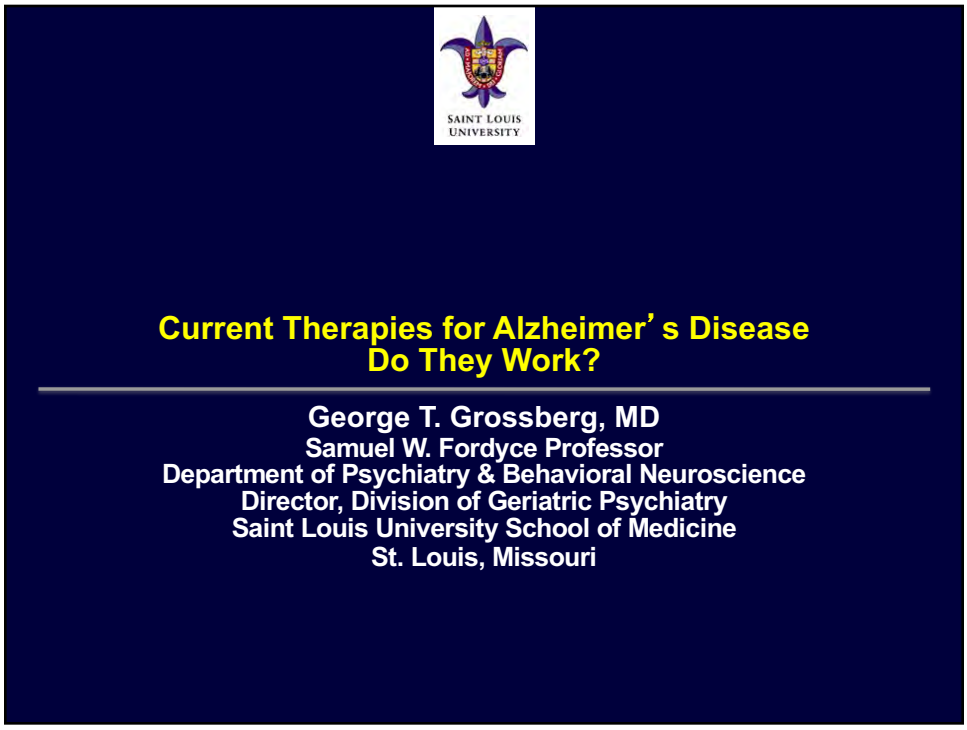
SAINT LOUIS UNIVERSITY
Current Therapies for Alzheimer's Disease
Do They Work?
George T. Grossberg, MD
Samuel W. Fordyce Professor
Department of Psychiatry & Behavioral Neuroscience
Director, Division of Geriatric Psychiatry
Saint Louis University School of Medicine
St. Louis, Missouri

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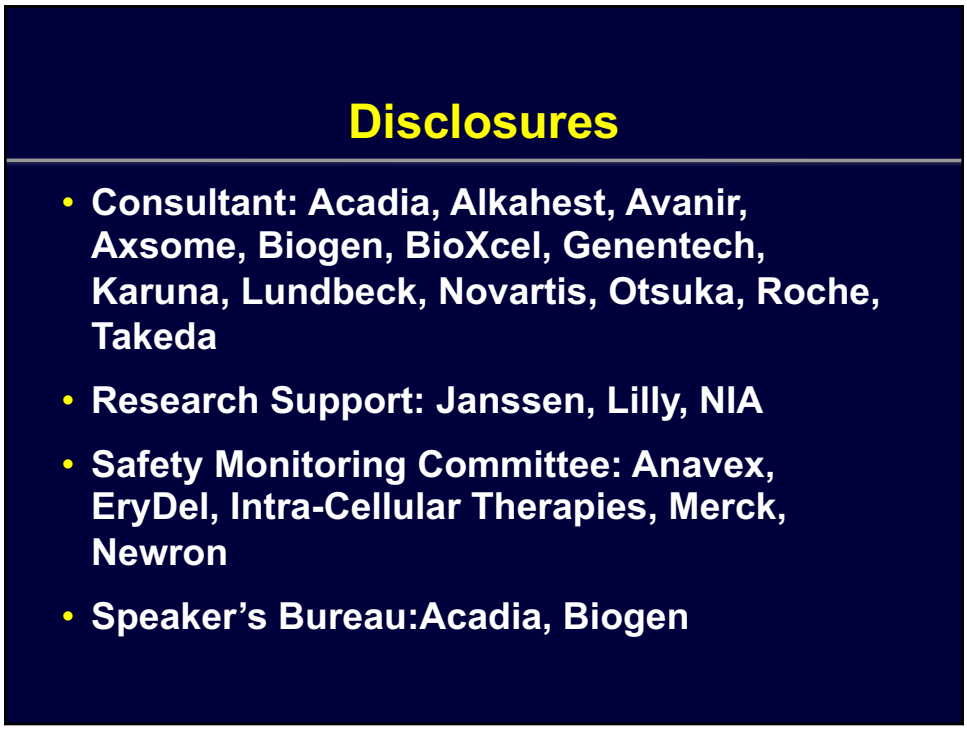

Disclosures
• Consultant: Acadia, Alkahest, Avanir, Axsome, Biogen, BioXcel, Genentech, Karuna, Lundbeck, Novartis, Otsuka, Roche, Takeda
• Research Support: Janssen, Lilly, NIA
• Safety Monitoring Committee: Anavex, EryDel, Intra-Cellular Therapies, Merck, Newron
• Speaker's Bureau:Acadia, Biogen

2

Learning Objectives

- Evaluate and contrast the pharmacologic therapies currently available for treating patients with mild- moderate to severe Alzheimer's disease
- Assess the evidence for the benefits of combination therapies for improving cognition, activities of daily living, global outcome, and behavior

3

Outline

- Impact of antidementia therapies on activities of daily living (ADLs), behavior, and cognition in mild-moderate–severe Alzheimer's disease (AD)
  - ChEIs (Cholinesterase inhibitors)
  - Memantine
  - Combination therapy
- Conclusions

4

Cholinesterase inhibitors and memantine (alone or in combination) produce statistically and clinically significant improvement in patients with moderate to severe AD when measured for

?

A. Cognition
B. Activities of daily living
C. Global measures
D. All of the above
E. None of the above

5

Cochrane Review of Memantine Concluded

- **A** Low incidence of adverse events
- **B** Significant benefits in mild to severe AD & VaD
- **C** In mod to severe AD, patients taking mementine were less likely to develop agitation
- **D** All are correct

6

Comparison of FDA-Approved Agents for the Treatment of AD (Conventional Oral Tablets)

Parameter	Donepezil[1]	Galantamine[2]	Galantamine ER[2]	Memantine[3]	Rivastigmine[4]	Rivastigmine Transdermal[4]
Stage	Mild, moderate, severe	Mild to moderate	Mild to moderate	Moderate to severe	Mild to moderate	Mild to moderate**
MOA(s)	AChEI	AChEI	AChEI	NMDA receptor antagonist	AChEI BuChEI	AChEI BuChEI
Dose titration	2 steps	2 to 3 steps	2 to 3 steps	4 steps	3 to 4 steps	2 steps
Starting dose	5 mg 1 × daily	4 mg 2 × daily	8 mg 1 × daily	5 mg 1 × daily	1.5 mg 2 × daily	4.6 mg every 24 hrs
Max dose	23 mg 1 × daily	12 mg 2 × daily	24 mg 1 × daily	10 mg 2 × daily XR 28 mg	6 mg 2 × daily	13.3 mg every 24 hours

Tacrine is an FDA-approved therapy but is rarely used because of QID dosing and hepatotoxicity.
BuChEI, butyrylcholinesterase inhibitor
** Mild to Mod AD or PDD

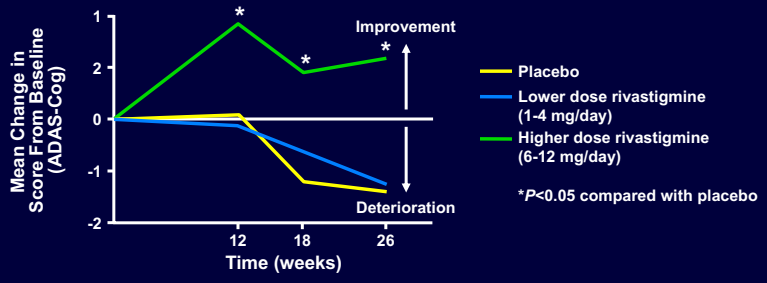
1. *Physicians' Desk Reference®*. 62nd ed. Montvale, NJ: Thomson PDR;2008:1075.
2. *Physicians' Desk Reference®*. 62nd ed. Montvale, NJ: Thomson PDR;2008:2373.
3. *Physicians' Desk Reference®*. 62nd ed. Montvale, NJ: Thomson PDR;2008:1181.
4. *Physicians' Desk Reference®*. 62nd ed. Montvale, NJ: Thomson PDR;2008:2214.

7

Response to ChEI Therapy: Cognition

- ADAS-Cog data (shown) was statistically significant but did not show improvement in cognition clinically
- Clinically important improvements were seen using CIBIC-plus data (not shown)

Rivastigmine (observed cases, ADAS-Cog)

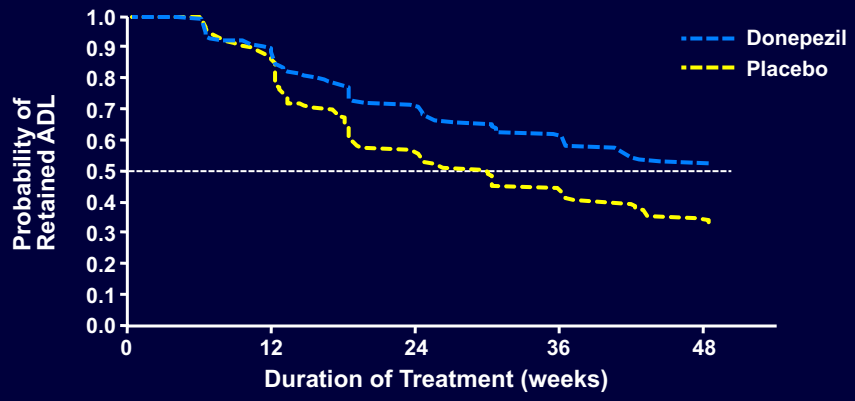


Reprinted with permission from the BMJ Publishing Group. Rösler M et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *Br Med J*. 1999;318(7184):633-640.
Qaseem A et al. *Ann Intern Med*. 2008;148:370.

8

ChEI Treatment and ADL in Mild-to-Moderate AD

Greater proportion of patients maintain ADL over 1 year.

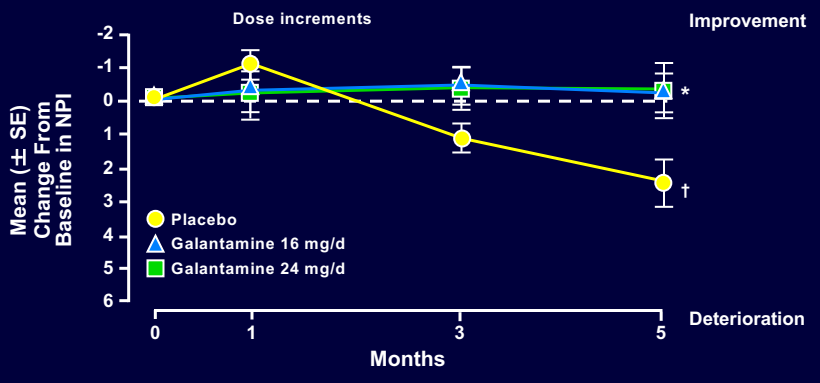


Criteria-based definition of ADL preservation; intent-to-treat population.

Adapted with permission from Mohs RC et al. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology.* 2001;57(3):481-488.

9

Behavioral Responses in Mild to Moderate AD: Delayed Adverse Behaviors With Galantamine



* *P*<0.05 vs placebo (both doses)
† *P*<0.05 vs baseline

NPI, neuropsychiatric inventory

Adapted with permission from Tariot PN et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. *Neurology.* 2000;54(12):2269-2276.

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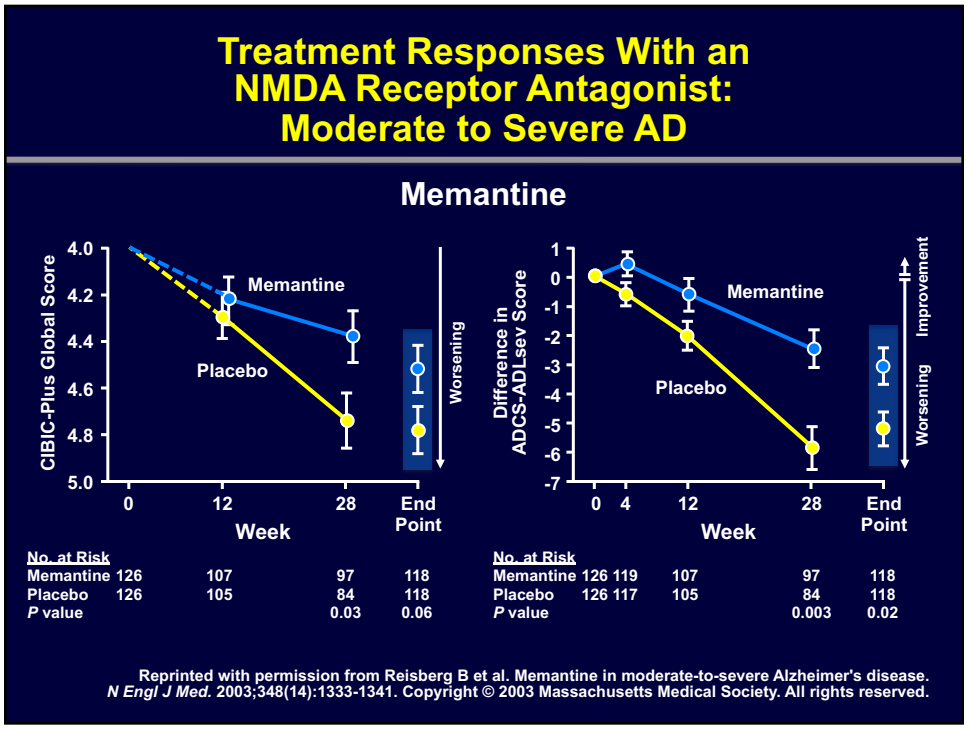
Treatment Responses With an NMDA Receptor Antagonist: Moderate to Severe AD
Memantine
CIBIC-Plus Global Score
4.0
4.2
4.4
4.6
4.8
5.0
Memantine
Placebo
Worsening
0
12
28
End Point
Week
No. at Risk
Memantine 126 107 97 118
Placebo 126 105 84 118
P value 0.03 0.06
Difference in ADCS-ADLsev Score
1
0
-1
-2
-3
-4
-5
-6
-7
Memantine
Placebo
Improvement
Worsening
0 4 12 28 End Point
Week
No. at Risk
Memantine 126 119 107 97 118
Placebo 126 117 105 84 118
P value 0.003 0.02
Reprinted with permission from Reisberg B et al. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med. 2003;348(14):1333-1341. Copyright © 2003 Massachusetts Medical Society. All rights reserved.

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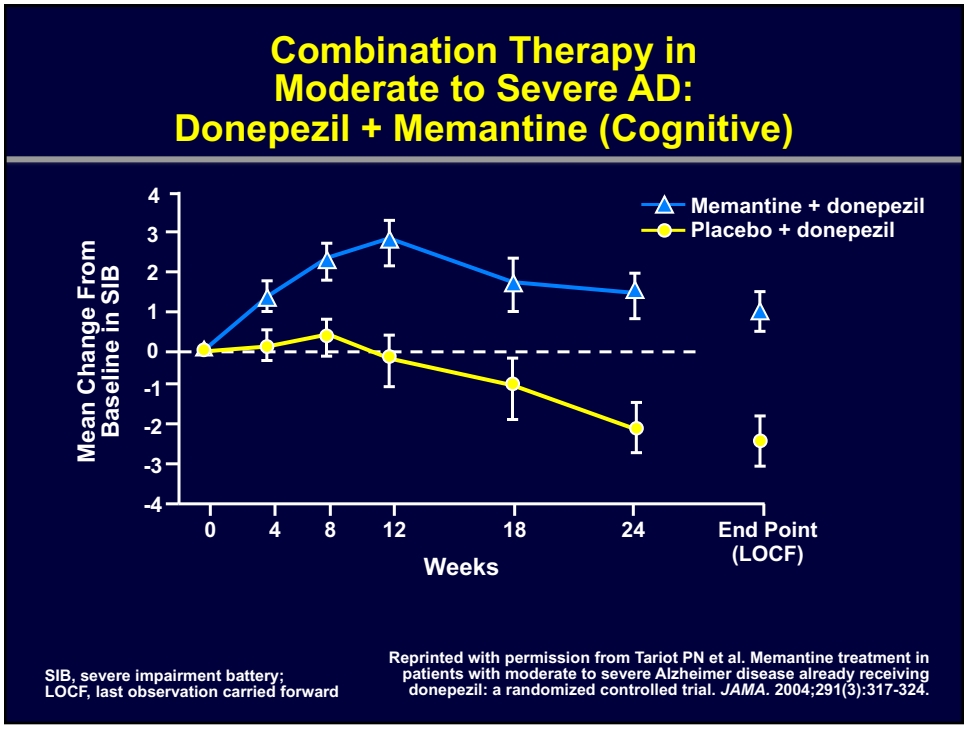
Combination Therapy in Moderate to Severe AD: Donepezil + Memantine (Cognitive)
Mean Change From Baseline in SIB
4
3
2
1
0
-1
-2
-3
-4
Memantine + donepezil
Placebo + donepezil
0
4
8
12
18
24
End Point (LOCF)
Weeks
SIB, severe impairment battery; LOCF, last observation carried forward
Reprinted with permission from Tariot PN et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA. 2004;291(3):317-324.

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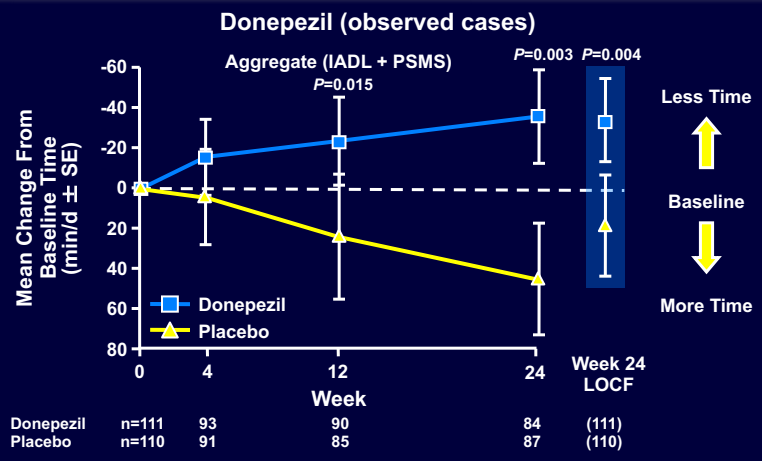
Treatment With a ChEI Reduces Caregiver Burden



IADL, instrumental activities of daily living; PSMS, physical self-maintenance scale

Reprinted with permission from Feldman H et al. Efficacy of donepezil on maintenance of activities of daily living in patients with moderate to severe Alzheimer's disease and the effect on caregiver burden. *J Am Geriatr Soc.* 2003;51(6):737-744.

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Data on Combination Therapy for AD

- NIH-sponsored analysis of 382 patients over the course of 15 years
- Study supports the benefits of combination therapy

Long-term Course and Effectiveness of Combination Therapy in Alzheimer's Disease

Alireza Atri, M.D., Ph.D., Lynn W. Shaughnessy, B.S., Joseph J. Locascio, Ph.D., and John H. Growdon, M.D.
From the Department of Neurology and Massachusetts Alzheimer's Disease Research Center, Massachusetts General, Hospital and Harvard Medical School, Boston, MA (AA, LWS, JJL, JHG), and the Massachusetts School of Professional Psychology, West Roxbury, MA (LWS)

NIH, National Institute of Health

Atri A et al. *Alzheimer Dis Assoc Disord.* 2008;22:209.

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Objectives

- To compare the real-world clinical effectiveness and long-term clinical trajectory in patients with AD who received
  - No treatment
  - Cholinesterase inhibitor (ChEI) alone
  - Memantine HCl + ChEI (combo)
- To compare the cognitive and functional differences between the 3 treatment groups

Atri A et al. *Alzheimer Dis Assoc Disorder*. 2008;22:209.

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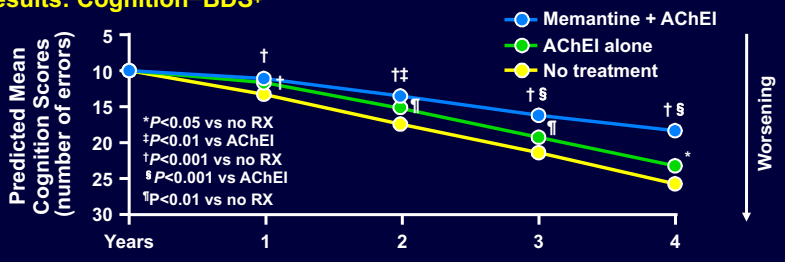
Results: Cognitive Performance* Over Time†

Results: Cognition–BDS‡



- Patients receiving combination therapy may experience significantly slower cognitive decline
- The data show that the mean deterioration for an untreated patient is 3 to 4 errors per year; combination therapy decreased the deterioration by 2 errors per year

*Based on predictive values from regression models of actual patient data. Actual patient data were used in a statistical model to generate these predicted values that account for patient differences such as duration of illness, time entering study, education, and baseline BDS and ADL scores.
†Mean cumulative medication treatment time was 1.9 years.
‡Blessed Dementia Scale (Information-Memory-Concentration subscale) is a brief mental status best administered by a physician to assess cognitive impairment.

Atri A et al. *Alzheimer Dis Assoc Disorder*. 2008;22:209.
Blessed G et al. *Br J Psychiatry*. 1968;114:797.

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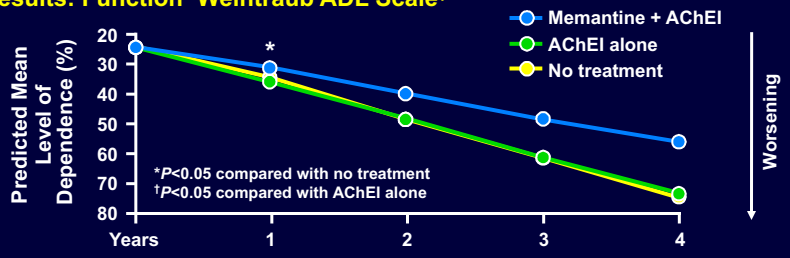
Results: Functional Dependence* Over Time†

Results: Function–Weintraub ADL Scale‡



- Patients receiving combination therapy may experience less dependence compared with a ChEI alone and not treatment

*Based on predictive values from regression models of actual patient data. Actual patient data were used in a statistical model to generate these predicted values that account for patient differences such as duration of illness, time entering study, education, and baseline BDS and ADL scores.
†Mean cumulative medication treatment time was 1.9 years.
‡Weintraub ADL Scale (Weintraub Activities of Daily Living scale) is a 31-item questionnaire on both basic and instrumental ADLs.

Atri A et al. *Alzheimer Dis Assoc Disorder.* 2008;22:209.
Johnson M et al. *Alzheimer Dis Assoc Disord.* 2004;13;223.
Weintraub S. *Am J Alzheimers Dis Other Demen.* 1986;1:35.

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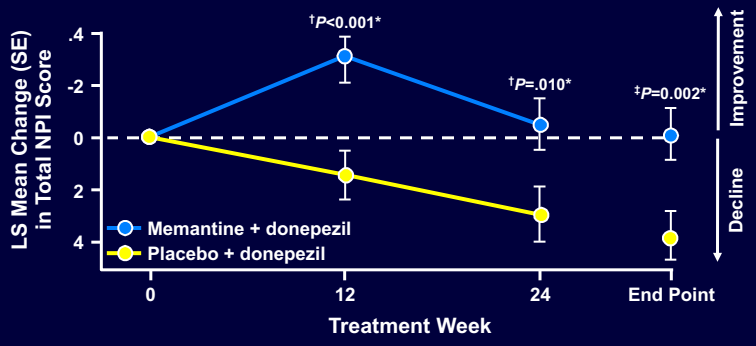
Behavioral Effects of Combination Therapy

Memantine + donepezil produced significant improvements in behavior compared with placebo + donepezil.



n=	198	186	171	193
n=	197	175	152	189

*Statistically significant; †OC analysis; ‡LOCF analysis.

LS, least square; SE, standard error

Tariot P et al. *JAMA.* 2004;291:317.
Cummings JL et al. *Neurology.* 2006;67:57.

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Persistent Treatment With ChEI and/or Memantine Slows Clinical Progression of AD

- 641 AD patients followed over 20 years
- Persistent drug treatment produced statistically and clinically significant impact on AD progression as assessed by measures of:
  - Cognition
  - ADLs
  - Global measures
- Positive treatment effects even seen in advanced AD

Roundtree SD et al. *Alzheimers Res Ther.* 2009 Oct 21;1:7.

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Management of Neuropsychiatric Symptoms

- Nonpharmacologic
  - Behavioral
  - Environmental
- Psychotropics
  - Antidepressants (SSRIs, SNRIs)
  - Atypical antipsychotics, conventional neuroleptics
  - Mood-stabilizing anticonvulsants (valproate, gabapentin)
- Antidementia agents
  - Cholinesterase inhibitors
  - Memantine

SSRI, selective serotonin reuptake inhibitor; SSNI, selective norepinephrine reuptake inhibitor

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Outline of Presentation

- Use of cholinesterase inhibitors
- Use of memantine

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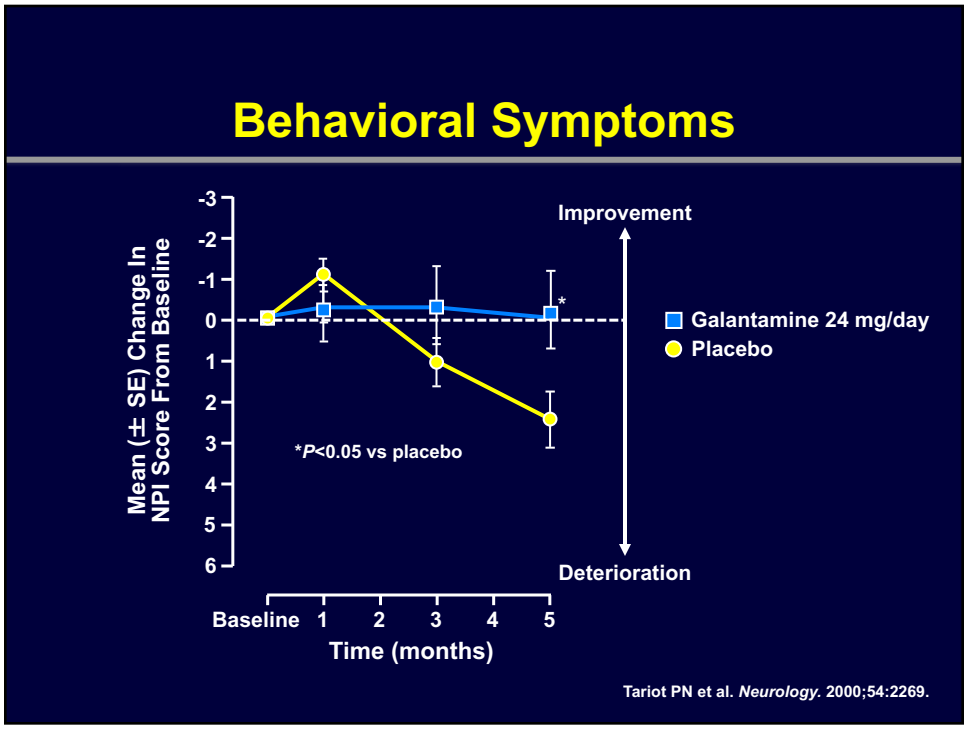
Outline of Presentation

- Use of neuroleptics
- Use of cholinesterase inhibitors
- Use of memantine

22


Behavioral Symptoms
Mean (± SE) Change In NPI Score From Baseline
-3
-2
-1
0
1
2
3
4
5
6
Improvement
Deterioration
Galantamine 24 mg/day
Placebo
*P<0.05 vs placebo
Baseline 1 2 3 4 5
Time (months)
Tariot PN et al. Neurology. 2000;54:2269.

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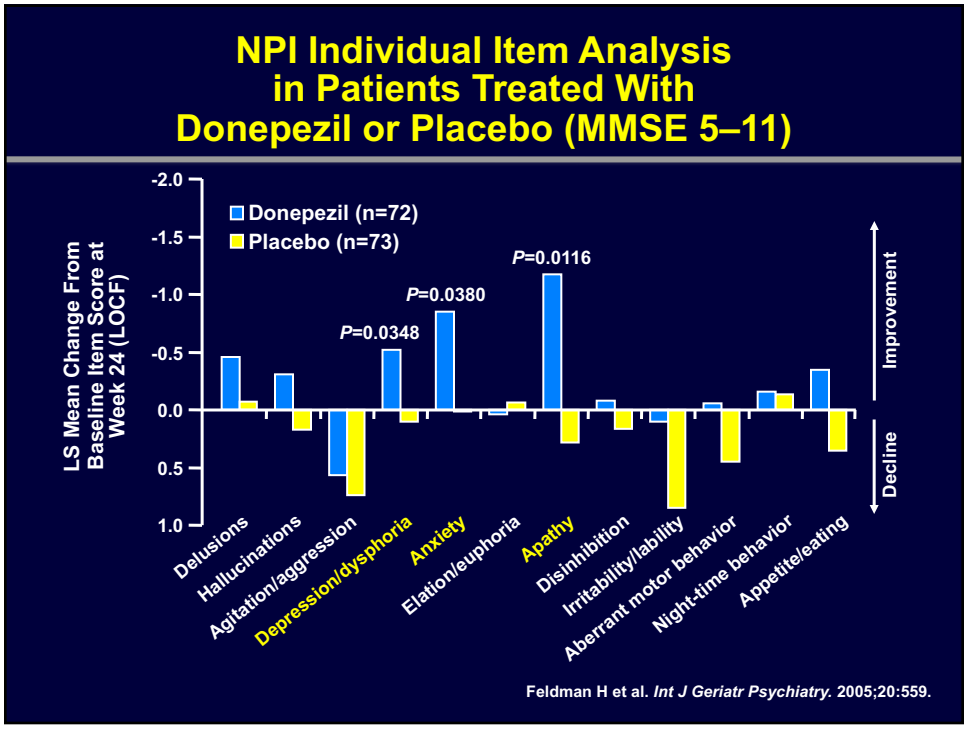
NPI Individual Item Analysis in Patients Treated With Donepezil or Placebo (MMSE 5–11)
LS Mean Change From Baseline Item Score at Week 24 (LOCF)
-2.0
-1.5
-1.0
-0.5
0.0
0.5
1.0
Donepezil (n=72)
Placebo (n=73)
P=0.0348
P=0.0380
P=0.0116
Improvement
Decline
Delusions
Hallucinations
Agitation/aggression
Depression/dysphoria
Anxiety
Elation/euphoria
Apathy
Disinhibition
Irritability/lability
Aberrant motor behavior
Night-time behavior
Appetite/eating
Feldman H et al. Int J Geriatr Psychiatry. 2005;20:559.

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Outline of Presentation

- Use of neuroleptics
- Use of cholinesterase inhibitors
- Use of memantine

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Cochrane Review of Memantine

Objectives

- To determine efficacy and safety of memantine for people with AD, vascular dementia (VaD), and mixed dementia

Conclusions

Moderate to severe AD:

- Pooled data indicate a beneficial effect of memantine at 6 months on cognition, ADLs, and behavior
- Supported by a significant improvement in the clinical impression of change
- Patients taking memantine appeared to be less likely to develop agitation

Mild to severe dementia (AD, VaD):

- Significant benefit of memantine on global impression, cognition, function, and behavior

Tolerability:

- Memantine is well tolerated and the incidence of adverse effects is low

McShane R et al. *Cochrane Database Syst Rev.* 2006 Apr 19:CD003154.

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Effects of Memantine on Behavior

Meta-analysis, six studies:

- Memantine produced a statistically significant beneficial effect on behavior (*P*=0.01 vs placebo) in patients with moderate to severe AD (MMSE <20)

Pooled data, six studies in moderate to severe AD:

- Memantine significantly improved NPI scores (vs placebo) from week 12 onwards

Winblad B et al. *Dement Geriatr Cogn Disord.* 2007;24:20.

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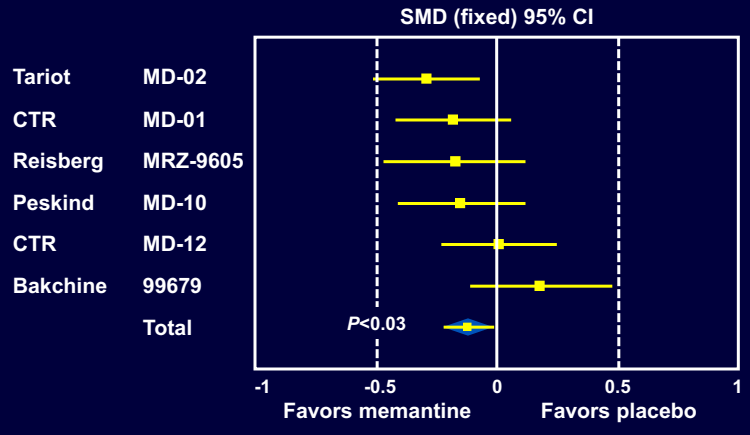
Meta-Analysis on 6 Studies: Behavior (NPI), OC Analysis (MMSE <20)

NPI, week 24/28 (LOCF) – moderate to severe AD



SMD, standardised mean difference;
CTR, Forest Clinical Trial Registry

Winblad B et al. *Dement Geriatr Cogn Disord.* 2007;24:20.

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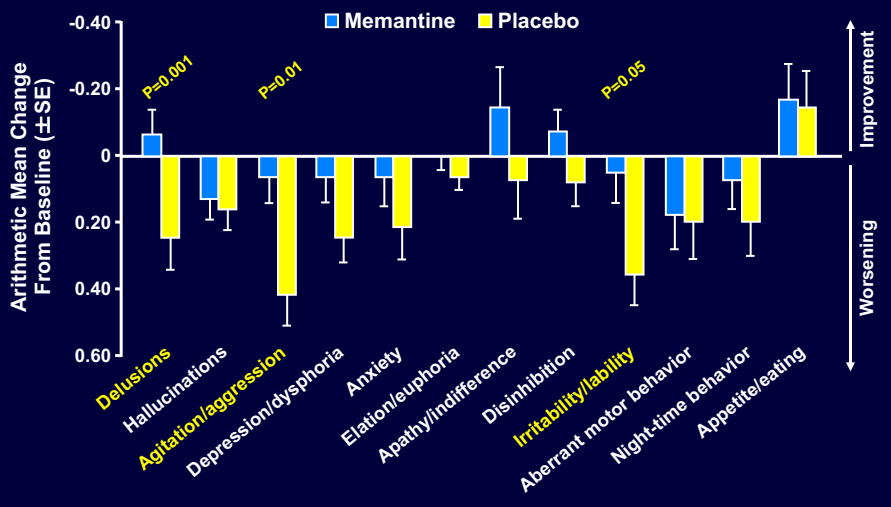
Effects of Memantine on Behavior

Pooled Data From 6 Phase III, Placebo-Controlled Studies (MMSE <20), NPI Single Items (LOCF)



Gauthier S et al. *Int Journal Geriatric Psychiatry*. 2008;23:537.

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Conclusions

- **ChEIs and memantine (alone or in combination) produce statistically and clinically significant improvement in patients with mild- moderate to severe AD when measured for cognition, ADLs, behavior, and global measures**

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