Mahidol University
Faculty of Medicine
Siriraj Hospital

Rational Drug Used For Cognitive Treatment of Alzheimer Disease And Related Dementia

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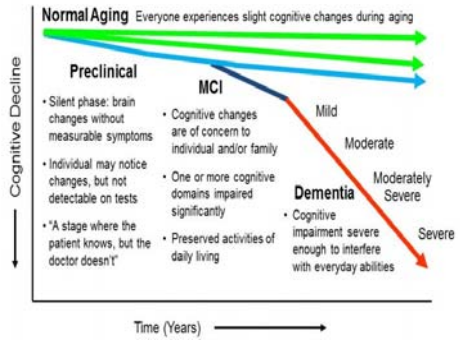
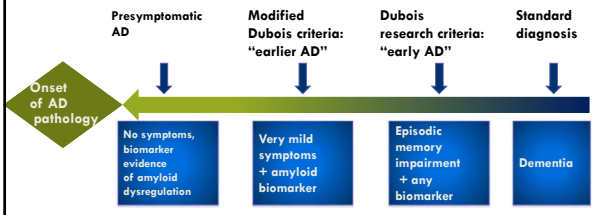
Spectrum of AD



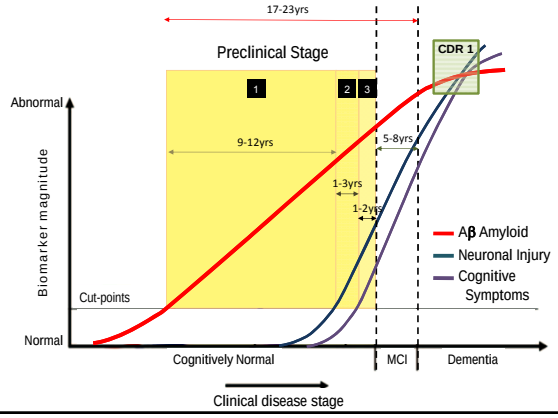
MCI, mild cognitive impairment

https://www.mind.uci.edu/alzheimers-disease/what-is-

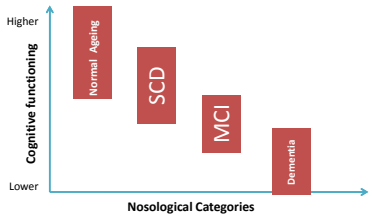
AD Diagnosis Marching Away from Dementia



Aisen PS. *Alzheimers Res Ther.* 2009;1:2. doi:10.1186/alzrt2.



Spectrum of Cognitive Disorders



Normal ageing-SCD-MCI -dementia

MCI mild cognitive impairment; **SCD subjective** cognitive impairment

Modified from Feldman H, Jacova C. *Am J Geriatr Psychiatry* 2005; 13(6):645-55

National Institute on Aging-Alzheimer's Association Criteria (2011)

Probable AD: Core Clinical Criteria

- Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days
- Clear-cut history of worsening of cognition by report or observation; and
- The initial and most prominent cognitive deficits are
  - Amnestic presentation (most common)
  - Nonamnestic presentation

Probable AD with evidence of the AD pathophysiological process

- Biomarker supported diagnosis
- Biomarkers for amyloid-beta (Aβ) protein
  - low CSF Aβ42
  - positive PET amyloid imaging
- Biomarkers of neuronal degeneration
  - elevated CSF tau
  - decreased 18-FDG uptake on PET in temporo–parietal cortex
  - disproportionate atrophy on structural MRI in medial, basal, and lateral temporal lobe, and medial parietal cortex

AD, Alzheimer's Disease; CSF, cerebrospinal fluid; FDG, Fludeoxyglucose; MRI, magnetic resonance Imaging;
PET, position emission tomography

McKhann GM et al, *Alzheimers Dement.* 2011;7(3):263-269

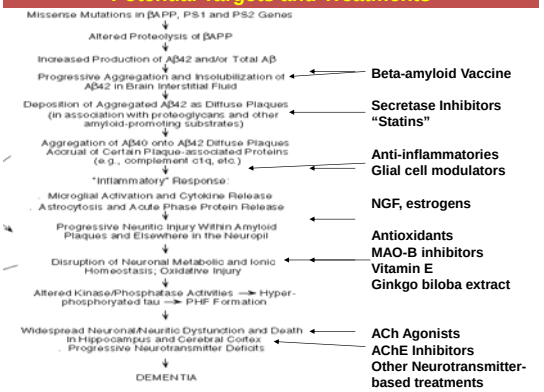
Goals of treatment based on stage of cognitive disorder

Preclinical stage
- main goal is to target pathology to prevent progression to prodromal stage
- this is essentially what we mean by delaying dementia

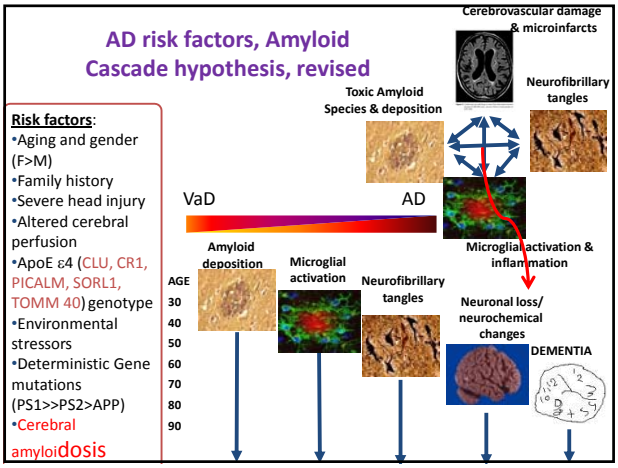
Prodromal stage
- main goals are to both slow the pathology and to improve symptoms

Dementia stage
- main goal is to improve/stbilize symptoms
- we are increasingly recognizing that by this stage it is too late to realistically modify or prevent disease progression

Molecular Pathogenesis of AD : Potential Targets and Treatments



AD risk factors, Amyloid Cascade hypothesis, revised



DEMENTIA
SYMPTOMATIC TREATMENTS

- Cholinergic drugs
  - Acetylcholinesterase inhibitors
    - 1st generation
      - » Tacrine)
    - 2nd generation
      - » Donepezil, Galantamine, Rivastigmine
- Glutaminergic drugs
  - Memantine
- Anti-psychotic drugs
- Anti-psychotics
- Anti-depressants
- Anxiolytics

Alzheimer's Disease Is a Complex Disorder Associated with Deficits in Cognition, Function, Behavior, and Other Domains

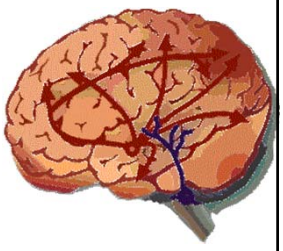
Representative Assessment Scales in Dementia				
Domain[1]	**Considerations**[1]	**Example Scale(s)**[1,2]		
Cognition	• Key change of interest in dementia	ADAS-cog SIB	MoCA MMSE	SLUMS
Function	• Ability to carry out ADL	ADCS-ADL	FAQ	IADL
Behavior	• Often referred to as BPSD • Can be hazardous; related to institutionalization and caregiver stress	NPI		
Staging	• Staging of dementia	CDR	GDS	
Quality of life	• Multidimensional; reflects patient's perception of impact of illness on everyday functioning	ADRQL PDS		
Depression	• Common, but challenging to assess	Cornell Depression in Dementia Scale		
Caregiver burden	• Major issue in dementia	General Health Questionnaire Zarit Caregiver Burden Interview (ZBI)		
Global Impression	• Designed to assign a level of severity to a patient's condition	ADCS-CGIC CIBIC-Plus		

ADAS-cog, Alzheimer's Disease Assessment Scale, cognitive subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; ADCS-CGIC, Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change; ADRQL, Alzheimer Disease-related Quality of Life assessment instrument; BPSD, behavioral and psychotic symptoms of dementia; CDR, Clinical Dementia Rating; CIBIC-Plus, Clinician's Interview-Based Impression of Change – Plus Caregiver Input; FAQ, Functional Activities Questionnaire; GDS, global deteriorating scale; IADL, Instrumental Activities of Daily Living; MoCA, Montreal Cognitive Assessment; MMSE, Mini–Mental State Examination; NPI, Neuropsychiatric Inventory; PDS, Progressive Deterioration Scale; SIB, Severe Impairment Battery; SLUMS, St Louis University Mental Status Exam.

1. Sheehan B. *Ther Adv Neurol Disord*. 2012;5(6):349-358. 2. Robert P, et al. *Alzheimers Res Ther*. 2010;2(4):24.

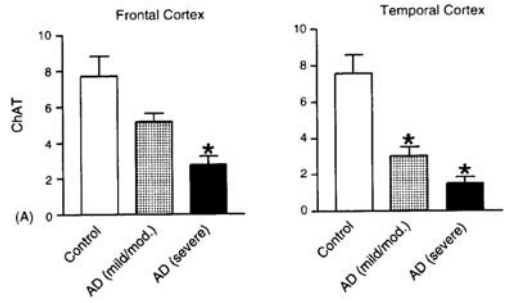
Cholinergic hypothesis

- Cholinergic neurons are essential for memory in animal models
  - scopolamine → cognitive loss
  - cholinergic lesions → cognitive loss
  - nicotine → information processing
  - cholinergic-rich grafts restore memory functioning
- Cholinergic neurons are lost first and most in AD
  - choline acetyltransferase (ChaT) markers lost in AD
  - reduced choline uptake and ACh release in AD
  - neuronal loss in cholinergic nuclei in AD



Blokland (1995); Dunnett (1991); Francis *et al* (1999)

THE CHOLINERGIC SYSTEM IN ALZHEIMER'S DISEASE :
ChAT ACTIVITY AND COGNITION

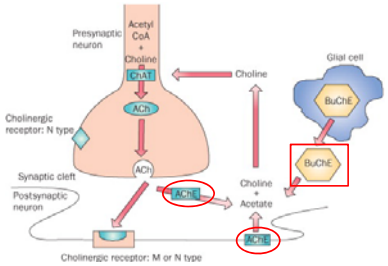


Tsang et al, 2005

Treatment	Dosing	Level I Evidence	Side Effects	Other
Donepezil	5mg or 10mg or 23mg	Multiple R DB PC trials 3-12 months. Mild, mod, severe	Low incidence GI esp diarrhea and nausea	ODT and Generic available for 5 and 10 mg doses
Rivastigmine	Oral: 3mg-6mg BID Patch: 9.5-13.3 mg/24h	Multiple R DB PC trials 6 months. Mild to moderate	Low-moderate GI incl anorexia, diarrhea & vomiting w/ oral; rash w/ TP	Start doses not effective. 13.3 mg/24h patch better when pt declines
Galantamine	8mg or 12mg BID 8, 16, 24 mg ER QD	Multiple R DB PC trials 6-24 months. Mild to moderate	Low incidence GI esp diarrhea and nausea	ER available for QD. Start dose not effective. Generic available
Memantine	10mg BID 28 mg XR QD	Multiple R DB PC trials 6 months. Moderate to severe	Few AE's; occ. mild transient confusion ~weeks3-5	4-step titration to max dose, one week apart
Combination Tx (Memantine added to stable donepezil)	10 mg BID or 28 mg XR QD memantine added to chronic ChEI therapy	Two R DB PC moderate to severe trials	Few AE's; mild transient confusion ~weeks3-5	RTC data in mild AD lacking; observational studies support long-term benefits
Vitamin E	1000 IU BID	Two R DB PC trials moderate to severe trial	Few AE's	More robust effects on slowing functional than on cognitive decline; "Controversy" re: Survival data

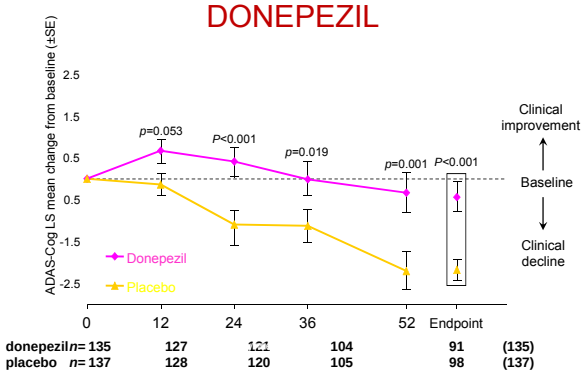
The cholinergic hypothesis of AD

Acetylcholine (ACh), a neurotransmitter essential for processing memory and learning, is decreased in both concentration and function in patients with AD

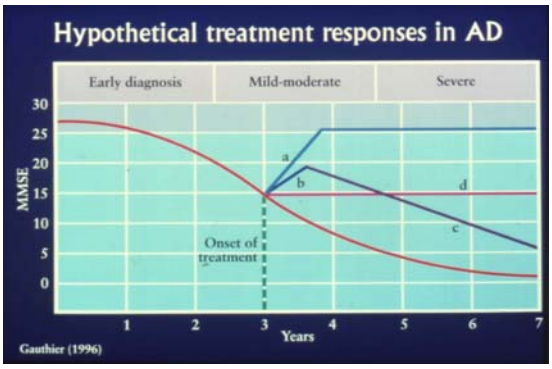


Scarpini E, et al. *The Lancet Neurology*.2003; 2(9): 539–547.

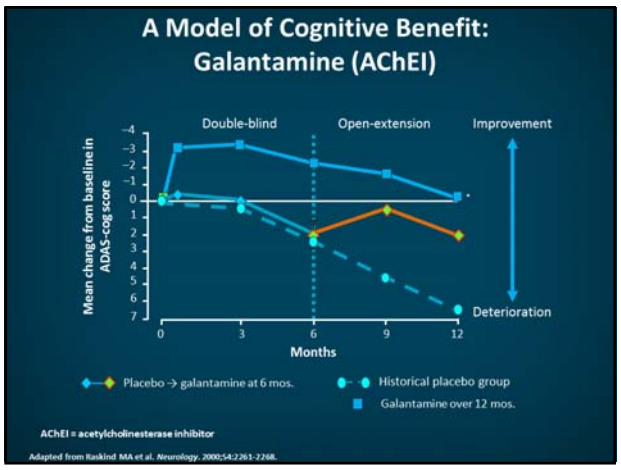
COGNITIVE EFECTS OF DONEPEZIL



Winblad et al, Neurology



a = Cure (aka the Holy Grail) symptomatic and disease modifying
b = symptomatic treatment
c = no treatment
d = disease modifying

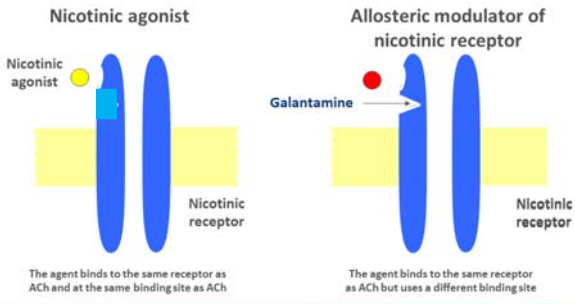


AChEIs FOR AD
Modest but significant therapeutic effect

Global Response	n	Mean % difference (95% CI)	NNT (95% CI)
Stable / Improvement	3128	15 (11-18)	7 (6-9)
Improvement	4468	9 (6-12)	12 (9-16)
>Minimal Improvement	1523	2 (1-4)	42 (26-114)
Cognitive Response ≥4 ADAS-Cog	2419	10 (4-17)	10 (8-15)

Lanctot 2003, CMAJ 169:557

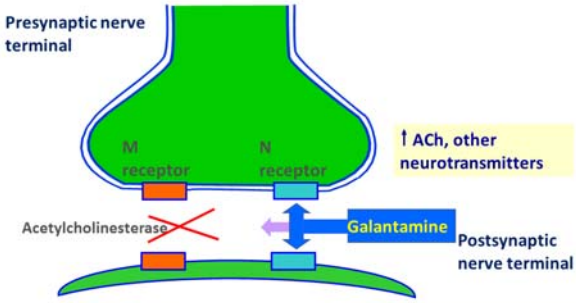
Difference between a nicotinic agonist and an allosteric modulator of nicotinic receptors



AChEIs FOR AD
Modest but significant therapeutic effect

- By comparison,
  - antipsychotics for schizophrenia NNT = 3
  - antihypertensives for prevention of major vascular events 5 year NNT = 29-86
- Definition of treatment response
- Possible ethnic variation in treatment response
  - Homma et al showed a large (28%) treatment effect using low dose donepezil in Japanese

Dual mechanism of action



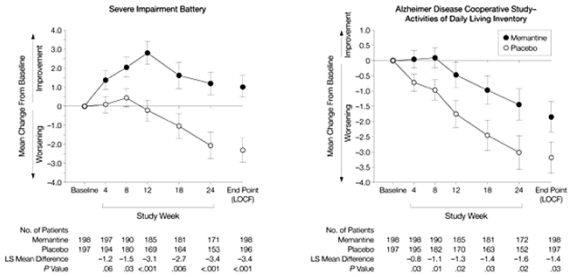
Nicotinic allosteric modulator

21

MEMANTINE FOR AD

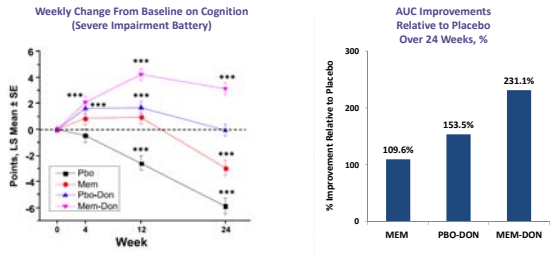
- NMDA receptor antagonist
- Blocks pathological activation of NMDA receptors by excessively high synaptic levels of glutamate while preserving physiological activation required in learning and memory formation
- Indicated for the treatment of moderate to severe AD

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



Tariot et al., JAMA 2004

AUC Analysis: Monotherapy or Adjunctive Therapy × 6 Months on Measure of Cognition



AUC analysis showed advantage of memantine-donepezil combination vs donepezil alone or memantine alone

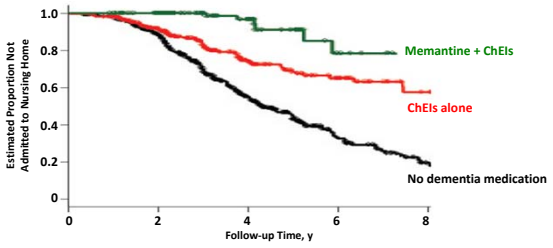
- However, baseline to endpoint change analysis underestimated this effect

*P <0.05 **P <0.01 ***P <0.001. vs within-group basline score
DON, donepezil; MEM, memantine; PBO, placebo.
Atri A, et al. *Alzheimers Res Ther*. 2015;7(1):28.

Using Higher Doses of Donepezil

- A matrix type (sustained-release [SR]) tablet of 23 mg donepezil was developed to provide a higher once-daily dose while avoiding a sharp daily increase in peak concentration.
  - The drug exposure with the SR formulation is ~92% (95% CI, 89.1–94.7; dose adjusted) that of the IR formulation
  - Tmax <2-fold greater (6–9 hours with SR vs 3–4 hours with IR)
  - AUC 0–∞ that is >2-fold greater

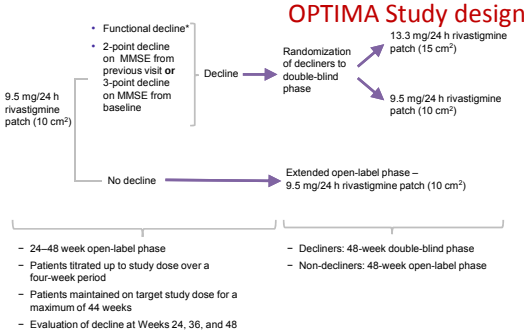
Pharmacotherapy Delays Admission to Nursing Home



- Patients taking anti-AD medications were less likely to be placed in a nursing home than patients receiving usual care but without medications
  - However, treatment does not prolong life

Adapted from Lopez et al. *J Neurol Neurosurg Psychiatry*. 2009;80(6):600-607.

OPTIMA Study design

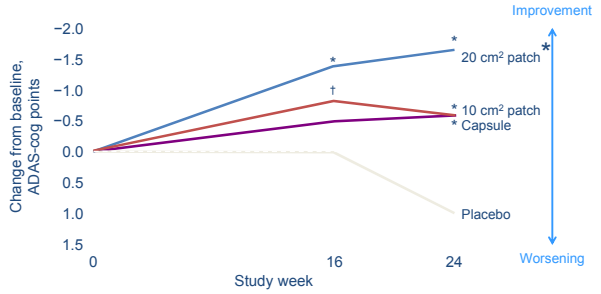


- 24–48 week open-label phase
- Patients titrated up to study dose over a four-week period
- Patients maintained on target study dose for a maximum of 44 weeks
- Evaluation of decline at Weeks 24, 36, and 48

- Decliners: 48-week double-blind phase
- Non-decliners: 48-week open-label phase

[redacted] Cummings J et

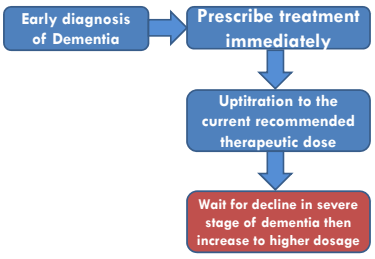
IDEAL Study : Rivastigmine Patch Superior to Placebo, At Least as Effective as Capsule on Cognition (ADAS-cog)



Baseline ADAS-cog scores: 27.0, 27.4, 27.9 and 28.6 in the 10cm², 20 cm², capsule and placebo groups, respectively

Winblad B et al,

Management strategies : Bringing in higher AChEI **later**



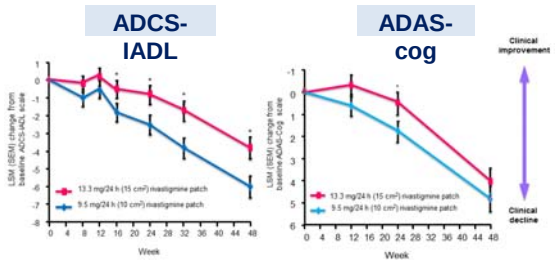
Titration/Starting dose
5 mg Donepezil Oral
4.6 mg/24 hr Rivastigmine path
8 mg Galantamine oral

Increase dose
10 mg Donepezil Oral
9.5 mg/24 hr Rivastigmine path
24 mg Galantamine oral

Increase dose
23 mg Donepezil Oral
13.3 mg/24 hr Rivastigmine path
Optional of Combination therapy to Memantine

Adapted from Small, Bullock: Alzheimers Dement 2011;7:177-84

Cognitive and Functional Outcomes



Cummings J et

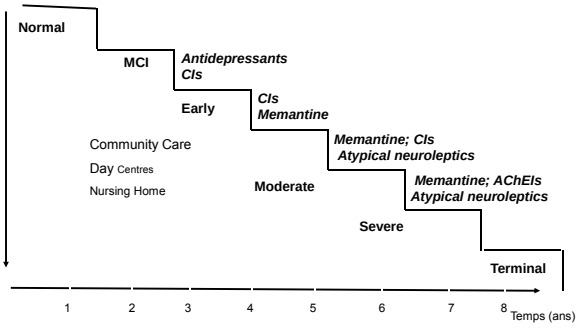
Other Neurotransmitter Based Treatments

- A number of other neurotransmitters are affected in AD
- However no new agents have emerged
- **Medivation's Dimebon (histamine) fails Phase III for Alzheimer's, shares collapse (2010)**
- **Phase III Alzheimer's flop (5HT6 antagonist) takes chunk out of Lundbeck (2016)**

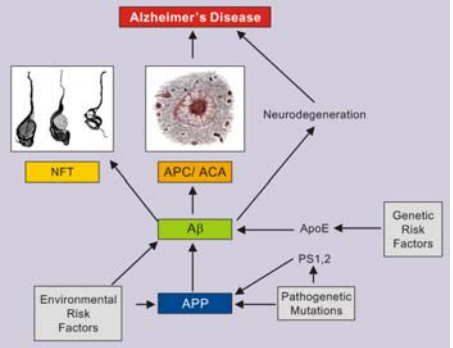
CURRENT PERCEPTIONS OF AChEI FOR AD

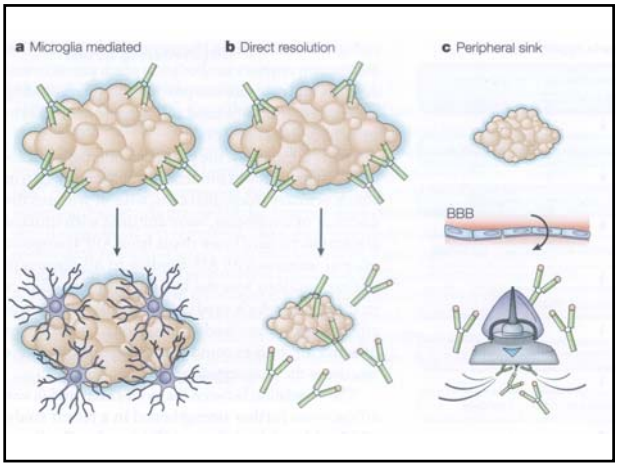
- AChEIs are perceived as *"symptomatic""* and not **"disease modifying"** treatments
- Hence AChEIs are
  - Inferior
  - Temporary
  - Costly
- Increasing therapeutic nihilism
  - unfounded

NATURAL HISTORY OF AD AND CURRENT Rx

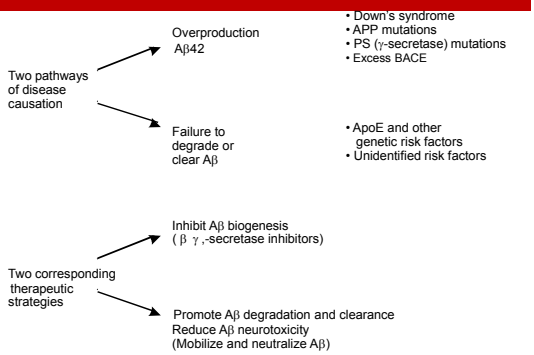


The Amyloidocentric Pathways in Alzheimer's Disease





Testing the Aβ theories of AD



A Decade of Disappointments

Lilly's Gamma Secretase Inhibitor for Alzheimer's: Worse Than Nothing (2010)

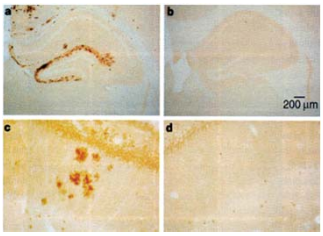
Pfizer, J&J scrap Alzheimer's studies as drug (bapineuzumab) fails (2012)

Lilly's Phase III data for solanezumab disappoint yet tantalize (2014)

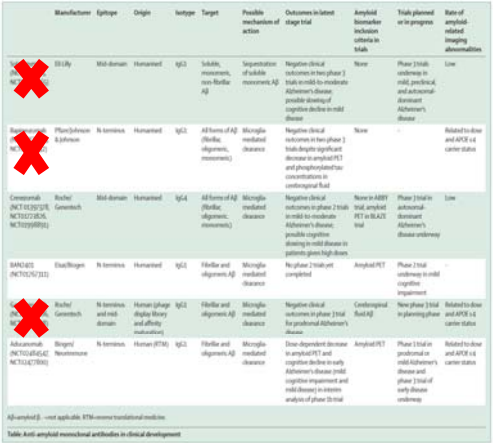
Solanezumab has failed to meet its primary endpoints in two pivotal Phase III studies in Alzheimer's disease. However, efficacy signals were discovered in prespecified secondary analyses : statistically significant effect on cognition in the mild Alzheimer's disease patient subgroup compared to placebo.

Alzheimer's hopes dashed as Lilly gives up on amyloid drug solanezumab (2016)

A VACCINE FOR AD?



Immunisation with ßA4 at 6 weeks of age attenuates plaque formation in 13 month old transgenic mice overexpressing APP (Schenk et al Nature 1999 : 400 ; 173-77)



ARTICLE

doi:10.1038/nature19323

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain Aβ in a dose- and time-dependent manner. This is accompanied by a slowing of clinical decline measured by Clinical Dementia Rating—Sum of Boxes and Mini Mental State Examination scores. The main safety and tolerability findings are amyloid-related imaging abnormalities. These results justify further development of aducanumab for the treatment of AD. Should the slowing of clinical decline be confirmed in ongoing phase 3 clinical trials, it would provide compelling support for the amyloid hypothesis.

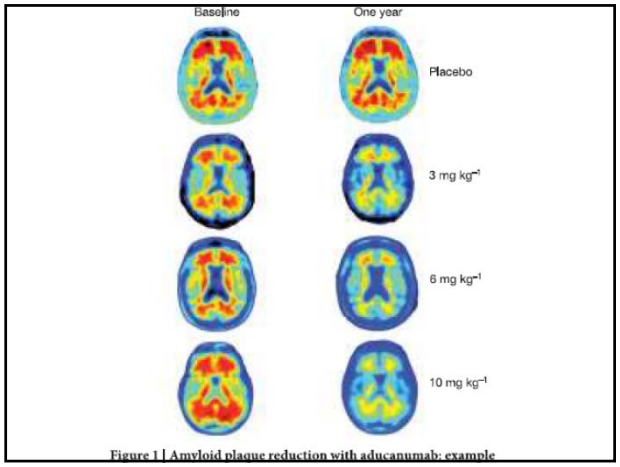
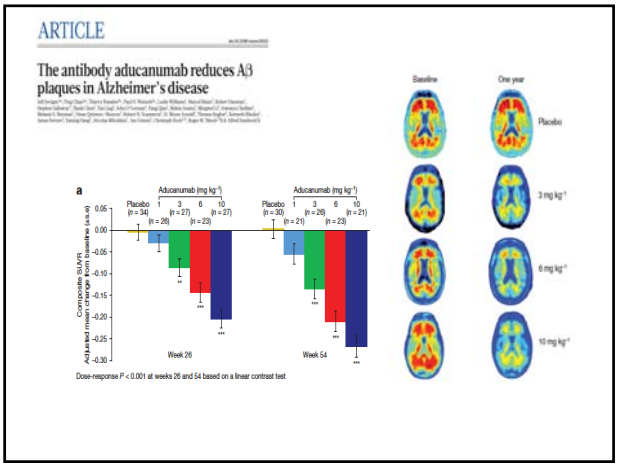
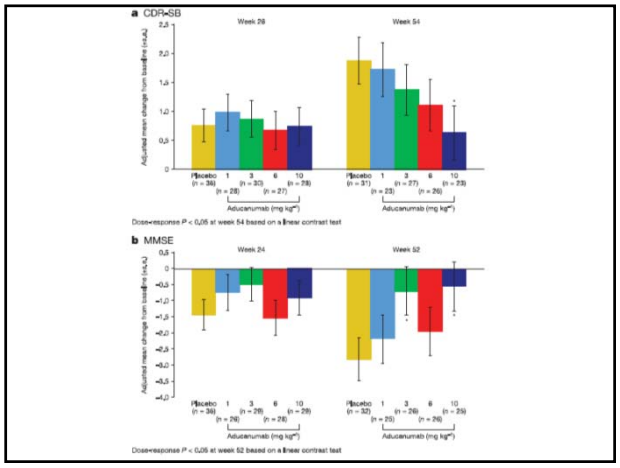
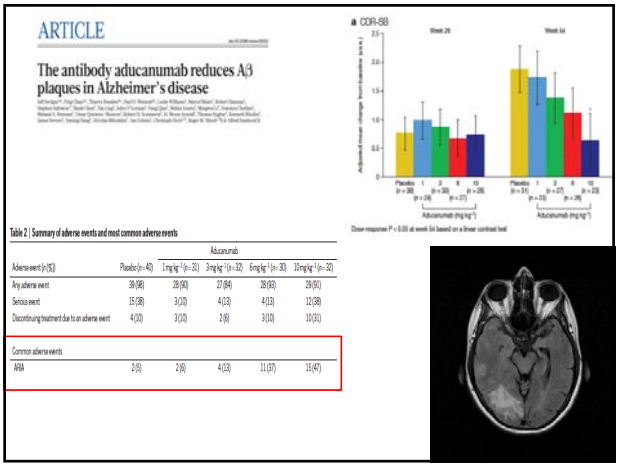


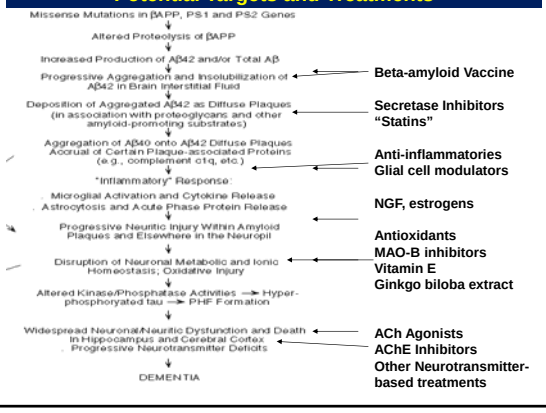
Figure 1 | Amyloid plaque reduction with aducanumab: example



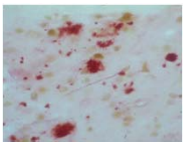
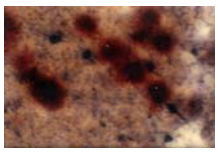
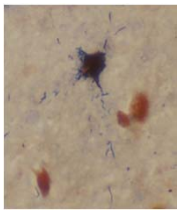




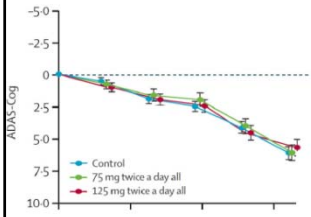
Molecular Pathogenesis of AD : Potential Targets and Treatments



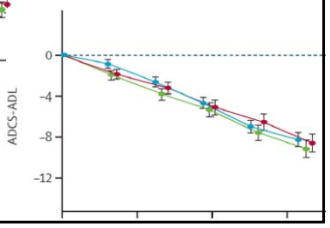
AMYLOID PLAQUES AND NEUROFIBRILLARY TANGLES

LMTM selective inhibitor of tau protein aggregation



Primary endpoints were neutral



AEs more frequent in treatment groups, especially gastrointestinal and urinary – leading to 9% discontinuation in high dose vs 2% in control

Lancet. 2016 December 10; 388(10062): 2873–2884. doi:10.1016/S0140-6736(16)31275-2.

Efficacy and safety of tau-aggregation inhibitor therapy in patients with mild or moderate Alzheimer's disease: a randomised, controlled, double-blind, parallel-arm, phase 3 trial

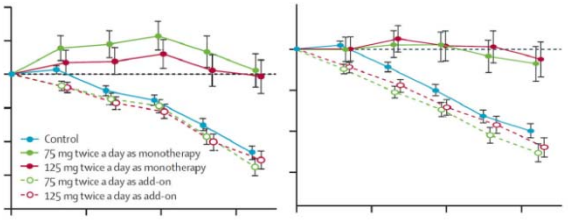
Serge Gauthier, Howard H Feldman, Lon S Schneider, Gordon K Wilcock, Giovanni B Frisoni, Jiri H Hardlund, Hans J Moebius, Peter Bentham, Karin A Kook, Damon J Wischik, Bjoern O Schelter, Charles S Davis, Roger T Staff, Luc Bracoud, Kohkan Shamsi, John M D Storey, Charles R Harrington, and Claude M Wischik

LMTM is a selective inhibitor of tau protein aggregation in vitro and in transgenic mouse models.

15 month placebo controlled RCT in Europe, North America, Asia and Russia. 891 mild to moderate AD recruited : 357 control, 268 to 75mg bd, 266 to 125mg bd added on to existing treatment

Co-primary endpoints were ADAS-Cog and ADCS-ADL

LMTM selective inhibitor of tau protein aggregation

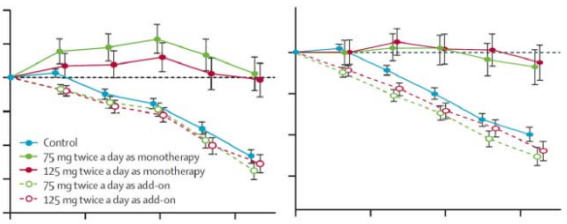


Exploratory pre-specified post hoc analysis showed that patients taking LMTM as monotherapy had lower rate of progression compared to controls or those taking LMTM as an add on

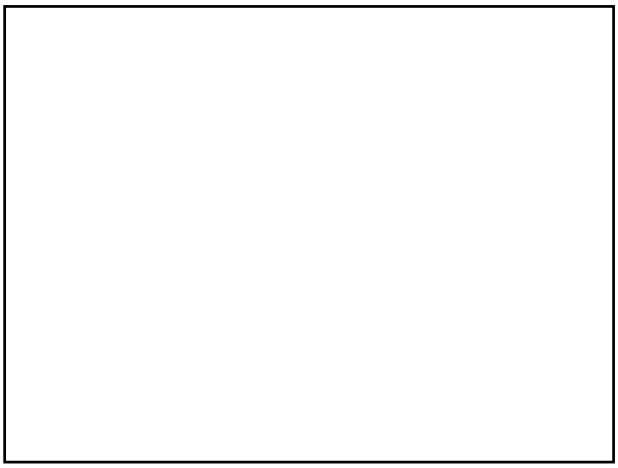
LMTM selective inhibitor of tau protein aggregation

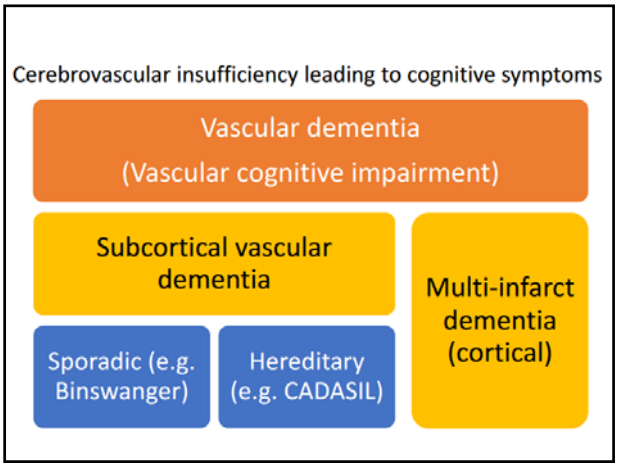
- Of the 891 randomized
  - 885 received at least one dose (safety population)
  - 855 had post-baseline efficacy assessment (modified ITT population)
  - 618 completed the study (579 on treatment)
  - MRI available from 880 at baseline and 554 at end of study
  - FDG PET available from 101 patients at end of study

LMTM selective inhibitor of tau protein aggregation



Exploratory pre-specified post hoc analysis showed that patients taking LMTM as monotherapy had lower rate of progression compared to controls or those taking LMTM as an add on




Cerebrovascular insufficiency leading to cognitive symptoms
Vascular dementia
(Vascular cognitive impairment)
Subcortical vascular dementia
Sporadic (e.g. Binswanger)
Hereditary (e.g. CADASIL)
Multi-infarct dementia (cortical)