Dementia

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Self-Assessment Question 1

Which of the following are required for a diagnosis of dementia?

A. Cognitive decline is ACQUIRED
B. MEMORY is affected
C. In addition to memory, ANOTHER cognitive function is affected.
D. Symptoms are not attributable to delirium or another psychiatric disorder.
E. All of the above

Self-Assessment Question 2

Which of the following cognitive or behavioral domains is affected in dementia?

A. Memory
B. Executive function
C. Behavior
D. Activities of daily living
E. All of the above

Self-Assessment Question 3

Which of the following statements is correct?

A. Alzheimer's Disease affects greater than 30% of adults older than 85 years of age.
B. Alzheimer's Disease is infrequent among adults less than 60 years of age.
C. Alzheimer's Disease is the most common cause of dementia.
D. All of the above
E. None of the above

Self-Assessment Question 4

Treatment of AD with cholinesterase inhibitors is based on which of these rationales?

A. Noradrenergic neurotransmission in the locus ceruleus is reduced in late AD
B. Pathological stimulation of NMDA receptors is associated with excitotoxic death of neurons.
C. The number of cholinergic neurons in the basal forebrain is reduced in late Alzheimer's disease.
D. All of the above
E. None of the above

Self-Assessment Question 5

Treatment of AD with memantine is based on which of these rationales?

A. Noradrenergic neurotransmission in the locus ceruleus is reduced in late AD
B. Pathological stimulation of NMDA receptors is associated with excitotoxic death of neurons.
C. The number of cholinergic neurons in the basal forebrain is reduced in late Alzheimer's disease.
D. All of the above
E. None of the above

Major Points

- Dementia is underrecognized and undertreated in primary care and in mental health settings
- Dementia can be recognized and treated beneficially in primary care and mental health settings
- Both pharmacological and nonpharmacological interventions may benefit overall brain health and dementia course

Major Points (cont.)

- **Neuroimaging with PET can show a pattern of regional glucose metabolism that improves early detection of Alzheimer's disease with greater specificity**
- **Novel approaches to *in vivo* plaque and tangle imaging will be useful in monitoring potential disease-modifying agents**

Definition of Dementia

- **Acquired syndrome of decline in memory and at least 1 other cognitive function (e.g., language) sufficient to affect daily life, not explainable by delirium or other mental disorder.**

Modified from Small GW et al. JAMA. 1997;278:1363-1371

Causes of Dementia

- Alzheimer's disease
  - (most frequent)
- Vascular disease
- Lewy Body Disease
- Parkinson's
- Huntington's
- Frontal dementias
- Head Injury
- Metabolic/Nutritional
  - B_{12}/Folate
  - Thiamine
  - Thyroid
  - Hepatic/Renal
- Medications
- Alcohol/Toxins
- Infectious
  - HIV
  - Syphilis
  - Meningitis
- Depression
- NPH
- Neoplasms
- Autoimmune disorders

Diagnostic Criteria for Alzheimer's Disease (1)

- Multiple cognitive deficits manifested by both of:
  - Memory impairment
  - One (or more) of the following cognitive disturbances: aphasia, apraxia, agnosia, disturbance in executive functioning
- Significant impairment in social or occupational functioning representing a significant decline from a previous level of functioning
- Gradual onset and progressive cognitive decline

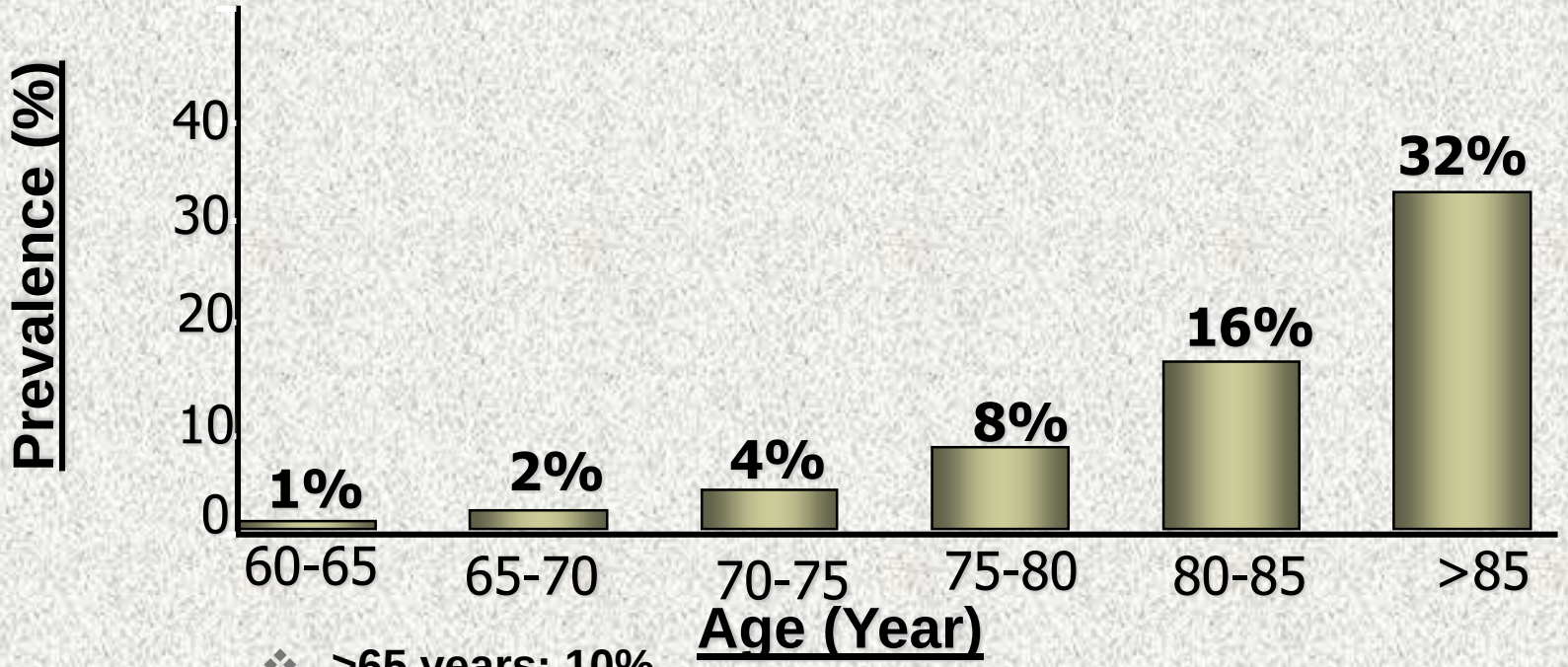
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. 1994:142-143.

Diagnostic Criteria for Alzheimer's Disease (2)

- Cognitive deficits are NOT due to any of the following:
  - Other central nervous system conditions that cause progressive deficits in memory and cognition
  - Systemic conditions known to cause dementia
  - Substance-induced conditions
- Deficits do not occur exclusively during delirium
- Disturbance is not better accounted for by another Axis I disorder

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. 1994:142-143.

Prevalence of Alzheimer's Disease in the U.S.



- >65 years: 10%
- >85 years: 32-47%
- 68% are women
- Today: ~4 million have AD
- 2050: >14 million will have AD

Diagnosing AD:
physical examination

* Life-threatening conditions, e.g. mass lesions, vascular lesions and infections
* Blood pressure and pulse
* Vision and hearing assessments
* Cardiac and respiratory function
* Mobility and balance
* Sensory and motor system examination (tone, reflexes, gait and coordination) and depressive symptoms (sleep and weight)

Physical examination

Diagnosing AD:
laboratory tests

All patients

* Complete blood count
* Thyroid function
* B12, folate, homocysteine
* BUN and creatinine
* Calcium
* Glucose
* Electrolytes
* Urinalysis
* Liver function tests
* Cholesterol, fasting HCY
* ESR

Most patients

* ECG

Many patients

* Neuropsychological testing
* Neuroimaging

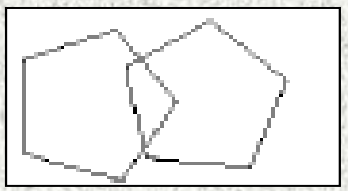
Diagnosing AD:
cognitive assessment with MMSE

Cognitive area	Score Maximum	Score Actual
Mini Mental State Examination: test outline and scoring		
Orientation		
***What is the (date, day, month, year, season)?**	**5**	
*** Where are you (clinic, town, country)?**	**5**	
Memory		
***Name three objects. Ask the patient to repeat them**	**3**	
Attention		
***Serial sevens. Alternatively ask the patient to spell world backwards (dlrow)**	**5**	

Cognitive Assessment **Folstein et al 1975**

Diagnosing AD:
cognitive assessment with MMSE (2)

Cognitive area	Score Maximum	Score Actual
Mini Mental State Examination: test outline and scoring		
Recall		
*Ask for the three objects mentioned above to be repeated	3	
Language		
*Name a pencil and watch	2	
*Repeat, 'No ifs, ands or buts'	1	
*A three stage command	3	
*Read and obey CLOSE YOUR EYES	1	
*Write a sentence	1	
*Copy a double pentagon	1	
	Total 30	



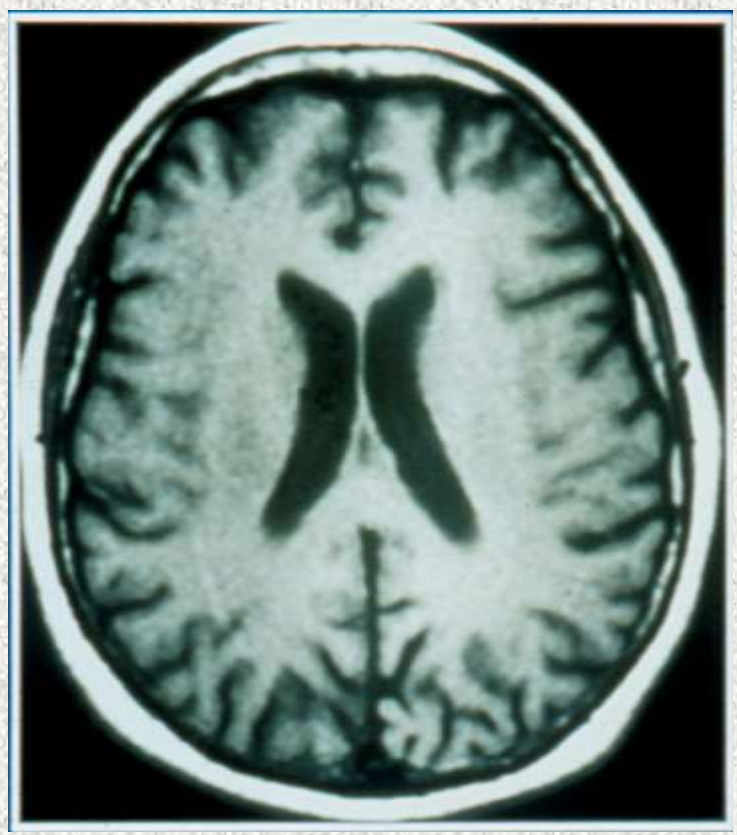
Cognitive Assessment **Folstein et al 1975**

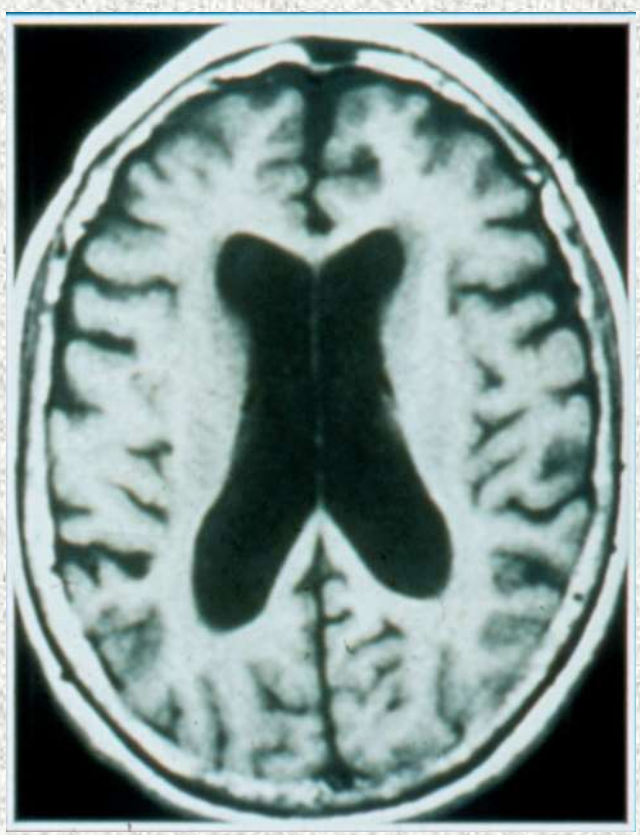
Diagnosing AD: Neuropsychological Assessment[1]

- No current "gold standard" single test identified
- Battery of tests improves sensitivity and specificity
- Typical neuropsychological battery:
  - RAVLT or CAVLT
  - WAIS-R
  - WMS-R
  - Rey-Osterrieth Complex Figure
  - Clock drawing / Trails
  - Mattis Dementia Rating Scale
- Predictive value of objective informant report is high

1. Petersen et al. 2001 and other sources

Diagnosing AD: Neuroimaging (Structural/Functional)

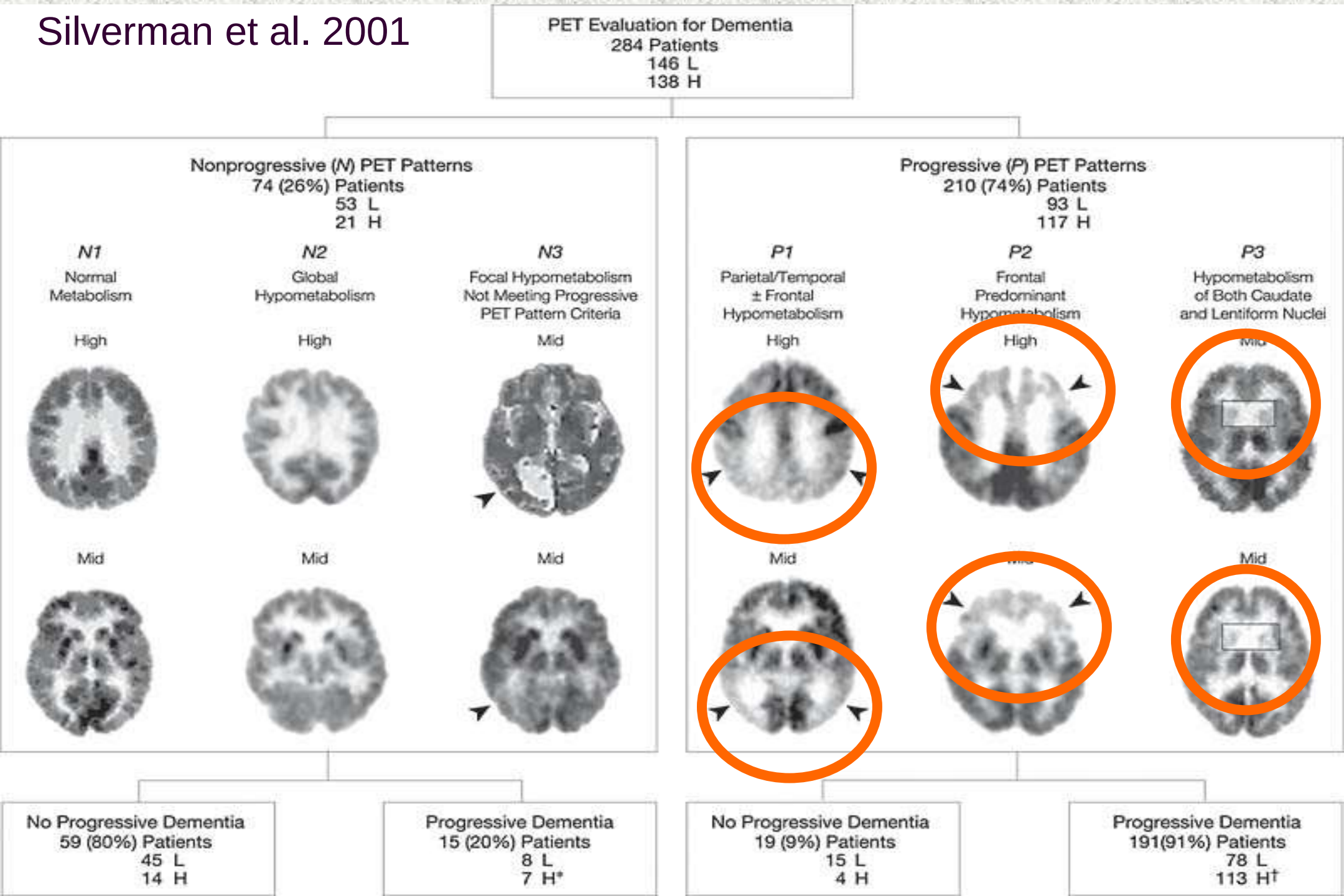




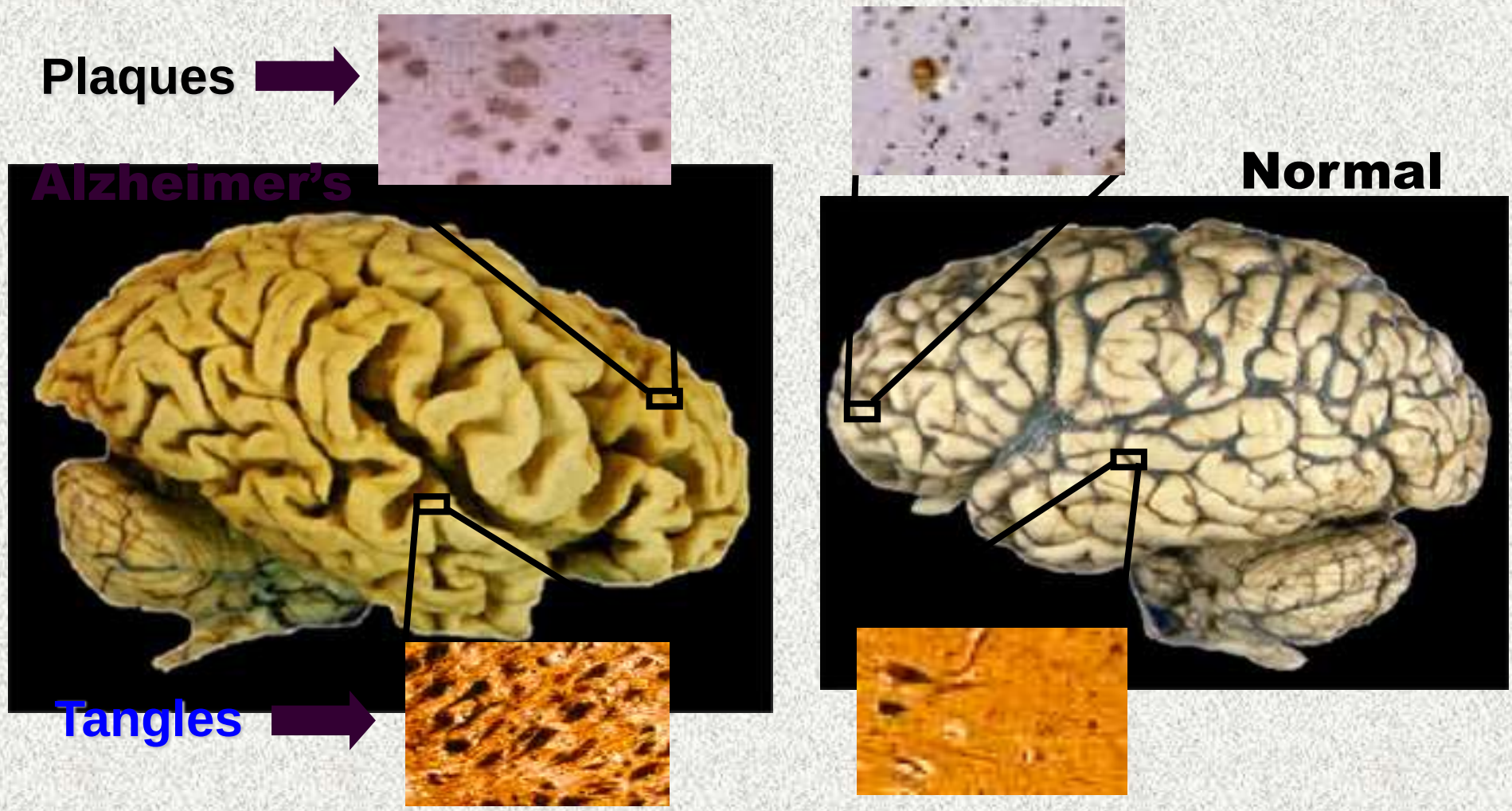
AD

Reproduced from Doraiswamy PM, 1998

Silverman et al. 2001



Amyloid Plaques and Neurofibrillary Tangles in Alzheimer's Disease and Normal Aging



Courtesy of Harry Vinters, M.D.

AAMI vs. MCI

- **AAMI: very mild impairment, 1%/yr progress to dementia**
- **MCI: memory complaint, objective memory impairment on neuropsychological testing, often corroborated by observer. Called "amnestic" when only memory affected, "other" when memory not affected, "multiple domain" when memory and other cognitive functions affected. Estimated 15%/yr progress to dementia.**

Risk/Protective Factors for Brain Aging

Definite risks

- Age
- Family history
- APOE-4 gene

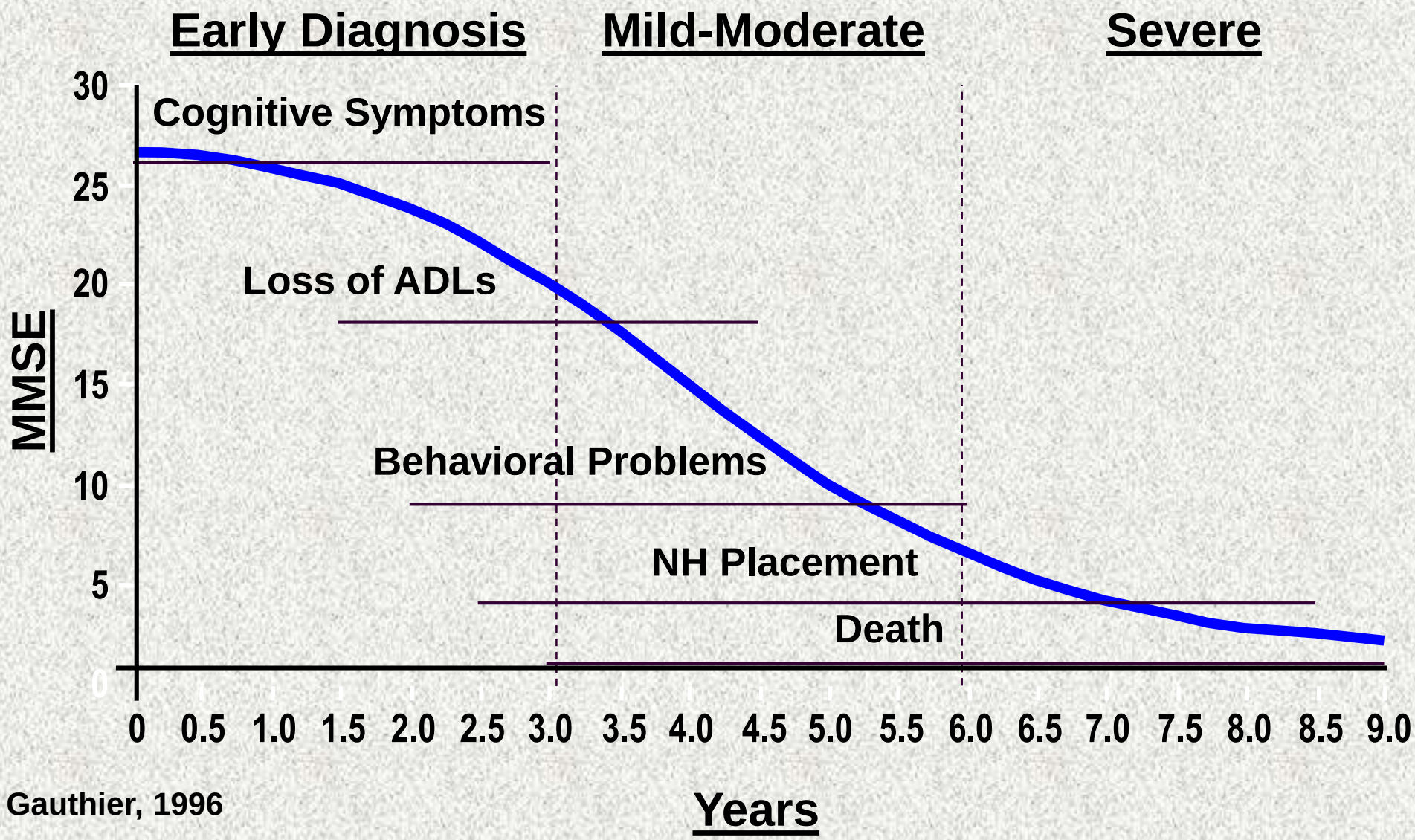
Possible risks

- Other genes
- Head trauma
- Lower educational achievement
- Chronic stress

Possible protections

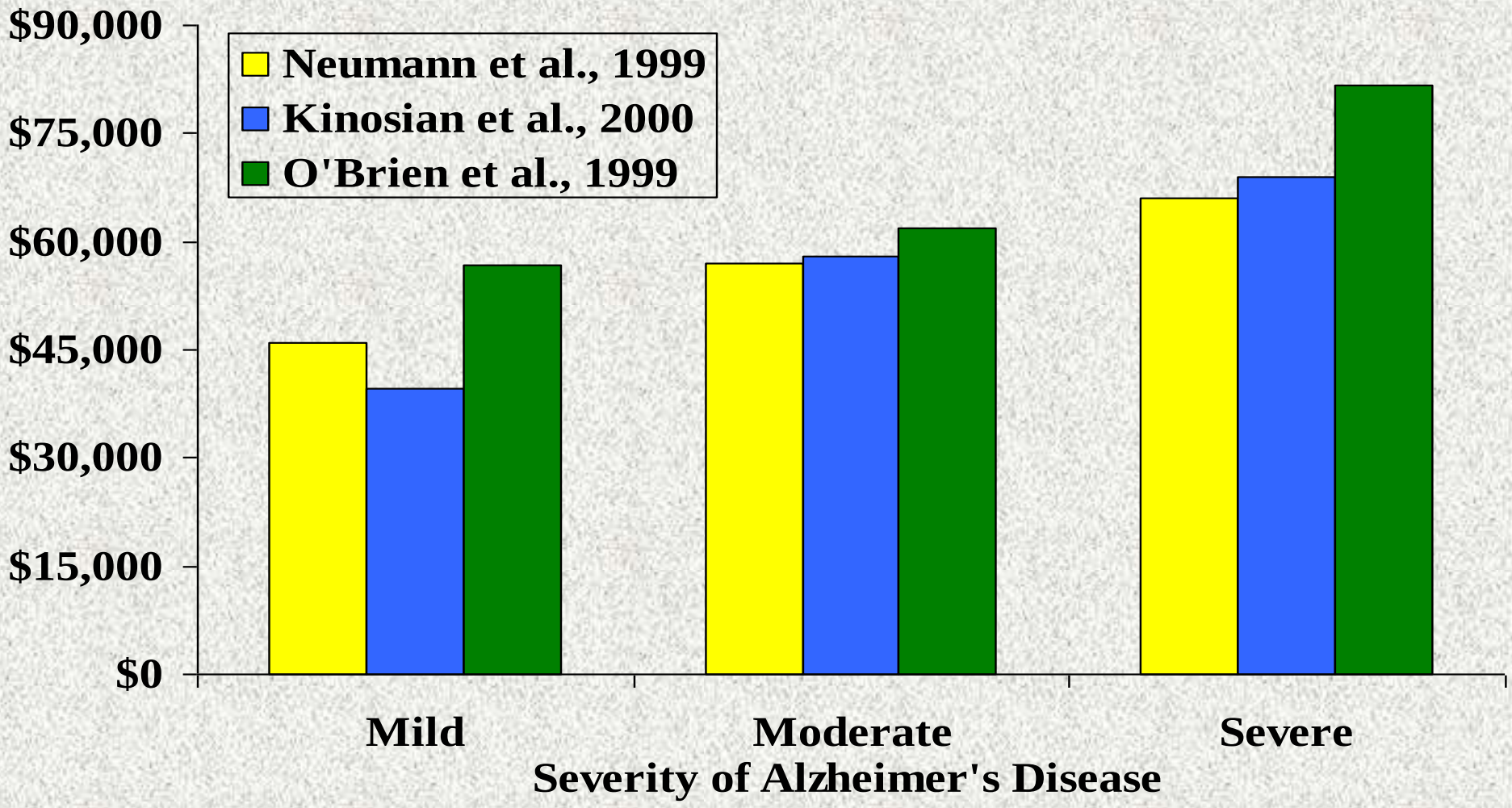
- Estrogen
- Anti-inflammatory drugs
- Antioxidants
- Low-fat diet
- Wine
- Aerobic exercise

The Progress of Alzheimer's Disease



Gauthier, 1996

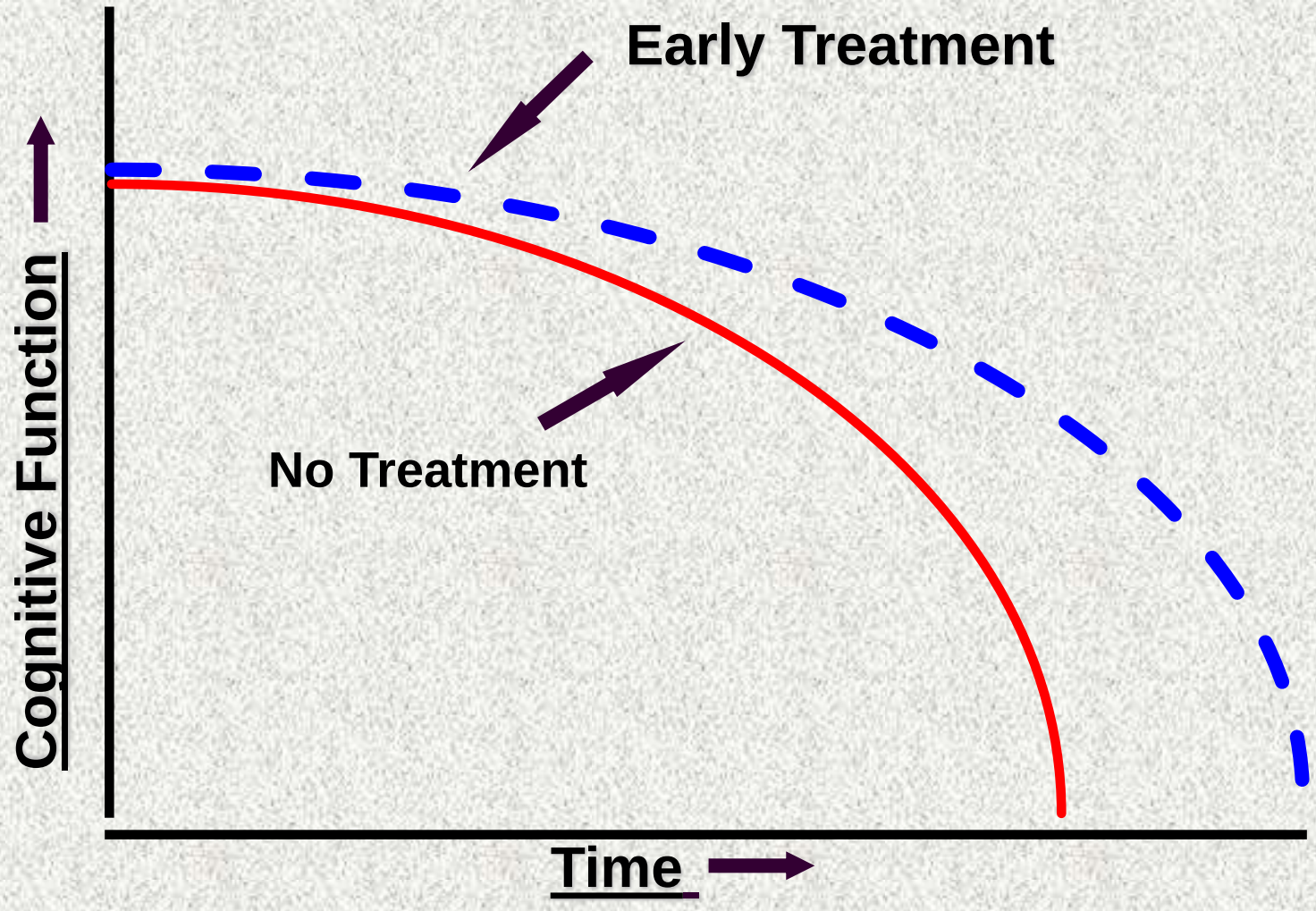
5 Year Cost of Care Models for Mild, Moderate, and Severe Alzheimer's Disease



* 10 year average costs may be as high as $109,000 for women and $67,000 for men.

Kinosian, et al., 2000, Journal of the American Geriatrics Society

Delaying Onset Reduces Prevalence/Costs



Current Challenges in Dementia Diagnosis

Primary care physicians (PCPs)

- PCPs care for most dementia patients (64%)
- Barrett et al, 1997 found that only 40% of PCPs knew Alzheimer's was most common cause of late-life memory loss (vs. 97% of experts)
- PCPs usually do not use standardized dementia diagnostic criteria

Missed diagnosis*

- 75% of patients with moderate dementia
- 97% of patients with mild dementia

Underrecognition of dementia leads to increased:

- Hospitalization rates
- Medication errors
- ER visits
- Mortality
- Motor vehicle accidents

*Callahan et al, 1995

When to Refer

Geriatric Psychiatrist

- Unclear dx, early onset, severe behavior/mood problem, non-responsive to tx, unable to tolerate drugs, caregiver stress

Neurologist

- Parkinson sx, early onset, focal neurological signs, rapid progression, atypical presentation

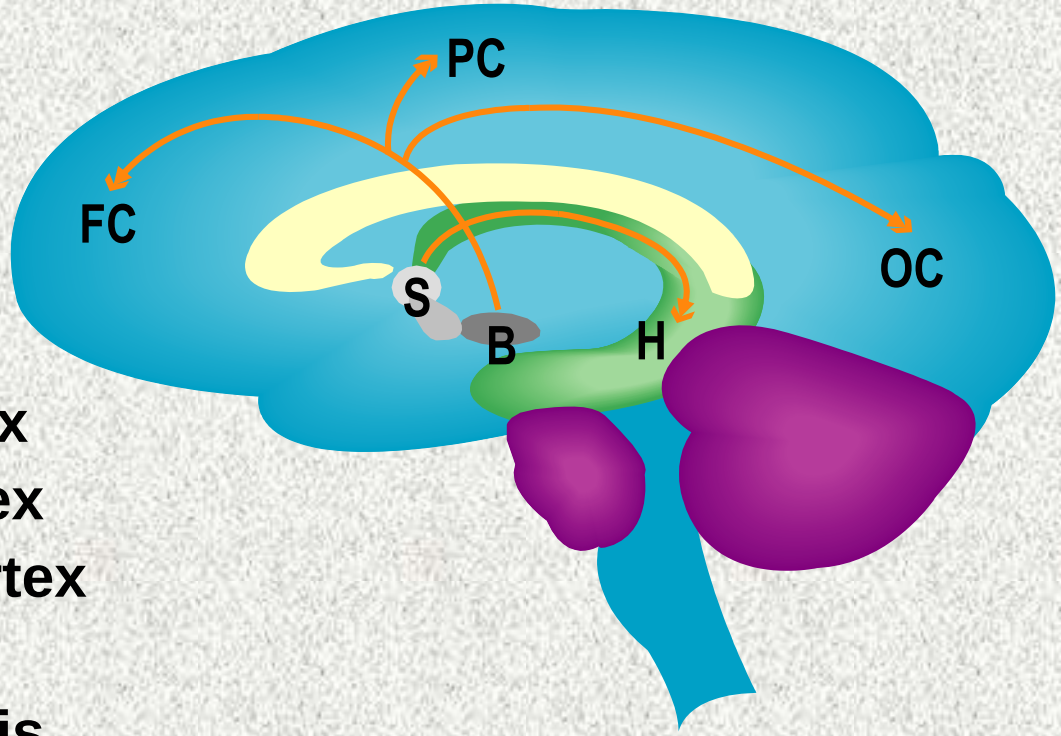
Geriatrician

- Complex medical problems, functional assessment

When to Hospitalize

- Imminent danger to self or others
- Severe mood problems
- Refusal to eat, severe sleep disturbance
- Psychiatric illness complicated by alcohol/drug addiction
- Need for drugs or tests requiring hospitalization
- Need for IV or frequent IM injections

Cholinergic System Innervates Areas Associated with Memory and Learning



FC = Frontal cortex
PC = Parietal cortex
OC = Occipital cortex
H = Hippocampus
B = Nucleus basalis
S = Medial septal nucleus

Adapted from: Coyle JT et al. Science. 1983;219:1184-1190

Rationale for Cholinergic Treatments of AD

- Cholinergic function including choline acetyltransferase (CAT) activity is reduced with aging[1]
- Number of cholinergic neurons (particularly in basal forebrain) is reduced in late AD[2]
- In AD, nicotinic receptors in hippocampus and cortex are reduced[1,3]

[1]Bartus RT et al. Science. 1982;217:408-414; [2]Whitehouse PJ et al. Science. 1982;215:1237-1239; [3]Guan ZZ et al. J Neurochem. 2000;74:237-243 (from Small G: Dementia. ACNP Curriculum)

Cholinesterase Inhibitor Properties

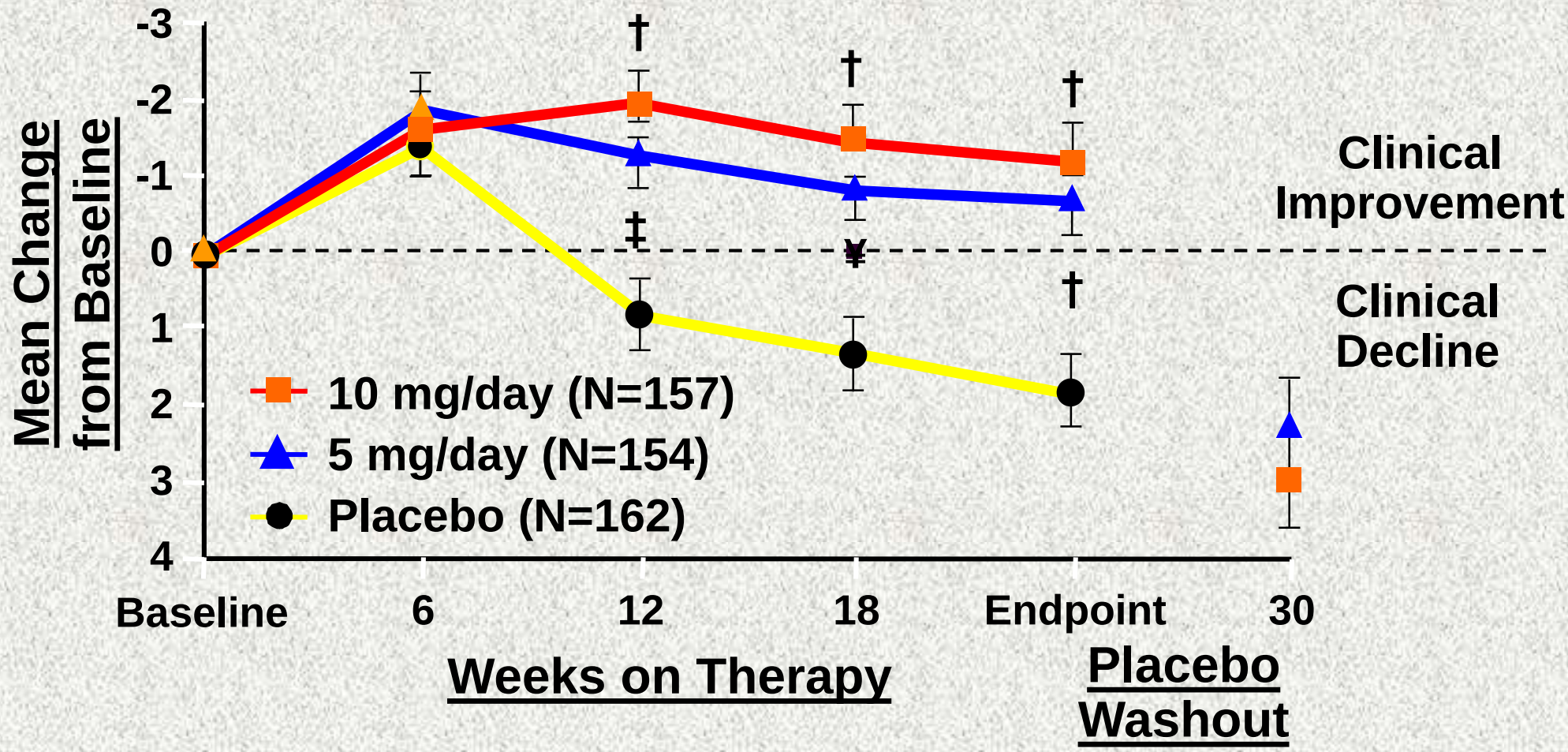
	Selectivity	Max serum conc	Absorbtion delay by food?	Serum Half-Life (hr)	Protein Binding %	Target Dose (mg/day)	Daily Dosing
Tacrine (Cognex)	**AChE &BuChE**	**1-2 hr**	**Yes**	**1.3-2**	**75**	**80-160**	**qid**
Donepezil (Aricept)	AChE	3-5 hr	No	70-80	96	5-10	qd
Rivastigmine (Exelon)	AChE &BuChE	0.5-2 hr	Yes	2	40	6-12	bid
Galantamine (Razadyne or Razadyne ER)	AChE & Nic Mod	30-60 min	Yes	5-7 ER is longer	10-20	16-24	bid or qd

Most Frequent Adverse Effects of Cholinesterase Inhibitors*

Nausea	13% to 35%
Anorexia	5% to 14%
Dizziness	1% to 10%
Diarrhea	0% to 11%
Cost	~$150/mo.

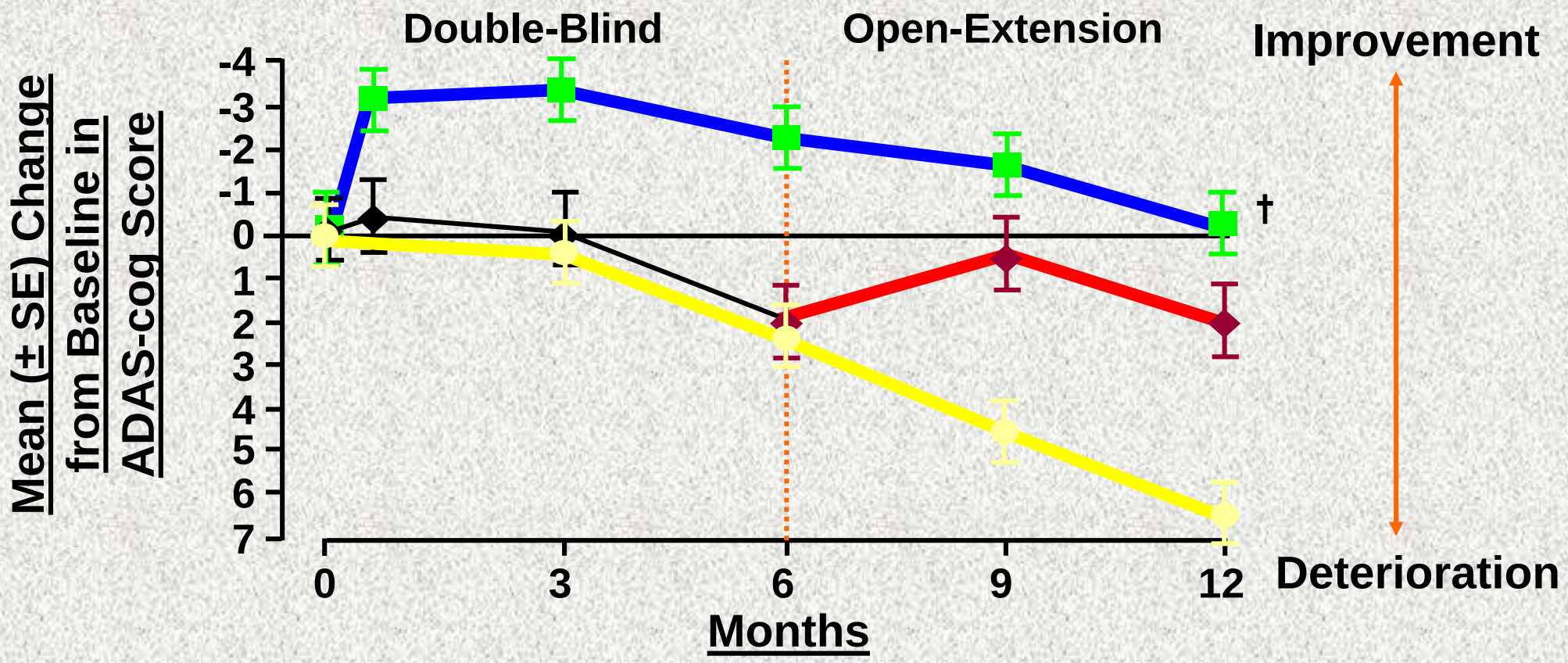
*These numbers are taken from package inserts for ChI's.

Effect of Donepezil on Cognition: ADAS-Cog*



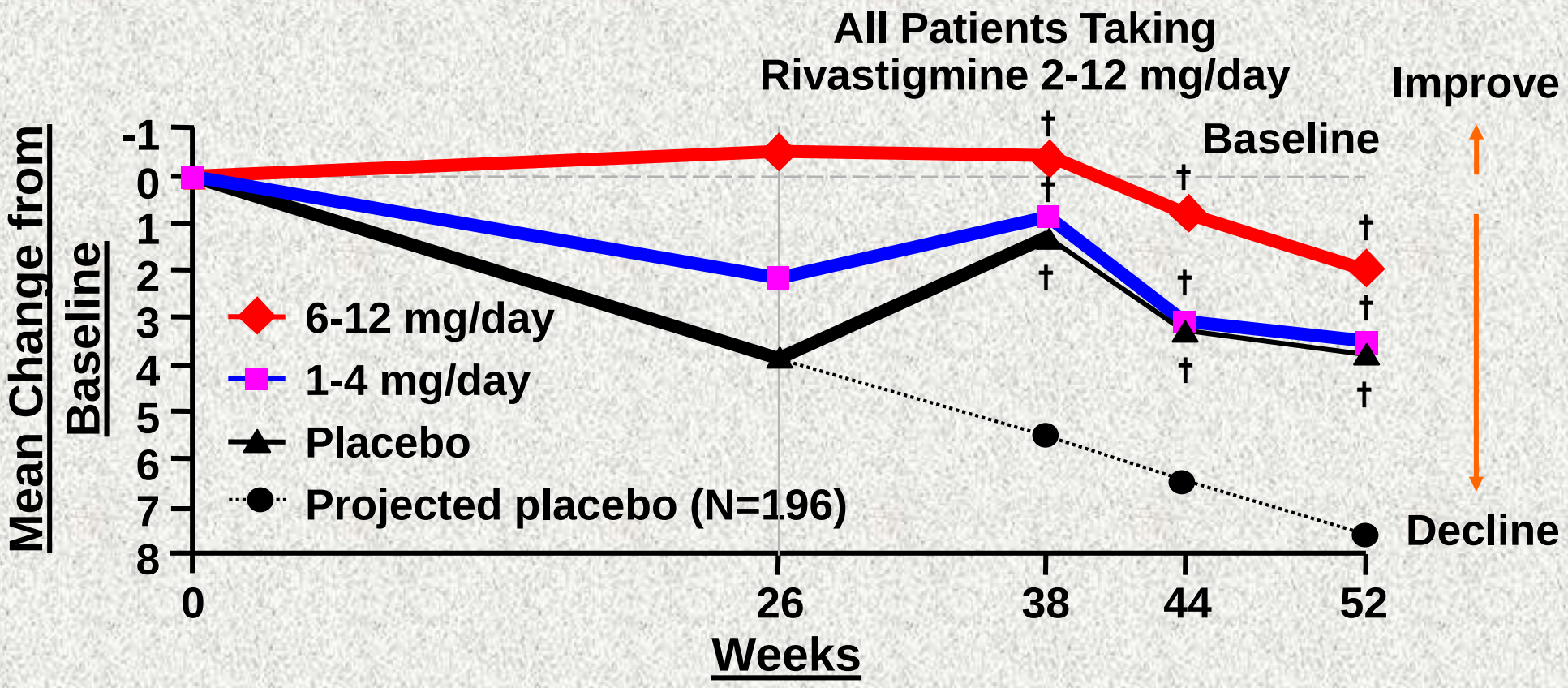
*Alzheimer's Disease Assessment Scale-Cognitive Subscale. †p<0.0001; ‡p<0.0007; ¥p<0.0012
Rogers SL et al. Neurology. 1998;50:136-145

Effect of Galantamine on Cognition: ADAS-Cog*



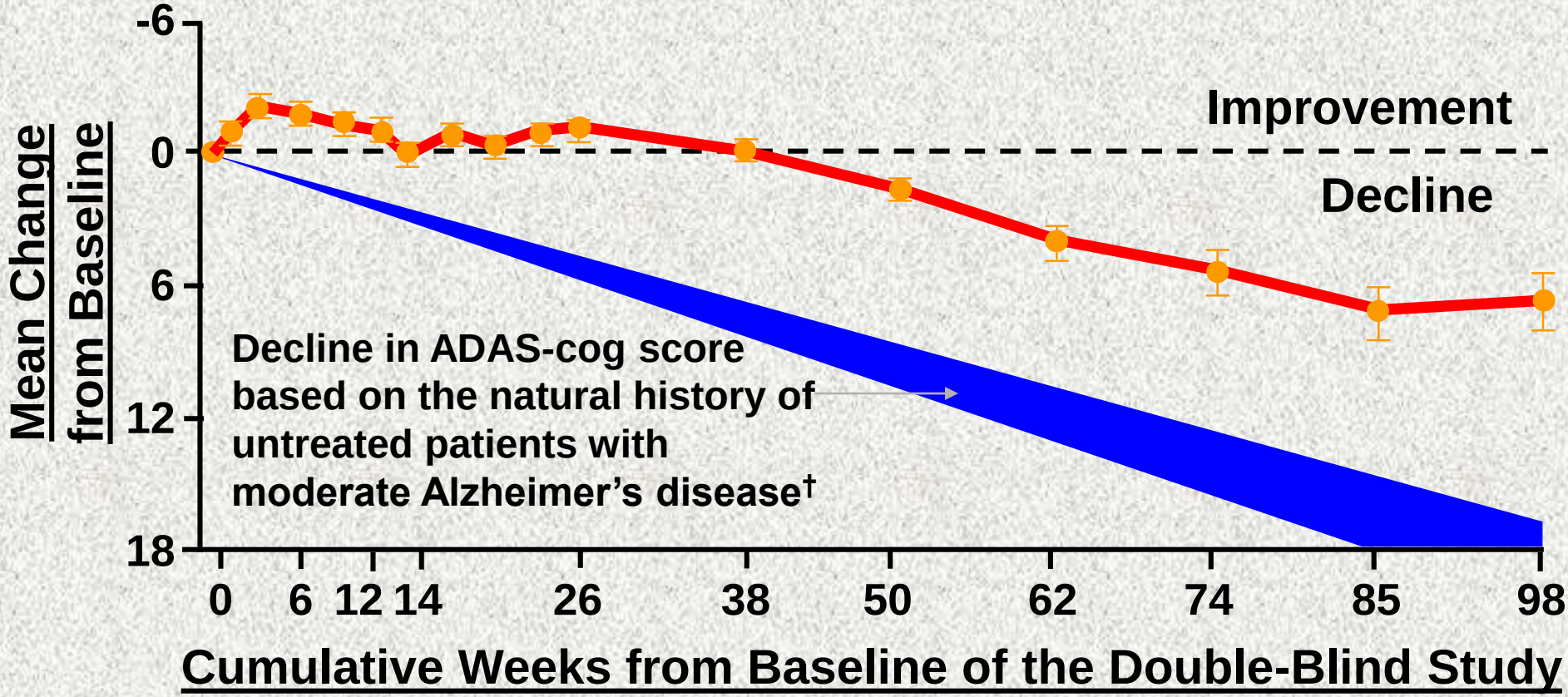
*ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; †p<0.05 vs. placebo/Galantamine and not statistically different from baseline; Raskind MA et al. Neurology. 2000;54:2261-2268

Efficacy of Rivastigmine on Cognition Through 52 Weeks: ADAS-Cog*



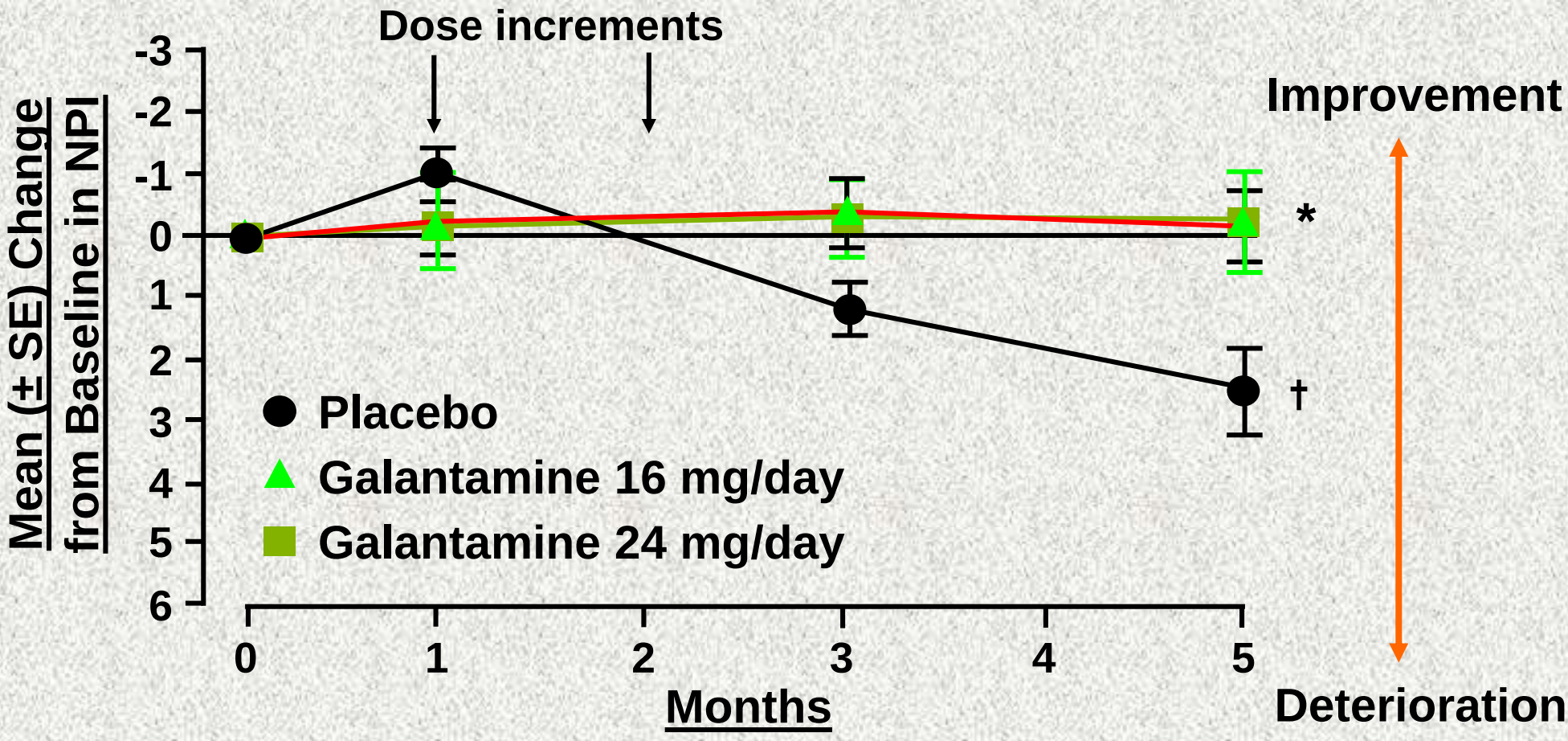
*Alzheimer's Disease Assessment Scale–Cognitive Subscale; †p<0.05 vs. projected placebo; Corey-Bloom J et al. Int J Geriatr Psychopharmacol. 1998;1:55-65; Adapted from: Messina J et al.
The 3rd Int'l Meeting for the College of Psychiatric and Neurologic Pharmacists. April 6-9, 2000. Washington, DC; Novartis Pharmaceuticals Corporation (Data on file)

Long-Term Effects of Donepezil on Cognition: ADAS-Cog*



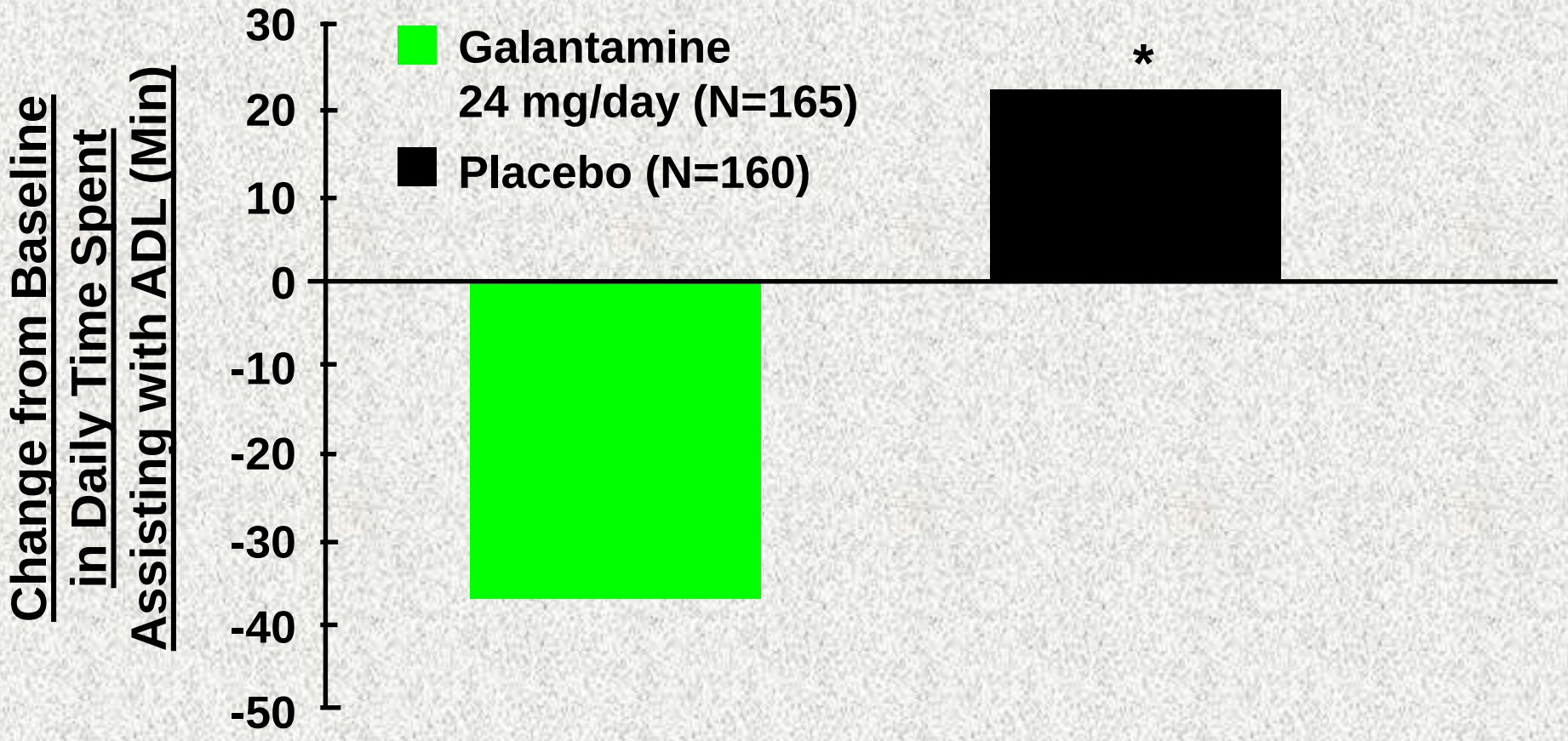
*Alzheimer's Disease Assessment Scale-Cognitive Subscale; Rogers SL, Friedhoff LT. Eur Neuropsychopharmacol. 1998;8:67-75; †Stern RG et al. Am J Psychiatry. 1994;151:390-396

Effect of Galantamine on Behavioral Symptoms: NPI



*p<0.05 vs. placebo (galantamine 16 mg and 24 mg); †p<0.05 vs. baseline; Adapted from: Tariot PN et al. Neurology. 2000;54:2269-2276

Change in Daily Time Spent by Caregiver Assisting with ADL



*p<0.05 vs. baseline; Lilienfeld S, Parys W. Dement Geriatric Cog Disord. 2000;11(suppl 1):19-27; Wilcock G et al. World Alzheimer Congress, 2000

Donepezil and Concomitant Treatments

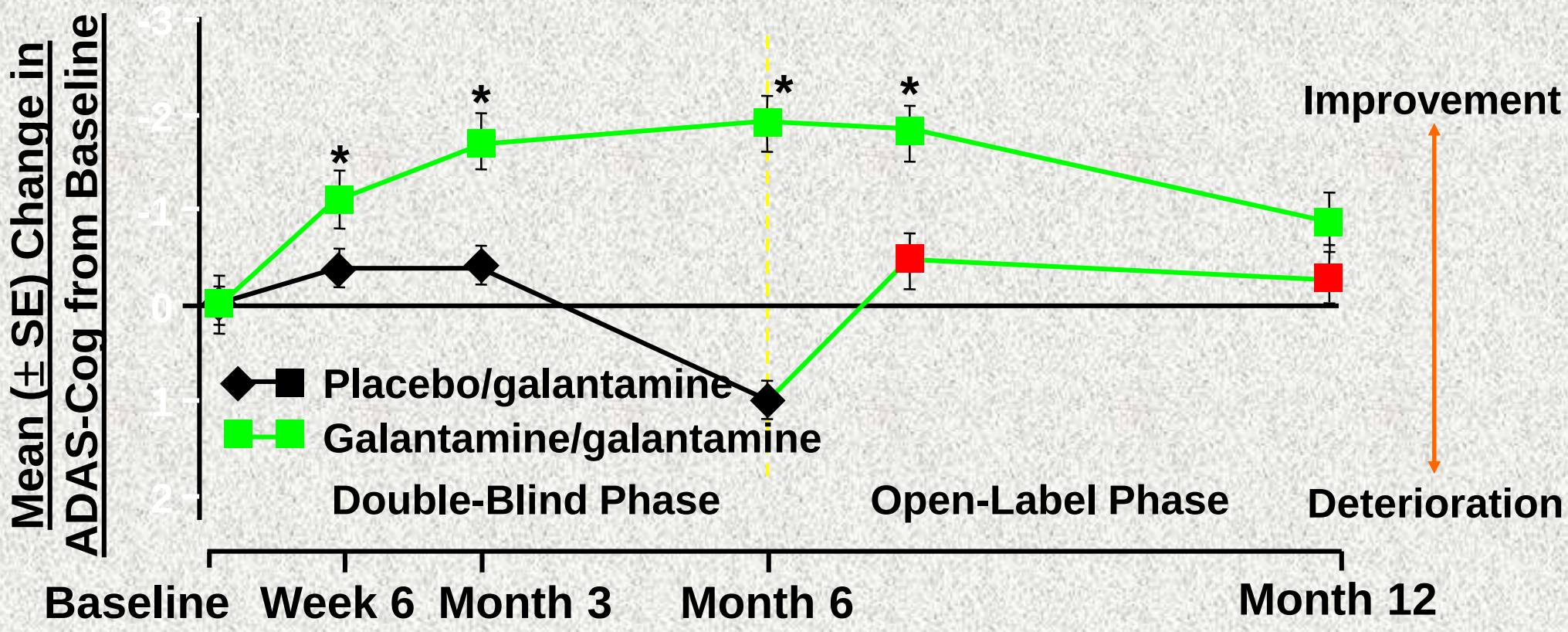
Percentage of Caregivers Reporting Patient's Drug Use, by Category

Drug Category	Donepezil (%) (N=108)	Nondonepezil (%) (N=268)
Antidepressant	25	43*
Antipsychotic	19	34*
Antianxiety	13	22†
Estrogen	10	8
Antiparkinsonian	5	7
Sedative-hypnotic	2	6†

*Pearson chi-square test, $p<0.05$; †Pearson chi-square test, $p<0.10$; Small GW et al. Clin Ther. 1998;20:838-850

Galantamine in the Study of Alzheimer's Disease, Vascular Dementia or Mixed Dementia

ADAS-Cog Change



*p<0.001 vs. placebo; Erkinjuntti T et al. Lancet. 2002;359:1283-1290; Janssen Pharmaceutica Products, L.P. (Data on file)

AD2000 Study (UK)

Randomized Clinical Trial of Donepezil / Placebo in 566 AD patients followed for up to 4 years

Cognition (MMSE) and ADLs improved by donepezil over the first 2 years

No significant benefits in risk of institutionalization or progression of disability

Conclusion: "Donepezil is not cost effective, with benefits below minimally relevant thresholds."

Lancet 2004;363:2105-15

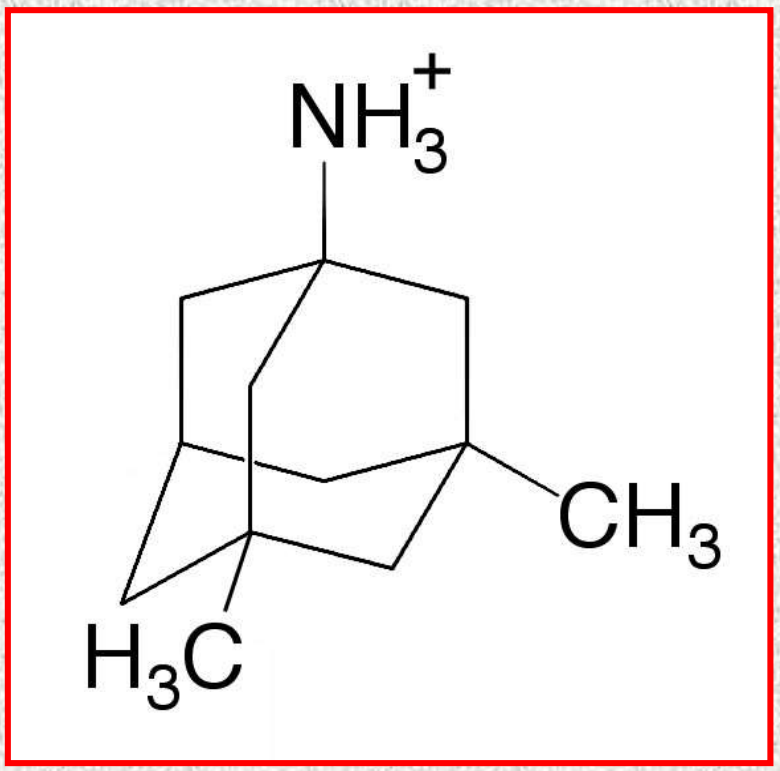
AD2000 Study - Limitations

- Underpowered: 566 / 3,000 subjects enrolled
- High attrition: 48% after 1 year, >80% after 2 years
- Lack of rigorous diagnostic criteria
- Repeated drug wash-out periods

Lancet 2004;363:2105-15

Pharmacology of Memantine

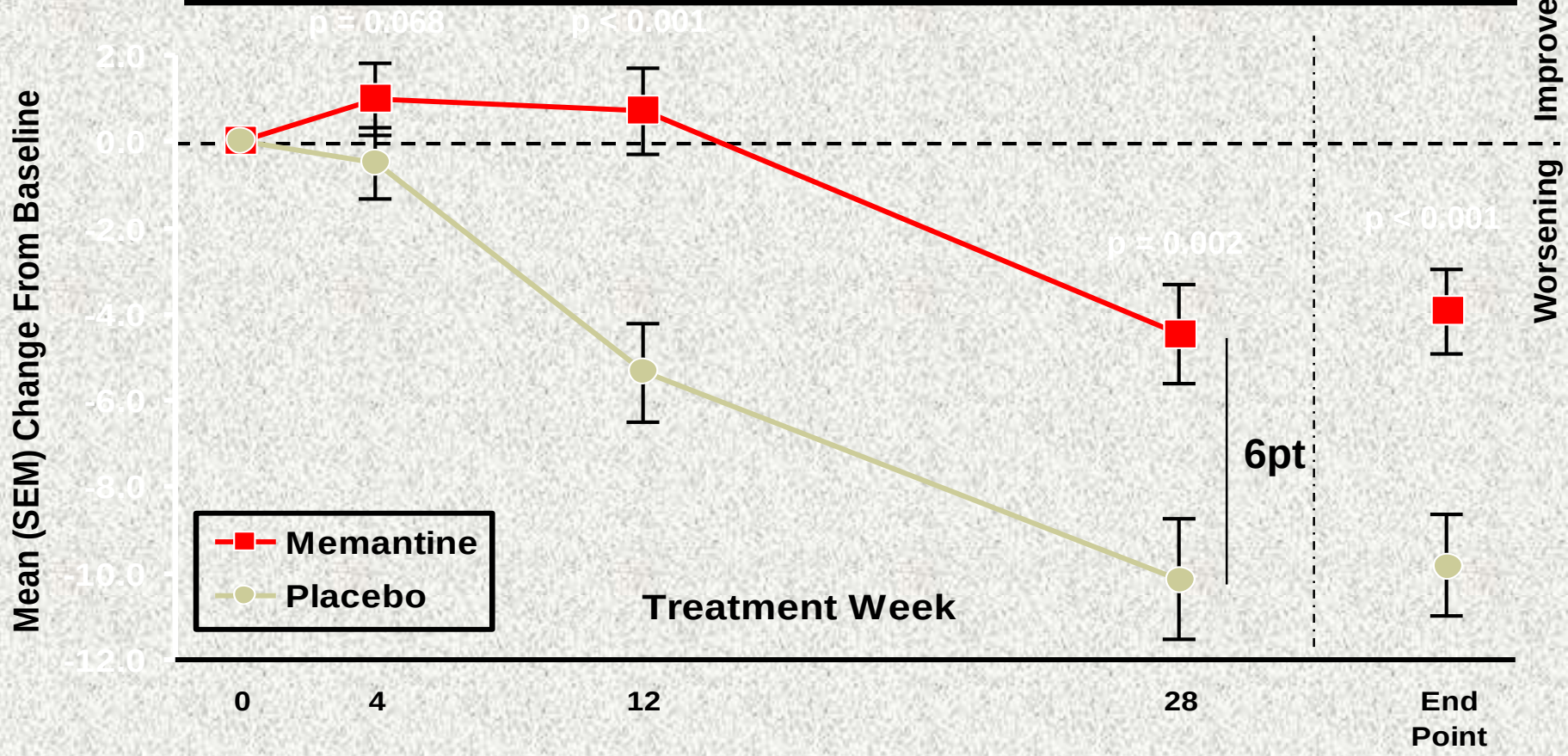
- Aminoadamantane derivative (1-amino-3,5-dimethyladamantane)
- NMDA receptor uncompetitive (open channel) antagonist – low/moderate affinity
- 5-HT_3 receptor allosteric antagonist of low/moderate affinity
- Binds with lower affinity to human nicotinic acetylcholine receptors – but may not be clinically relevant (does not alter AChE activity in the presence or absence of AChEIs)



Memantine: Clinical Pharmacokinetics

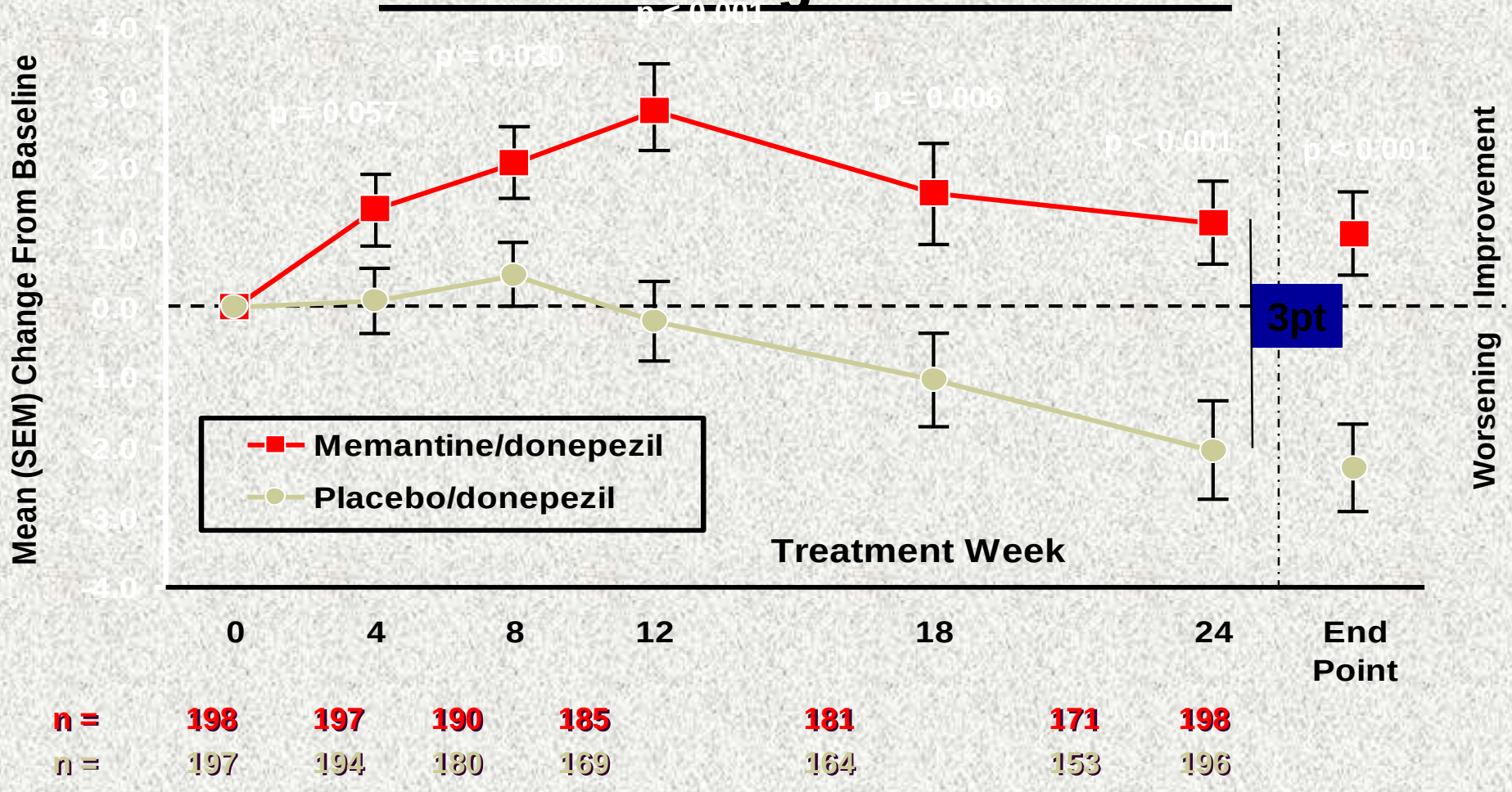
- 100% oral bioavailability
- Crosses blood-brain barrier rapidly
- No effects of food, age and gender
- Linear, dose-proportional kinetics (range 5- 40 mg)
- Elimination half-life of 60 - 80 hours
- Basis for dosing recommendation:
  - **BID dosing better tolerated than QD dosing in early trials**
  - **Up-titration improves tolerability**
- Metabolism:
  - Eliminated mostly in urine as parent drug and inactive metabolites
  - Lower dose recommended in moderate renal disease.
  - No or minimal effects on P450 isoenzymes
- No PK/PD interactions with donepezil

Memantine Improves Cognitive Function in Alzheimer's Disease



Reisberg et al. NEJM 2003;348:1333-1341

Memantine Added to Donepezil in AD Confers Additional Cognitive Benefits



Tariot et al. JAMA 2004;291:317-24

Adverse Events*

(Reported by ≥ 5% of Patients in Either Treatment Group)

Double-Blind, Placebo-Controlled Dementia Trials

	Placebo (N = 922) n (%)	Memantine (N = 940) n (%)
Any adverse event	624 (67.7)	662 (70.4)
Dizziness	49 (5.3)	64 (6.8)
Agitation	98 (10.6)	63 (6.7)
Confusion	42 (4.6)	58 (6.2)
Headache	31 (3.4)	54 (5.7)
Constipation	28 (3.0)	50 (5.3)
Fall	50 (5.4)	48 (5.1)
Inflicted Injury	64 (6.9)	44 (4.7)

- Lack of significant effect on vital signs, tested lab parameters, ECG

*** Adverse events were considered treatment emergent if not present at baseline or if present at baseline and increased in severity during the treatment period.**

Other Pharmacologic Treatments for AD

Anti-inflammatory drugs

- NSAIDs
- COX-2 inhibitors
- Statins

Anti-amyloid agents

- Vaccine
- Secretase inhibitors
- Alzhemed
- Flurizan

Trophic/Metabolic

- Leteprinim (Neotrofin)
- Ginkgo biloba

Symptomatic treatments

- Anticonvulsants
- Antipsychotics
- Antidepressants

Current Controversies over Pharmacotherapy of Behavioral and Psychological Symptoms of Dementia

- Use of Vitamin E: Still recommended?
- Use of antipsychotics for behavioral symptoms:
  - CVAE / Increased total mortality
  - Black box warnings
  - Shortcomings of data
- Anticonvulsants
- Antidepressants
- Cholinesterase inhibitors/ Memantine

Additional Material on Early Detection of Alzheimer's Disease

Neuropathological Studies of Nondemented Elderly

Morris et al[1]

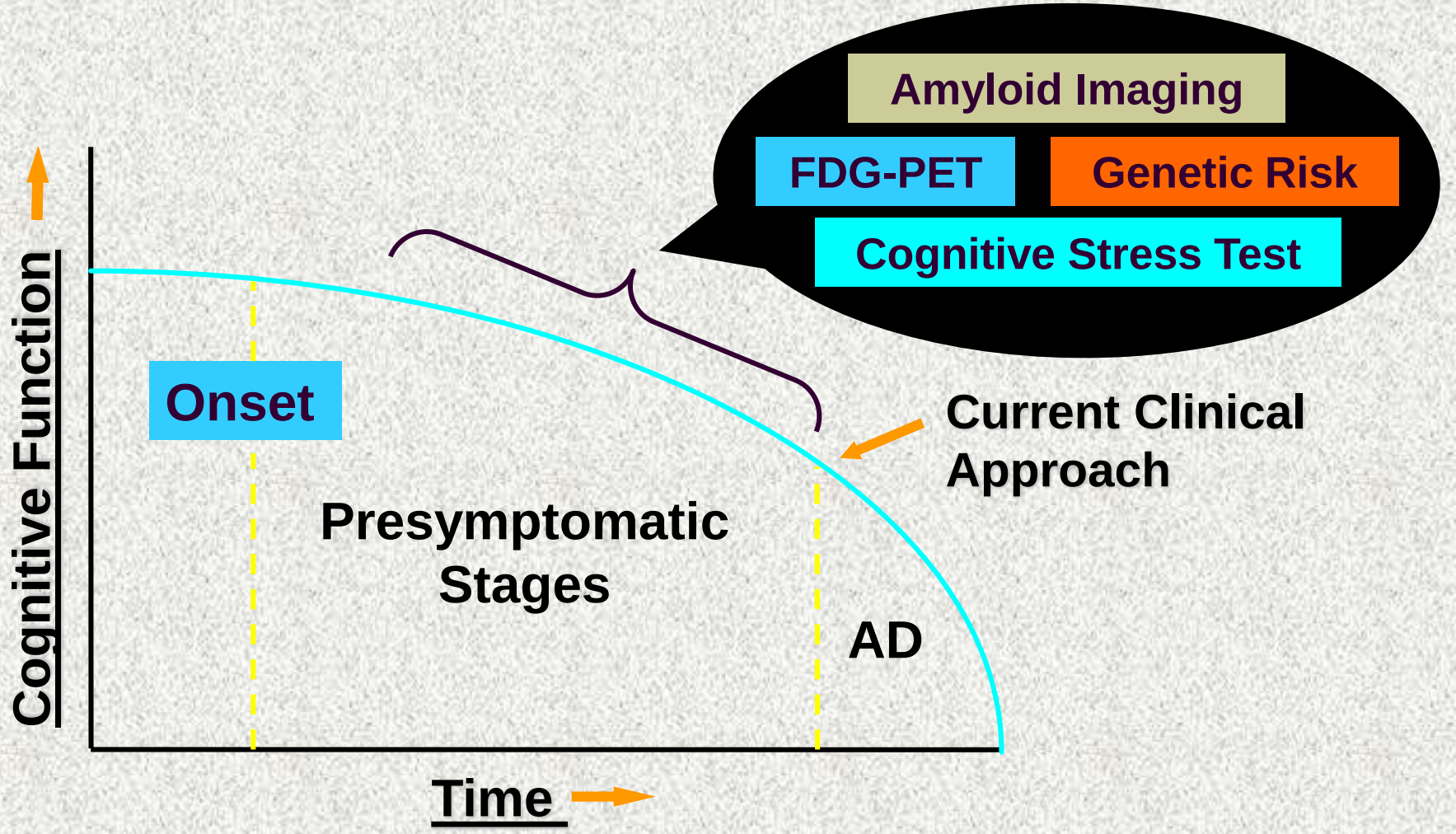
- Cerebral amyloid deposition in 21 elderly men, followed longitudinally
- 78% with high cortical plaque density had MCI
- Few or no plaques = cognitively intact

Braak & Braak[2]

- Neurofibrillary tangles appear to accumulate and extend from the entorhinal cortex as early as the third decade

1 Neurology. 1996;46:707-719; [2]Acta Neuropathol. 1991;82:239-259

Developing Tools for Early Detection of Alzheimer's Disease



Genetic Risk

- Apolipoprotein E (APOE)—gene on chromosome 19
- APOE-4 in 20% of population
- APOE-4 increases risk, lowers onset age for AD
- APOE-4 may have modest effect in predicting cognitive decline in older persons, but APOE alone not considered a useful predictive test

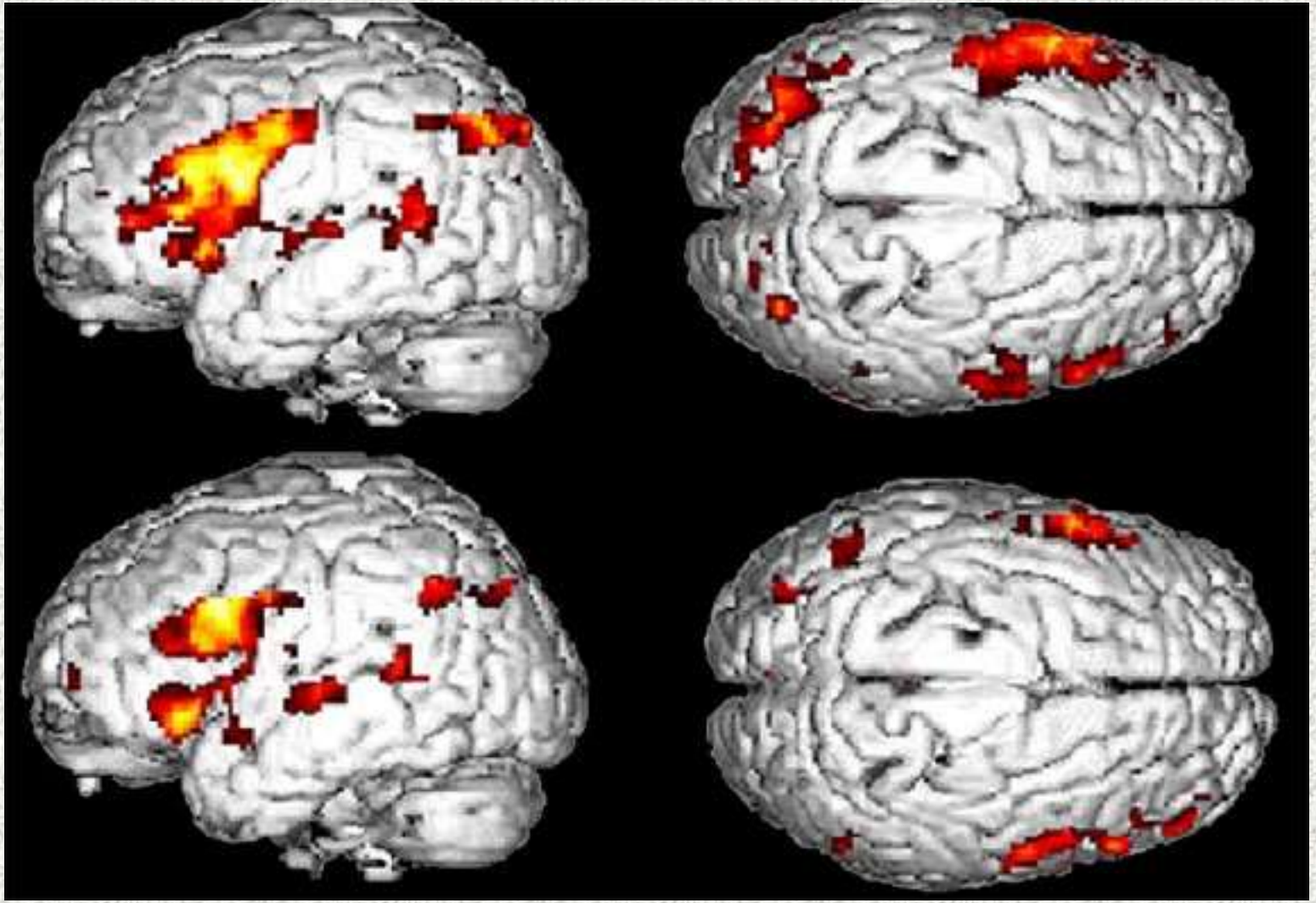
Cognitive Stress Test with fMRI

- Functional brain measures during memory performance may uncover subtle brain dysfunction not observed during mental rest (cf. treadmill ECG for cardiac disease)
- Combine neuroimaging and APOE-4 measures of genetic risk in order to identify abnormalities that may predict future cognitive decline

Bookheimer SY, Strojwas MH, Cohen MS, et al. N Engl J Med. 2000

Increase Brain Activity During Memory Tasks

E-4

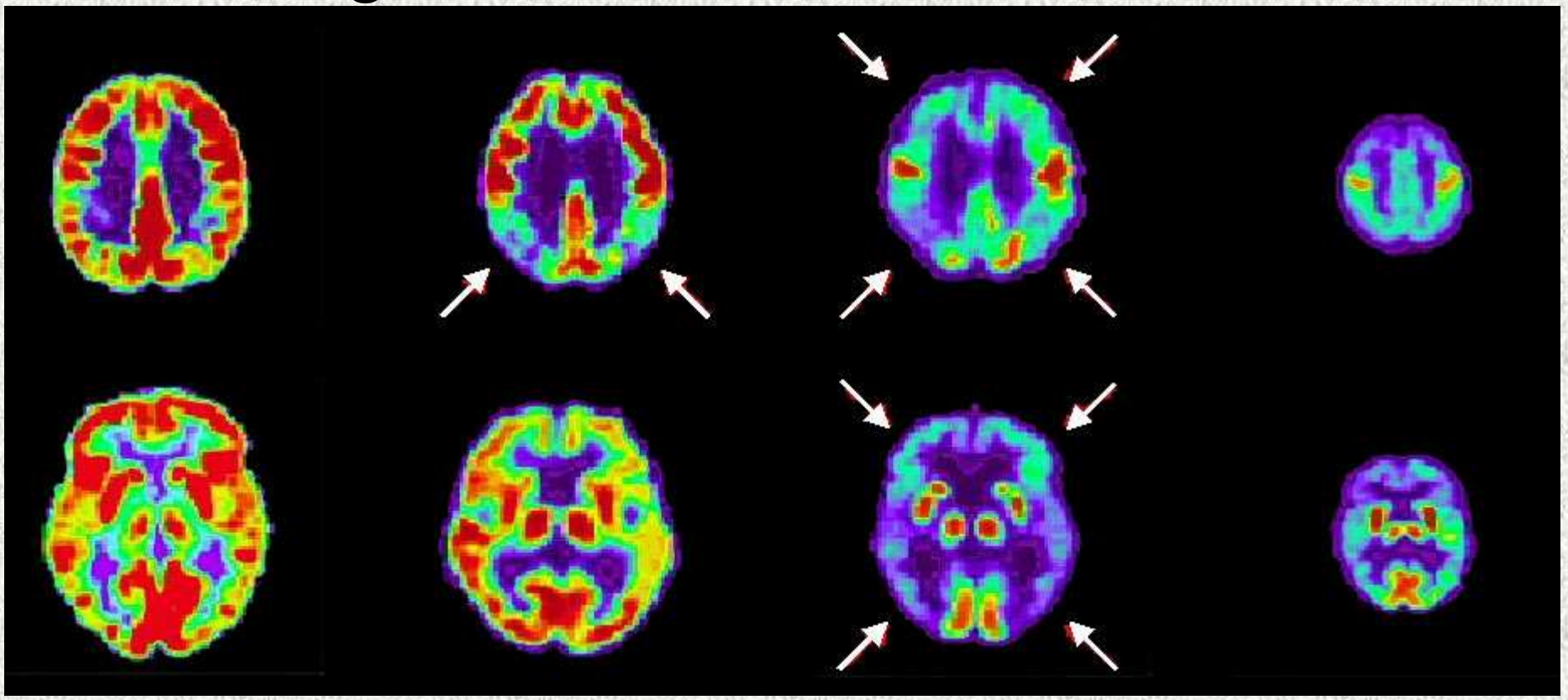


E-3

Bookheimer SY, Strojwas MH, Cohen MS, et al. N Engl J Med. 2000

Positron Emission Tomography (PET)

Cerebral Metabolism in Alzheimer's Disease Progression and in Normal Brains



Courtesy of Gary W. Small, M.D., UCLA

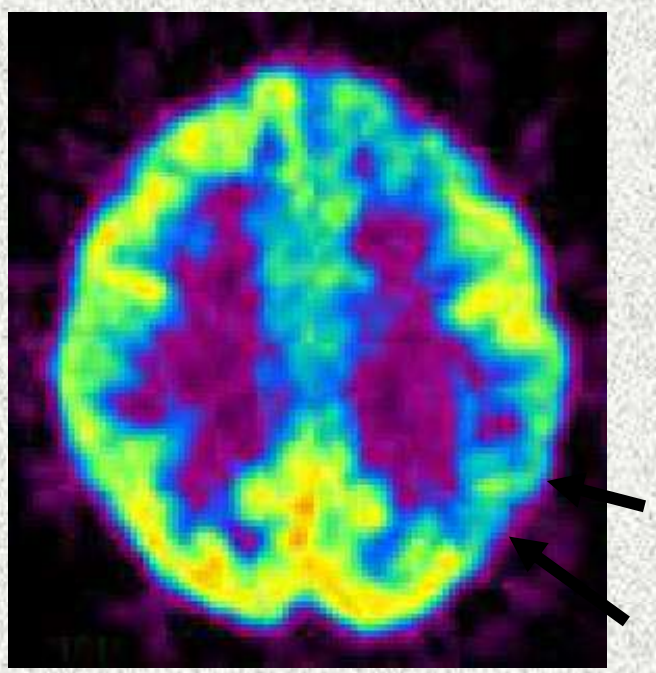
Accuracy of Early Diagnostic Assessment: Standard Clinical vs. FDG-PET

- Multiple clinical assessments over years in 134 patients
- Diagnostic accuracy[1]
  - Sensitivity: 83-85%
  - Specificity: 50-55%
- Single baseline PET scan in 284 patients (138 autopsy diagnosis)
- Diagnostic accuracy[2]
  - Sensitivity: 93-95%
  - Specificity: 73-78%

[1]Lim et al. J Am Geriatric Soc. 1999;47:564-569; [2]Silverman et al. JAMA. 2001;286:2120-2127

Case Example

- 65-year-old woman diagnosed with depression and attention deficit after
  2 1/2 years of multiple neuropsychiatric evaluations including serial MRI scans
- PET showed typical Alzheimer's pattern
- Symptoms improved with cholinergic treatment



FDG-PET shows parietal deficit

Silverman & Small, 2002. Am J Psychiatry. 2002;159:1482-1488

Practical Consequences of Improved Diagnostic Accuracy

- Accurate diagnostic information and education reduces family/caregiver burden
- Decreased likelihood of repeated diagnostic assessments and testing
- "Alzheimer's disease label" improves caregiver attitudes[1]
- Information about the disease improves quality of life for family/patient and delays nursing home placement[2]

[1]Wadley et al. J Gerontol. 2001;56:244-252; [2]Mittelman et al. JAMA. 1996;276:1725-1731

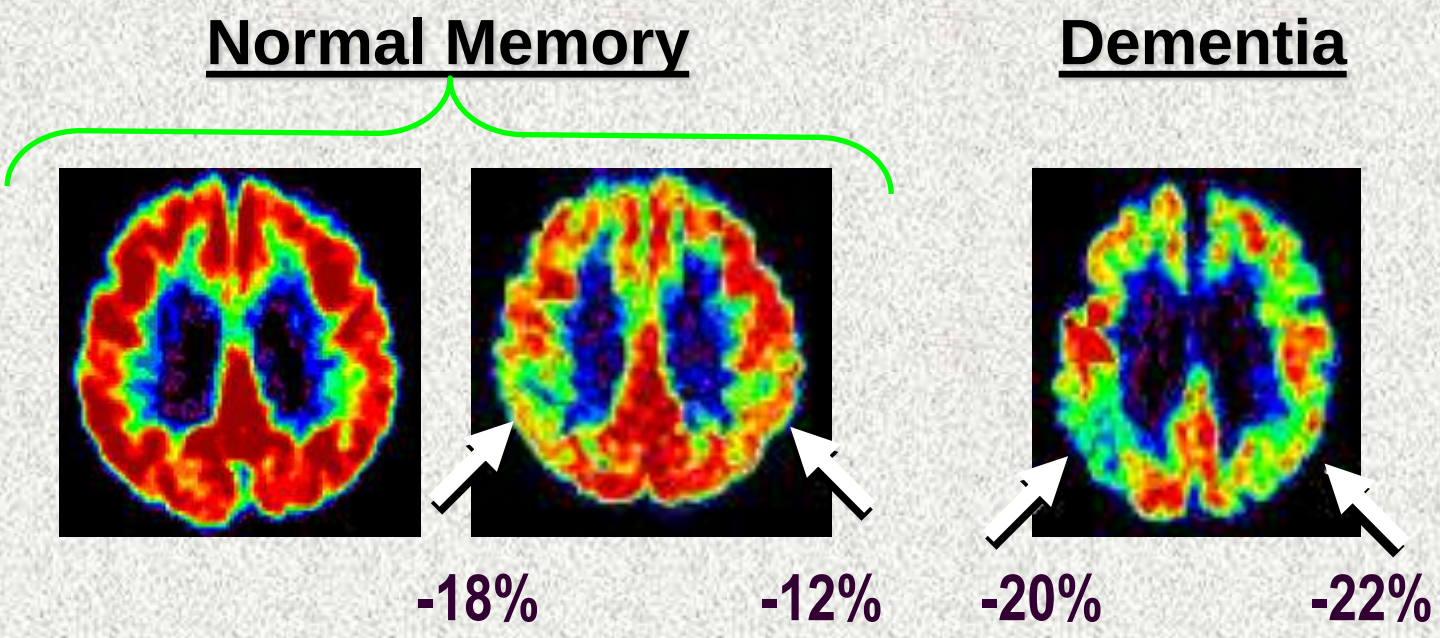
Practical Consequences of Improved Diagnostic Accuracy (Cont.)

Early, accurate diagnosis and treatment ...

- **Maintains patients at higher levels of functioning leading to fewer MD/hospital visits[1]**
- **Reduces caregiver burden[2]**
- **Delays nursing home placement[3]**
- **Reduces use of other psychotropic drugs[4]**

[1]Small et al. J Am Geriatr Soc. 2002;50:321-327; [2]Shikier et al. J Am Geriatr Soc. 2000;48:268-274; [3]Knopman et al. Neurology. 1996;47:166-177; [4]Small et al. Clin Therapeutics. 1998;20:838-850

Pet and Genetic Risk for Alzheimer Disease

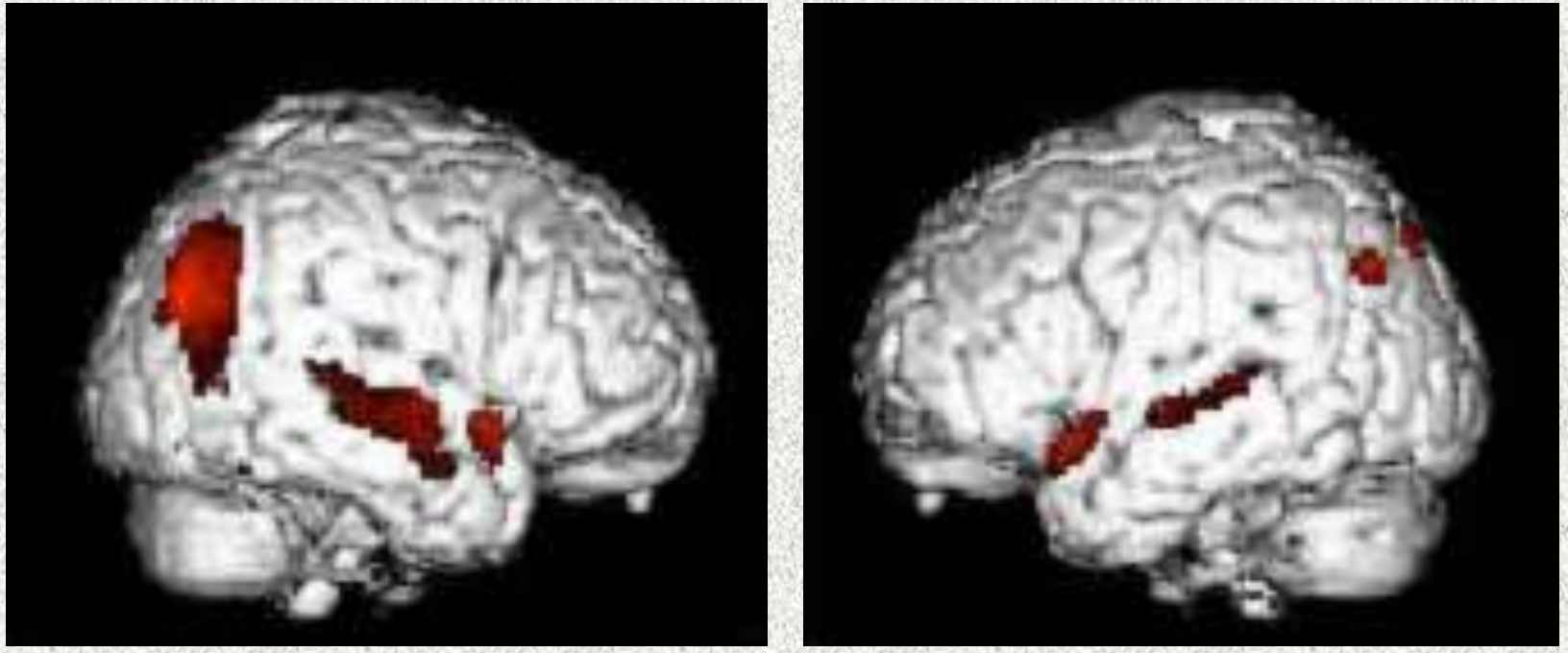


Genetic Risk **No APOE-4** **APOE-4**

- **Lower inferior parietal metabolism in nondemented persons with a single copy of APOE-4**

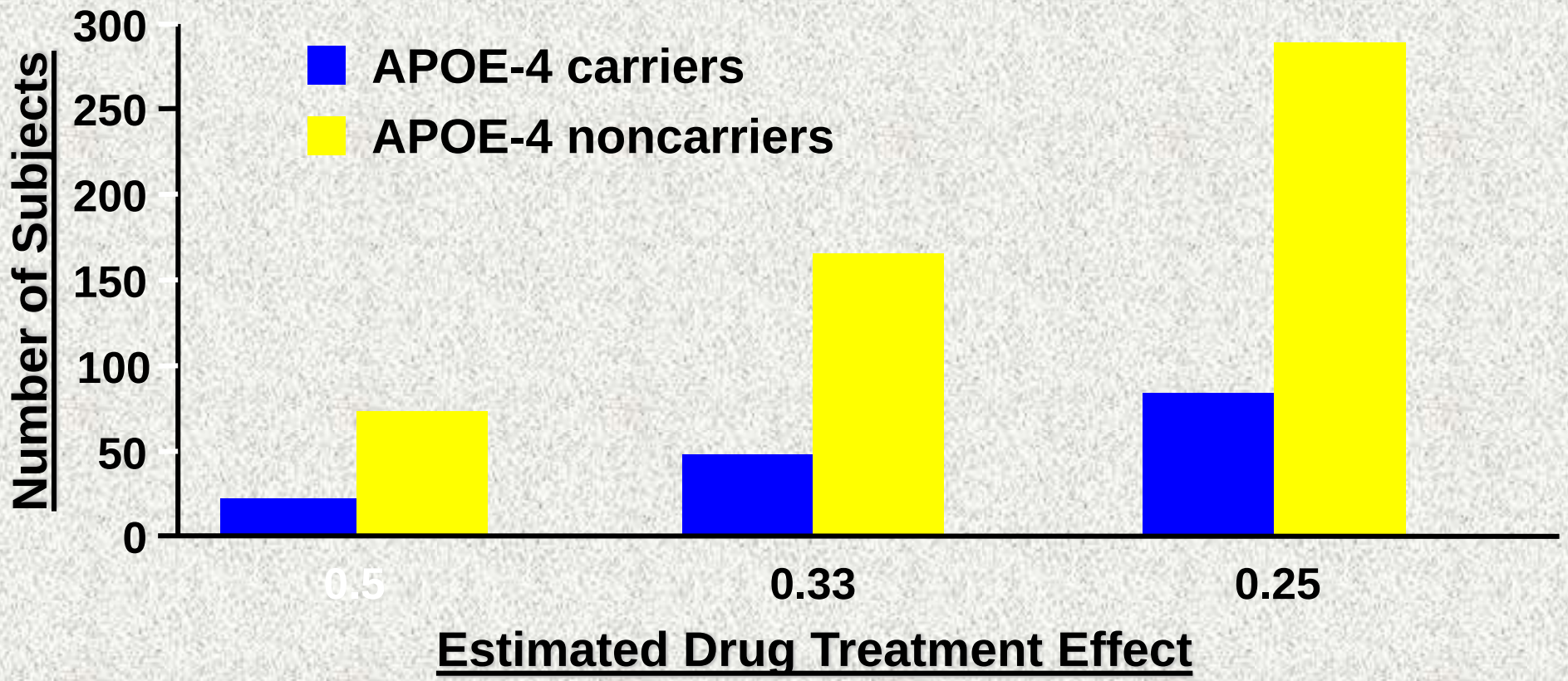
Small et al. PNAS. 2000;97:6037-6042

PET Scans Show Brain Function Decline in People at Genetic Risk for Alzheimer's Disease



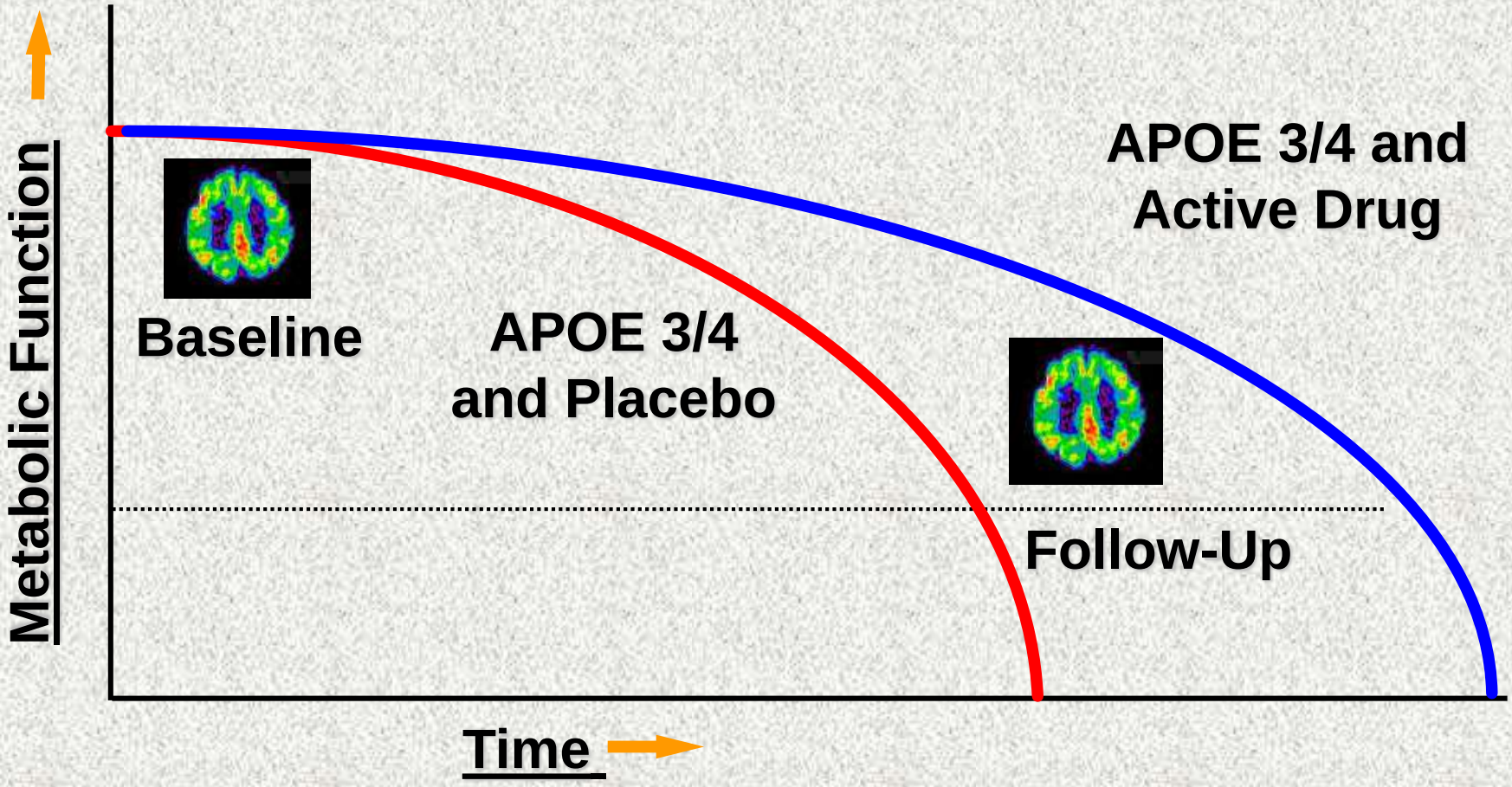
Small et al. PNAS. 2000;97:6037-6042

Number of Subjects Per Treatment Group Needed to Detect a Drug Effect in 2 Years Using PET*



*Posterior cingulate metabolism; Based on data from: Reiman et al. PNAS. 2001;98:3334-3339

Possible Outcomes Using PET as a Surrogate Marker in AAMI Clinical Trials



AAMI = age-associated memory impairment

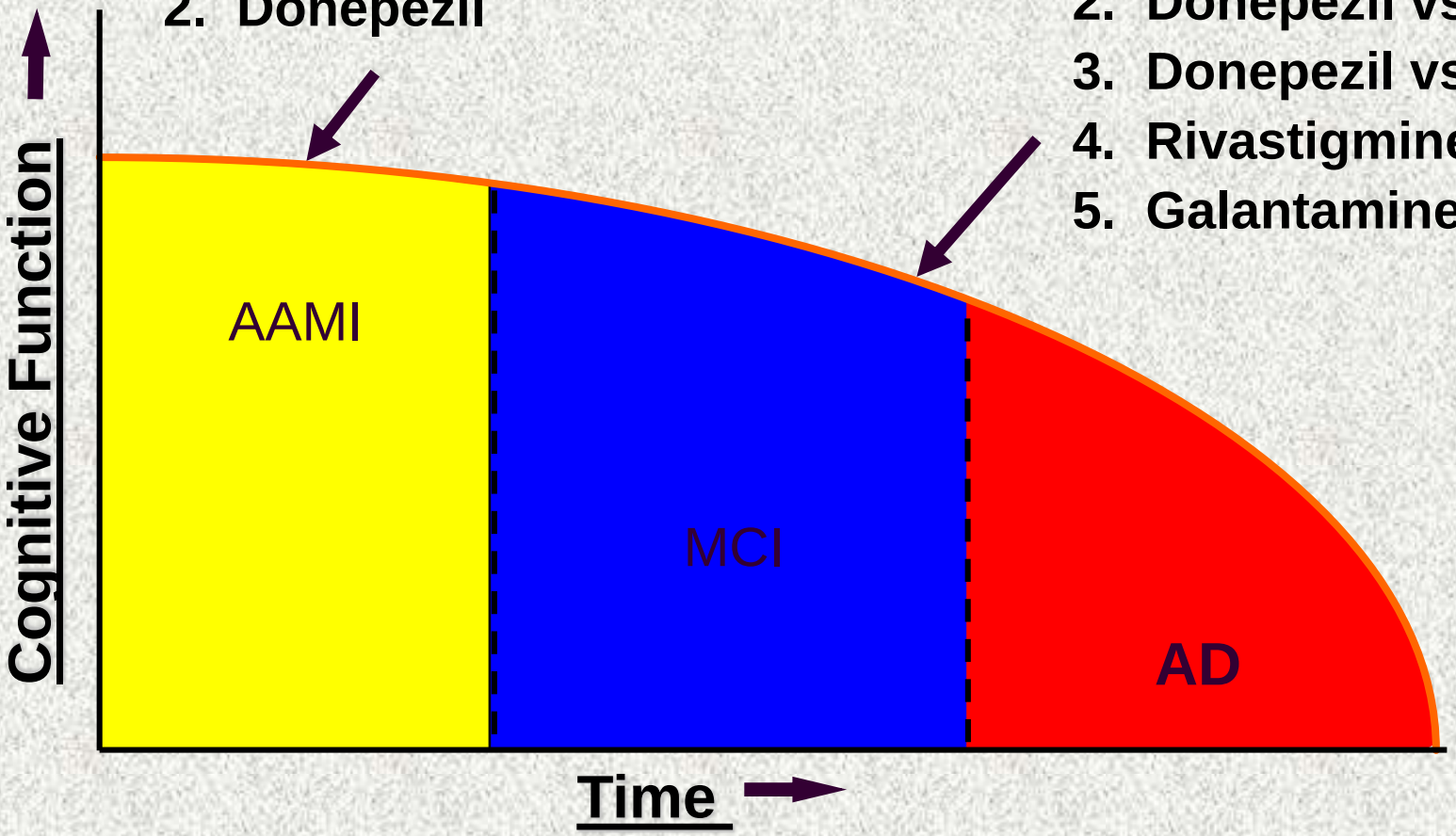
Early Detection and Intervention

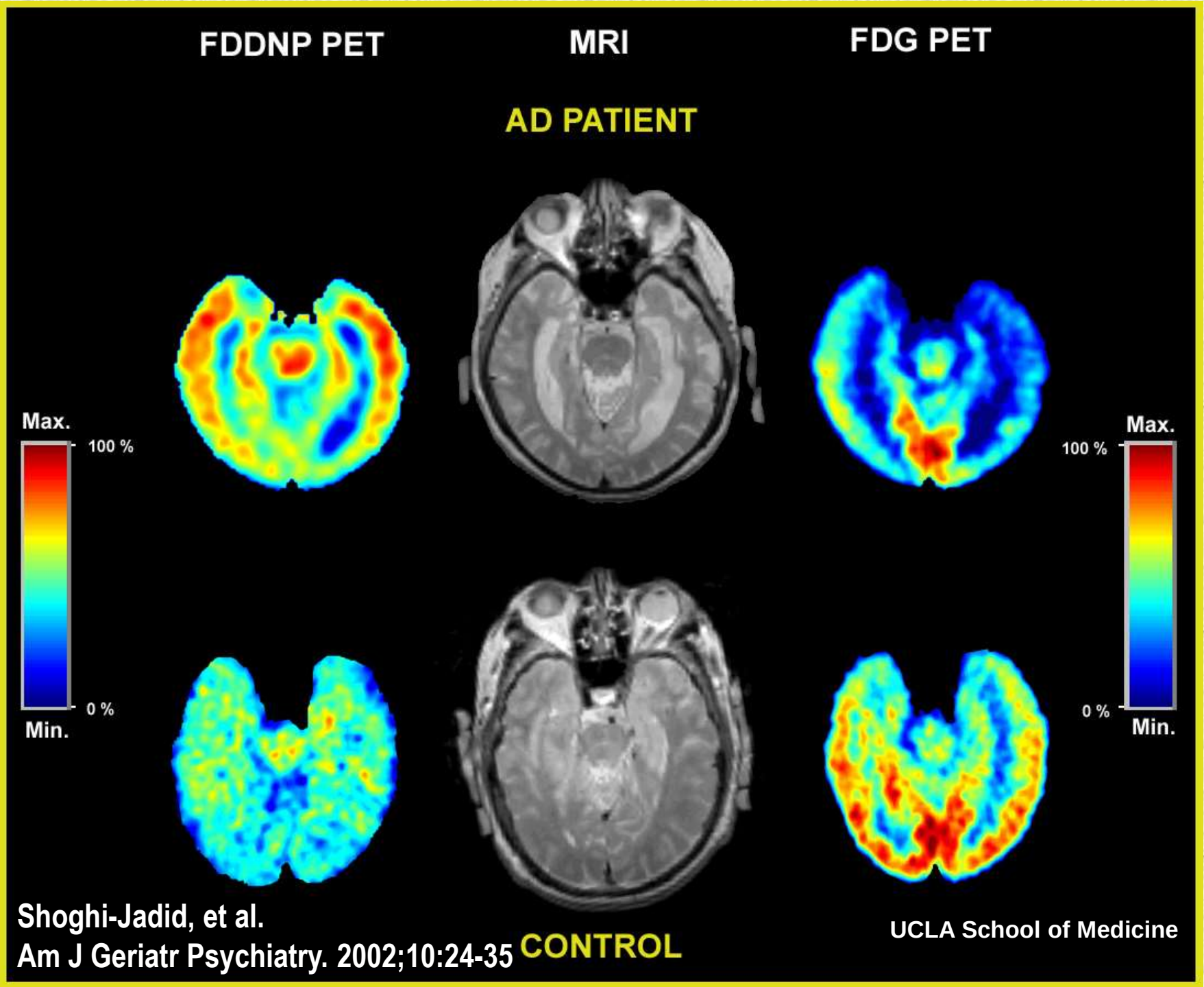
1º outcome: PET + APOE-4

1. Celecoxib
2. Donepezil

1º outcome: clinical exam

1. Donepezil vs. vitamin E
2. Donepezil vs. ginkgo
3. Donepezil vs. estrogen
4. Rivastigmine
5. Galantamine




FDDNP PET
MRI
FDG PET
AD PATIENT
Max.
100 %
0 %
Min.
Max.
100 %
0 %
Min.
Shoghi-Jadid, et al.
Am J Geriatr Psychiatry. 2002;10:24-35
CONTROL
UCLA School of Medicine

Slowing Down Brain Aging

- Minimize stress
- Mental aerobics
- Physical exercise
- Healthy brain diet
- Lifestyle choices
- Medicines
- Memory training skills

Small. BMJ. 2002; 324:1502-5

Major Points

- Dementia is underrecognized and undertreated in primary care and in mental health settings
- Dementia can be recognized and treated beneficially in primary care and mental health settings
- Neuroimaging with PET can show a pattern of regional glucose metabolism that improves early detection of Alzheimer's disease with greater specificity

Major Points (cont.)

- Both pharmacological and nonpharmacological interventions may benefit overall brain health and dementia course
- Novel approaches to *in vivo* plaque and tangle imaging will be useful in monitoring potential disease-modifying agents

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Major Points (cont.)

- Neuroimaging with PET can show a pattern of regional glucose metabolism that improves early detection of Alzheimer's disease with greater specificity
- Novel approaches to *in vivo* plaque and tangle imaging will be useful in monitoring potential disease-modifying agents

Suggested Readings

- Cummings JL. Alzheimer's disease: from molecular biology to neuropsychiatry. Seminars in Clinical Neuropsychiatry. 8:31-6, 2003
- Cummings JL. Cole G. Alzheimer disease. JAMA. 287:2335-8, 2002
- Small GW. Rabins PV. Barry PP. et al. Diagnosis and treatment of Alzheimer disease and related disorders. Consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. JAMA. 278:1363-71, 1997
- Small GW. What we need to know about age related memory loss. Br Med J 2002;324:1502-5.

Self-Assessment Question 1

Which of the following are required for a diagnosis of dementia?

A. Cognitive decline is ACQUIRED
B. MEMORY is affected
C. In addition to memory, ANOTHER cognitive function is affected.
D. Symptoms are not attributable to delirium or another psychiatric disorder.
E. All of the above

Self-Assessment Question 2

Which of the following cognitive or behavioral domains is affected in dementia?

A. Memory
B. Executive function
C. Behavior
D. Activities of daily living
E. All of the above

Self-Assessment Question 3

Which of the following statements is correct?

A. Alzheimer's Disease affects greater than 30% of adults older than 85 years of age.
B. Alzheimer's Disease is infrequent among adults less than 60 years of age.
C. Alzheimer's Disease is the most common cause of dementia.
D. All of the above
E. None of the above

Self-Assessment Question 4

Treatment of AD with cholinesterase inhibitors is based on which of these rationales?

A. Noradrenergic neurotransmission in the locus ceruleus is reduced in late AD
B. Pathological stimulation of NMDA receptors is associated with excitotoxic death of neurons.
C. The number of cholinergic neurons in the basal forebrain is reduced in late Alzheimer's disease.
D. All of the above
E. None of the above

Self-Assessment Question 5

Treatment of AD with memantine is based on which of these rationales?

A. Noradrenergic neurotransmission in the locus ceruleus is reduced in late AD
B. Pathological stimulation of NMDA receptors is associated with excitotoxic death of neurons.
C. The number of cholinergic neurons in the basal forebrain is reduced in late Alzheimer's disease.
D. All of the above
E. None of the above

Self-Assessment Question Answers

1. E
2. E
3. A
4. C
5. B