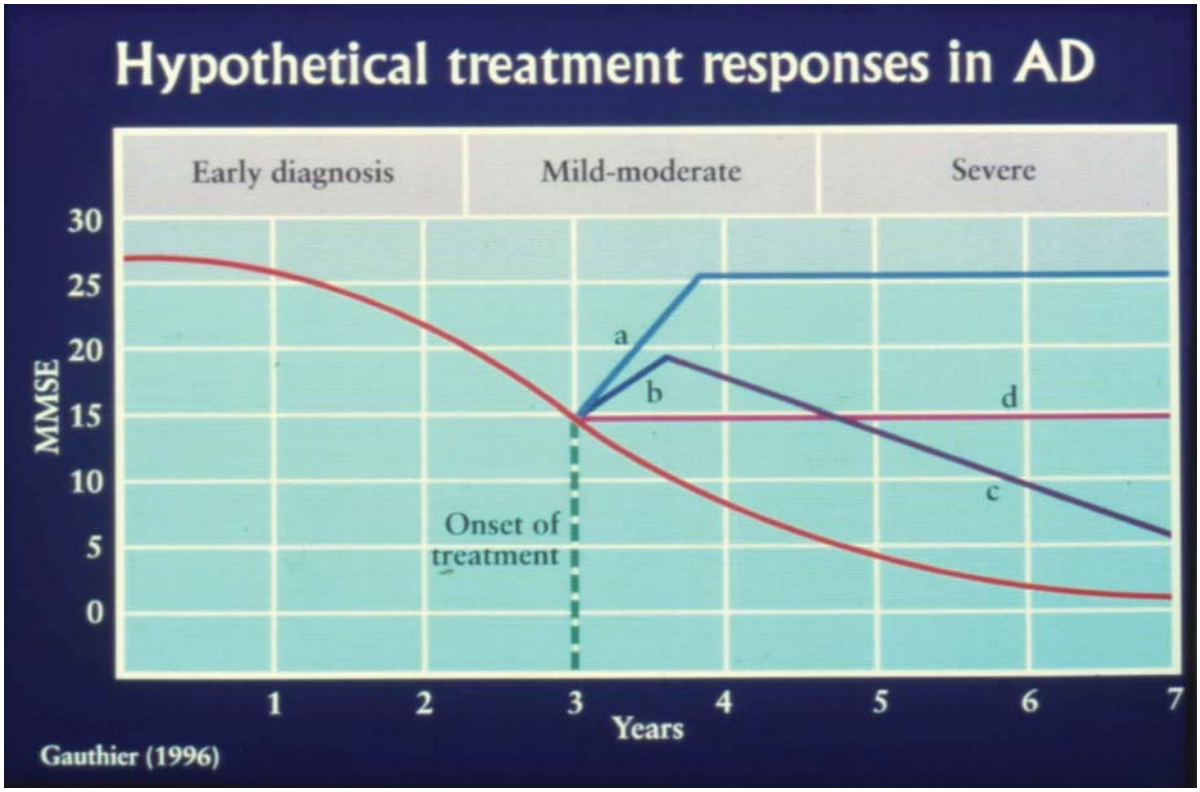
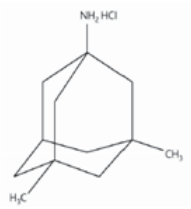
BEST USE OF AVAILABLE DRUGS FOR ALZHEIMER'S DISEASE

Serge Gauthier, C.M., C.Q., MD, FRCPC
McGill Centre for Studies in Aging



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



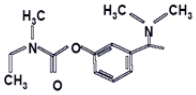
Memantine
NMDA
Uncompetitive
Receptor
Antagonist

1906 1910 1974 1982 1997 2004 2010 2020

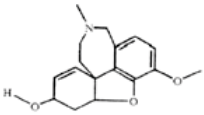
The cholinergic hypothesis

Acetylcholinesterase inhibitors

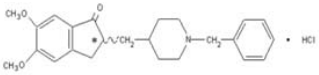
First Disease Modifying Rx?
Amyloid and tau lowering?
Next generation targets?



rivastigmine



galantamine



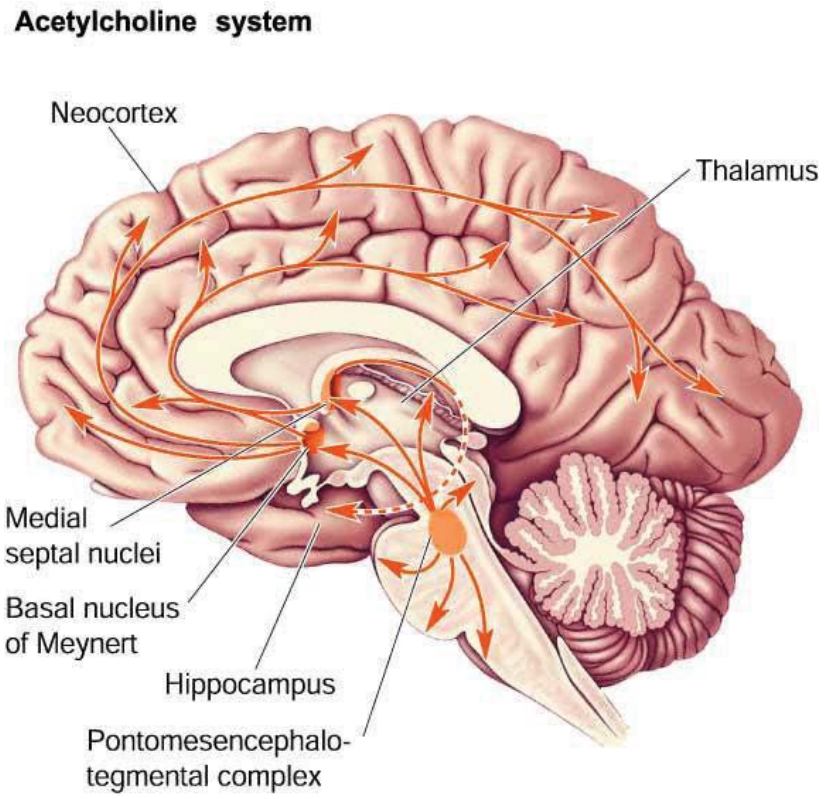
March 12, 2016 Bengt Winblad 3

SYMPTOMATIC DRUGS FOR DEMENTIAS

- Antidepressants (ex.escitalopram)
- Cholinesterase inhibitors (donepezil, rivastigmine, galantamine)
- NMDA receptor antagonist (memantine)
- Atypical antipsychotics (risperidone, olanzapine, quetiapine)

RATIONALE FOR CHOLINESTERASE INHIBITORS (CIs)

- Cholinergic deficit in AD, VaD and DLB
- Loss of neurons in Nucleus Basalis of Meynert



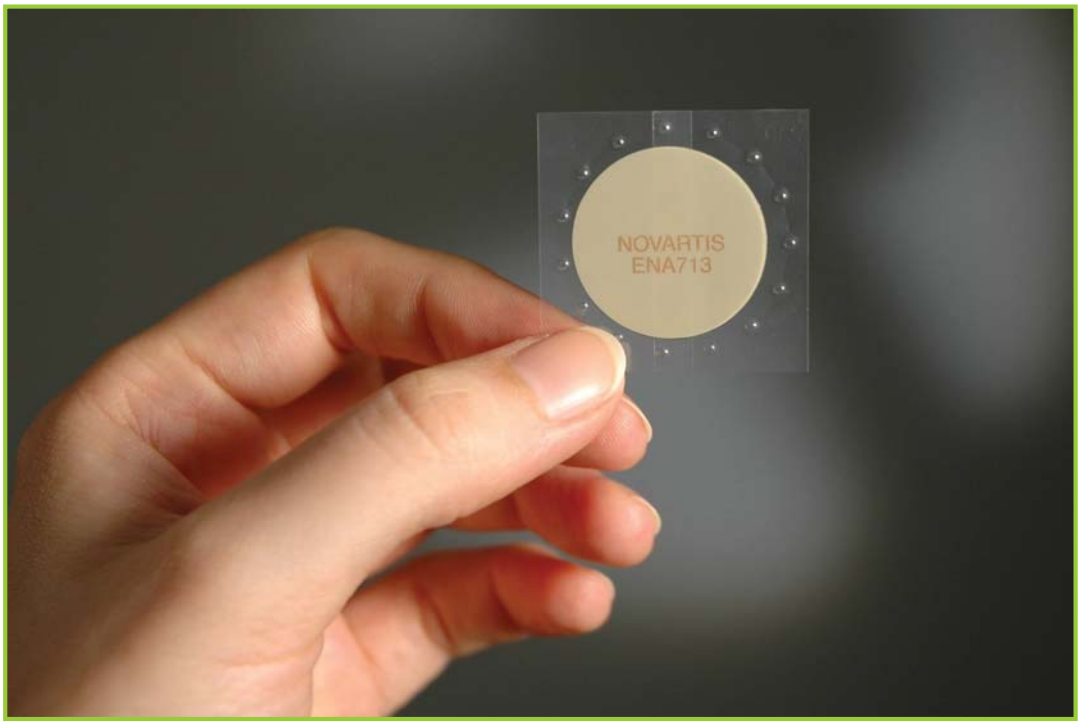
RATIONALE FOR CHOLINESTERASE INHIBITORS (CIs)

- Anticholinergic drugs interfere with memory, cholinergic drugs help
- Drugs that inhibit one or both cholinesterase enzymes improve or stabilize symptoms in dementia due to AD, DLB, PDD, mixed AD/Vasc

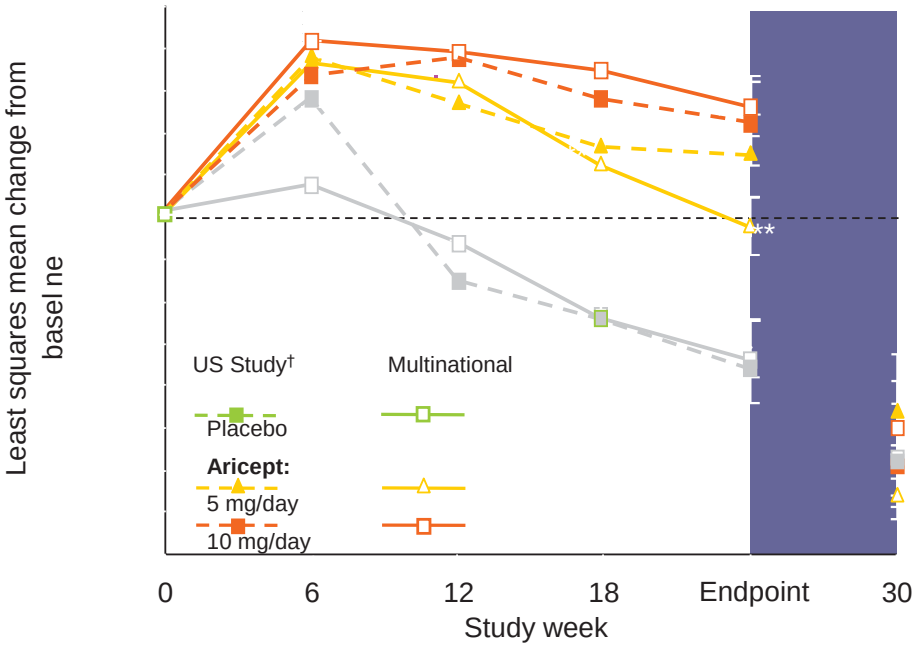
CIs: PHARMACOLOGICAL DIFFERENCES

	Donepezil	Rivastig-mine	Galanta-mine
Half-life & posology	70-80 hrs QD	0.6-2 hrs BID or patch QD	7-8 hrs BID or QD
Enzymes inhibited	AChE	AChE & BuChE	AChE
Nicotinic effects	+	+	+++

Rivastigmine Patch

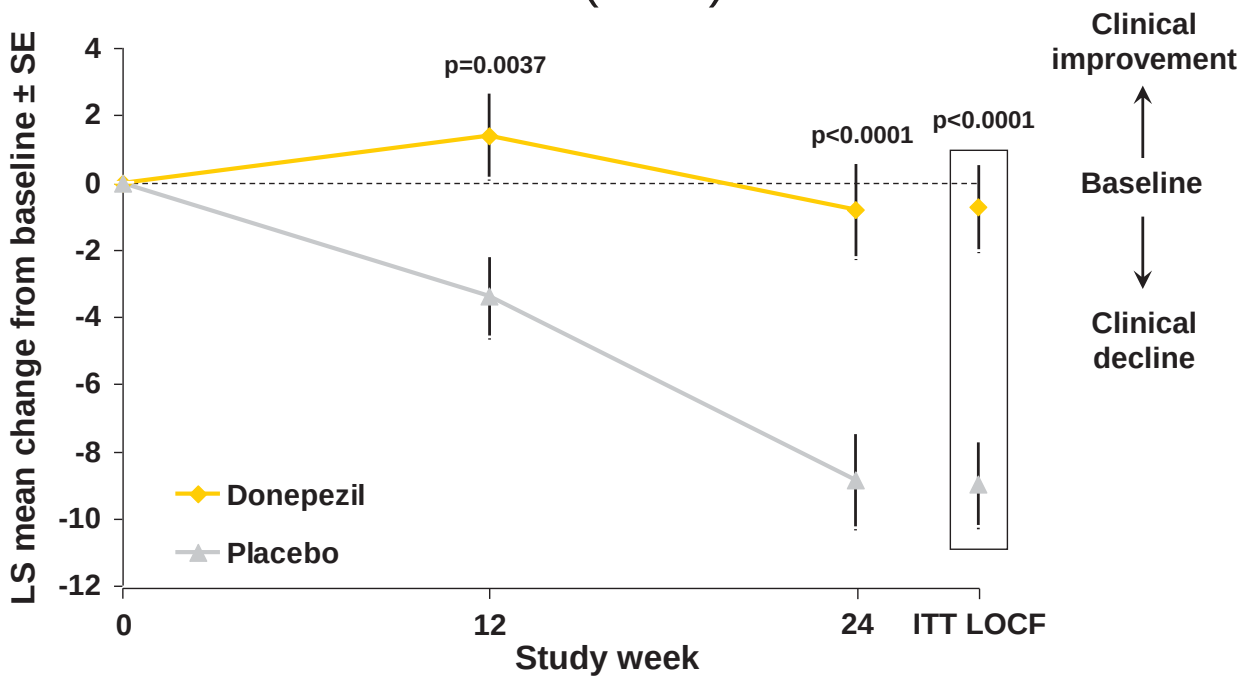


DONEPEZIL VS PLACEBO
COGNITION (ADAS-cog)



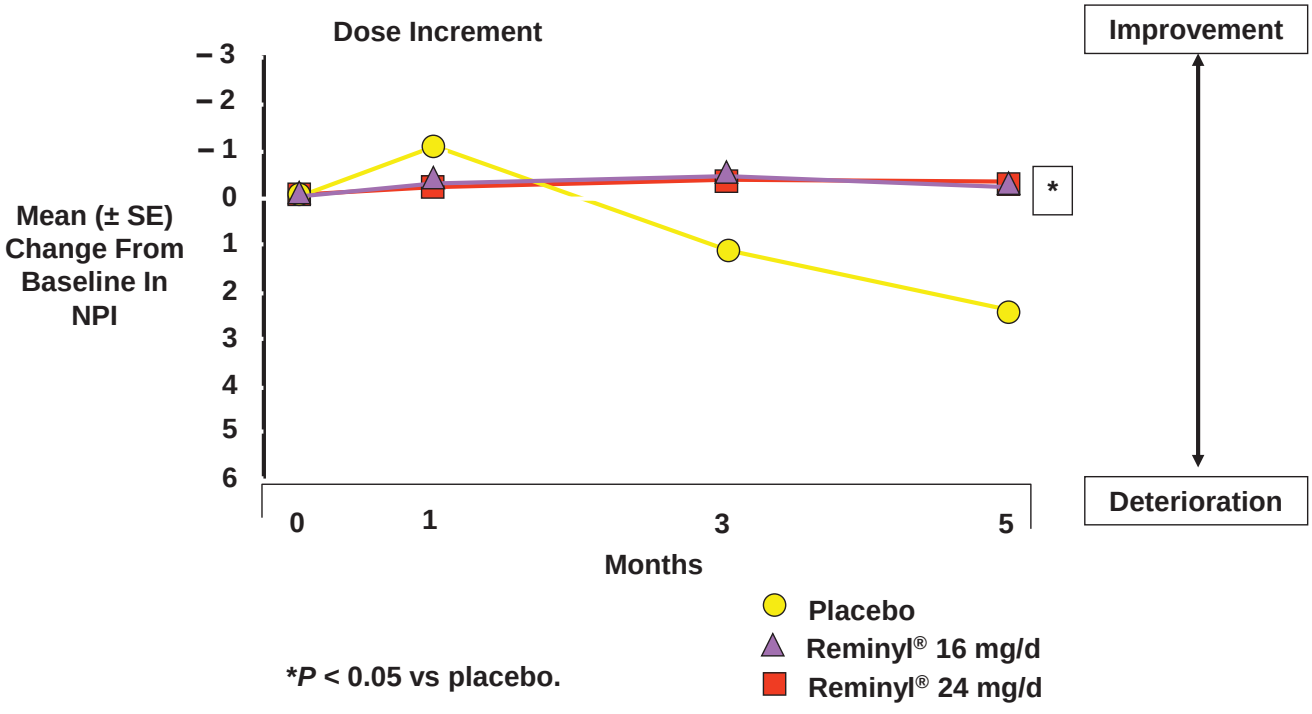
ITT-LOCF analysis; **p≤0.001 for Aricept versus placebo
†Rogers *et al*. *Neurology* 1998;**50**:136–145; ‡Burns *et al*. *Dement Geriatr Cogn Disord* 1999;**10**:237–244

DONEPEZIL VS PLACEBO ADL (DAD)



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

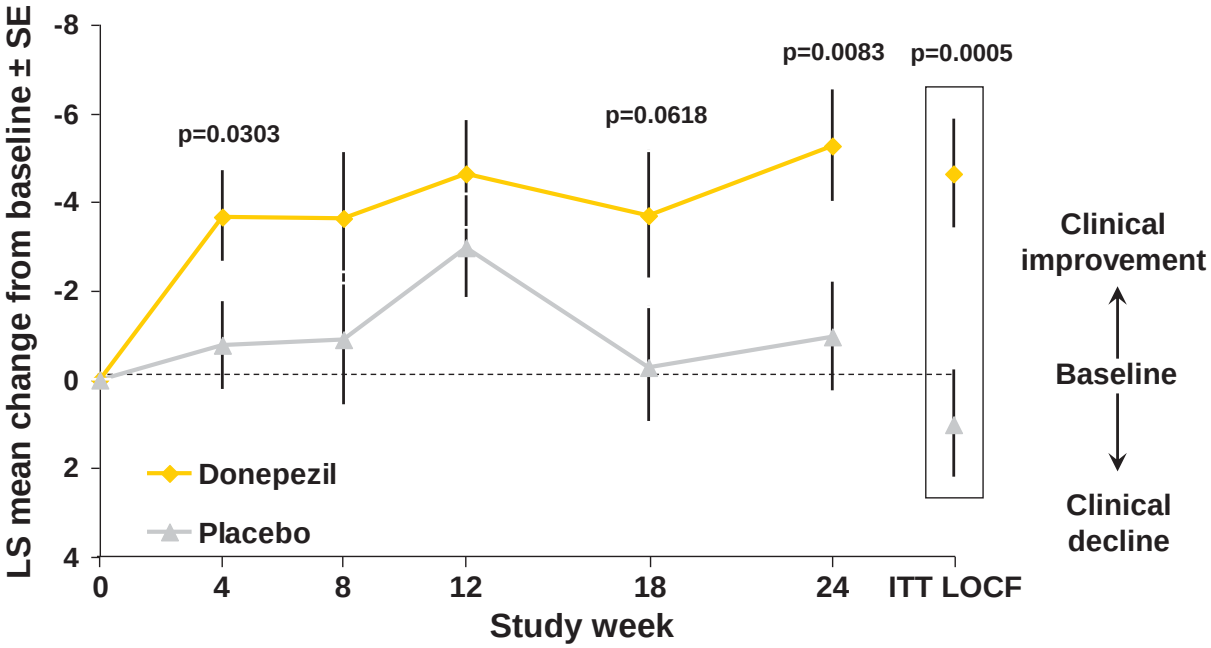
GALANTAMINE VS PLACEBO BEHAVIOR (NPI)



******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)

CIs STANDARD TITRATION AND DOSES

- Donepezil 5mg QD for 4 weeks then 10mg (23mg not approved in Canada)
- Rivastigmine patch #5 for 4 weeks then #10 (#15 not widely used), or oral 1.5mg BID titrated up to 6.0mg BID as tolerated
- Galantamine 8mg QD for 4 weeks, then increase to 16mg QD then 24mg QD as tolerated

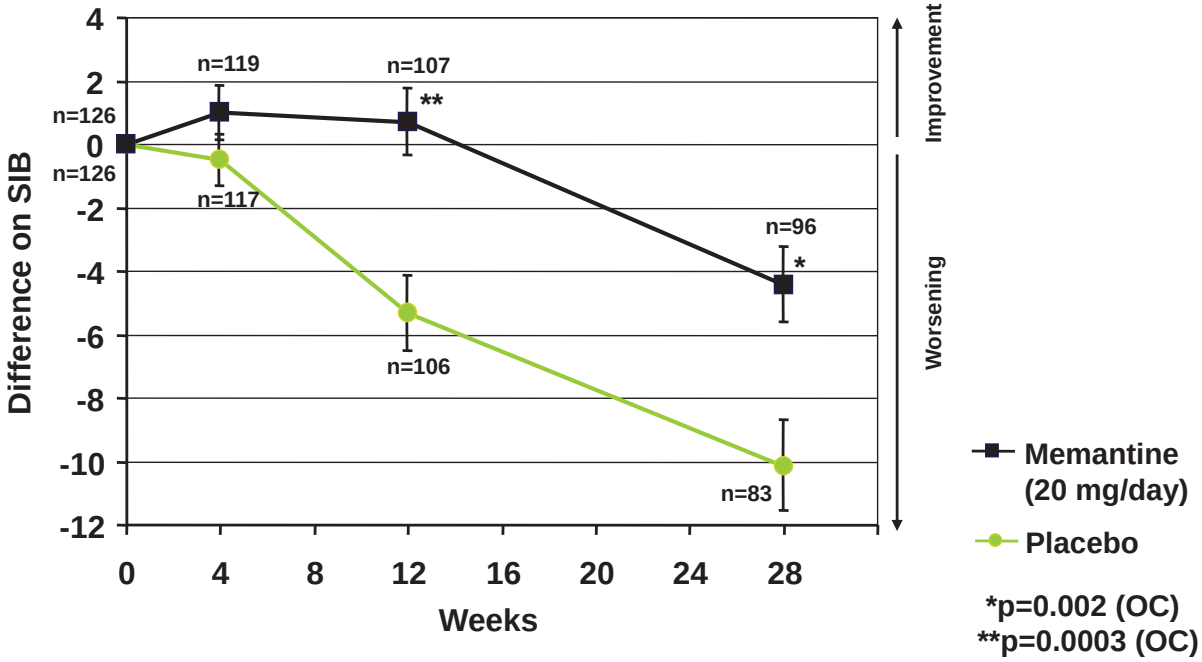
SIDE EFFECTS OF CIs
from parasympathetic activation

- Gastrointestinal: nausea, vomiting, diarrhea, anorexia
- Cardiovascular: bradycardia, syncope (attention with sick sinus syndrome)
- Neuromuscular: cramps
- Central: insomnia, REM Behavior Disorder, worsening of depression
- Urinary: increase voiding
- Other: rhinorrhea

MEMANTINE FOR AD

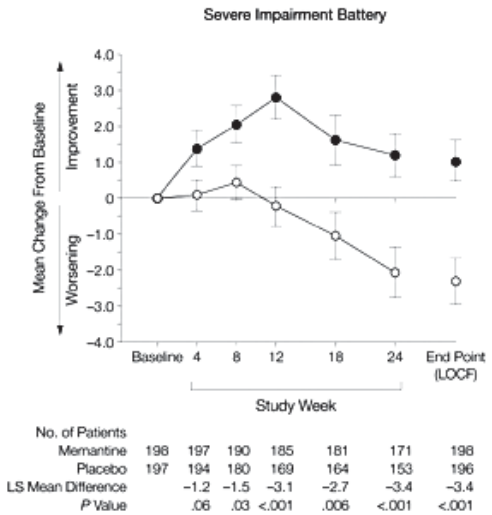
- NMDA receptor antagonist
- Blocks pathological activation of NMDA receptors by excessively high synaptic levels of glutamate while preserving physiological activation required in learning and memory formation
- Indicated for the treatment of moderate to severe AD

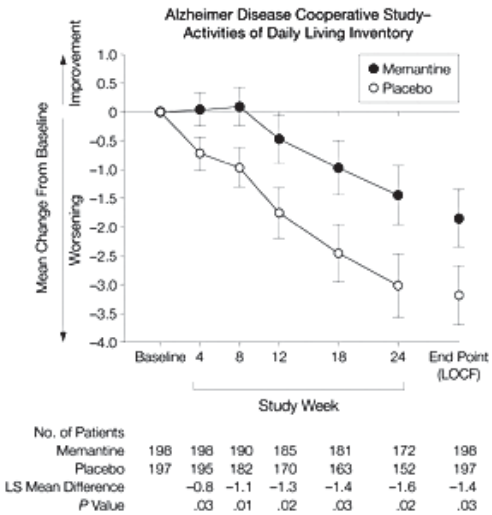
SIB to measure cognition



Reisberg et al 2003; H. Lundbeck A/S,

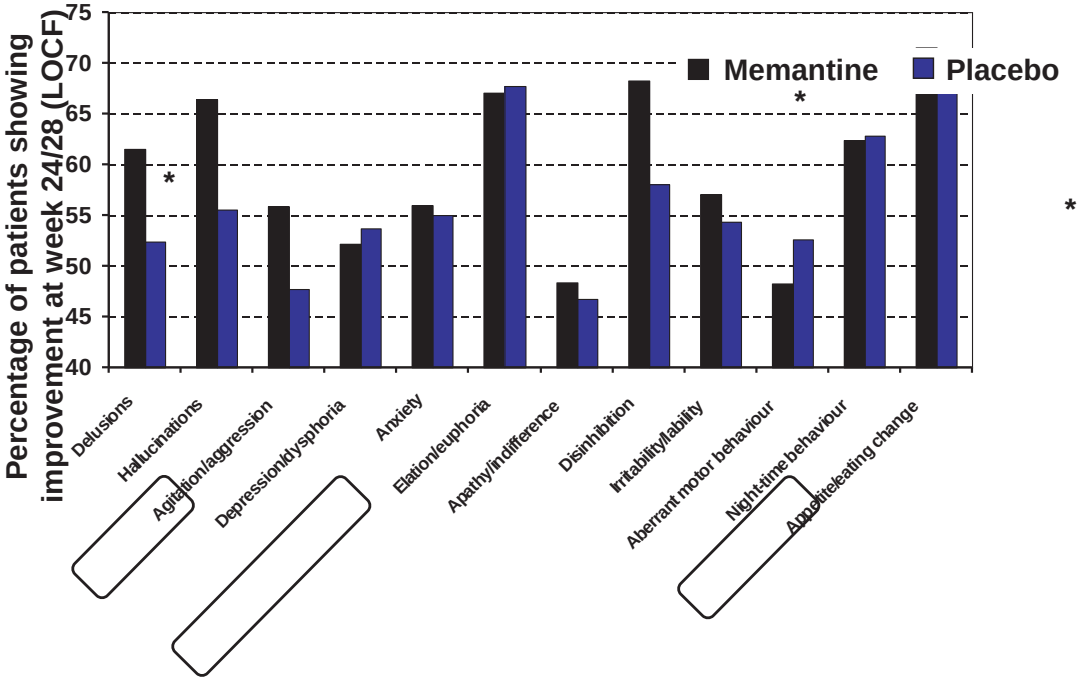
SIB to measure cognition and ADCS-ADL to measure function





Tariot et al., JAMA 2004

NPI TO MEASURE BEHAVIORAL SYMPTOMS PRESENT AT BASELINE



*p<0.05

Gauthier et al. Int J Geriatr Psych 2007

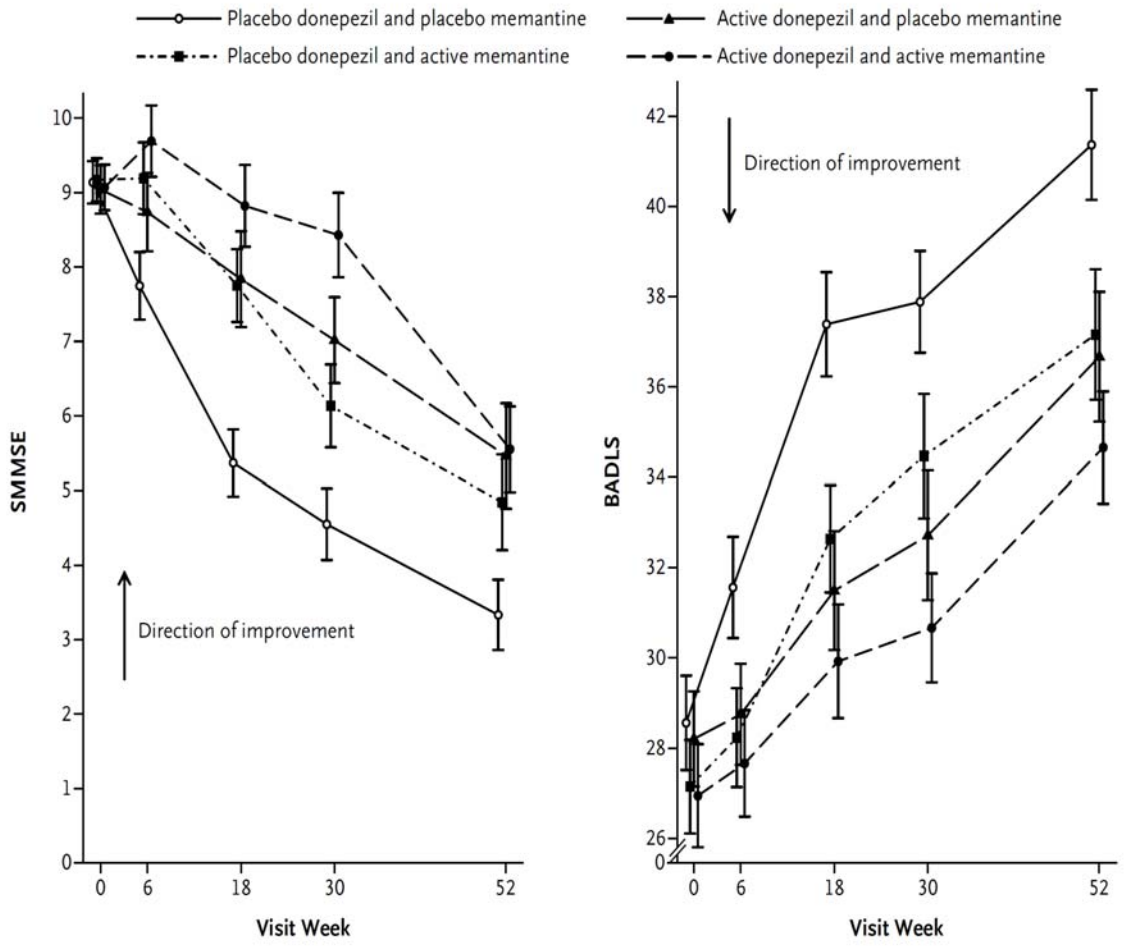
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

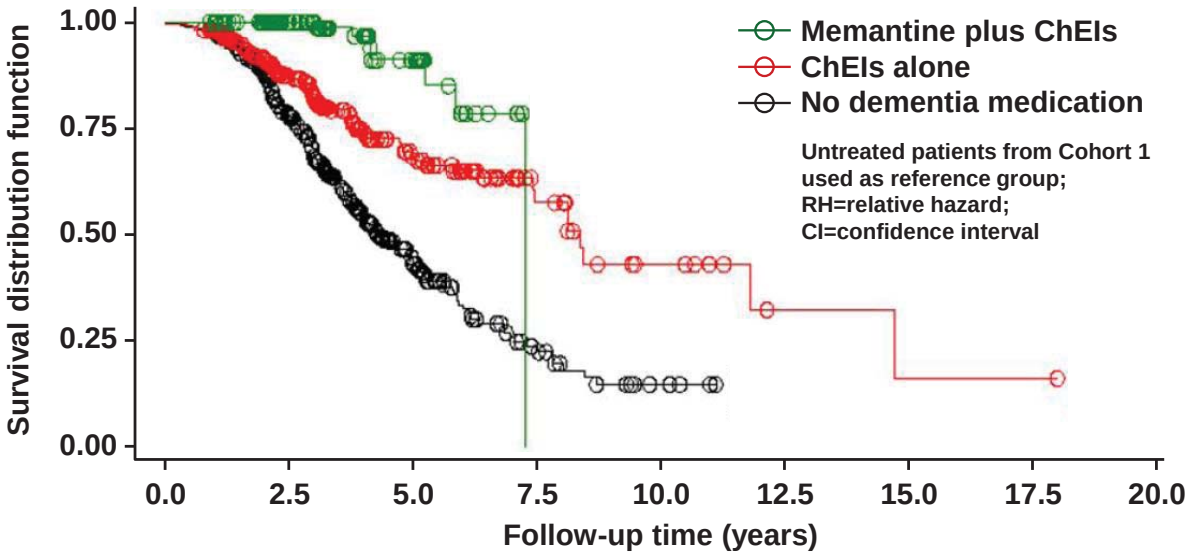
Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease

Robert Howard, M.D., Rupert McShane, F.R.C.Psych., James Lindesay, D.M., Craig Ritchie, M.D., Ph.D., Ashley Baldwin, M.R.C.Psych., Robert Barber, M.D., Alistair Burns, F.R.C.Psych., Tom Dening, F.R.C.Psych., David Findlay, M.B., Ch.B., Clive Holmes, Ph.D., Alan Hughes, M.B., Ch.B., Robin Jacoby, D.M., Rob Jones, M.B., Ch.B., Roy Jones, M.B., Ian McKeith, F.Med.Sc., Ajay Macharouthu, M.R.C.Psych., John O'Brien, D.M., Peter Passmore, M.D., Bart Sheehan, M.D., Edmund Juszczak, M.Sc., Cornelius Katona, M.D., Robert Hills, D.Phil., Martin Knapp, Ph.D., Clive Ballard, M.D., Richard Brown, Ph.D., Sube Banerjee, M.D., Caroline Onions, P.G.Dip., Mary Griffin, R.G.N., Jessica Adams, B.Sc., Richard Gray, M.Sc., Tony Johnson, Ph.D., Peter Bentham, M.B., Ch.B., and Patrick Phillips, Ph.D.

N Engl J Med 2012;366:893-903.



TIME TO NURSING HOME IN CLINICAL PRACTICE, CI ± MEMANTINE



- **Patients receiving ChEIs had a significant delay to nursing home placement; this effect was significantly augmented with the addition on memantine**
- **Memantine reduced the risk of nursing home placement by a factor of 3.4, relative to the group taking ChEIs alone**

Lopez et al. J Neurol Neurosurg Psychiatry 2009;80;600-607

MEMANTINE TITRATION

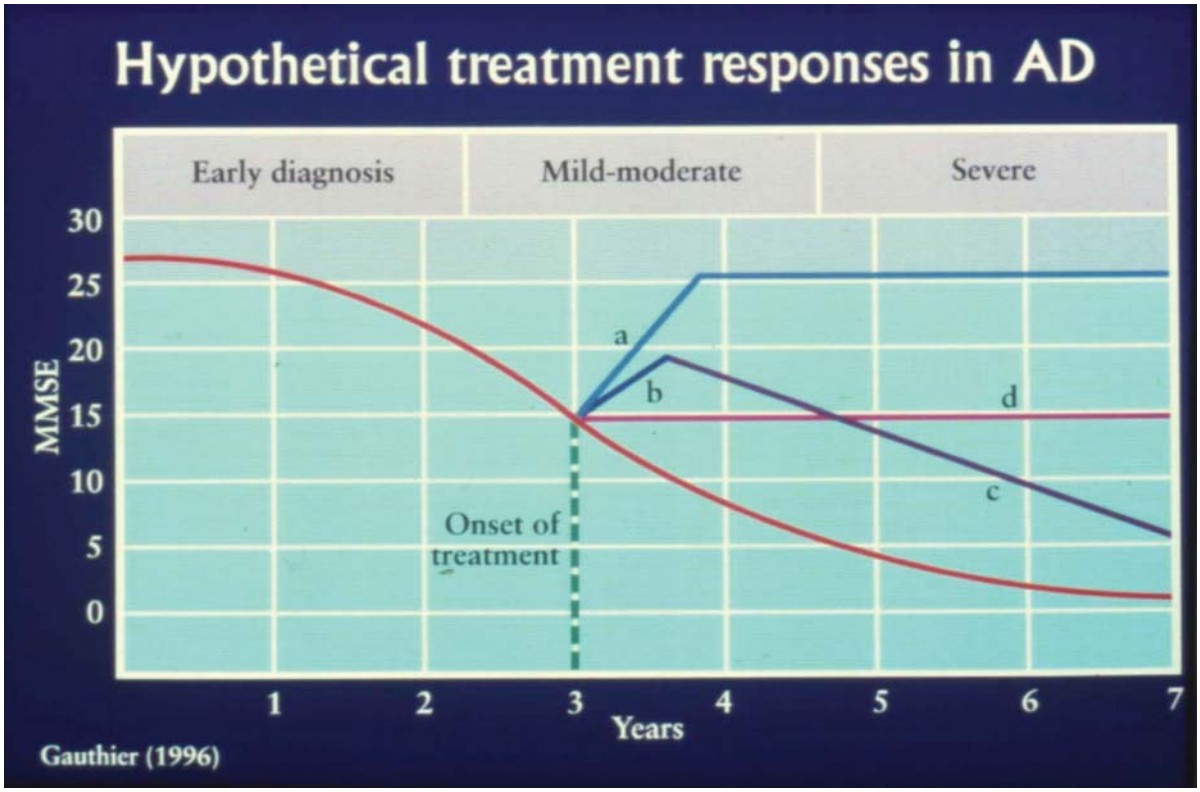
- 5mg QD for one week
- 5mg BID for one week
- 10mg + 5mg for one week
- 10mg BID

SIDE EFFETS OF MEMANTINE

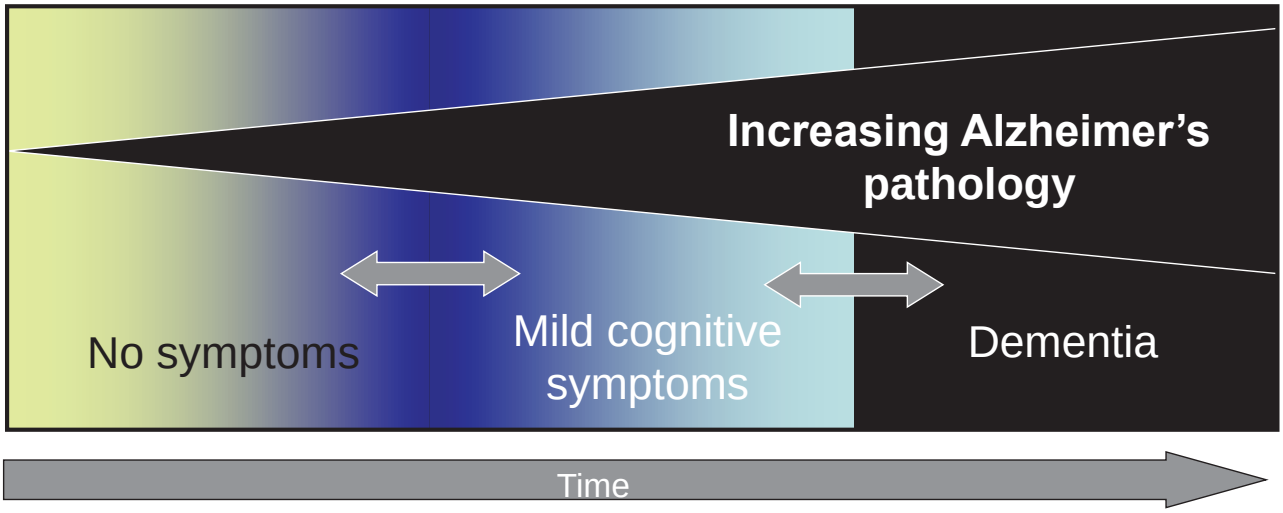
- Excreted by the kidneys
- Confusion, agitation (may be related to dose)
- Constipation
- Visual hallunications
- Increased appetite and weight

INDICATIONS FOR MEMANTINE IN COMBINAISON WITH A CI

- Clinical decline despite a well tolerated therapeutic dose of a CI, at least for the month of titration of memantine

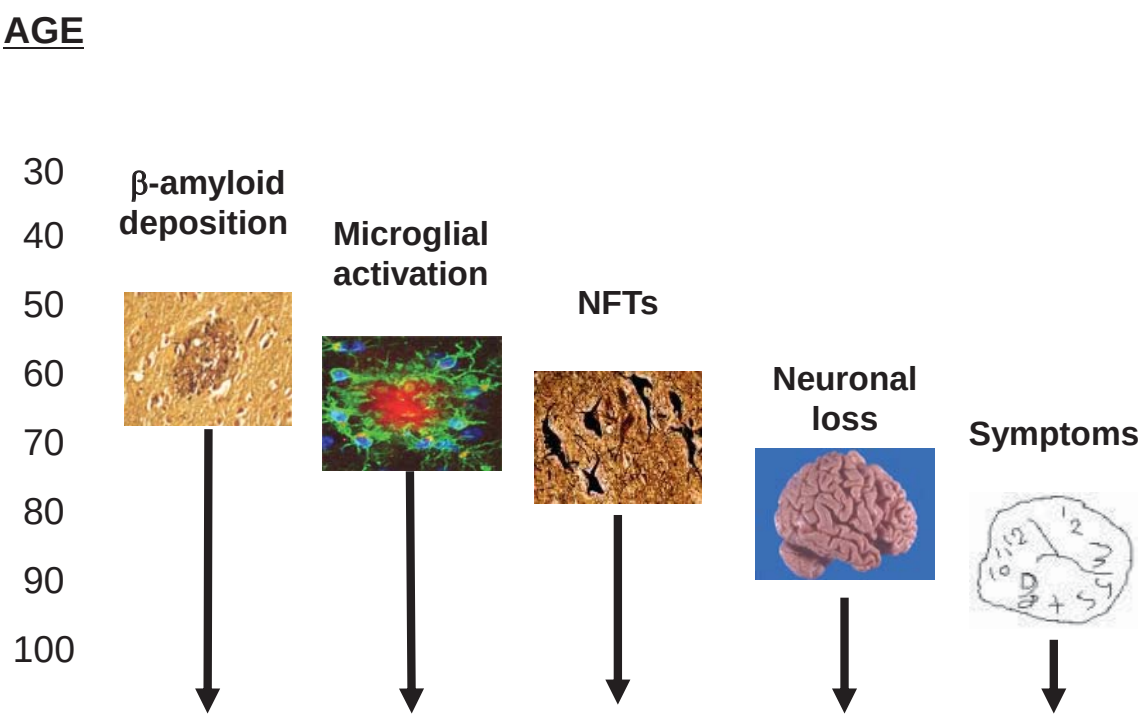


Alzheimer's disease exists on a spectrum from minimal symptoms to dementia



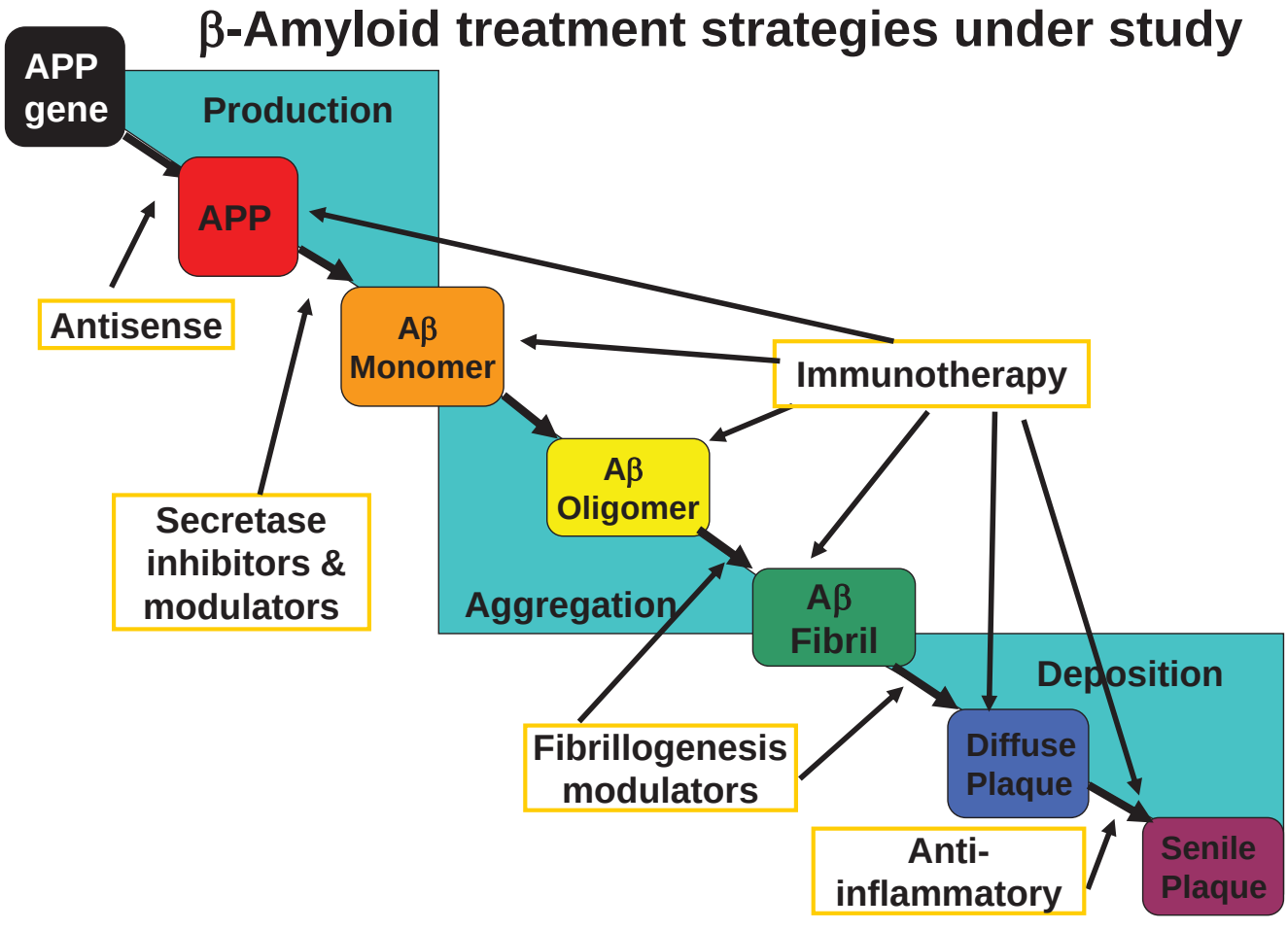
- Increasingly severe phenotype
- Biomarkers assist in identifying the underlying pathology
- Biomarker changes may precede clinically detectable changes

PATHOLOGIES ASSOCIATED WITH AD

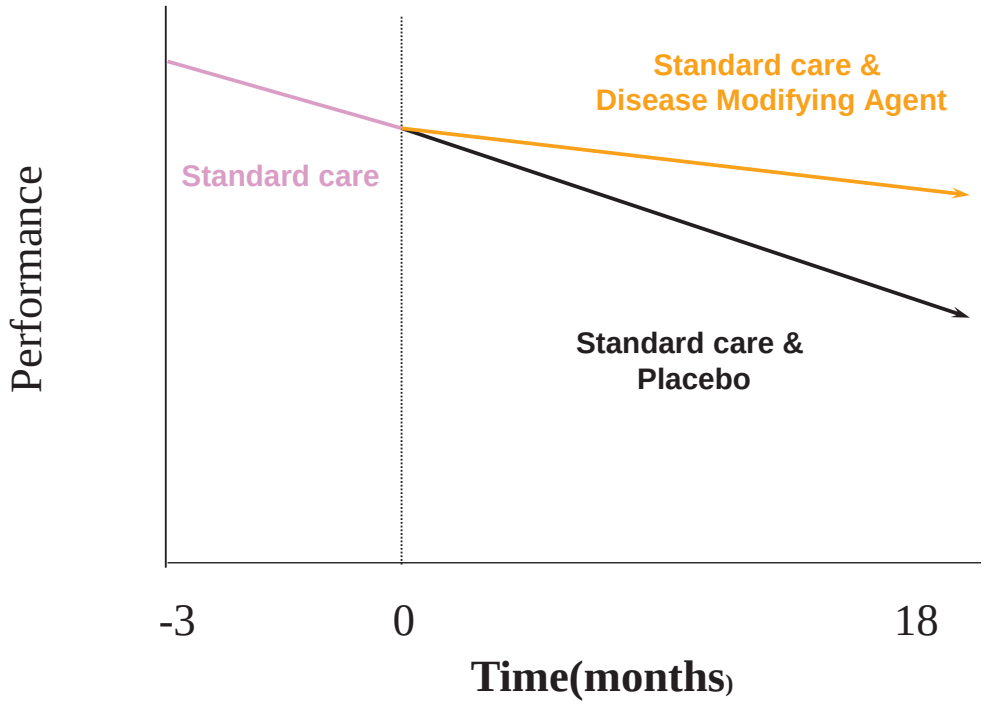


TESTABLE HYPOTHESIS

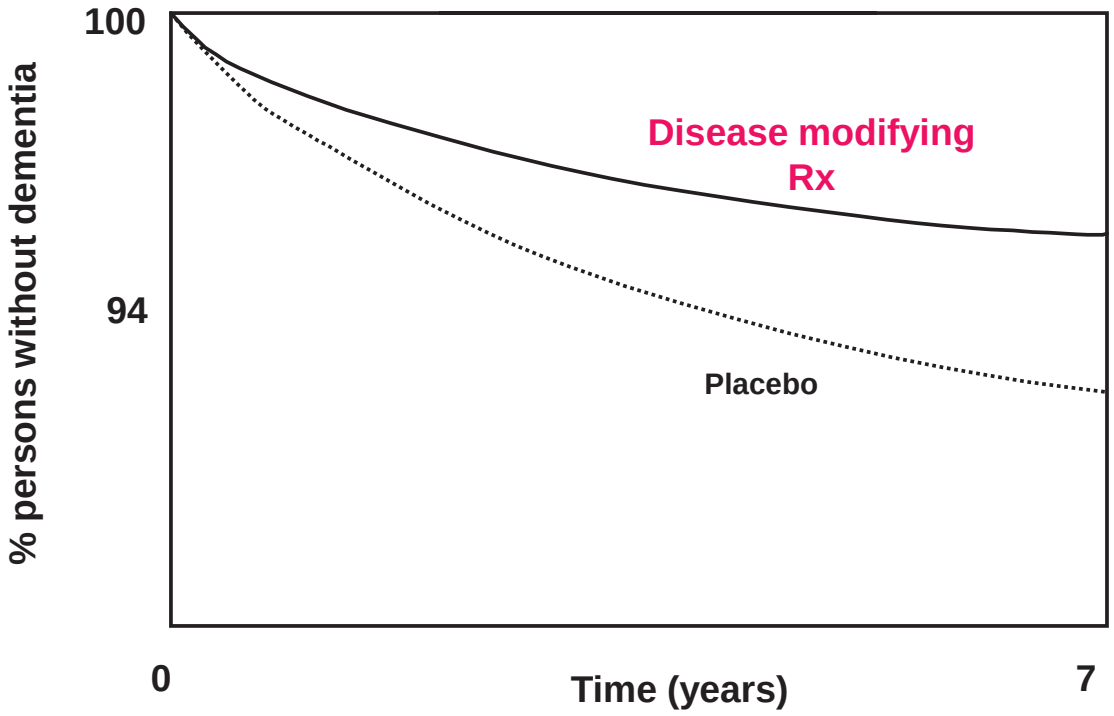
- Beta-amyloid deposition
- Tau hyperphosphorylation
- Excessive brain inflammation
- Insufficient brain plasticity



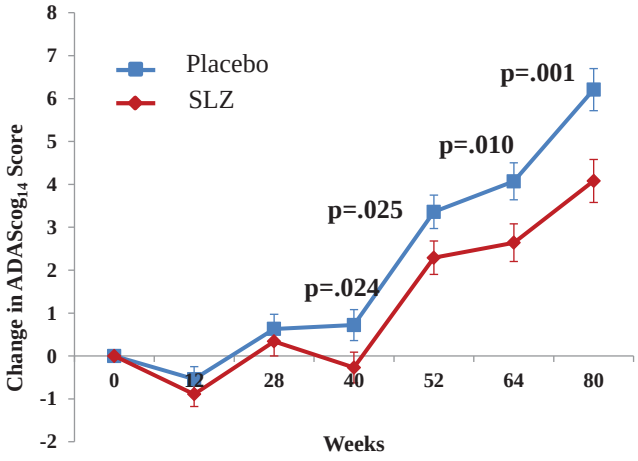
Add On Design in persons with AD

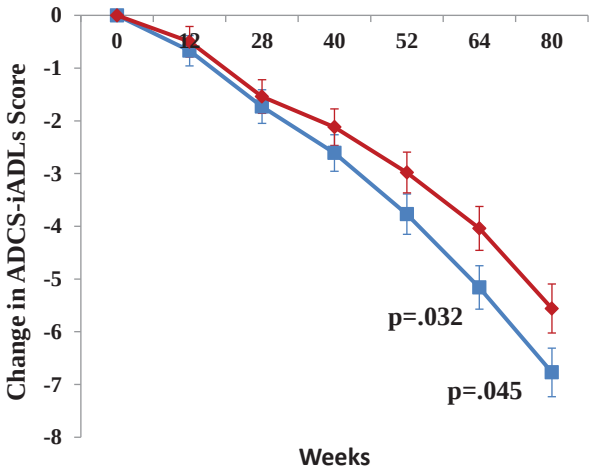


Survival design from CN to DEMENTIA



Pooled Mild AD Patients: EXP1 + EXP2





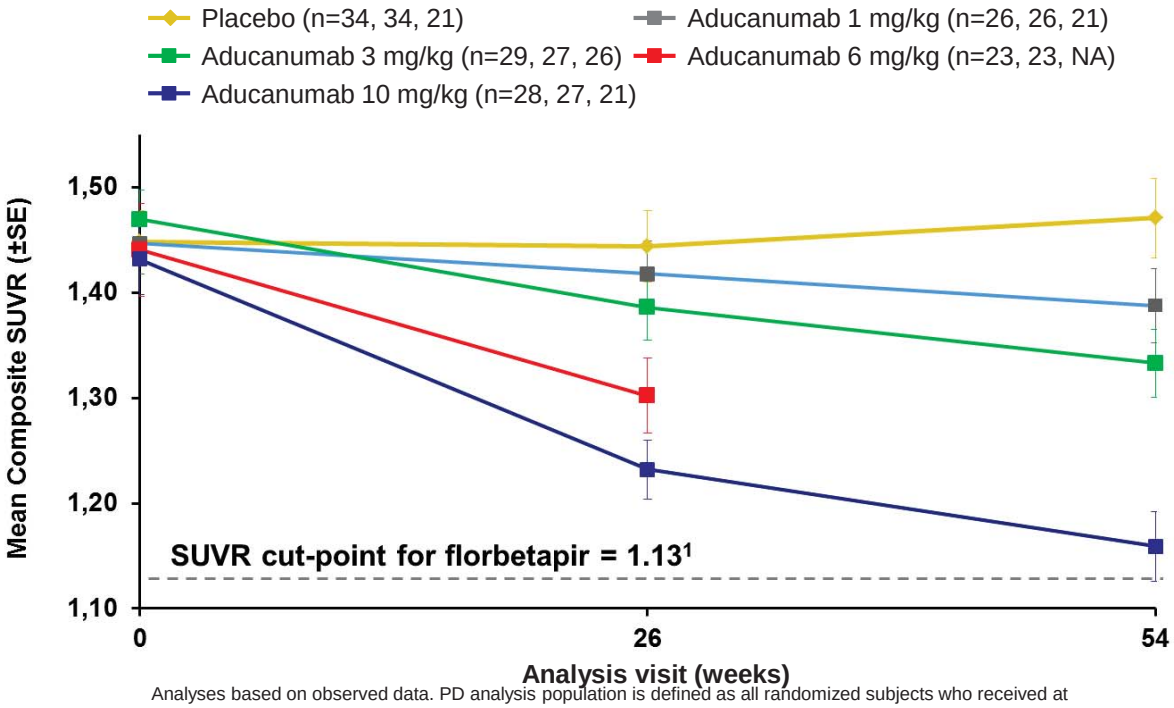
ADAS-Cog$_{14}$: 34% slowing in cognitive decline at Week 80

ADCS-iADLs: 18% slowing in functional decline at Week 80

Negative Phase III Amyloid Study

- Solanezumab, in mild AD (still tested in familial early-onset AD, asymptomatic E4/4): is the dose to low, or given to late?

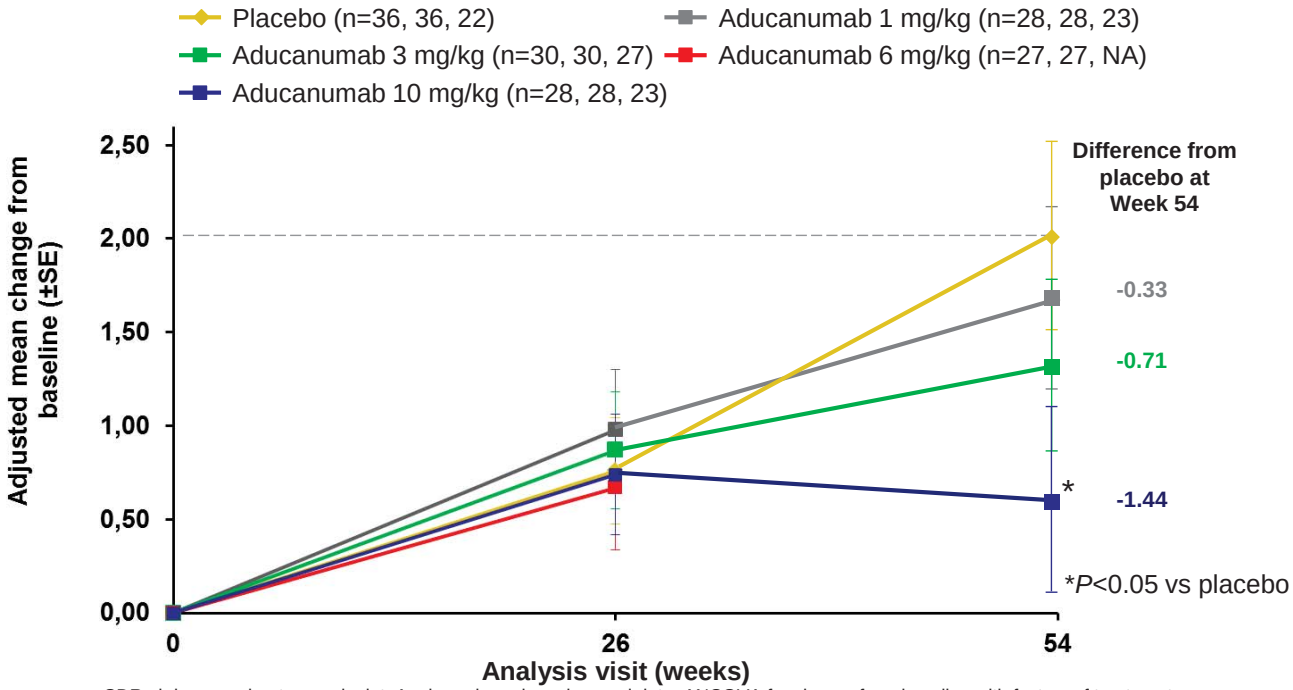
Amyloid Plaque Reduction with Aducanumab



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

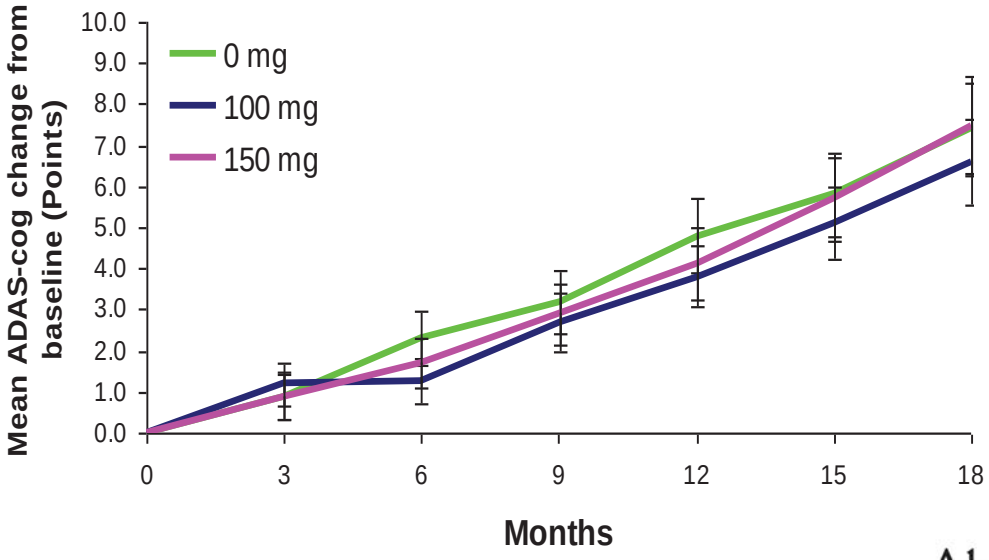


CDR-sb is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-sb. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study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

New look at old drugs - 1

- Tramiprosate was tested in mild to moderate AD: reanalysis showed a potential disease stabilization effect in E4/4 homozygous patients

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

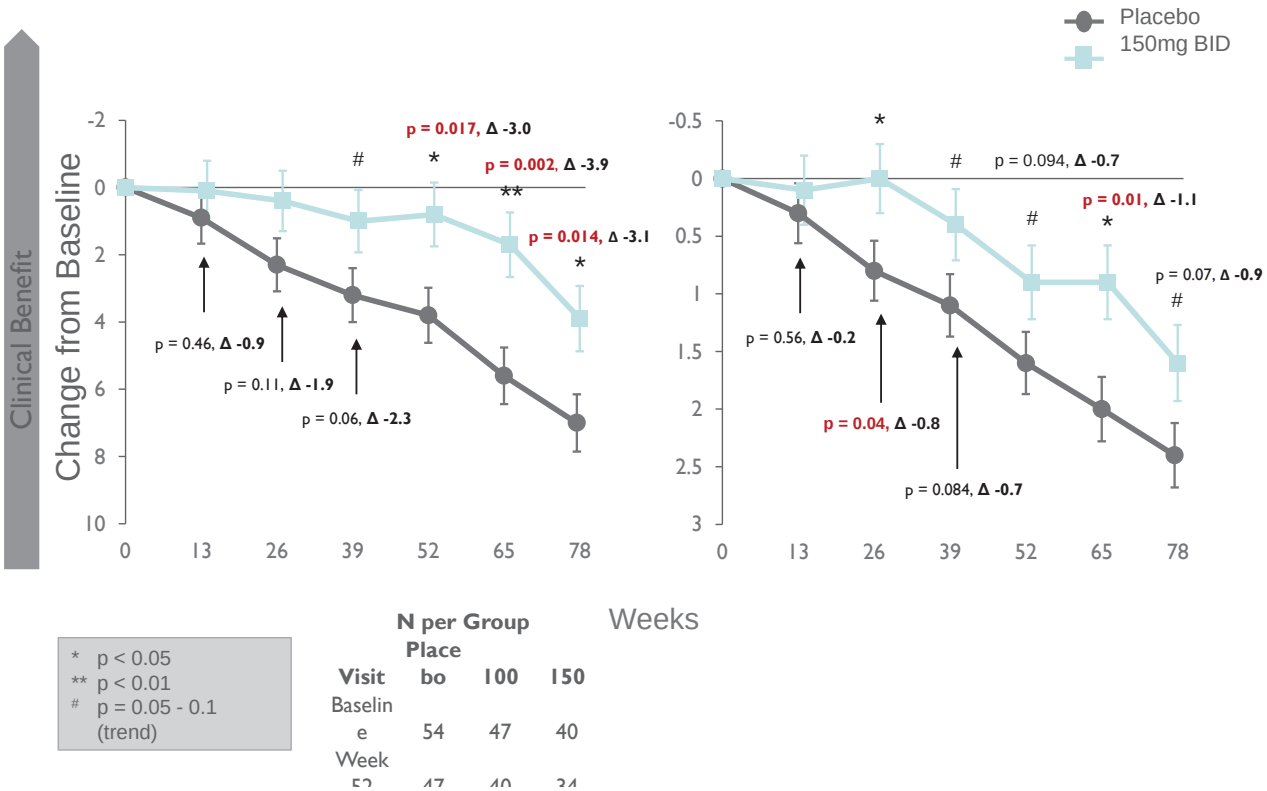


*Arithmetic mean +/- 95% CI

Alphase III Study

Effects in Mild to Moderate AD E4/4

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

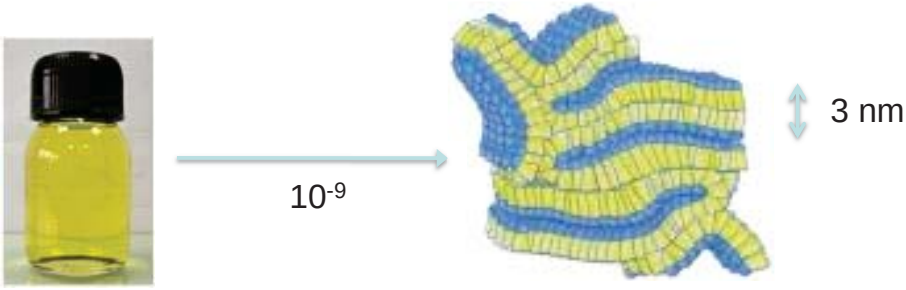


* p < 0.05
** p < 0.01
\# p = 0.05 - 0.1 (trend)

N per Group	Placebo	100	150
Visit			
Baseline	54	47	40
Week 52	47	40	34

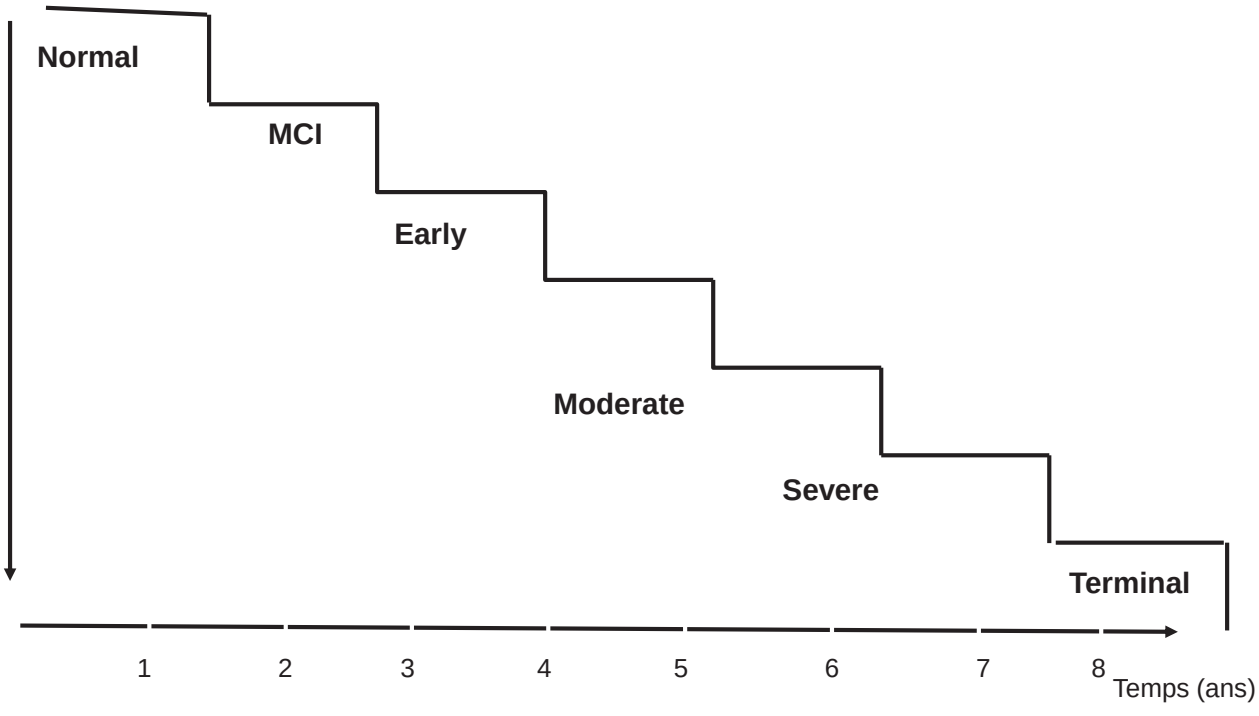
New look at old drugs - 2

- 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

NATURAL HISTORY OF AD AND CURRENT Rx



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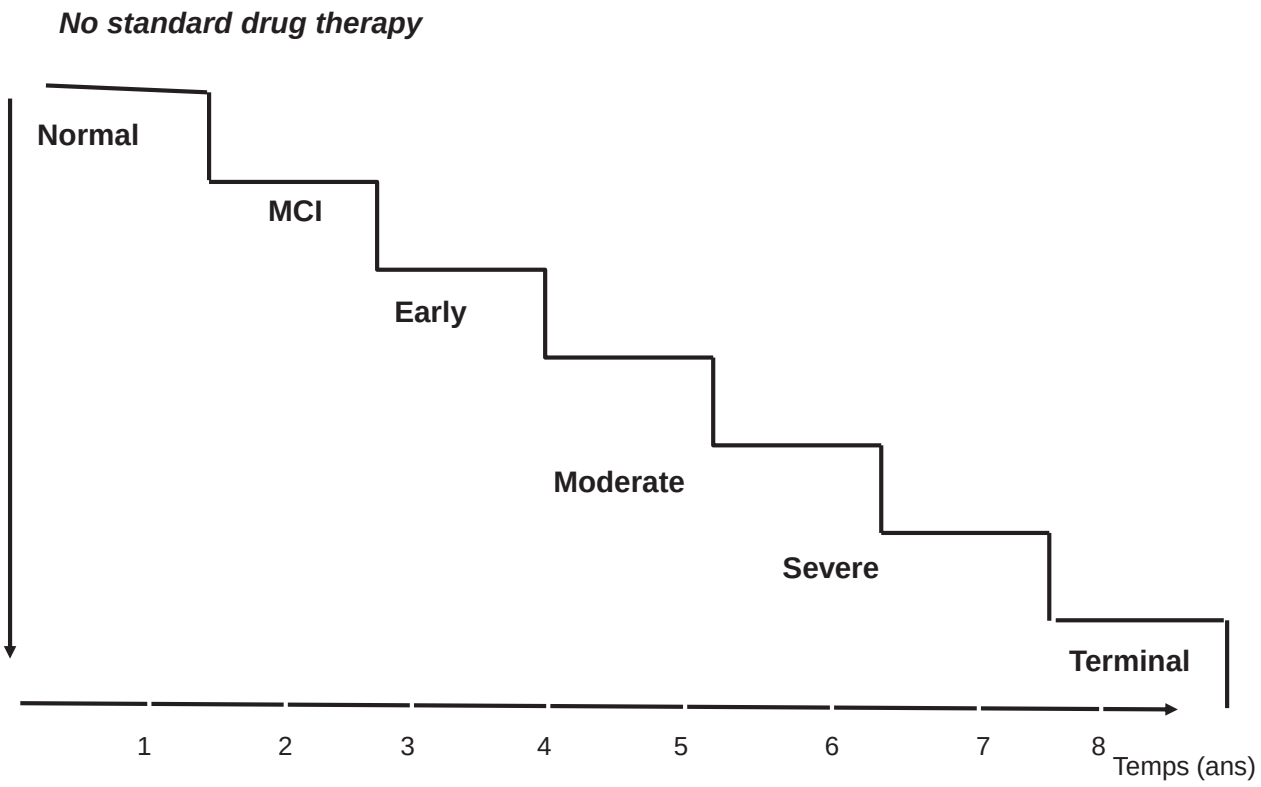

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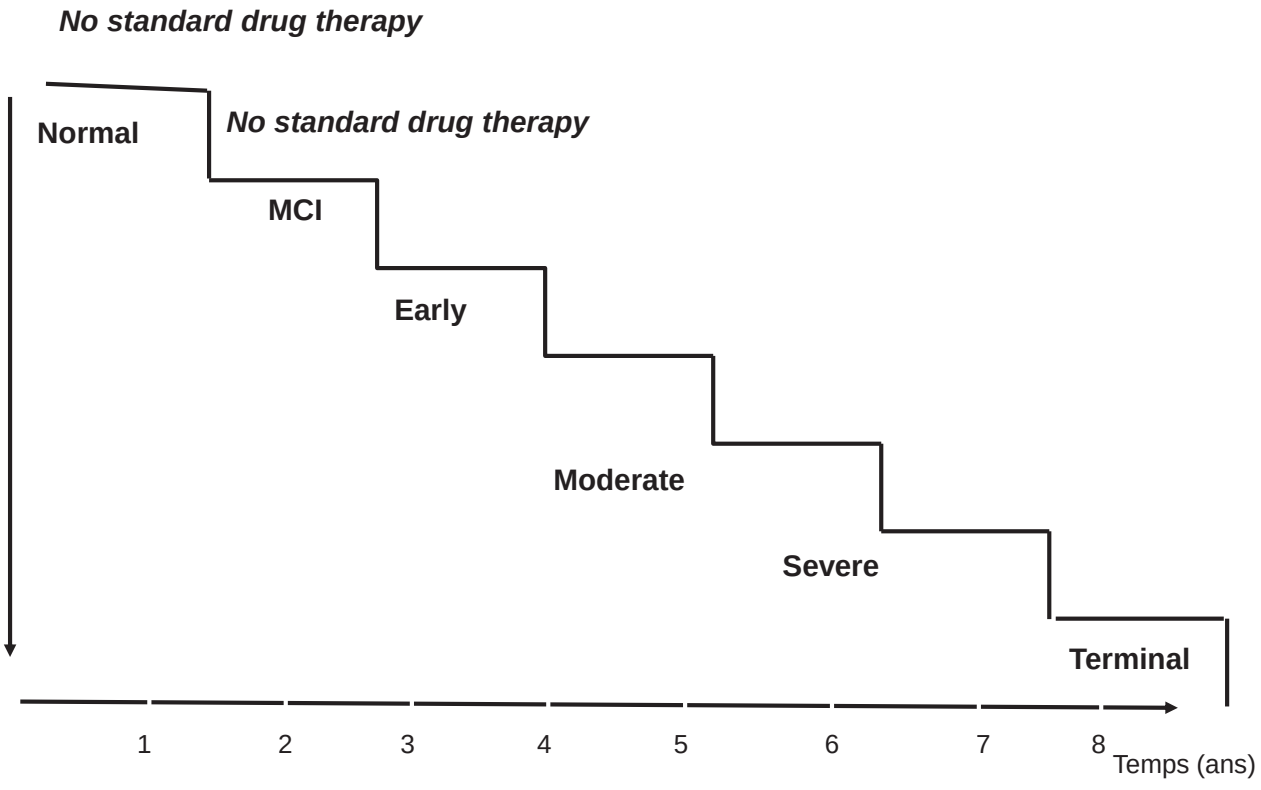

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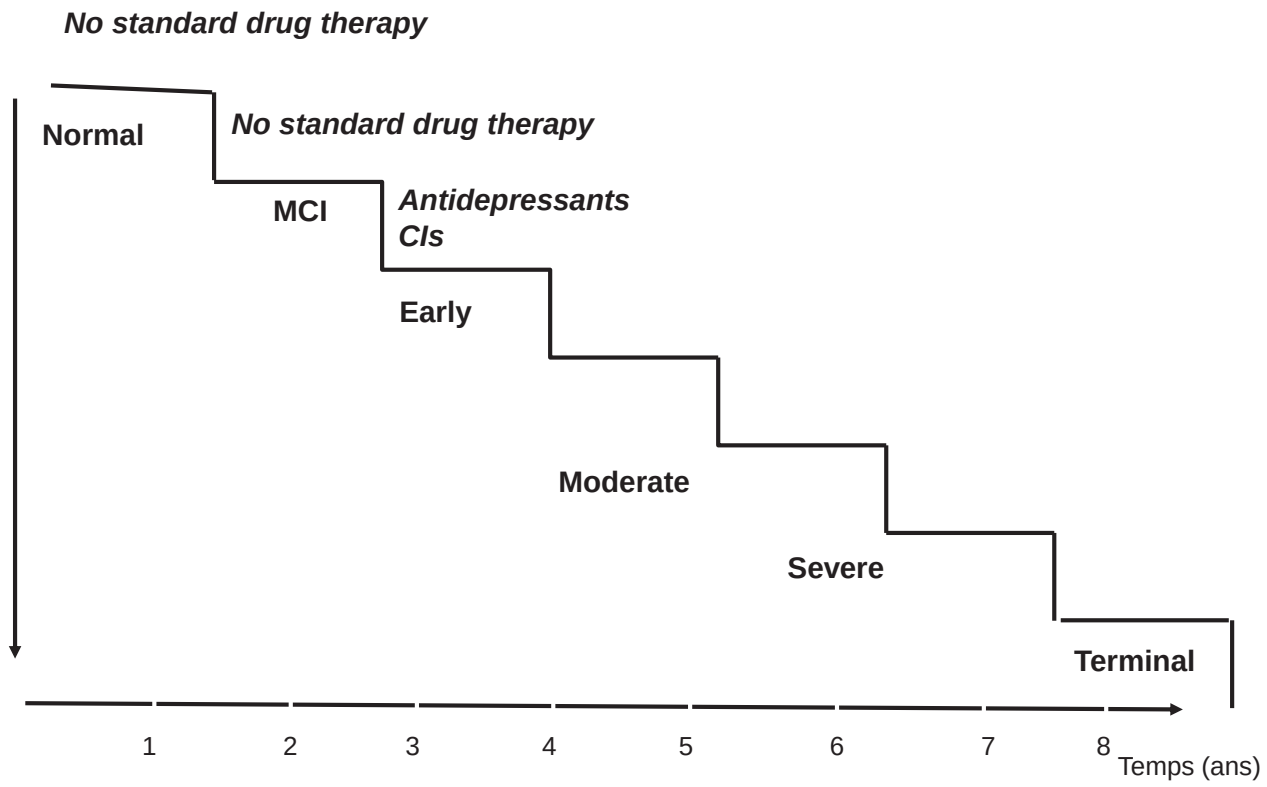
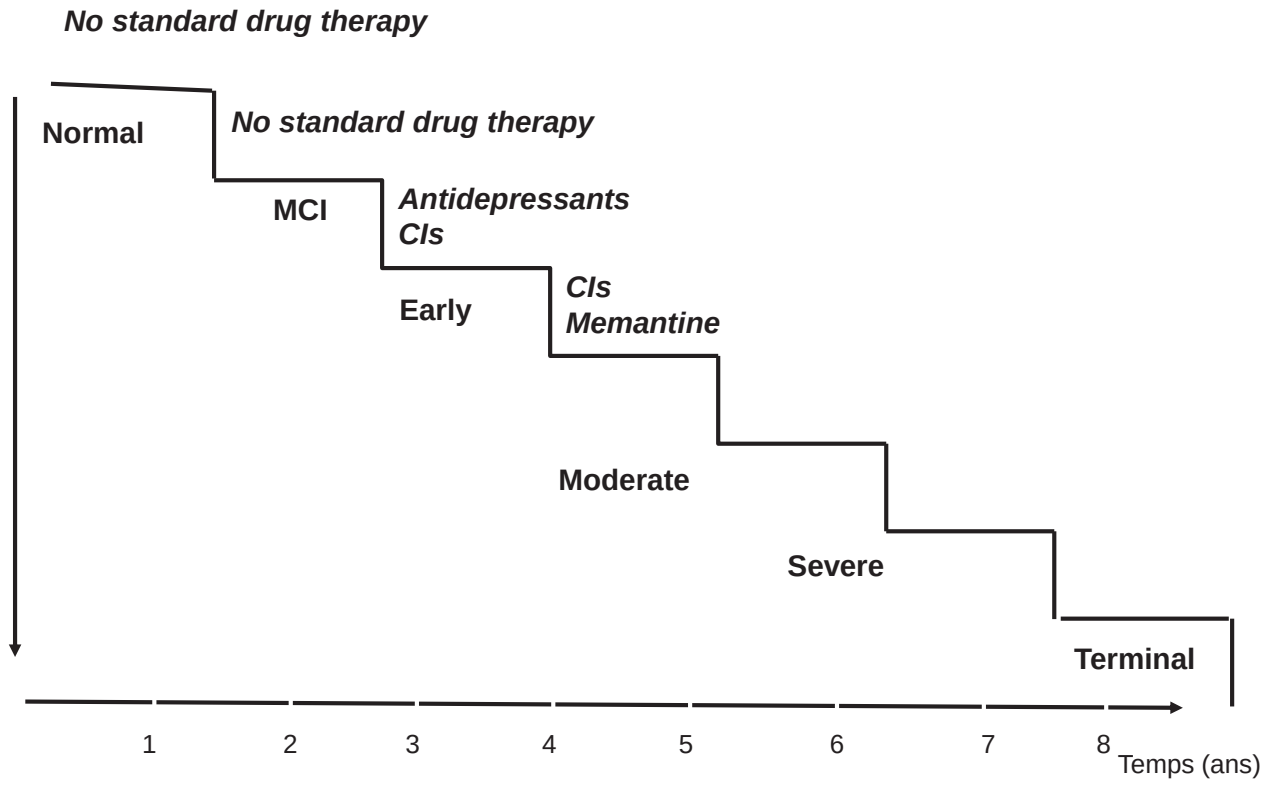
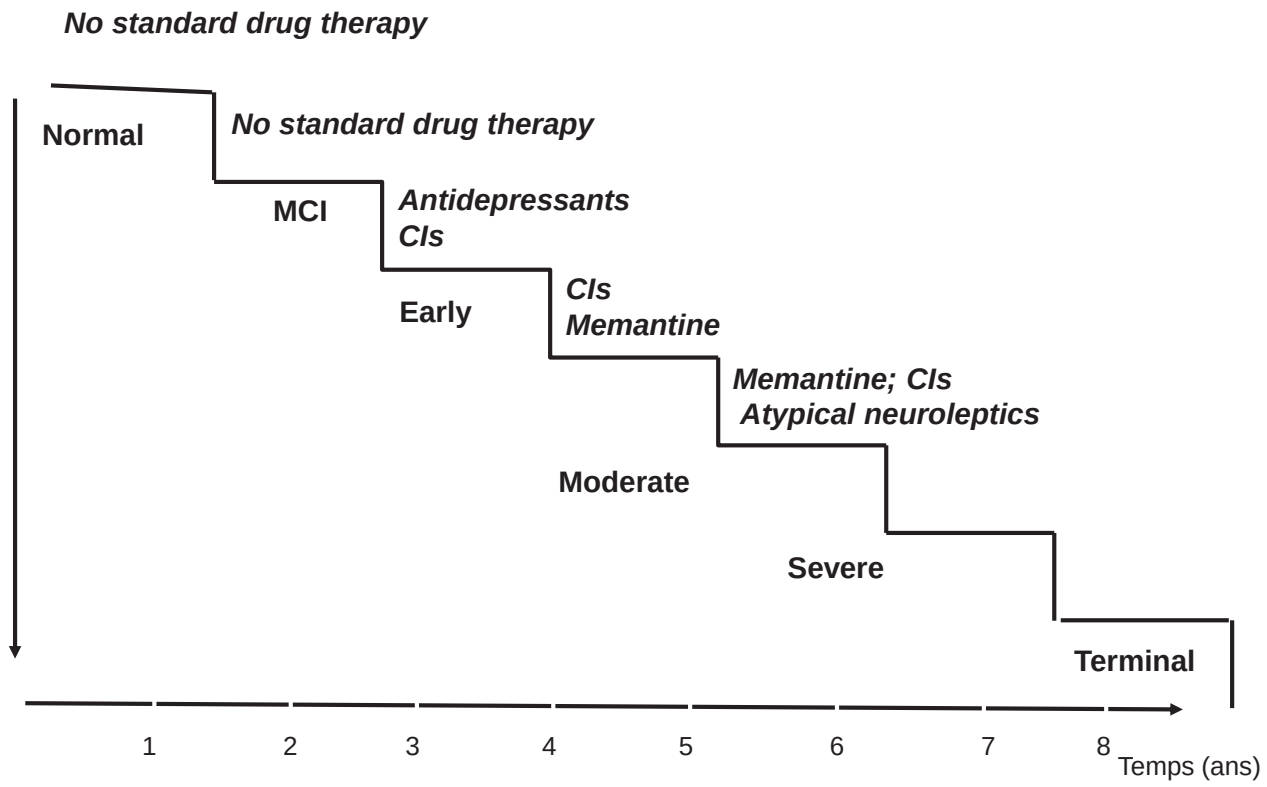


NATURAL HISTORY OF AD AND CURRENT Rx



NATURAL HISTORY OF AD AND CURRENT Rx



NATURAL HISTORY OF AD AND CURRENT Rx