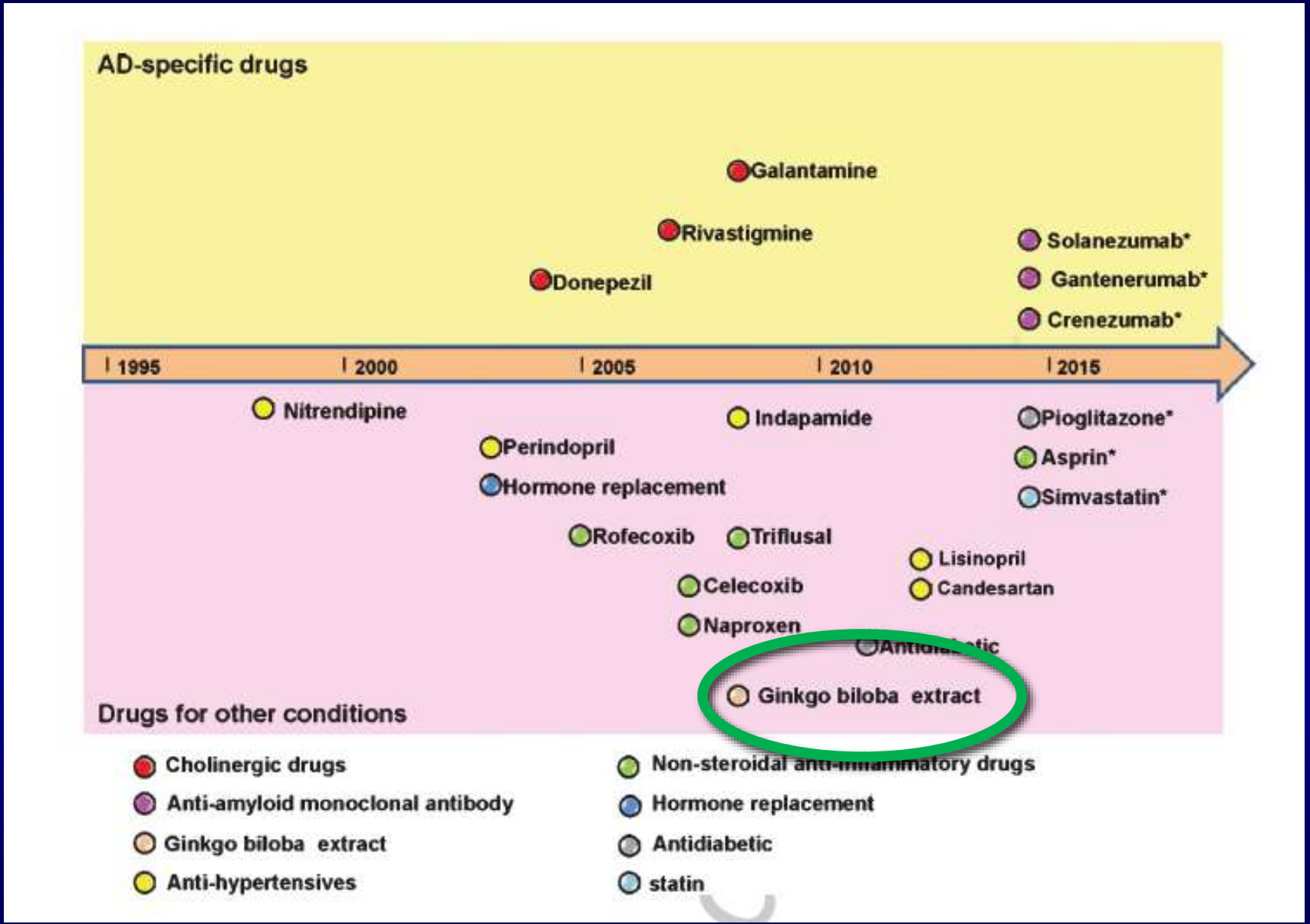
[3]*Geriatric Unit and Laboratory of*

Among active and passive anti-β-amyloid (Aβ) immunotherapies for Alzheimer's disease (AD), bapineuzumab and solanezumab, two humanized monoclonal antibodies, failed to show significant clinical benefits in mild-to-moderate AD patients in large Phase III clinical trials. Another ongoing Phase III trial of solanezumab aims to confirm positive findings in mild AD patients. Gantenerumab is the first fully human anti-Aβ monoclonal antibody directed to both N-terminal and central regions of Aβ. A 6-month PET study in 16 AD patients showed that gantenerumab treatment dose-dependently reduced brain Aβ deposition, possibly stimulating microglial-mediated phagocytosis. Two ongoing Phase III trials of gantenerumab in patients with prodromal or mild dementia due to AD will determine if any reduction in brain Aβ levels will translate into clinical benefits. An ongoing secondary prevention trial of gantenerumab in presymptomatic subjects with genetic mutations for autosomal-dominant AD will verify the utility of anti-Aβ monoclonal antibodies as prevention therapy.

KEYWORDS: Alzheimer's disease • cognitive disorder • dementia • gantenerumab • monoclonal antibody • passive immunotherapy • solanezumab

Panza et al. Expert Rev Neurother 2014;14:973-986

Pharmacological Interventions in AD Prevention Trials



Wang et al. J Alzheimers Dis 2016 [Epub ahead of print]

Pharmacological Interventions in AD Prevention Trials

Studies	Sample size	Including criteria	Age at enrollment	Intervention	Duration	Outcomes	
						Primary	Secondary
AD-specific drugs							
API [24]	300	Members of families with early-onset AD; no cognitive impairment; Carriers of a mutated PS1 gene, non-carriers will also be included to ensure double-blinding of the genetic status	≥30 years	Anti-amyloid monoclonal antibody: crenezumab	5 years, (interim analysis at 2 years)	cognition	Change in AD biomarkers;
DIAN [24]	240	Members of families with early-onset AD; subjects can be asymptomatic or have very mild memory and cognitive problems including mild dementia; carriers of mutation in PS1, PS2, or AβPP, non-carriers will also be included to ensure double-blinding of the genetic status	18–80 years	Two anti-amyloid therapies:the anti-amyloid monoclonal antibodies: gantenerumab and solanezumab	2 years + 3-year extended follow-up	Initial phase (2 years): change in AD biomarkers; Follow-up phase (3 years): cognition	–
ADCS-A4 [24]	1000	No cognitive impairment; evidence of brain amyloid accumulation (PET); subjects with no evidence of amyloid burden will also be included	65–85 years	Anti-amyloid monoclonal antibody: solanezumab	3 years + 2-year extended follow-up	cognition	Changes in AD biomarkers
Other pharmacological interventions							
TOMMORROW [48] NCT01931566	5800	No cognitive impairment; subjects at risk of developing MCI due to AD within 5 years. The risk stratification is based on an algorithm including age and TOMM40 and APOE genotype	65–83 years	Pioglitazone	5 years	Time to onset of MCI due to AD	Cognitive decline

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Pharmacological Interventions in AD Prevention Trials

KEEPS-Cog [49]	720	perimenopausal and recently-postmenopausal women	42–58 years	Conjugated equine estrogens + progesterone or transdermal estradiol + oral progesterone	4 years	Change in cognition and mood	–
ASPREE [50]	19000	free of dementia, disability and cardiovascular disease	≥65 or 70 years	Aspirin	5 years	Composite endpoint (including Incident dementia)	Composite endpoint (including Incident dementia)
SIMaMCI NCT00842920	520	Amnestic MCI, high cholesterol level	55–90 years	Simvastatin	2 years	Change in cognition (CDR-SB)	Change in cognition; time to conversion to AD
SimBio NCT01142336	120	Cognitively normal	45–64 years	Simvastatin	1 year	Changes in AD biomarkers in CSF	Measures of inflammation and oxidative stress in CSF
SHARP NCT00939822	90	Family AD history	45–65 years	Simvastatin	18 months	Changes in CSF Aβ levels	–

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EXPERT REVIEWS

Amyloid-based immunotherapy for Alzheimer's disease in the time of prevention trials: the way forward

Expert Rev. Clin. Immunol. Early online, 1–15 (2014)

Francesco Panza*[1,2], Vincenzo Solfrizzi[5], Bruno P Imbimbo[3], Rosanna Tortelli[1,2], Andrea Santamato[4] and Giancarlo Logroscino[1,2]

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[2]*Department of Clinical Research in Neurology, University of Bari Aldo Moro, "Pia Fondazione Cardinale G. Panico", Tricase, Lecce, Italy*
[3]*Research & Development Department,*

Both active and passive anti-β-amyloid (Aβ) immunotherapies for the treatment of Alzheimer's disease (AD) have demonstrated dearance of brain Aβ deposits. Among passive immunotherapeutics, two Phase III dinical trials in mild-to-moderate AD patients with bapineuzumab, a humanized monoclonal antibody directed at the N-terminal sequence of Aβ, were disappointing. Also solanezumab, directed at the mid-region of Aβ, failed in two Phase III trials in mild-to-moderate AD. Another Phase III trial with solanezumab is ongoing in mildly affected AD patients based on encouraging results in this subgroup. Second-generation active Aβ vaccines (CAD106, ACC-001, and Affitope AD02) and new passive anti-Aβ immunotherapies (gantenerumab and crenezumab) have been developed and are under clinical testing. These new anti-Aβ immunotherapies are being tested in prodromal AD, in presymptomatic subjects with AD-related mutations, or in asymptomatic subjects at risk of developing AD. These primary and secondary prevention trials will definitely test the Aβ cascade hypothesis of AD.

KEYWORDS: active immunotherapy • Alzheimer's disease • cognitive disorders • dementia • gantenerumab • monoclonal antibody • passive immunotherapy • solanezumab

Panza et al. Expert Rev Clin Immunol 2014;10:405-19

Upcoming trials for preventive immunotherapies

Name	Drug Used vs. Placebo	Patient Group	Trial Start Date	Responsible Party
Dominantly Inherited Alzheimer Network (DIAN)	Use of three different dugs: gantenerumab *, solanezumab *, beta-secretase (BACE) inhibitor	Families with carriers for autosomal dominant Alzheimer's disease	Early 2013	Washington University School of Medicine
Treatment of Asymptomatic Alzheimer (A4)	Solanezumab *	Clinically older individuals with amyloid positive PET scan	Mid 2013	Harvard Medical School and Brigham and Women's Hospital, Boston, MA
Alzheimer Prevention Initiative (API)	Crenezumab *	cognitively healthy individuals who are cariers for genes causing familial Alzheimer's disease	Early 2013	Banner Alzheimer's Institute, Phoenix, AZ

Discov Med 2013; 15: 319–326

Multi-domain Interventions in AD Prevention Trials

Concurrent management of risk factors based on lifestyle changes and marketed pharmacological products

1) The Finnish Geriatric Intervention Study to Prevent Cognitive impairment and Disability (FINGER)

2) Multi-domain Alzheimer Prevention Study (MAPT)

3) Prevention of Dementia by Intensive Vascular Care (PreDIVA)

The Finnish Geriatric Intervention Study to Prevent Cognitive impairment and Disability (FINGER)

A 2-year multi-domain intervention (diet, exercise, cognitive training, vascular risk monitoring) or a control group (general health advice)

This multidomain intervention could improve or maintain cognitive functioning in at-risk older people from the general population

(between-group difference in the change of NTB total score per year was: 0·022, 95% CI 0·002-0·042, p=0·030)

Ngandu et al. Lancet. 2015;385(9984):2255-2263

Nutraceutical and bioactive compounds with published studies

Name of nutraceutical formula	Institution	Active ingredient	Clinical trials batteries
AXONA AC-1200® [12]	Nestlé	Caprilic acid	ADAS-Cog
Perceptiv® [76]	Sevo Nutraceuticals	– 3-deaza-adenosine – Acetyl-L-cysteine – S-adenosylmethionine	CVLTII
Cognitex® [77]	LifeExtension	– Phosphatidyl serine – Omega 3	– Rey Auditory Verbal Learning Test – Computerized Cognitive Battery Test
Resveratrol [83]		3,4,5-trihydroxystilbene	In preclinical trials (both *in vitro* and *in vivo*)
Ginkgo Biloba [69, 70]	Ipsen, Boulogne, France. (GuidAge) US National Institutes of Health (GEM)	Ginkgo extract EGb761	Conversion to AD – GuidAge: MMSE, CDR, FCSRT, TMT, verbal fluency, visual analogue scales, instrumental activities of daily living, geriatric depression scale. – GEM: MMSE, CDR, or ADAS-Cog. GEM Study Neuropsychological Battery in cases of cognitive deterioration.
Brain – Up10® [61]	Neuroinnovation	– Complex B vitamins – Andean Compound (*Shilajit andino*)	– MMSE – Boston naming test – ADAS-Cog – TMT-A – NPI-12 – GDS
Souvenaid® [84]	Nutricia	– Uridine monophosphate – Phospholipid – Choline and omega-3 fatty acids – Vitamins antioxidants	– WMS-r – ADAS-Cog – MMSE

ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; CVLTII, California Verbal Learning Test II; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; FCSRT, The Free and Cued Selective Reminding Test, TMT-A, Trail-making Test A; NPI, Neuropsychological Inventory; GDS, Global Deterioration Scale; WMS-r, Wechsler Memory Scale-Revised; GEM, Ginkgo Evaluation of Memory trial.

Journal of Alzheimer's Disease 42 (2014) 357–367

Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-141887
IOS Press

Commentary

Plant-Based Nutraceutical Interventions against Cognitive Impairment and Dementia: Meta-Analytic Evidence of Efficacy of a Standardized *Gingko biloba* Extract

Vincenzo Solfrizzi[a,b,c,d,1,*] and Francesco Panza[a,b,c,d,1,*]
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[b]*Neurodegenerative Disease Unit, Department of Basic Medicine, Neuroscience, and Sense Organs, University of Bari Aldo Moro, Bari, Italy*
[c]*Department of Clinical Research in Neurology of the University of Bari Aldo Moro at "Pia Fondazione Card G. Panico", Tricase, Lecce, Italy*
[d]*Geriatric Unit & Laboratory of Gerontology and Geriatrics, Department of Medical Sciences, IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Foggia, Italy*

Solfrizzi and Panza. J Alzheimers Dis 2015;43:605-611

Principal nutraceuticals and bioactive compounds for the treatment of AD and late-life cognitive disorders

Groups	Subgroups	Molecules
Antioxidant vitamins		Vitamins A, C, and E
Homocysteine-related vitamins		Vitamins B6, B12, and B9
Flavonoids	Flavanols	Catechin, epicatechin, epigallocathechin, and epigallocatechingallate (EGCG)
	Flavonols	Quercetin and kaempferol
	Flavones	Luteolin and apigenin
	Isoflavones	Daidzein and genistein
	Flavanones	Esperetin and naringenin
	Anthocyanidins	Pelargonidin, cyanidine, and malvidin
Non-flavonoid polyphenols		Resveratrol and curcumin
Carotenoids		Lutein, lycopene, and β-carotene
Diterpenes		Carnosic acid and rosmarinic acid

Solfrizzi and Panza. J Alzheimers Dis 2015;43:605-611

Gingko biloba properties for treating symptoms of dementia

Flavonoids (e.g., quercetin and ginkgetin)

Pro- coagulant and pro-inflammatory properties, possibly vasodilatory and anti-oxidant properties in the central nervous system

Diterpene ginkgolides A, B, and C

Improved peripheral and cerebral blood flow, with also anti-inflammatory and antioxidant properties

Sesquiterpene ginkgolide bilobalide

Antioxidant activity, promoting expression of growth factors

Gb may influence different neurotransmitter systems

Inhibition of monoamine oxidase A and uptake of norepinephrine

Increased synaptosomal uptake of 5-hydroxytryptamine and extracellular levels of dopamine and noradrenaline

Solfrizzi and Panza. J Alzheimers Dis 2015;43:605-611

Standardized Gingko biloba extract:

EGb 761

24% of flavonol glycosides

Quercetin, kaempferol, and isorhamnetin derivatives

6% of *terpenes*

Divided into diterpenes (ginkgolides) and sesquiterpenes (bilobalide)

Solfrizzi and Panza. J Alzheimers Dis 2015;43:605-611

Standardized Gingko biloba extract:

EGb 761

Repeated administration of 600 mg/kg of EGb 761 for 8 days led to 4.5-fold, 11.5-fold, and 10-fold increases in plasma concentration of quercetin, kaempferol, and isorhamnetin

In animal AD models, EGb 761 demonstrated a protective effect against Aβ1-42-induced dysfunction and death of hippocampal neurons, inhibiting Aβ aggregation, and enhancing also neurogenesis

Solfrizzi and Panza. J Alzheimers Dis 2015;43:605-611

COCHRANE META-ANALYSES 2002-2007-2009

Gingko biloba for cognitive impairment and dementia

Evidence of improvement of clinical global change, functional status, and cognition on 33 pooled RCTs with daily dose ranged from 80 to 600 mg/day, usually less than 200 mg/day, and treatment periods ranging from 3 to 52 weeks

Birks J et al (2002) Cochrane Database Syst Rev 4, CD003120

Pooled data on 35 RCTs (total participants = 4247), although only 29 studies contributed data to the meta-analyses, showed benefits associated with EGb 761 in subjects with cognitive impairment and dementia for clinical global change (dose greater than 200 mg/day) at 24 weeks, for cognition at any dose but only at 12 weeks, and for functional status at 12 weeks and 24 weeks but only with a dose less than 200 mg/day

Birks J et al (2007) Cochrane Database Syst Rev 2, CD003120

Pooled data on 36 RCTs suggested inconsistent results of EGb 761 for cognition, functional status, mood, depression and caregiver burden in subjects with cognitive impairment and dementia

A subgroup analysis of this last Cochrane meta-analysis including only AD patients (925 patients from 9 trials) also showed no consistent pattern of any benefit associated with Gb extracts

Birks J et al (2009) Cochrane Database Syst Rev 1, CD003120

PREVENTIVE TRIALS WITH EGb 761

The Ginkgo Evaluation of Memory (GEM)

The GuidAge Trial

The Ginkgo Evaluation of Memory (GEM)

In 3,069 participants with a follow-up of 6.1 years, EGb 761, at a dose of 120 mg twice a day, did not reduce the incidence of AD in healthy individuals and those suffering from Mild Cognitive Impairment (MCI)

DeKosky et al; GEM Study Investigators (2008) JAMA 300, 2253-2262

The GuidAge Trial

In 2,854 participants aged 70 years and older in the GuidAge trial, EGb 761 did not decrease the AD risk over 5 years in subjects with a memory complaint who might be mildly cognitively impaired

Vellas et al; GuidAge Study Group (2012) Lancet Neurol 11, 851-859

TRIALS WITH EGb 761 IN DEMENTED PATIENTS WITH NEUROPSYCHIATRIC SYMPTOMS (NPS)

EGb 761 IN DEMENTED PATIENTS WITH NPS

The regulatory trial of Schneider and colleagues led to the hypothesis that AD patients with NPS may decline more rapidly than average and would benefit more from EGb761

Schneider et al. Curr Alzheimer Res 2, 541–551

Three recently performed RCTs showed a beneficial effect of a dose of 240 mg/day of EGb761 in dementia, AD, and MCI patients accompanied by NPS

Int J Geriatr Psychiatry 2011; 26: 1186-1194
J Psychiatr Res 2012; 46: 716-723
Int J Geriatr Psychiatry 2014; doi: 10.1002/gps.4103

Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-140837
IOS Press

Efficacy and Adverse Effects of Ginkgo Biloba for Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis

Meng-Shan Tan[a], Jin-Tai Yu[a,b,c,d,*], Chen-Chen Tan[b], Hui-Fu Wang[c], Xiang-Fei Meng[b], Chong Wang[b], Teng Jiang[c], Xi-Chen Zhu[c] and Lan Tan[a,b,c,*]

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[b]*Department of Neurology, Qingdao Municipal Hospital, School of Medicine, Qingdao University, China*
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Handling Associate Editor: Francesco Panza

Tan et al. J Alzheimers Dis 2014; DOI: 10.3233/JAD-140837

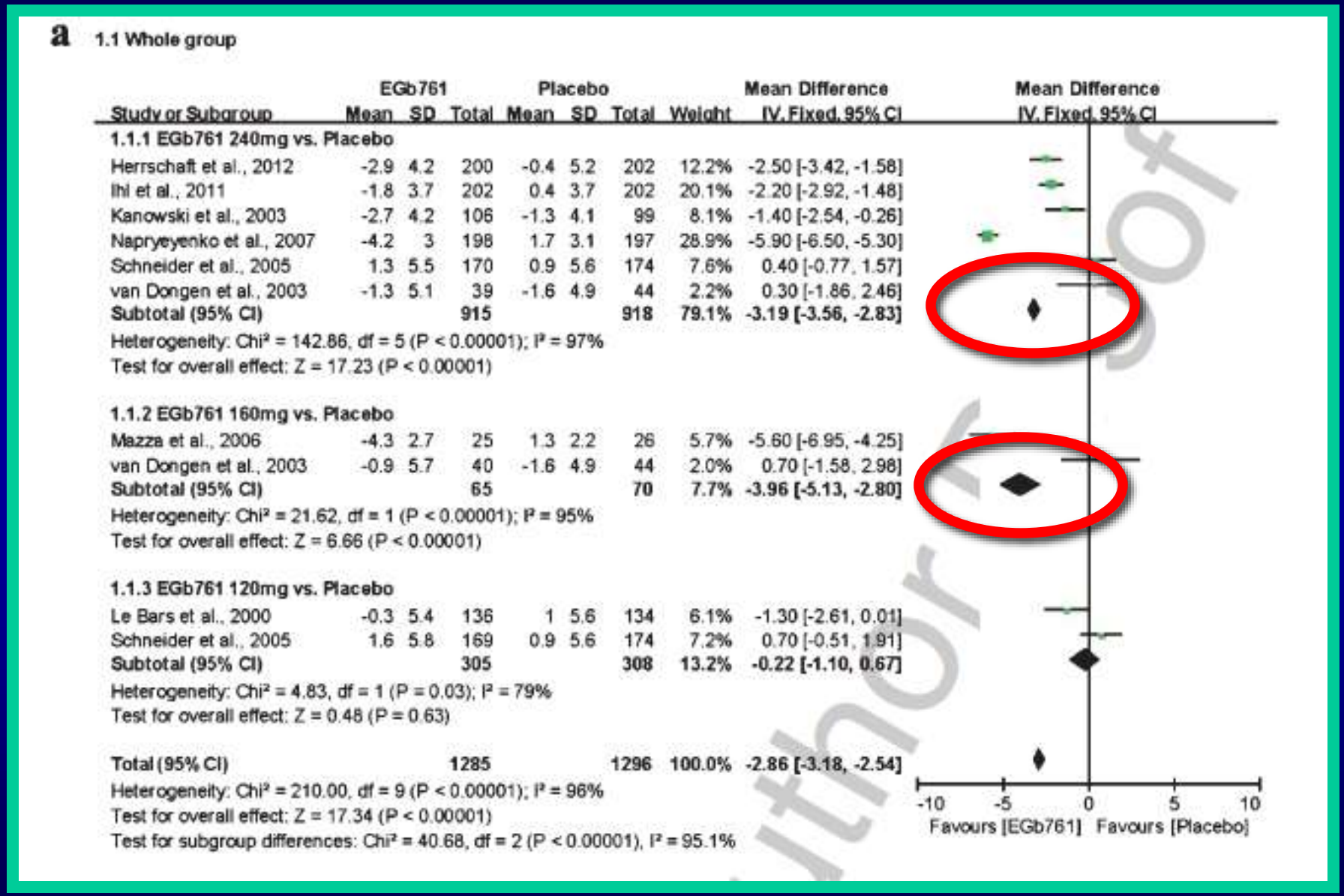
Table 1
Summary of ginkgo biloba EGb761 trials in patient with dementia and cognitive impairment

Study	Criteria	Patients	Groups (*n*)	Age, y (SD)	Gender (% men)	Disease severity	Baseline MMSE (SD)	Duration (weeks)	Outcomes				Dropout rate (%)
									Cognition	Function	Behavior	Global	
Kanowski et al., [41, 51]	DSM-III-R	AD or VaD	240 mg daily (106)	72 (10)	32	Mild to moderate	21.6 (2.6)	24	SKT ADAS-cog	NAB	–	CGI	25.5
			Placebo (99)	72 (10)	29		21.5 (2.4)						22.2
		Only AD	240 mg daily (79)	72 (10)	29	Mild to moderate	21.5 (2.3)	24	SKT ADAS-cog	NAB	–	CGI	–
			Placebo (79)	72 (10)	27		21.6 (2.7)						–
Le Bars et al., [40]	DSM-III-R ICD-10	AD or VaD	120 mg daily (155)	69 (10)	49	Mild to severe	21.1 (5.8)	26	ADAS-cog	GERRI	–	CGIC	21.3
			Placebo (154)	69 (10)	44		21.2 (5.5)						20.8
		Only AD	120 mg daily (120)	68 (10)	46	Mild to severe	21.1 (5.9)	26	ADAS-cog	GERRI	–	CGIC	–
			Placebo (116)	68 (11)	38		21.3 (5.6)						–
Mazza et al., [42]	DSM-IV	AD	160 mg daily (25)	66.2 (6)	48	Mild to moderate	18.8 (3.6)	24	SKT	–	–	CGI	20.0
			Placebo (26)	69.8 (3)	39		18.8 (3.6)		MMSE				23.1
van Dongen et al., [37]	DSM-III-R ICD-10	AD or VaD AAMI	160/240 mg daily (79)	82.6 (5.1)	14	Mild to moderate	18.0 (4.9)	24	SKT	NAA	–	CGI	16.9
			Placebo(44)	82.5 (5.8)	18		18.7 (4.6)						8.3
Schneider et al., [38]	DSM-IV NINCDS/ADRDA	AD	240 mg daily (170)	78.1 (7.0)	44	Mild to moderate	17.9 (4.0)	26	ADAS-cog	GERRI	–	CGIC	17.6
			120 mg daily (169)	78.6 (7.0)	50		18.2 (4.1)						20.1
			Placebo (174)	77.5 (7.4)	48		18.2 (4.1)						22.4
		AD with NPS	240 mg daily (42)	79.3 (6.6)	33	Mild to moderate	17.4 (3.8)	26	ADAS-cog	–	–	CGIC	–
			120 mg daily (51)	79.6 (7.3)	37		17.9 (4.5)						–
			Placebo (47)	77.2 (7.8)	32		17.6 (3.9)						–
Napryeyenko et al., [39, 45]	NINCDS/ADRDA NINDS/AIREN	AD or VaD with NPS	240 mg daily (198)	65 (8)	28	Mild to moderate	14–25	22	SKT	GBS-ADL	NPI	GBS	2.0
			Placebo (197)	63 (8)	28		14–25						2.5
		Only AD with NPS	240 mg daily (104)	66 (8)	33	Mild to moderate	14–25	22	SKT	GBS-ADL	NPI	GBS	1.9
			Placebo (110)	64 (8)	29		14–25						3.6
Ihl et al., [19, 44]	NINCDS/ADRDA NINDS/AIREN	AD or VaD with NPS	240 mg daily (202)	65 (10)	31	Mild to moderate	14–25	24	SKT	ADL-IS	NPI	CGIC	7.9
			Placebo (202)	65 (9)	34		14–25						5.9
		Only AD with NPS	240 mg daily (163)	64.9 (9.5)	33	Mild to moderate	14–25	24	SKT	ADL-IS	NPI	CGIC	–
			Placebo (170)	64.2 (8.7)	35		14–25						–
Herrschaft et al., [18]	NINCDS/ADRDA NINDS/AIREN	AD or VaD with NPS	240 mg daily (200)	65.1 (8.8)	31	Mild to moderate	14–25	24	SKT	ADL-IS	NPI	CGIC	3.4
			Placebo (202)	64.9 (9.4)	31		14–25						2.4
Gavrilova et al., [21]	International consensus criteria*	aMCI with NPS	240 mg daily (80)	65 (7)	28	Mild	25.6 (1.3)	24	TMT	–	NPI	CGI	2.5
			Placebo (79)	63 (7)	16		25.7 (1.5)						3.8

AAMI, age-associated memory impairment; AD, Alzheimer's disease; ADAS-cog, Alzheimer's Disease (AD) Assessment Scale, cognitive subscale; ADL-IS, Alzheimer's Disease Activities-of-Daily-Living International Scale; CGI, Clinical Global Impression; CGIC, Clinical Global Impression of Change; GBS-ADL, Gottries-Bräne-Steen-Activities of daily living scale; GERRI, Geriatric Evaluation by Relative's Rating Instrument; MMSE, Mini-Mental State Examination; NAA, Nürnberger Alters-Alltagsaktivitäten-Skala; NAB, Nurnberger-Alters-Beo-bachtungs-Skala; NPI, Neuropsychiatric Inventory; NPS, neuropsychiatric symptoms; SKT, Syndrom-Kurz test; TMT, Trail-Making Test; VaD, vascular dementia. *Criteria proposed by Winblad et al. [27]. – Not available.

Tan et al. J Alzheimers Dis 2014; DOI: 10.3233/JAD-140837

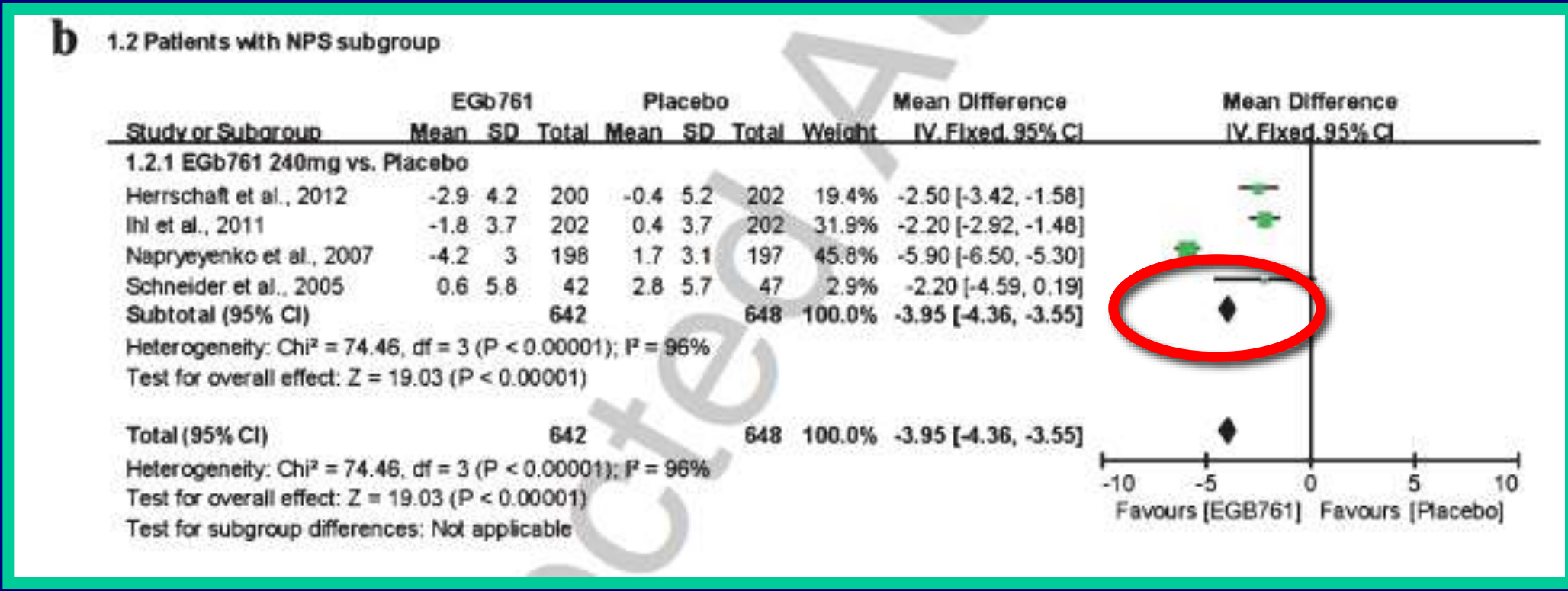
Cognition outcome: *EGb 761 vs. placebo*



Tan et al. J Alzheimers Dis 2014; DOI: 10.3233/JAD-140837

Cognition outcome: *EGb 761 vs. placebo*

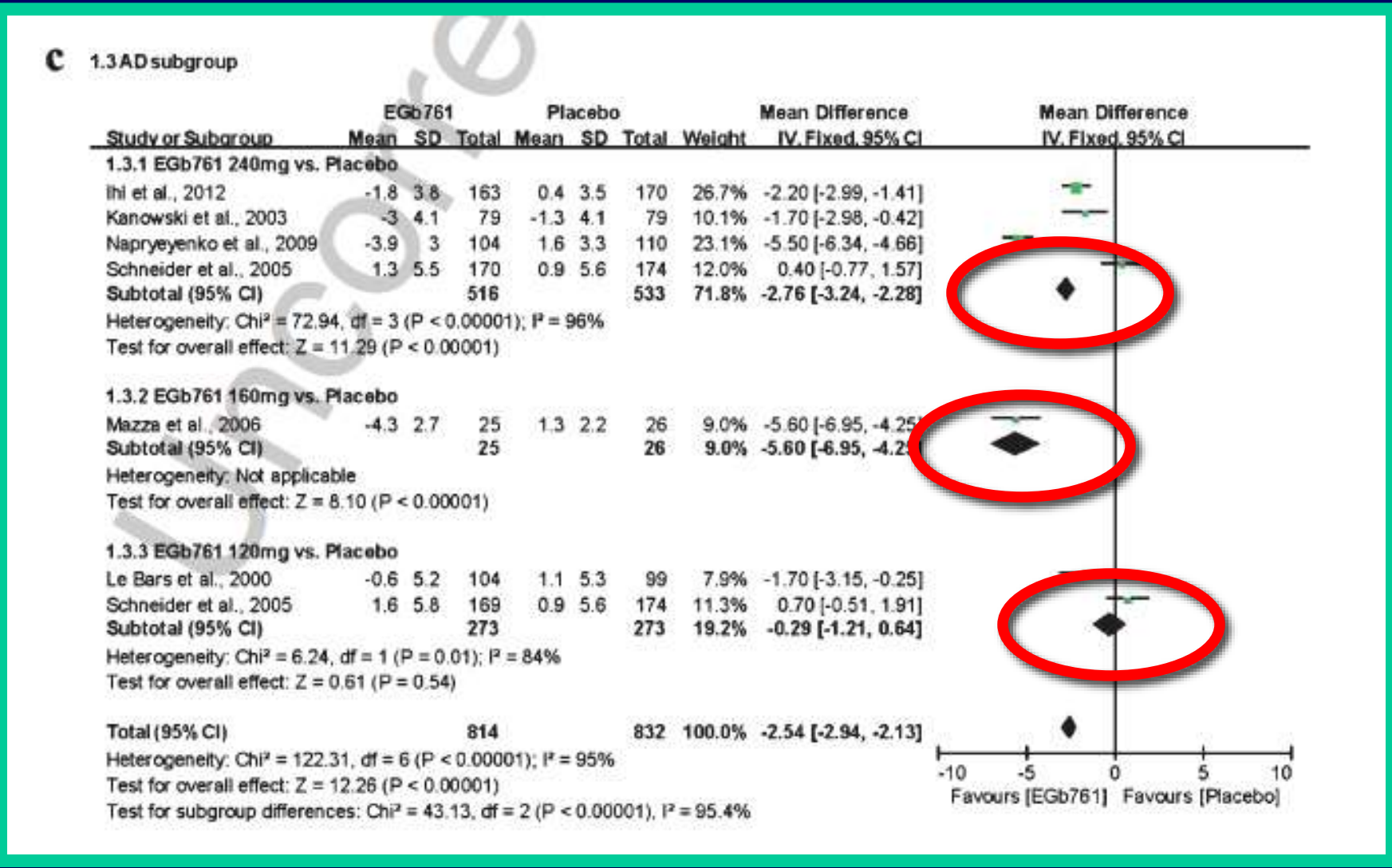
Subgroup with neuropsychiatric symptoms



Tan et al. J Alzheimers Dis 2014; DOI: 10.3233/JAD-140837

Cognition outcome: *EGb 761 vs. placebo*

Subgroup with Alzheimer's disease



Tan et al. J Alzheimers Dis 2014; DOI: 10.3233/JAD-140837

Gingko biloba for cognitive impairment and dementia

Treatment effects of EGb 761 on 2,561 patients with cognitive impairment and dementia from 9 RCTs with a duration of 22 to 26 weeks showed the overall benefits of EGb 761 for stabilizing or slowing decline in cognition, function, behavior, and clinical global change of subjects with cognitive impairment and dementia

Subgroup analyses revealed the differences in effects of different doses, although all these clinical benefits of EGb 761 were mainly associated with the 240 mg/day dose. In AD subgroup analysis, the advantage of EGb 761 compared to placebo was similar to that obtained on the whole group

Tan et al. J Alzheimers Dis 2014; DOI: 10.3233/JAD-140837

Gingko biloba for cognitive impairment and dementia

EGb 761 showed pooled benefits at a dose of 240 mg/day in improving cognition, functional status and clinical global change, and NPS in the treatment of dementia, AD, and MCI patients with also NPS

The safety and tolerability of EGb761 appeared to be excellent at different doses, with only few and minor adverse events perfectly balanced between EGb 761 and placebo, which were in line with findings from previous meta-analyses and long-standing clinical experience

Tan et al. J Alzheimers Dis 2014; DOI: 10.3233/JAD-140837

Principal nutraceuticals and bioactive compounds for the treatment of AD and late-life cognitive disorders

Groups	Subgroups	Molecules
Antioxidant vitamins		Vitamins A, C, and E
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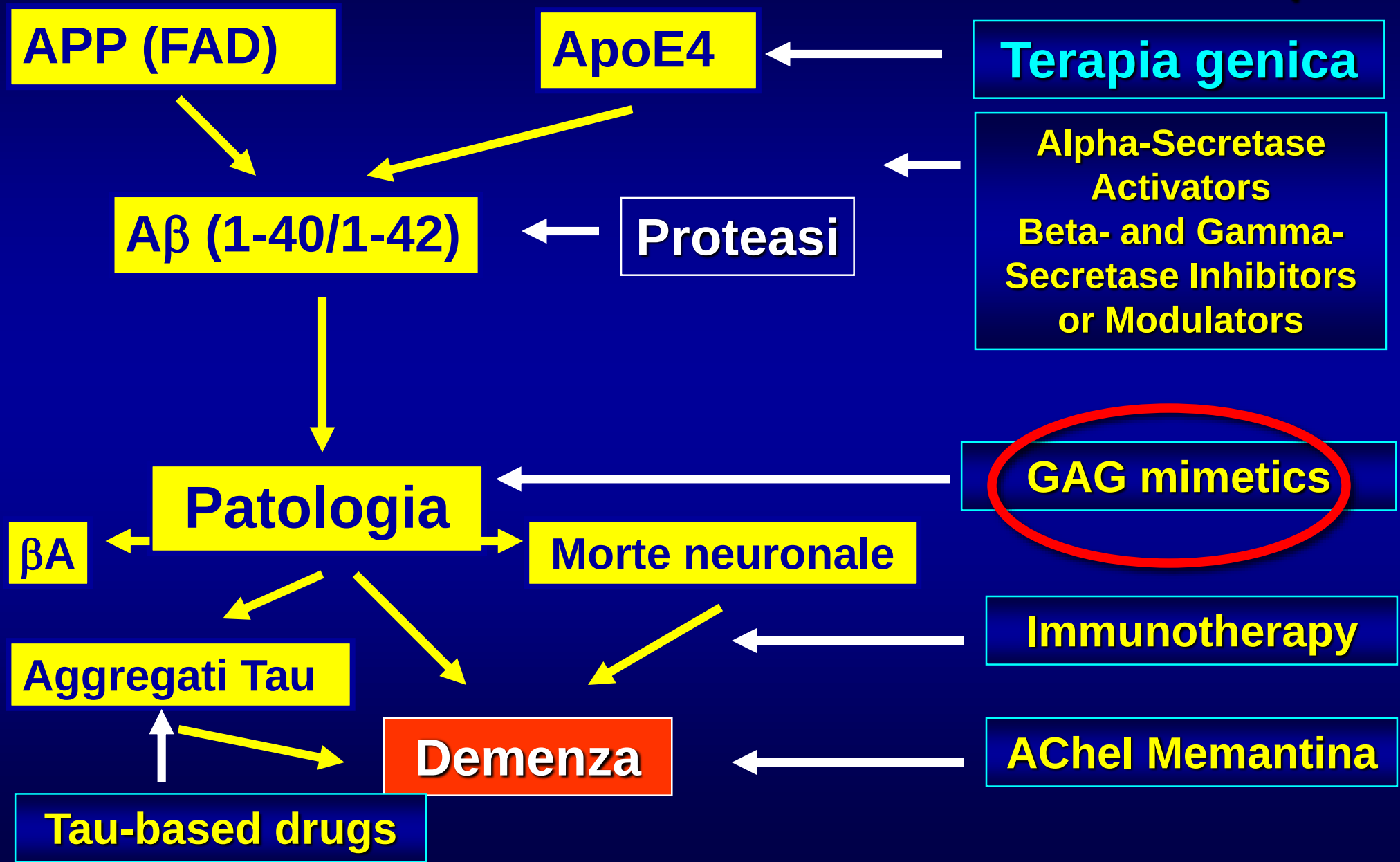
Carotenoids		Lutein, lycopene, and β-carotene
Diterpenes		Carnosic acid and rosmarinic acid

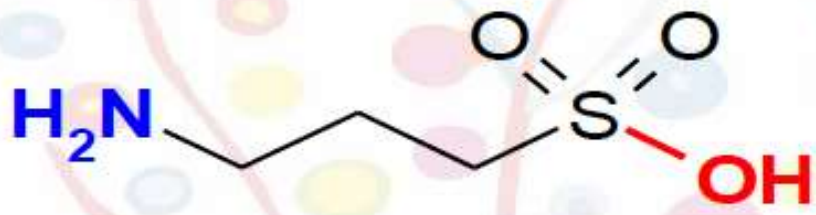
Solfrizzi and Panza. J Alzheimers Dis 2015;43:605-611

RIDUZIONE DELLA CONCENTRAZIONE E DEPOSITO EXTRACELLULARE DELLA Aβ



Homotaurine: Structure and Mechanisms of Action

Homotaurine Naturally Found in Seaweeds



Natural Form ⟺ Synthesized Form

Seaweed containing homotaurine

Homotaurine

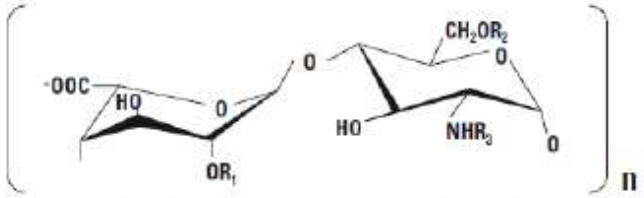
Forma sintetica vs molecola d'estrazione:

- Identica chimicamente
- Stessa attività biologica

Homotaurine: Structure and Mechanisms of Action

Omotaurina: Struttura e meccanismo d'azione

Glycosaminoglycans accelerate amyloid aggregation



Amyloid Precursor Protein (brain)

↓

↑Amyloid Aβ → X ← Amyloid fibril → Amyloid plaque

↓ X

Homotaurine

Neurotoxicity

↓

Brain cell damage/death

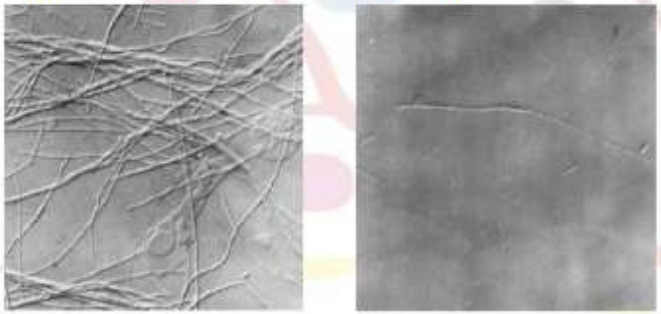
↓

Brain volume loss

↓

Memory Loss & Cognitive Decline

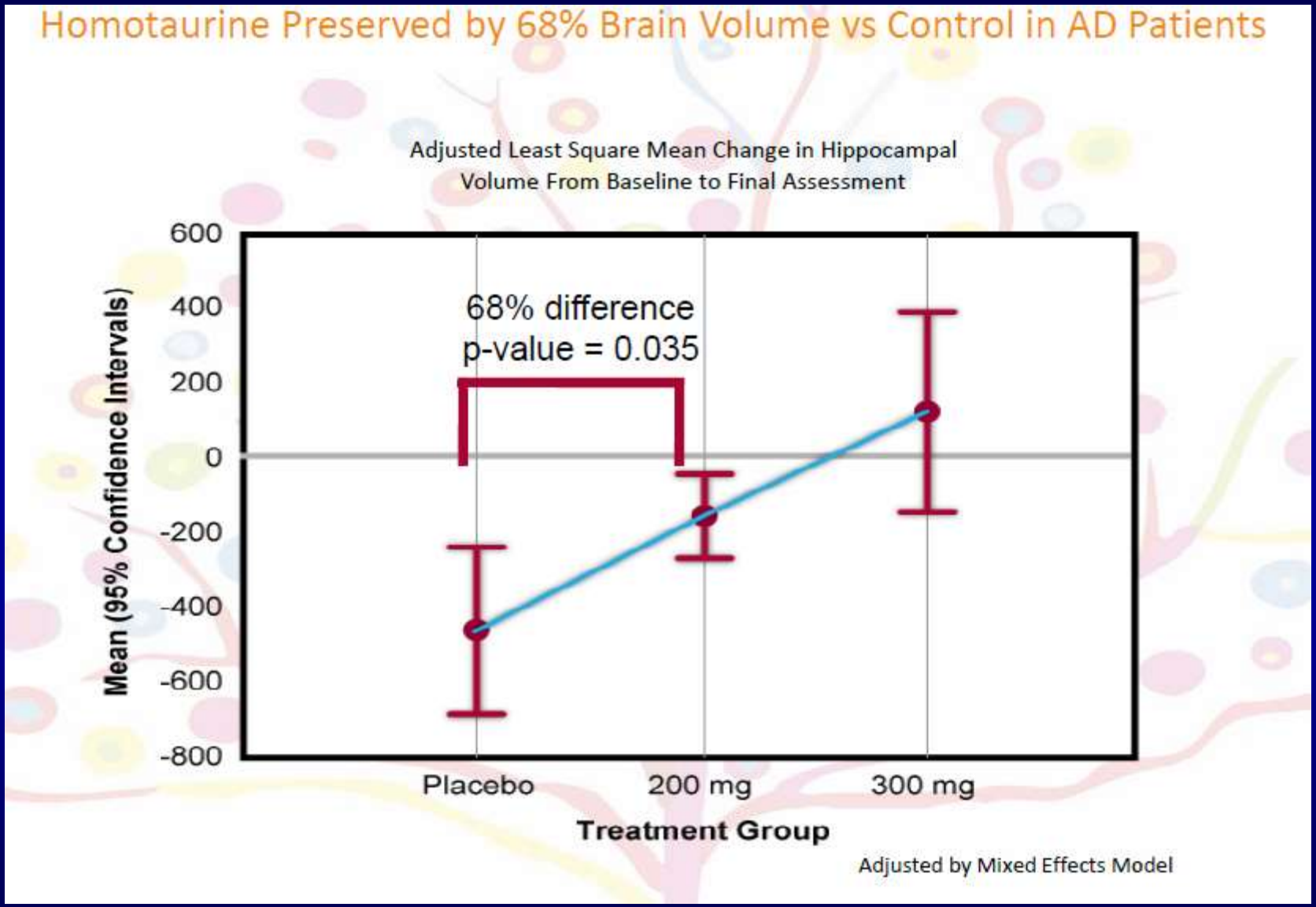
L'omotaurina inibisce la formazione in vitro delle fibrille di amiloide



Amyloid Aß — Amyloid Aß + homotaurine

24-hour incubation

Homotaurine: Volumetric MRI in AD



Saumier et al. J Nutr Health Aging 2009;13:370-372

Effects of Homotaurine on Specific Types of Cognitive Performance

ADAS-cog subtest	Change in scores in 1 yr (100 mg homotaurine vs placebo)	Conclusion
Remembering Test Instructions	66.7% better*	Preserves memory
Language Comprehension	38.9% better	Maintains verbal skills and comprehension ability
Spoken Language Ability	40.0% better	
Ideational Praxis	33.0% better	Supports planning & execution of tasks

*Statistically significant

Saumier et al. J Nutr Health Aging 2009;13:808-812

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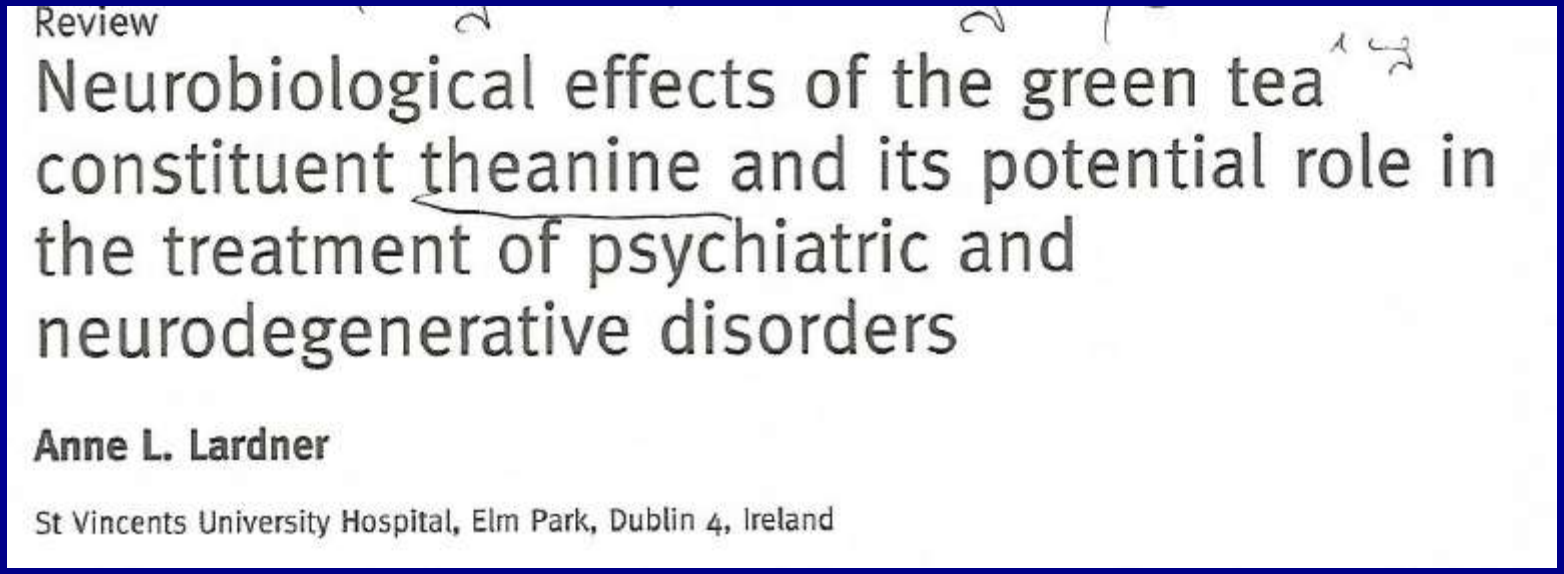
Solfrizzi and Panza. J Alzheimers Dis 2015;43:605-611

L-theanine: Potential Neurobiological Effects



Review

Neurobiological effects of the green tea constituent theanine and its potential role in the treatment of psychiatric and neurodegenerative disorders

Anne L. Lardner

St Vincents University Hospital, Elm Park, Dublin 4, Ireland

Nutr Neurosci 2014;17:145-155

J Nutr Health Aging
Volume 19, Number 3, 2015

COFFEE, TEA, AND CAFFEINE CONSUMPTION AND PREVENTION OF LATE-LIFE COGNITIVE DECLINE AND DEMENTIA: A SYSTEMATIC REVIEW

F. PANZA[1,2,3], V. SOLFRIZZI[4], M.R. BARULLI[1,2], C. BONFIGLIO[5], V. GUERRA[6], A. OSELLA[5], D. SERIPA[3], C. SABBÀ[4], A. PILOTTO[3,7], G. LOGROSCINO[1,2]

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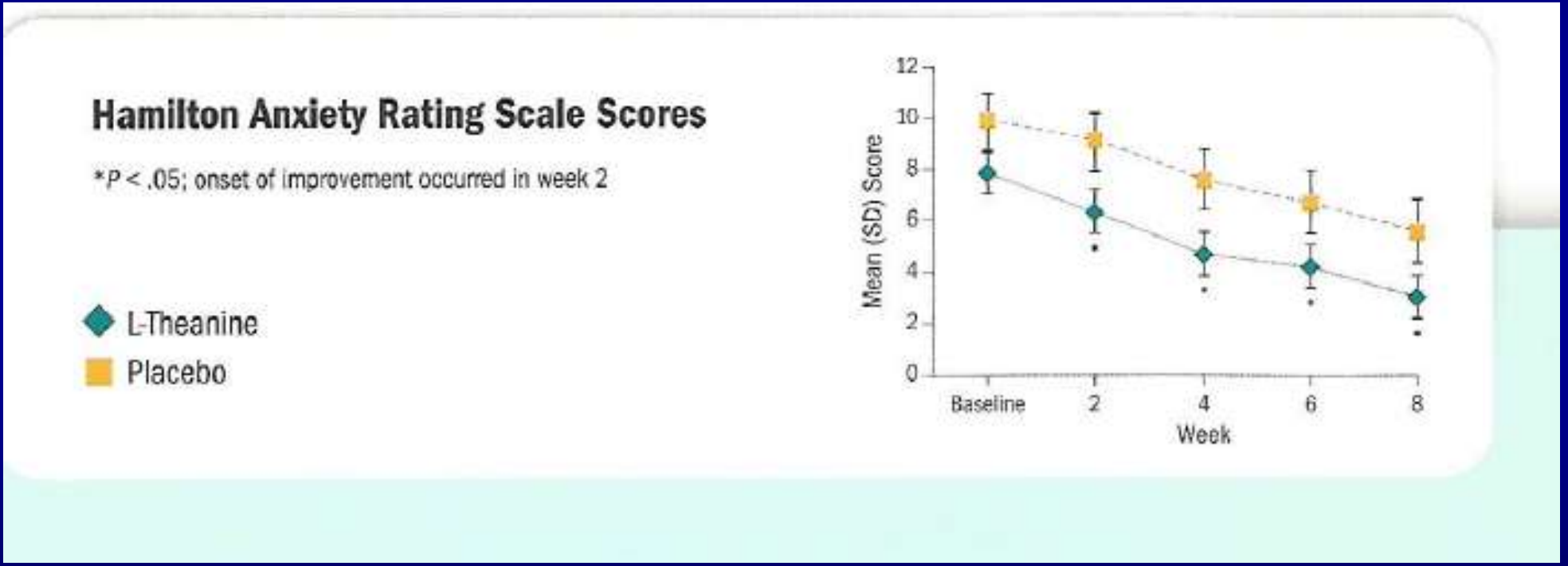
J Nutr Health Aging 2015;19:313-328

L-theanine relieves positive, activation, and anxiety symptoms in patients with schizophrenia and schizoaffective disorder: an 8-week, randomized, double-blind, placebo-controlled, 2-center study



Ritsner et al. J Clin Psychiatry 2011;72:34-42