Morningside Ministries

# Ask the Geriatrician

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# ALZHEIMER'S DISEASE UPDATE

# OUTLINE

I. HISTORY
II. DEFINITION
III. EPIDEMIOLOGY
IV. COURSE
V. GENETICS AND RISK FACTORS
VI. BIOMARKERS AND TESTING
VII. IMAGING
VIII. EVALUATION
IX. TREATMENT –CURRENT AND FUTURE
X. CAREGIVER SUPPORT

# SIRACH 3, 2-5

- “My sons, take care of your father when he is old. Grieve him not as long as he lives. Even if his mind fail be consoling to him. Revile him not. Kindness to a father will not be forgotten.”

# THE CASE OF AUGUSTE D.

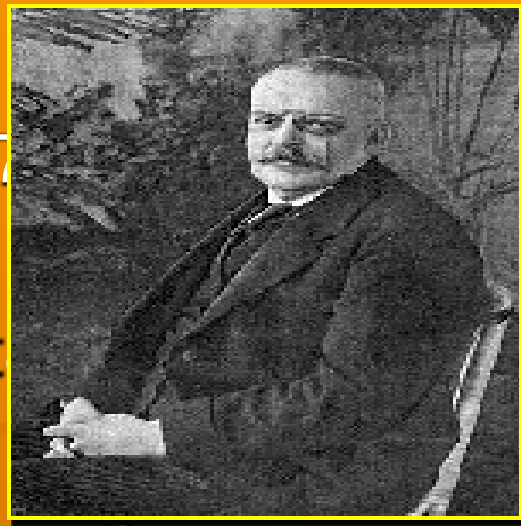
51 y/o WF admitted 1902, expired 4/8/06; case presented Nov 3, 1906. No questions or comments at conclusion.

CC " I have lost myself"

S/Sxs: poor memory, aphasia, confusion, paranoia, negativism, wandering

Treatment plan: dietary, activity, exercise, massage, balneotherapy. Alcohol, and later chloral hydrate for sleep

# Alzheimer's Disease



First described by Alois Alzheimer, a German neuropathologist, in 190

Observed in a 51-year-old female patient with memory loss, disorient and hallucinations

Postmortem studies characterized senile plaques and neurofibrillary tangles (NFTs) in the cerebral cortex

- Senile plaques: Extracellular accumulation of insoluble fragments of beta-amyloid ($A\beta_{1-42}$)
- NFTs: Intracellular accumulation of hyperphosphorylated tau strands

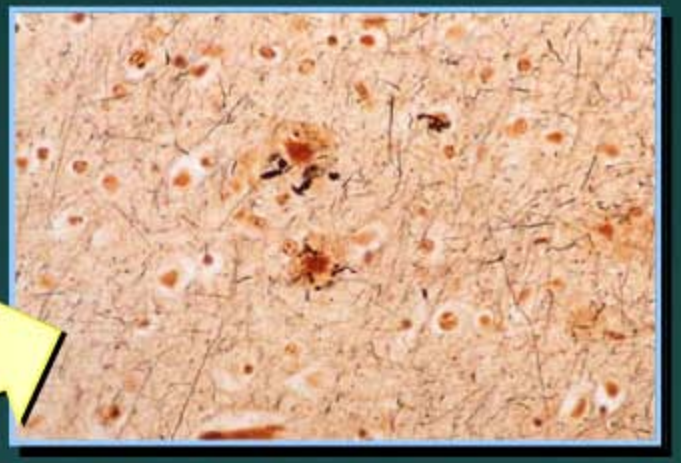
# Barriers to Diagnosis and Treatment

- Cognitive impairment overshadowed by other comorbid medical/psychiatric illnesses
- Time for diagnosis
- Lack of understanding of diagnostic tests
- Therapeutic nihilism
- Cost associated with diagnosis and treatment
- Perception that lack of improvement equates to lack of efficacy

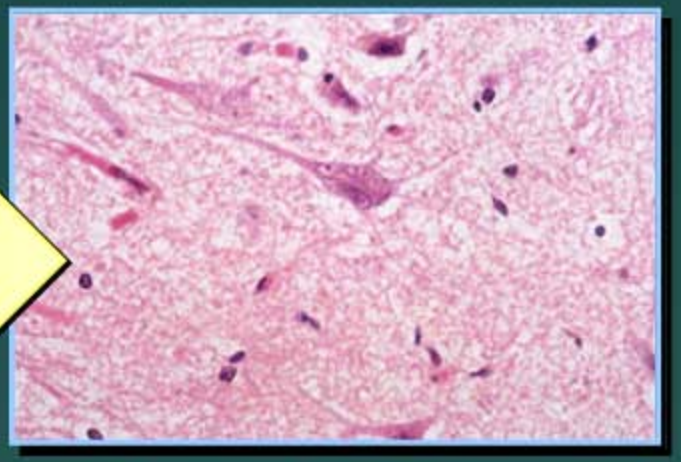
# Pathology

*AD is a progressive neurodegenerative disorder associated with:*

- Accumulation of extracellular senile (beta-amyloid [Aβ]) plaques



- Accumulation of intracellular NFTs



NFTs = neurofibrillary tangles.

# HISTORY

1906 A. Alzheimer reports “Auguste D.”

1950s Identity of senile dementia

1970s Cholinergic deficit discovered

“Coming epidemic”

1980s Amyloid pathology; genetic influences

1990s Present treatments introduced

Non-AD identified

MCI

Disease-modification- interfere with APP processing; decrease AB accumulation or increase AB clearance

# DSM-IV Definition of Alzheimer's Disease

Development of multiple cognitive deficits manifested by both memory impairment and 1 or more of the following cognitive disturbances: aphasia, apraxia, agnosia, or disturbance in executive functioning

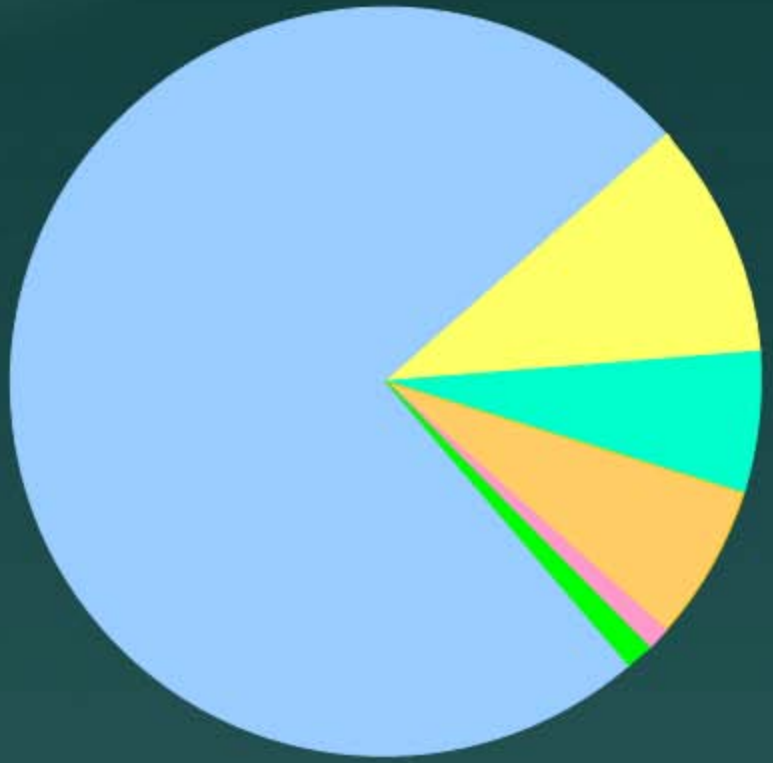
Cognitive deficits cause significant impairment in social functioning and represent a significant decline from a previous level of functioning

Course is gradual in onset with continuing cognitive decline

Deficits are not due to any other CNS disorder, systemic illness, or substance-induced condition

- Deficits do not occur exclusively during the course of delirium

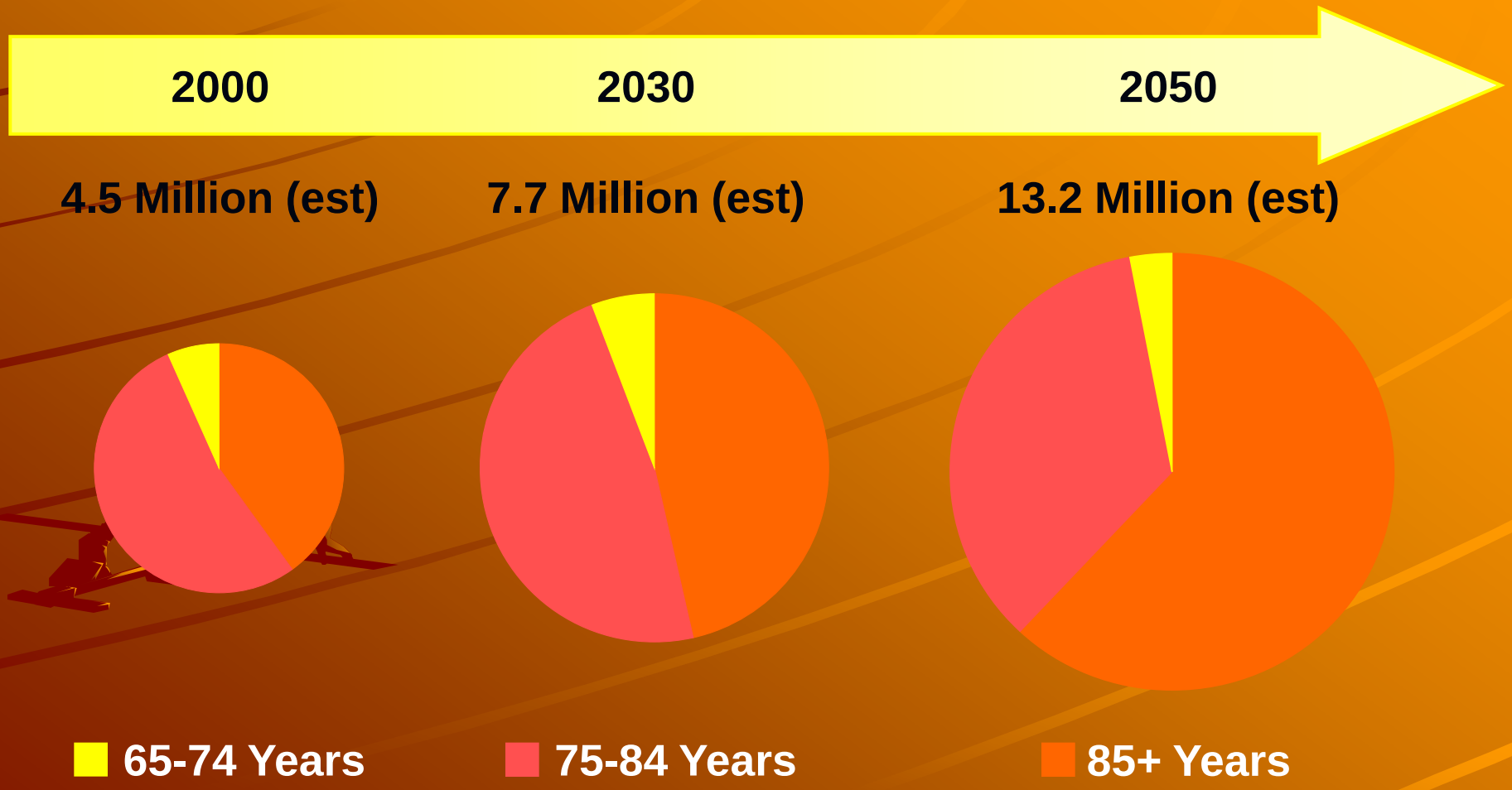
# Differential Diagnosis: Dementia Etiology



- Alzheimer's disease (AD)
- Vascular dementia (VaD) + AD
- VaD
- Lewy body dementia
- Frontal lobe dementia/ other degenerative dementias
- Depression, tumor, hydrocephalus, metabolic disorders, and other potentially reversible dementias

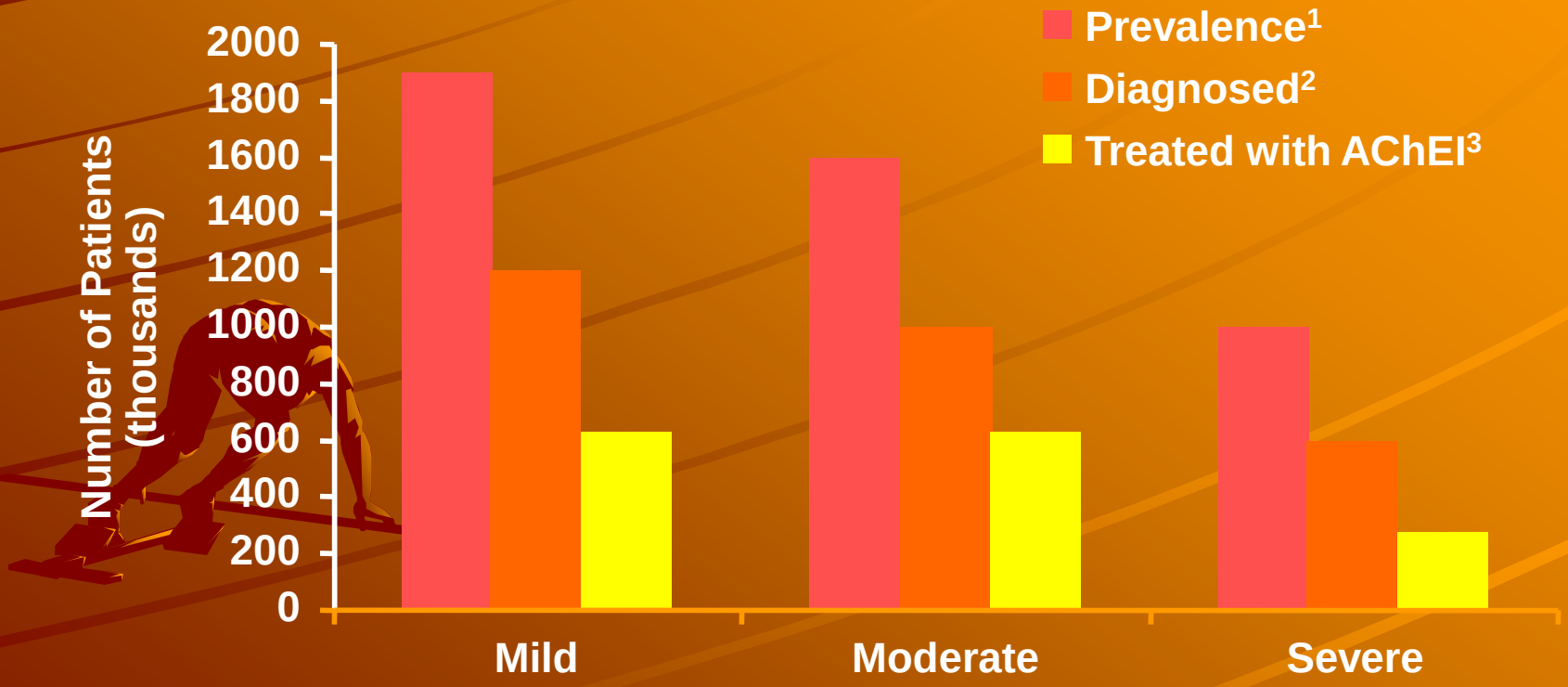
Adapted from: Green RC. *Diagnosis and Management of Alzheimer's Disease and Other Dementias.* Caddo, Okla: Professional Communications; 2005.

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



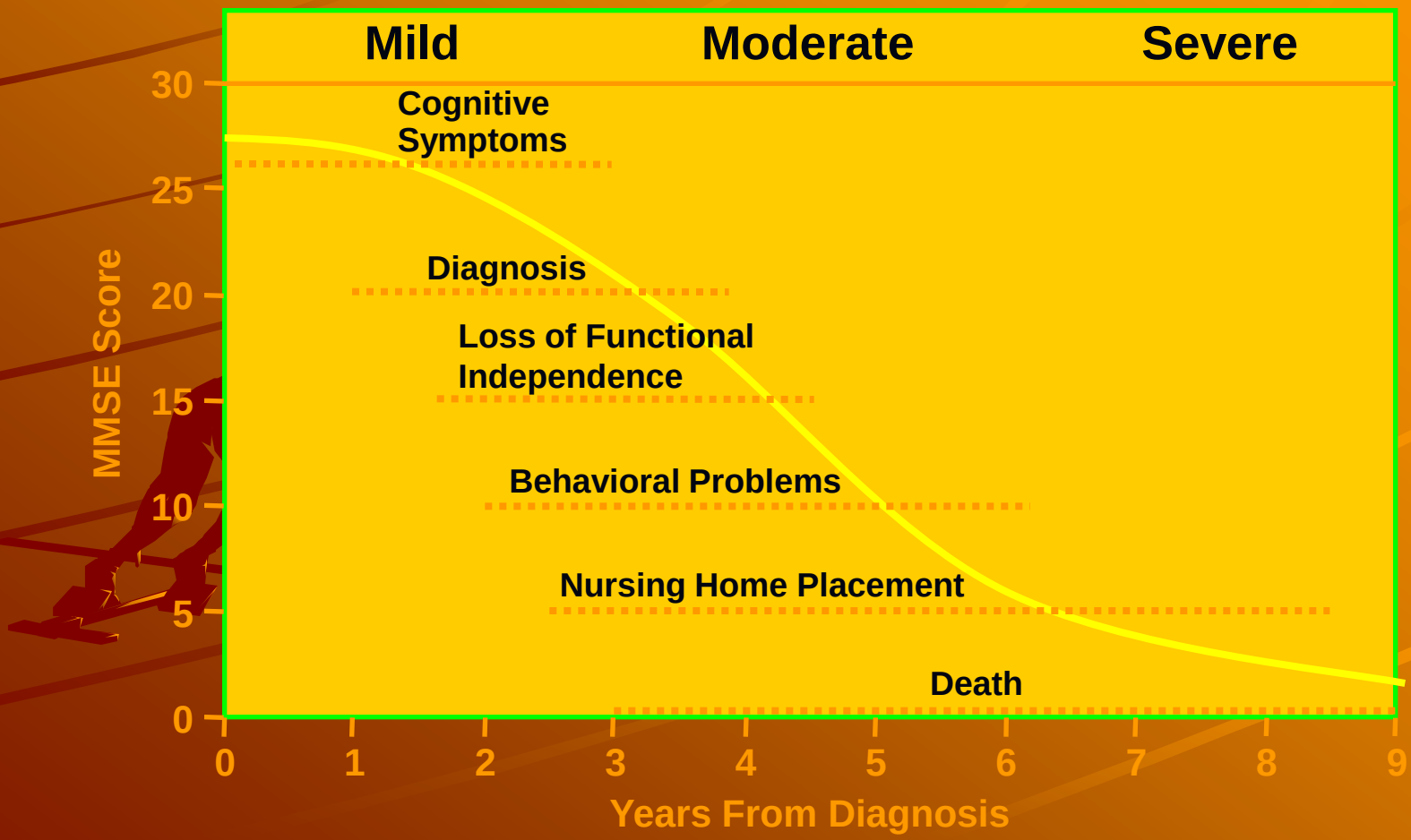

Source: Hebert LE, et al. *Arch Neurol*. 2003;60:1119-1122.

# Prevalence and Treatment Rates

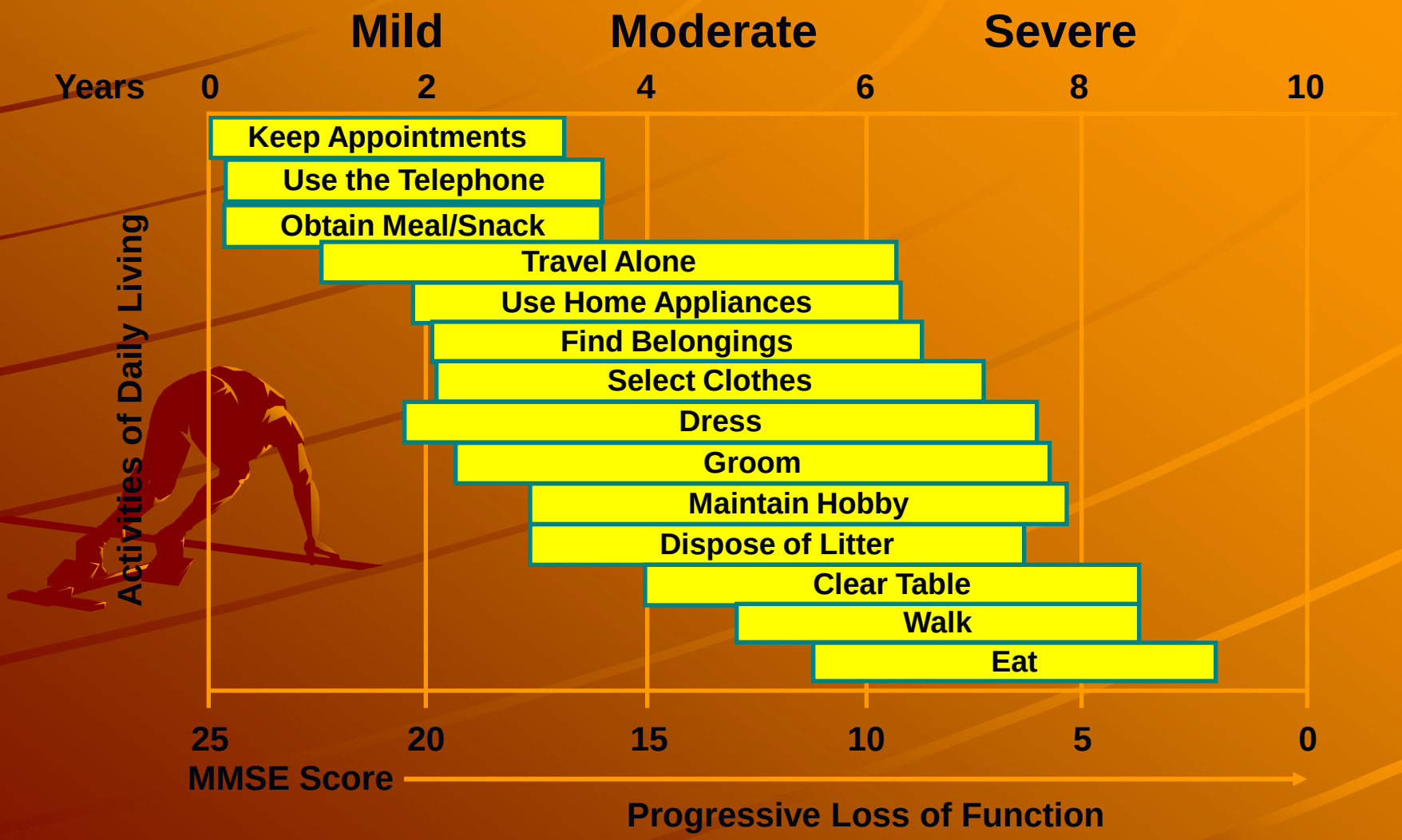



Sources: 1. Hebert LE, Scherr PA, Bienias J, et al. *Arch Neurol*. 2003;60:1119-1122.
2. Datamonitor AD Treatment Algorithms. 2002.
3. Market Measures. 2003.

# Clinical Disease Progression



# Progressive Loss of Activities of Daily Living




Adapted from Galasko D, et al. *Eur J Neurol*. 1998;5(suppl 4):S9-S17.

# EMERGING CLINICAL TARGETS DIAGNOSIS

*Genetics*: APOE4, SORL1

*Imaging*: MRI (volume), FDG-PET (metabolism), FDGNP-PET/ PET-PIB

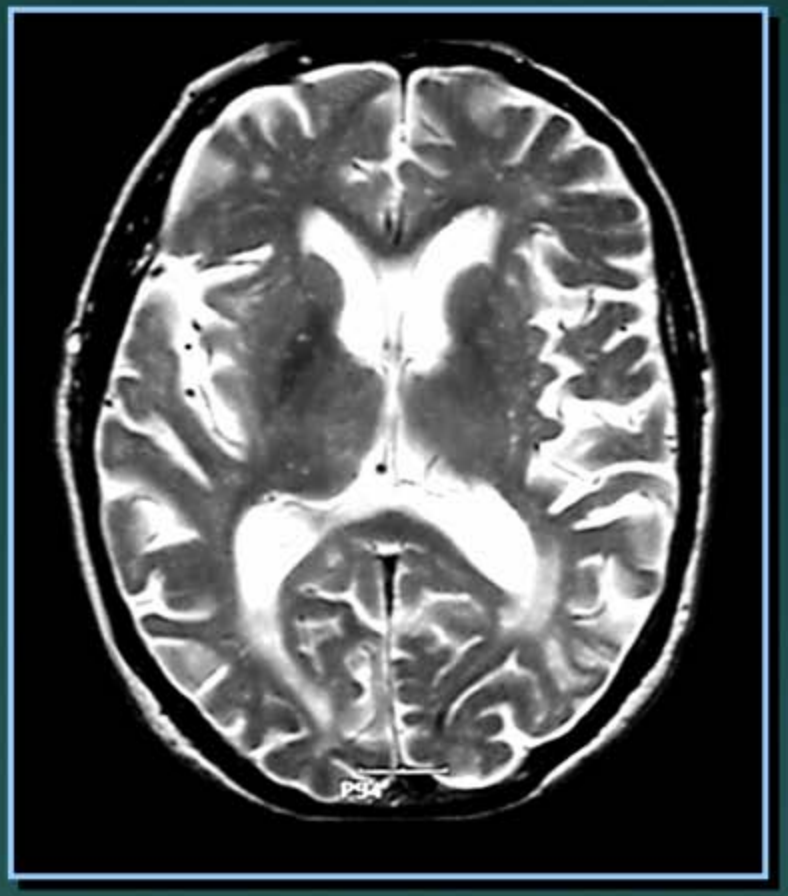
*Biomarkers*: CSF
Serum measures

*Testing*: Memory screens- MOCA
SLUMS

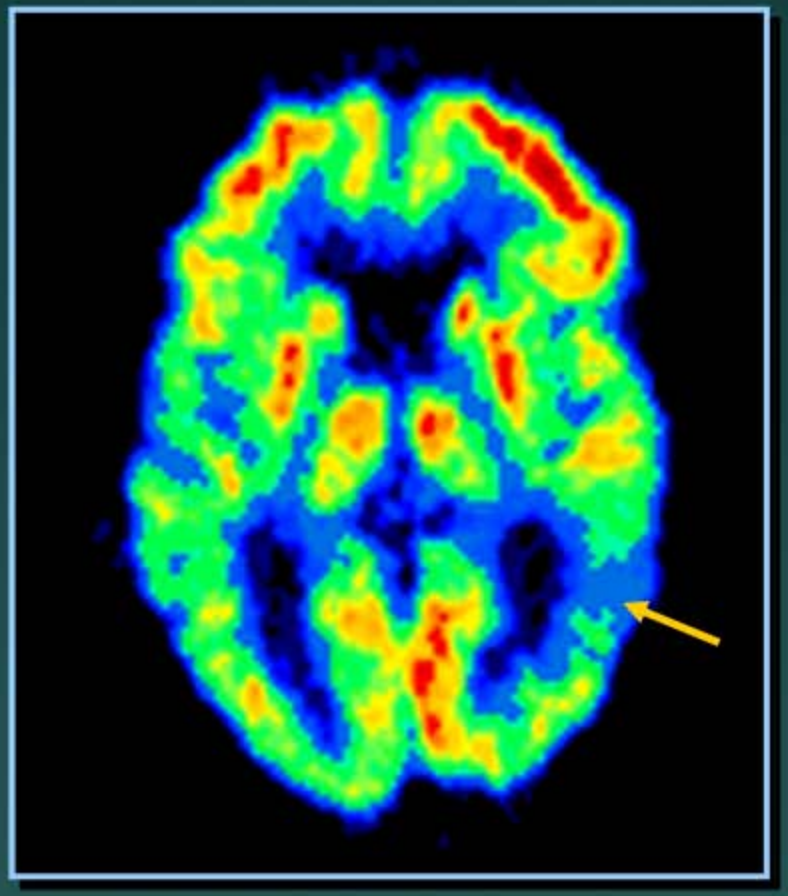
*MCI*: Amnestic type

# MRI and PET Scan of Patient With Alzheimer's Disease

*MRI*

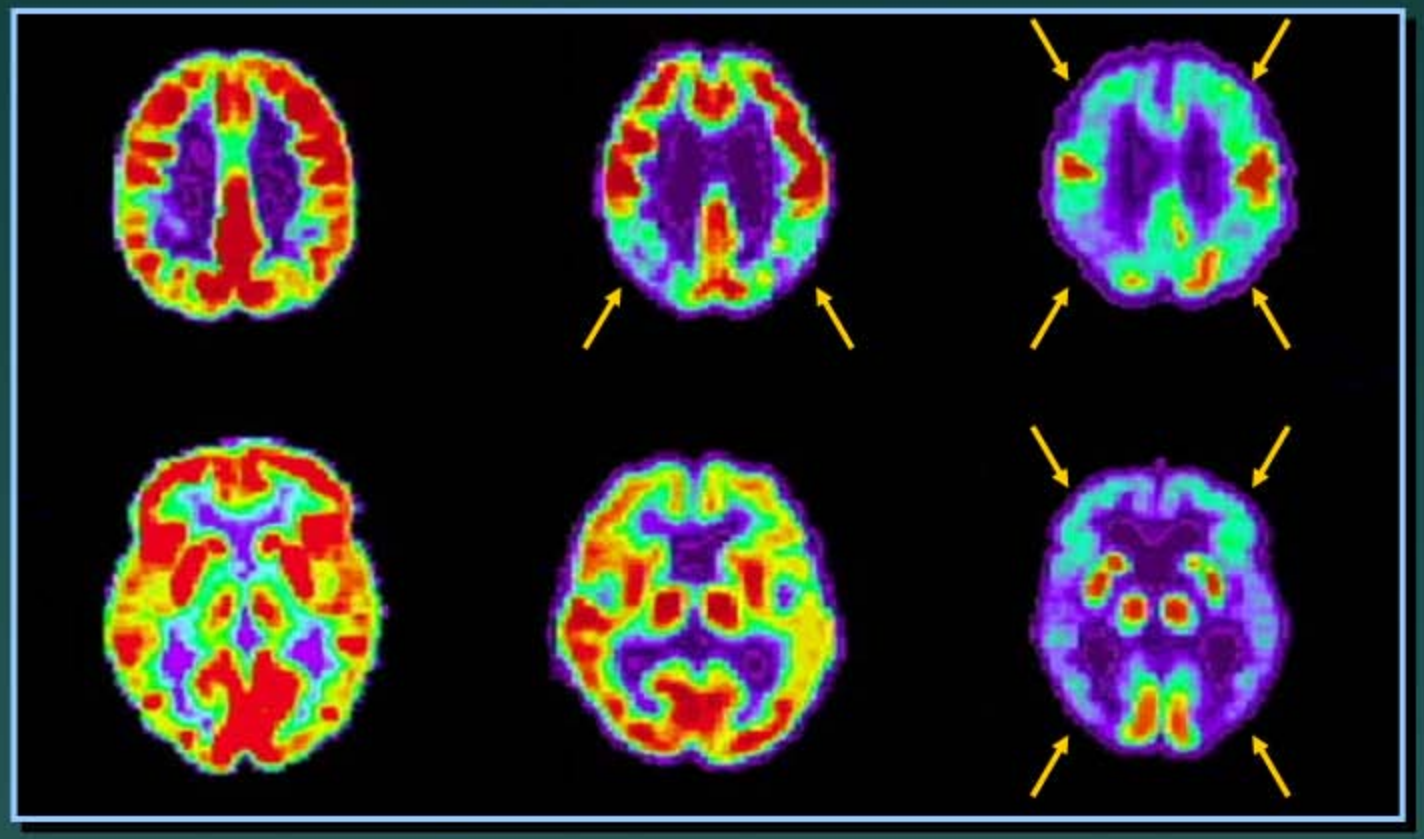


*PET*



Used with permission from GW Small, UCLA School of Medicine.

# Positron Emission Tomography (PET): Cerebral Metabolism in Alzheimer's Disease Progression and in Normal Brains

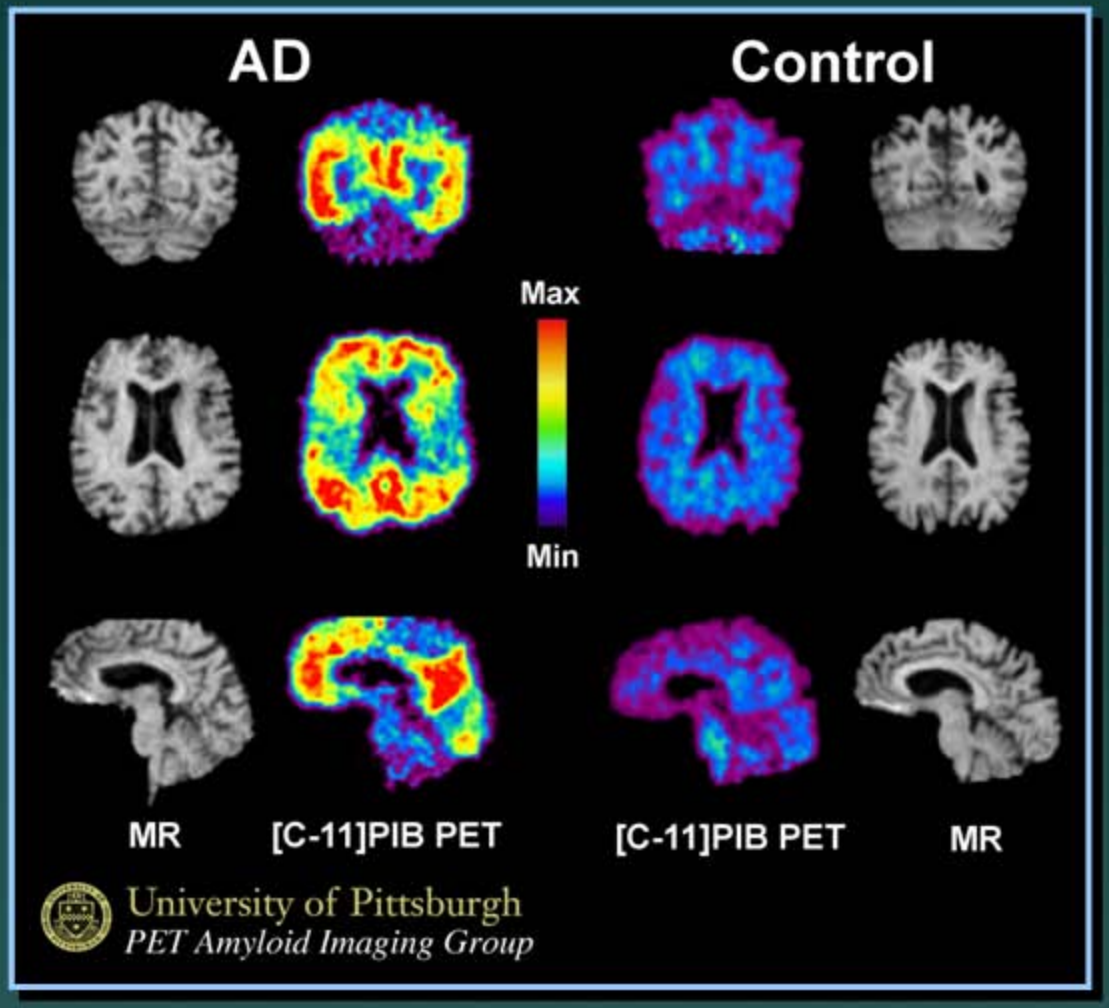



Used with permission from GW Small, UCLA School of Medicine.

# Human Amyloid Imaging Using Pittsburgh Compound-B

Appearance in expected gray matter areas

Absence in areas where there is no amyloid




Very little labeling

Absence of labeling in gray matter

# Dementia in Long-Term Care: Suggested Diagnostic Workup

- Patient and informant interviews
- Clinical assessment
  - Comprehensive physical exam
  - Brief neurological and mental status exams
  - Brief, quantified cognitive function evaluation (eg, MMSE)
  - Laboratory evaluation (CBC, chemistries, RPR, liver function, thyroid, vitamin $B_{12}$)
  - Optional imaging studies (eg, CT head scan, MRI)
- Neuropsychological testing can be beneficial

MMSE = Mini-Mental State Examination; CBC = complete blood count; RPR = Rapid Plasma Reagin.

# Conditions/Factors That Mimic and/or Exacerbate Alzheimer's Disease Symptoms

- **D** Drug use
- **E** Emotional disorders
- **M** Metabolic disorders
- **E** Eye and ear disorders
- **N** Nutritional disorders and normal-pressure hydrocephalus
- **T** Tumors and trauma
- **I** Infection
- **A** Atherosclerosis and alcoholism

Source: Gambert SR. *Postgrad Med.* 1997;101(6):42-43,48-49,52-54 passim.

# Overview of Assessment Methods Useful in the Long-Term Care Setting

*Cognition:*
- MMSE
- Clock Drawing Test
- Mini-Cog

*Function:*
- Instrumental ADL

*Mood:*
- GDS
- Cornell Scale for Depression

*Behavior:*
- NPI-NH
- BPRS

*Caregiver stress:*
- Burden Interview

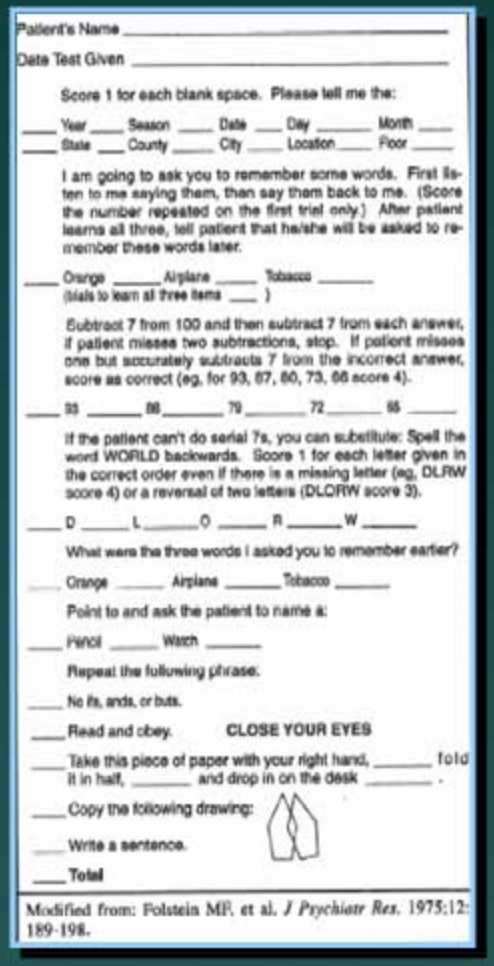
*Global monitoring:*
- CIBIC-Plus

GDS = Geriatric Depression Scale; NPI-NH= Neuropsychiatric Inventory–Nursing Home version;
BPRS = Brief Psychiatric Rating Scale; CIBIC-Plus = Clinician's Interview-Based Impression of Change Plus Caregiver Input.

# Brief Mental Status Assessments

## *Mini-Mental State Examination*

- Brief, structured cognitive screener
- Sections evaluate
  - Orientation
  - Registration
  - Attention
  - Recall
  - Language/comprehension
  - Praxis
- 10 to 15 minutes to administer
- Scores range from 0 (worst) to 30 (best)



Patient's Name _____

Date Test Given _____

Score 1 for each blank space. Please tell me the:

___ Year ___ Season ___ Date ___ Day ___ Month ___
___ State ___ County ___ City ___ Location ___ Floor ___

I am going to ask you to remember some words. First listen to me saying them, then say them back to me. (Score the number repeated on the first trial only.) After patient learns all three, tell patient that he/she will be asked to remember these words later.

___ Orange ___ Airplane ___ Tobacco ___
(trials to learn all three items ___ )

Subtract 7 from 100 and then subtract 7 from each answer, if patient misses two subtractions, stop. If patient misses one but accurately subtracts 7 from the incorrect answer, score as correct (eg, for 93, 87, 80, 73, 66 score 4).

___ 93 ___ 86 ___ 79 ___ 72 ___ 65 ___

If the patient can't do serial 7s, you can substitute: Spell the word WORLD backwards. Score 1 for each letter given in the correct order even if there is a missing letter (eg, DLRW score 4) or a reversal of two letters (DLORW score 3).

___ D ___ L ___ O ___ R ___ W ___

What were the three words I asked you to remember earlier?

___ Orange ___ Airplane ___ Tobacco ___

Point to and ask the patient to name a:

___ Pencil ___ Watch ___

Repeat the following phrase:

___ No ifs, ands, or buts.

___ Read and obey. CLOSE YOUR EYES

___ Take this piece of paper with your right hand, ___ fold it in half, ___ and drop in on the desk ___ .

___ Copy the following drawing:

___ Write a sentence.

___ Total

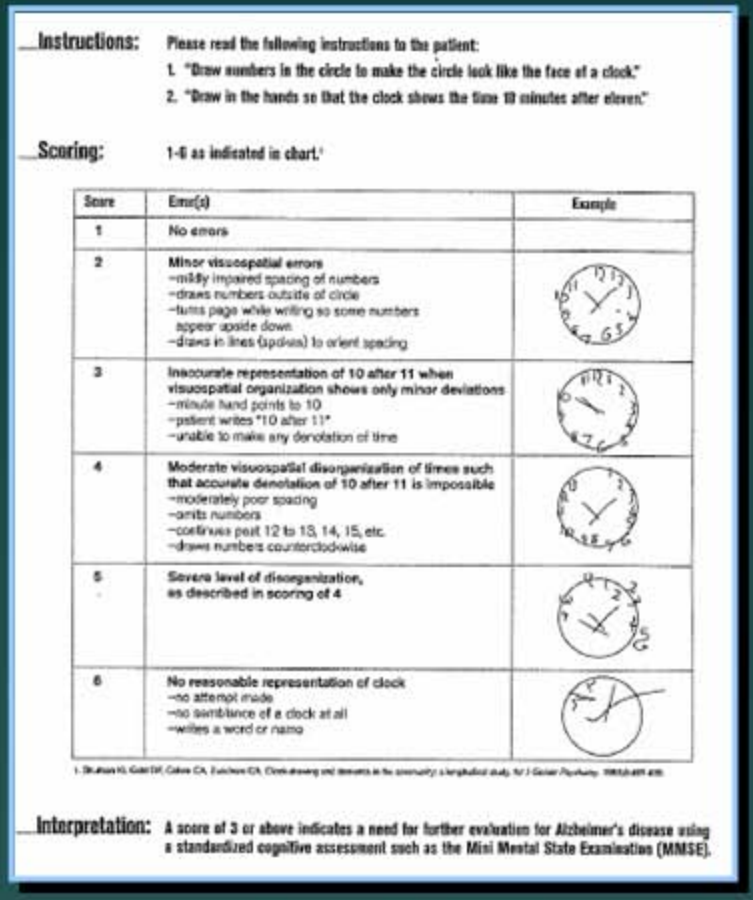
Modified from: Folstein MF, et al. *J Psychiatr Res.* 1975;12:189-198.

Source: Folstein M, et al. *J Psychiatr Res.* 1975;12:189-198.

# Brief Mental Status Assessments (cont)

## *Clock Drawing Test*

- Quick screening tool
- Brief (1-5 minutes)
- Minimal language requirement
- Does not require specialized testing materials



**Instructions:** Please read the following instructions to the patient:

1. "Draw numbers in the circle to make the circle look like the face of a clock."
2. "Draw in the hands so that the clock shows the time 10 minutes after eleven."

**Scoring:** 1-6 as indicated in chart.[1]

| Score | Error(s) | Example |
|---|---|---|
| 1 | No errors | |
| 2 | **Minor visuospatial errors**<br>–mildly impaired spacing of numbers<br>–draws numbers outside of circle<br>–turns page while writing so some numbers appear upside down<br>–draws in lines (spokes) to orient spacing | |
| 3 | **Inaccurate representation of 10 after 11 when visuospatial organization shows only minor deviations**<br>–minute hand points to 10<br>–patient writes "10 after 11"<br>–unable to make any denotation of time | |
| 4 | **Moderate visuospatial disorganization of times such that accurate denotation of 10 after 11 is impossible**<br>–moderately poor spacing<br>–omits numbers<br>–continues past 12 to 13, 14, 15, etc.<br>–draws numbers counterclockwise | |
| 5 | **Severe level of disorganization, as described in scoring of 4** | |
| 6 | **No reasonable representation of clock**<br>–no attempt made<br>–no semblance of a clock at all<br>–writes a word or name | |

1. Shulman KI, Gold DP, Cohen CA, Zucchero CA. Clock-drawing and dementia in the community: a longitudinal study. *Int J Geriatr Psychiatry*. 1993;8:487-496.

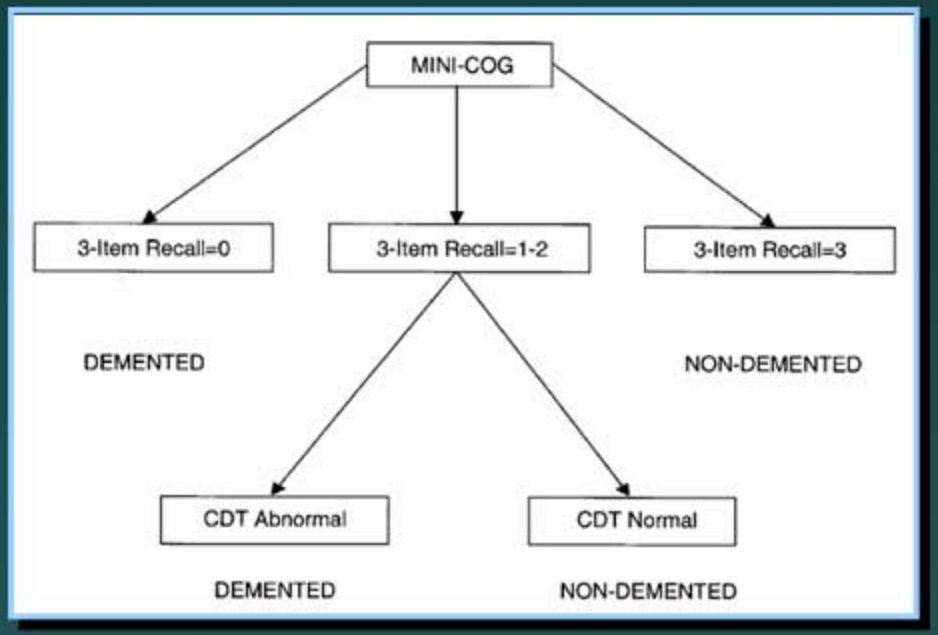
**Interpretation:** A score of 3 or above indicates a need for further evaluation for Alzheimer's disease using a standardized cognitive assessment such as the Mini Mental State Examination (MMSE).

Source: Shulman KI, et al. *Int J Geriatr Psychiatry*. 1993;8:487-496.

# Brief Mental Status Assessments (cont)

## *Mini-Cog*

- Brief (3 minutes)
- Includes 3-word recall and Clock Drawing Test
- Relatively little bias by language or educational level




CDT = Clock Drawing Test.
Figure used with permission from: Borson S, et al. *Int J Geriatr Psychiatry*. 2000;15:1021-1027.

# Assessment of Function

## *Instrumental Activities of Daily Living*

- Assess the ability to perform the following:
  - Telephoning
  - Shopping
  - Preparing food
  - Keeping house
  - Doing laundry
  - Getting transportation
  - Taking care of finances
  - Taking medication
- Rated by caregiver
- Scores range from 4 to 30 points, and higher scores indicate better functioning

Source: Lawton M. *Gerontologist*. 1969;9:179-186.

# TREATMENT

- Cholinesterase inhibitors-new developments
- New formulations-
  - Galantamine ER
  - Rivastigmine patch(EU)
  - Donepezil ODT
  - Memantine ER (in trials)

- Expanded indications- Donepezil for severe AD
- New indications- Rivastigmine for PDD

# TREATMENT

- NMDA antagonist- Memantine
- Moderate to severe AD
- Monotherapy
- Combination therapy with ChEIs
- Few drug-drug interactions (DDIs)
- Well tolerated
- Multiple effects: cognitive, ADLs, behavior

# PATHOGENESIS

AMYLOID PRECURSOR PROTEIN (APP)

- PRODUCTION AB42
- ACCUMULATION
- CONSOLIDATION (senile plaques)
- TRANSFORMATION (microglia)
- DEGENERATION
- SYMPTOMS

# TREATMENT

Disease-modifying therapies:

Anti-amyloid: "active" –AN 1792

"passive" – IVIG

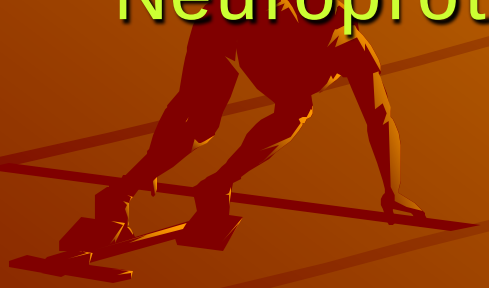
Neuroprotective: Tau-related agents

Antioxidants

Anti-inflammatory agents

Homocysteine-lowering agents

Anti-excititoxic agents



# DEVELOPMENTS

- 1) Late-onset AD causing gene: SORL1
- 2) Neurochem's Alzhemed (Transiposate)-binds to soluble Abeta; keeps it nonfibrillar
- 3) Myriad Genetics Flurizan (Tarenflurbil) –selectively lowers Abeta 42 in animals and humans
- 4)Sanofi-Aventis Xaliproden-neurotrophic and neuroprotective effects

# AAGP RECOMMENDATIONS FOR CAREGIVERS

1) Education
2) Teach problem-solving
3) Access resources
4) Long range planning
5) Emotional support
6) Respite

# What do you think?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# Ask the Geriatrician

- Next Webcast: April 28 at 10:30 a.m. CST
- Topic: Substance Abuse and Older Adults
- Presenter: Thomas Weiss, MD

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