Alzheimer's Treatment

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Alzheimer's Treatment

- Introduction
- Nonpharmacologic / Pharmacologic Treatment
- Cholinesterase Inhibitors
- Memantine
- Immunization
- Antioxidants , HRT, Ginkgo biloba
- Dimebon
- New Anti Amyloid Agent, BAN 2401

Introduction

- Alzheimer's disease is the most common neurodegenerative disorder.
- Aging is amongst the major risk factors for the disease.
- Alzheimer's disease progressively impairs cognitive abilities and behavior, leading to gradual functional decline

Update on Dementia therapy

Basic principles:

- Make the correct diagnosis (be familiar with the different types of dementia)
- Look for reversible causes ! (depression, metabolic, drugs, etc..)
- Dementia specific therapy
- Symptomatic and supportive care (patients and caregiver)

Remember to do !

- Comprehensive geriatric assessment.
- Look after behavioral issues.
- Management of medical problems are more complex and needs careful analysis.

Remember !

- Decreased ability to make decisions.
- Adherence to treatment plans.
- Report adverse effects of therapy.
- Close discussion with the patient's caregiver is essential.
- Patients with advanced stages of dementia appear to have diminished survival when faced with acute illnesses .

Goals of Therapy

- Holistic approach
- Promote function
- Maintain independence
- Improve quality of life
- Decrease caregiver burden

Alzheimer's Treatment

Nonpharmacologic

Pharmacologic

Nonpharmacologic Treatment

- Cognitive Training
- Supportive individual and group therapy
- Physical and mental activity
- Family and caregiver education and support
- Attention to safety:

  Needs for supervision, wandering, driving etc.

Nonpharmacologic Treatment

- Environmental modification
  - Supportive strategies such as clocks, calendars, to-do list, visual clues, simple and compassionate communication style
  - Structure activities to match patient abilities

Nonpharmacologic Treatment

- Behavior modifications, scheduled toileting, & promoted toileting for UI.
- Graded assistance (as little help as possible to perform ADLs, practice, & positive reinforcement to improve independence)

Nonpharmacologic Treatment

- Use orienting stimuli (clocks, calendar, radio)
- Provide adequate socialization
- Use eyeglasses & hearing aids appropriately
- Mobilize patient ASAP
- Ensure adequate intake of nutrition & fluids, by hand feeding if necessary
- Educate & support the patient, Caregiver, & family
- Cognitive Rehabilitation
- Physical & Mental Activity

Sleep Hygiene

- Establish a stable routine for going to bed and awakening
- Pay attention to noise, light, and temperature
- Increase daytime activity and light exercise
- Reduce or eliminate caffeine, nicotine, alcohol
- Reduce evening fluid consumption to minimize nocturia
- Give activating medications early in the day if patient unable to eliminate
- Control nighttime pain
- Limit daytime napping to brief periods of 20 to 30 minutes
- Use relaxation, stress management, and breathing techniques to promote natural sleep

Caregiver Support

- Ensure that the caregiver has adequate respite.
- Educate caregivers about practical aspects of dementia care and about behavioral disturbances.
  - Advice family about sources of care & support, financial, & legal issues.
  - Intensive education & support of caregivers may delay institutionalization.

Alzheimer's Treatment

- **No cure therapy.**
- **Mainly Symptomatic therapy & supportive care.**
- **Available therapies have modest effect.**

Alzheimer's Treatment

Cholinesterase inhibitors (FDA approved)

- Donepezil
- Rivastigmine
- Galantamine.

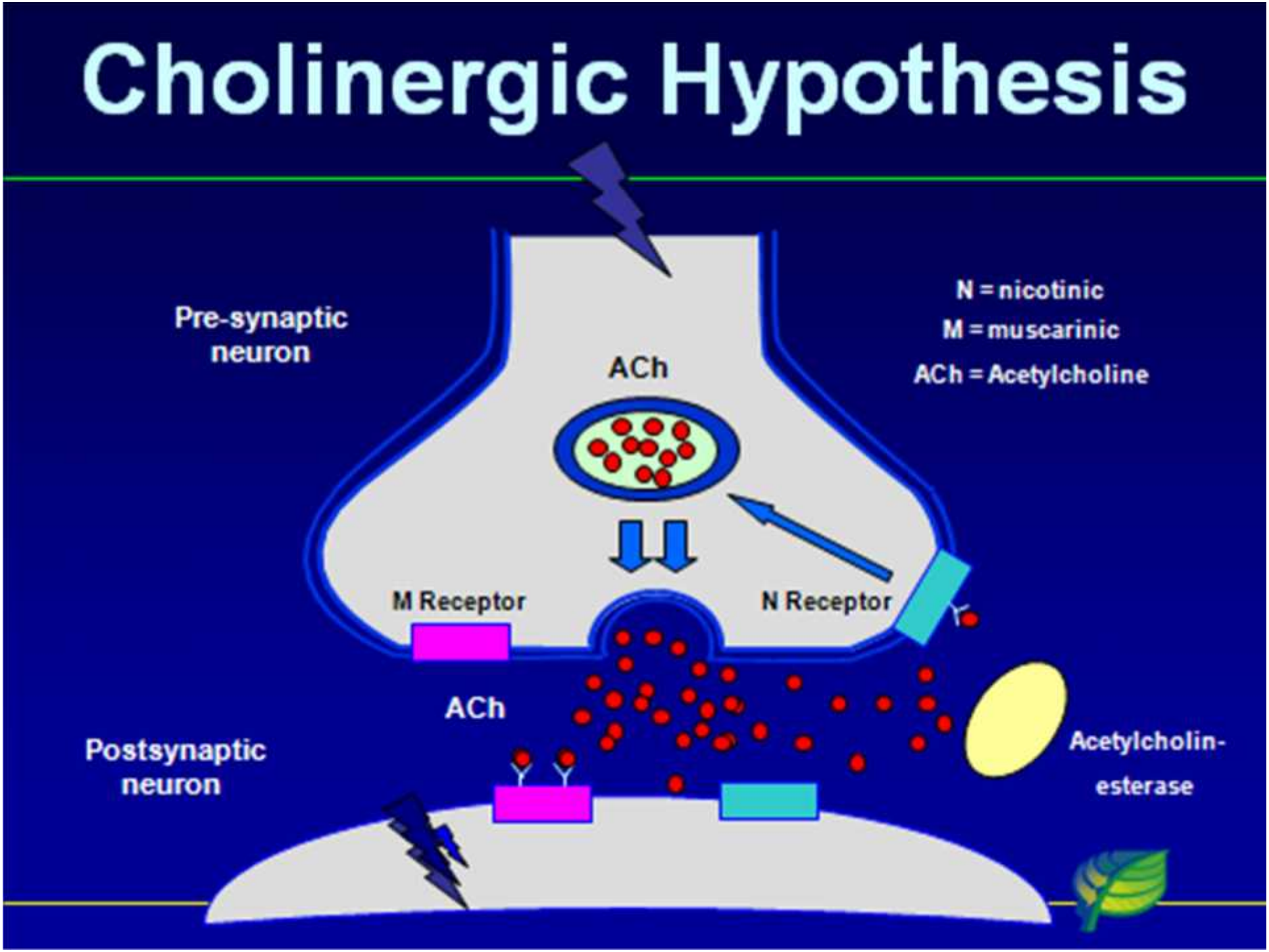
Alzheimer's Treatment

Cholinesterase inhibitors

- In AD, there is reduced cerebral production of choline acetyl transferase ⟶ decrease in acetylcholine synthesis and impaired cortical cholinergic function.

- cholinesterase inhibitors increase cholinergic transmission by inhibiting cholinesterase at the synaptic cleft.

Cholinergic Hypothesis



Alzheimer's Treatment

Donepezil

- Has relatively little peripheral anticholinesterase activity
- Generally well tolerated & Easy dosing(once a day).
- Mild to moderate AD and severe cases & VD
- Modest effect on cognition.
- Reduction in functional decline.
- Can be used for longer time.

- Neurology 1998 Jan;50(1):136-45 - Arch Neurol 2001 Mar;58(3):427-33.
- Lancet 2004 Jun 26;363(9427):2105-15..Neurology. 2007 Jul 31;69(5):459-69..
- Neurology 2001 Aug 28;57(4):613-20. Lancet. 2006 Apr 1;367(9516):1057-65.

Donepezil

Rogers and Friedhoff (1998); Rogers *et al* (2000)

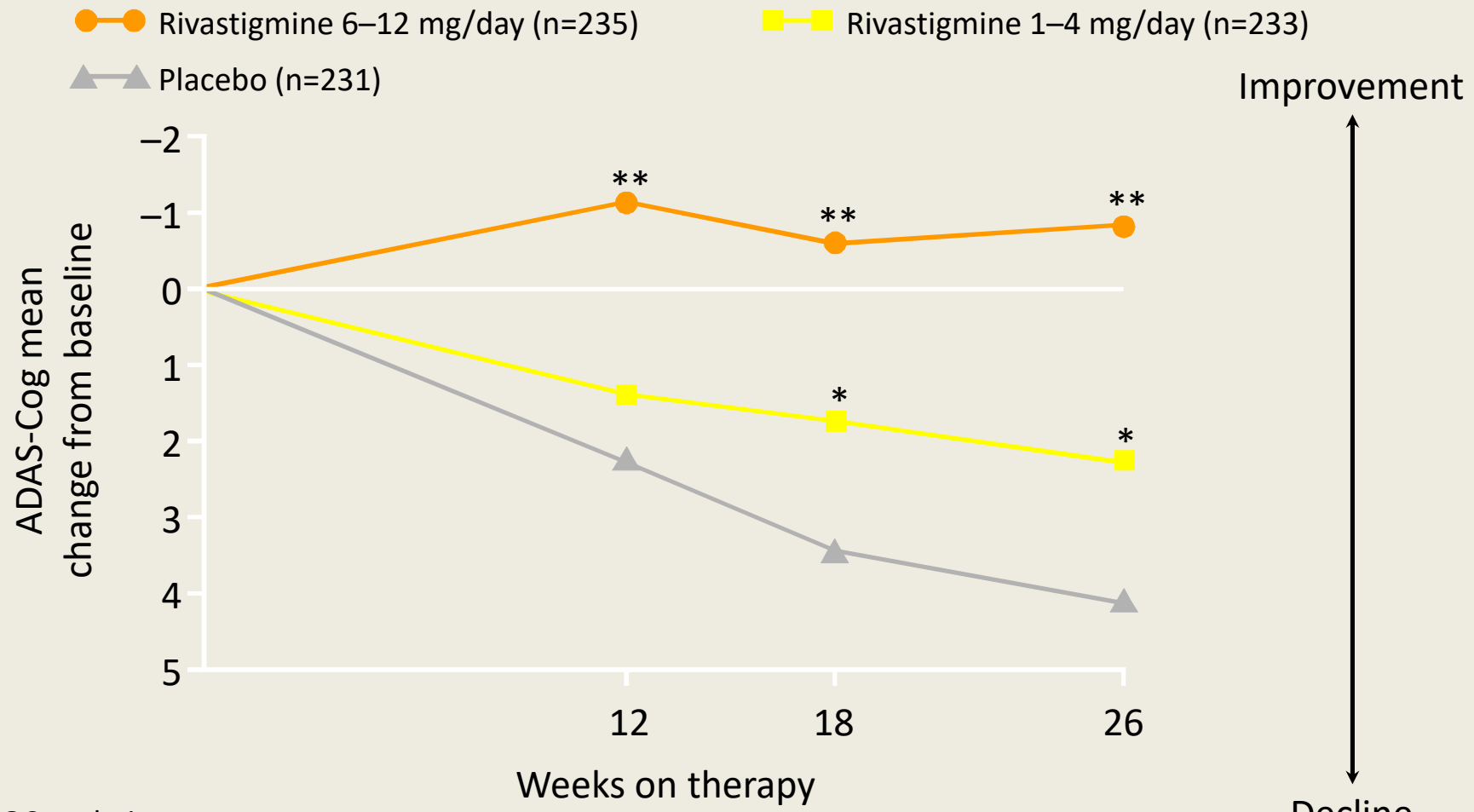
Alzheimer's Treatment

Rivastigmine

- Mild to moderate AD.
- Side effects (nausea, vomiting).
- Take it with meals.
- Start with 1.5 mg twice daily and titrate slowly every 2-4 wks to 6 mg twice daily.
- Modest effect on cognition.
- Improves behavior and function.

- Cochrane Database Syst Rev 2000;(4):CD001191
- BMJ 1999 Mar 6;318(7184):633-8

Effects of rivastigmine on cognition: ADAS-Cog changes from baseline



OC analysis
*p<0.05; **p<0.001 vs placebo

Corey-Bloom et al., 1998

Alzheimer's Treatment

Rivastigmine

- Transdermal patch formulation has been approved by the FDA.
- Less GI side effects.

- Int J Geriatr Psychiatry. 2007 May;22(5):456-67.
- Neurology. 2007 Jul 24;69(4 Suppl 1):S14-22

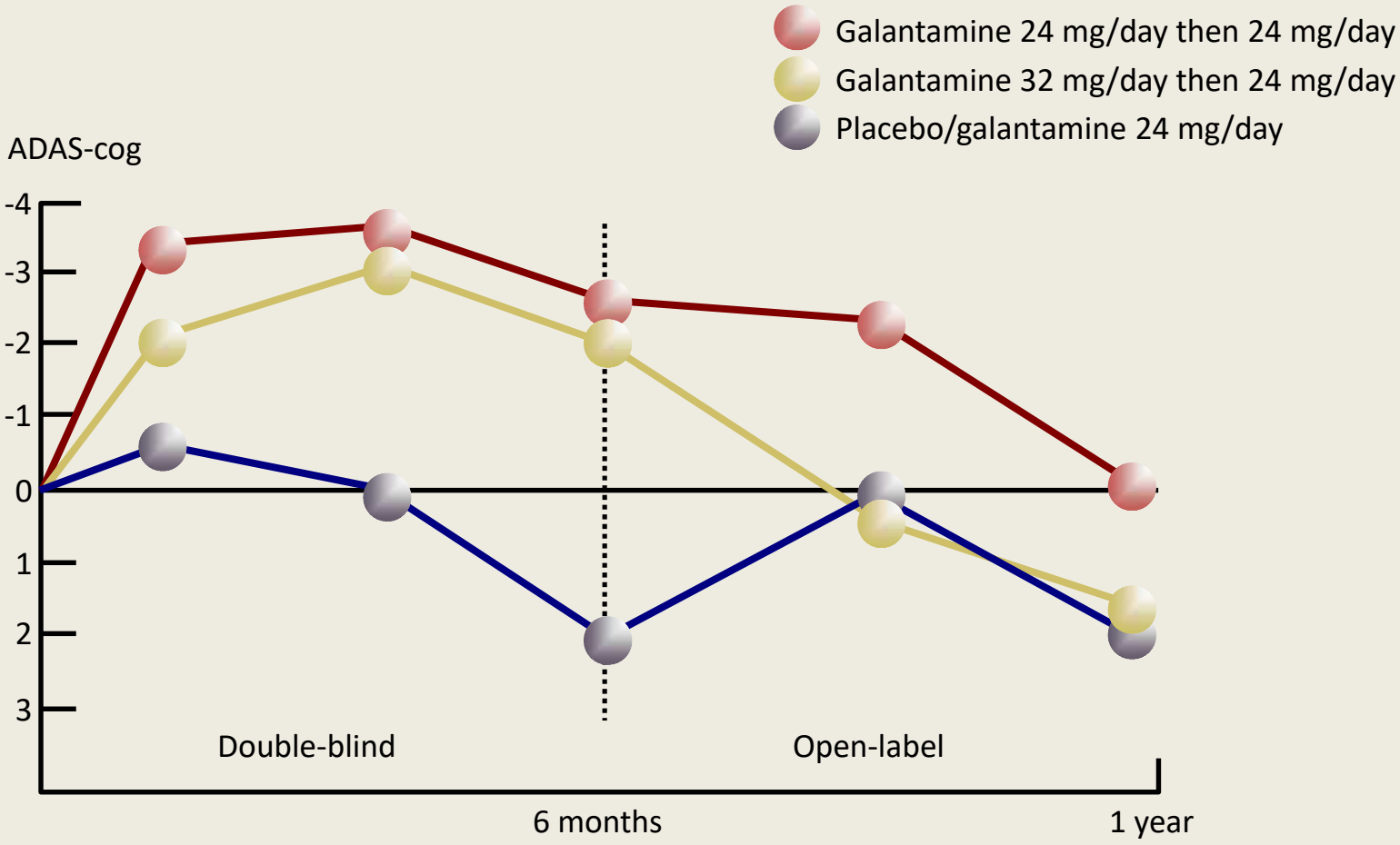
Alzheimer's Treatment

- **Galantamine**
- GI side effects.

  4 mg twice daily increase gradually every 4 weeks to 12 mg twice daily.
- Mild to moderate and moderate to severe dementia.
- Can be used in Vascular dementia.
- Slow the decline in both the disease and ADLS.

- Cochrane Database Syst Rev 2001;(1):CD001747
- Arch Neurol 2004 Feb;61(2):252-6.
- J Am Geriatr Soc 2004 Jul;52(7):1070-6.
- Lancet Neurol. 2009 Jan;8(1):39-47. Epub 2008 Nov 29.
- Stroke 2004 Apr;35(4):1010-7. Epub 2004 Mar 4.

Galantamine



Raskind *et al* (2000)

Alzheimer's Treatment

Mixed Dementia

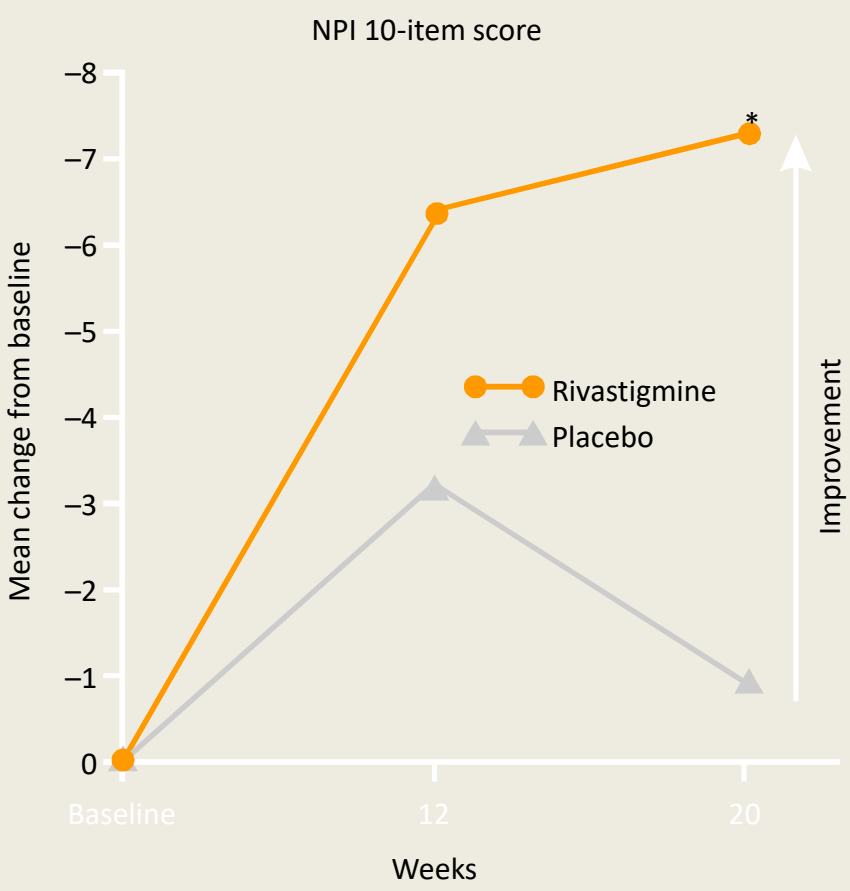
- Rivastigmine.
- Galantamine.

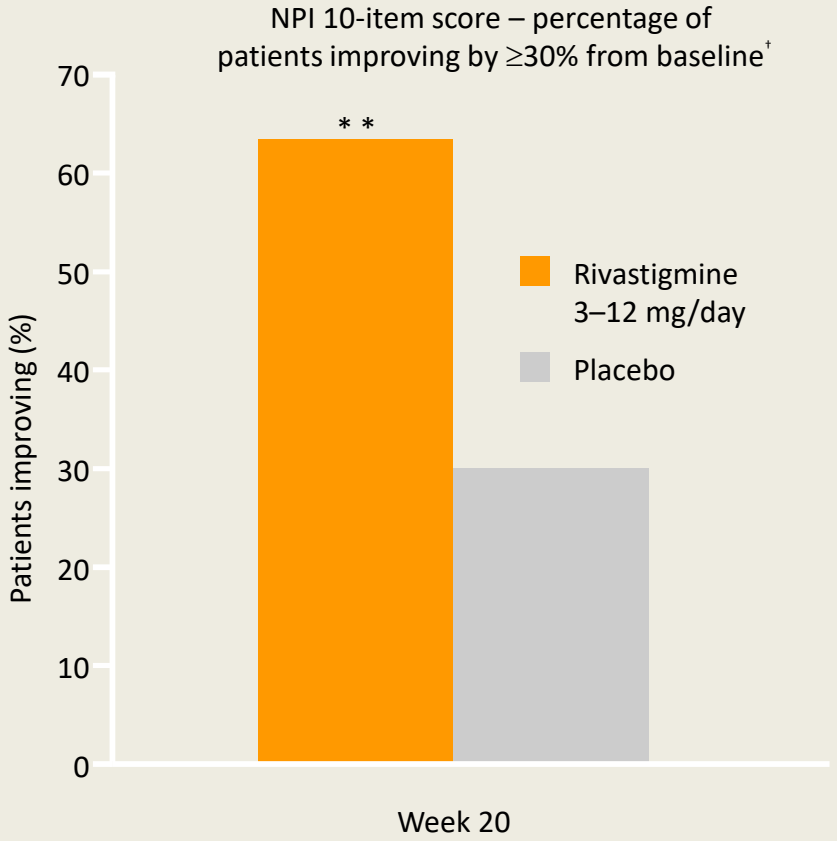
- Lancet 2002 Apr 13;359(9314):1283-90.
- Eur J Neurol 2000 Mar;7(2):159-69.

Dementia with Lewy bodies

- Patients who have dementia with DLB can have marked improvements in cognition as well as improvements in behavioral symptoms and hallucination.
- Rivastigmine
- Lancet 2000 Dec 16;356(9247):2031-6.

Effects of rivastigmine on behavioural disturbances in DLB





OC analysis
*p=0.005 vs placebo; **p=0.001 vs placebo
†Responder definition recommended by NPI author (J Cummings)

McKeith et al., 2000; Data on file, Novartis AG, 2000

Parkinson disease dementia

- Donepezil.
- Rivastigmine.
- Mild benefits.

- N Engl J Med 2004 Dec 9;351(24):2509-18.
- Neurology. 2005 Nov 22;65(10):1654-6.
- J Neurol Neurosurg Psychiatry 2005 Jul;76(7):934-9.
- J Neurol Neurosurg Psychiatry 2002 Jun;72(6):708-12.

Frontotemporal Dementia

- **Galantamine** may be effective in PPA.
- No effects on behavior.
- **Rivastigmine** has some benefits on behavior.

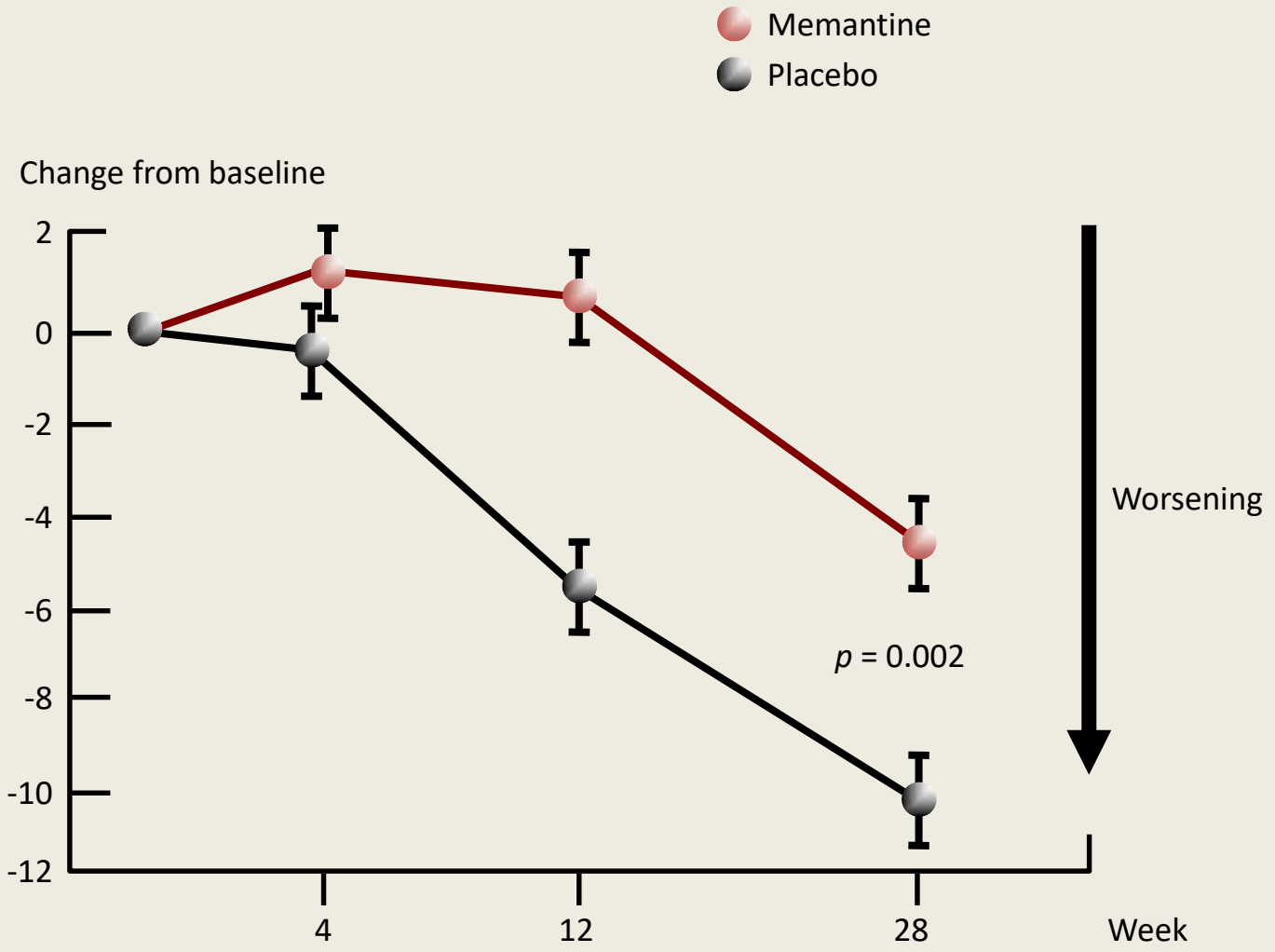
- Dement Geriatr Cogn Disord. 2008;25(2):178-85. Epub 2008 Jan 14.
- Drugs Aging. 2004;21(14):931-7

MEMANTINE

- N-methyl-D-aspartate (NMDA) receptor antagonist.
- FDA approved in October 2003 for moderate to severe AD.
- Modest effect on cognition.
- Improvement in quality of life not proven.
- Used in combination with AchEI or alone.
- Delusions and hallucinations in dementia with Lewy bodies: worsening with memantine.

Ann Intern Med. 2008 Mar 4;148(5):379-97
Neurology 2005 Aug 9;65(3):481-2.

Severe Impairment Battery (SIB)



Memantine plus Cholinesterase Inhibitors

- Memantine plus Donepezil in moderate to severe AD
- Improvement in Cognition, ADLs and Behavior.

- JAMA 2004 Jan 21;291(3):317-24

OTHER COGNITIVE ENHANCERS

- **Vitamin E** (α–tocopherol) may lower rate of functional decline, but no evidence of cognitive improvement in AD
  - ➢ The clinical efficacy and safety of vitamin E has yet to be fully established
- **Selegiline** may lower rate of functional decline, but no evidence of cognitive improvement in AD
- Neurology 2001 May 8;56(9):1154-66

Estrogen replacement

- Not recommended.
- large randomized trials have now shown that the use of hormone replacement therapy (HRT) with estrogen plus progestin or estrogen alone in women aged 65 and older who are free from dementia may increase the risk of developing dementia.

- JAMA 2003 May 28;289(20):2663-72.
- JAMA 2004 Jun 23;291(24):2947-58.
- JAMA 2004 Jun 23;291(24):2959-68

Ginkgo biloba

- A systematic review of ginkgo for cognitive impairment and dementia concluded that **ginkgo biloba**, while safe, has inconsistent and unconvincing evidence of benefit.

- Cochrane Database Syst Rev. 2007 Apr 18;(2):CD003120

Vitamin B supplementation

- High-dose B vitamin supplements does not slow cognitive decline in individuals with mild to moderate AD.
- JAMA. 2008 Oct 15;300(15):1774-83

Immunization

- Unfortunately not successful till now.
- Meningoencephalitis 18/298 patients.
- Neurology 2003 Jul 8;61(1):46-54

Dimebon (Latrepirdine)

- Nonselective antihistamine with weak cholinesterase, weak glutamatergic, and neuroprotective activity has been evaluated as a treatment for AD in a randomized, placebo-controlled, double-blind study of 183 patients with mild to moderate AD.

Dimebon

- Impressive result (phase II trial)
- Significant Improvement in cognition as compared with placebo.

- Lancet. 2008 Jul 19;372(9634):207-15.

Dimebon

- **The CONNECTION trial** has been a Phase III study looking at the effects of Dimebon in about 600 patients with mild-to-moderate AD in North America, Europe, and South America
- Disappointing results.

Finally, a Winner for Alzheimer's? Anti-amyloid Agent Shows Promise

Pauline Anderson

July 26, 2018

CHICAGO — Positive results for an anti-amyloid agent in patients with early-stage Alzheimer's disease (AD) is drawing praise, but experts are calling for caution.

Results from the new phase 2 study showed a statistically significant reduction in brain amyloid with a high dose of BAN2401 (Eisai Co. Ltd/Biogen Inc) at 18 months.

In addition, the study showed a dose-dependent, statistically significant, and clinically meaningful slower decline in cognition and function with the highest dose compared to placebo.

BAN2401

- BAN2401 is a humanized monoclonal antibody, selectively binds to amyloid beta.
- 856 patients, early stage AD, multicenter.
- Phase 2 study:
- Reduction in brain amyloid with high dose at 18 months.
- Slower decline in cognition and function.

SYMPTOM MANAGEMENT

- **Psychoactive medications**
  - Behavioral disturbances best managed nonpharmacologically, eg, reducing overstimulation, environmental modification
  - When meds are required, target symptoms should be identified, and therapy selected accordingly
- **Antidepressants**
  - Depressed mood, low appetite, insomnia, fatigue, irritability, agitation
  - A trial of high-dose citalopram demonstrated significant improvements in behaviors but also resulted in worsened cognition and QT prolongation.
  - **Caution: falls and anticholinergic effects that may worsen confusion (ie, paroxetine)**

SYMPTOM MANAGEMENT

- **1st/2nd-generation antipsychotics**
  - Limited evidence of efficacy and increased risk of all-cause mortality in dementia
  - Should be used with caution in targeting delusions, hallucinations, paranoia, and irritability — frequently attempt to taper off
- **Valproic acid and carbamazepine**
  - Possible options, but with limited evidence and increased risk of mortality
- **Benzodiazepines** and **anticholinergic medications** should be *avoided*

Remember !

- Don’t prescribe cholinesterase inhibitors for dementia without periodic assessment for perceived cognitive benefits and adverse gastrointestinal effects.

- Don’t use antipsychotics as first choice to treat behavioral and psychological symptoms of dementia.

Summary

- To date there is no cure therapy of the disease
- Nonpharmacologic intervention.
- Cholinesterase inhibitors in patients with dementia produce, on average, small improvements in measures of cognition and ADLS.
- There is some evidence of benefit of CEI for patients with vascular dementia (VaD), mixed dementia, dementia with Lewy bodies (DLB), and dementia in Parkinson disease (PD)

Summary

- In patients with moderate to advanced dementia, add MEMANTINE to a cholinesterase inhibitor, or use Memantine alone in patients who do not tolerate or benefit from a cholinesterase inhibitor.
- Patients with AD who have no significant heart disease take vitamin E 1000 IU twice daily.

Summary

- Dementia shortens life expectancy.
- Caregiver support

THANK YOU

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