

# Alzheimer's Disease

Michael A. Lobatz MD  
The Neurology Center  
Scripps Rehabilitation Center

# Terminology

- ▶ • Dementia
  - an acquired syndrome consisting of a decline in memory and other cognitive functions

# Forms of Dementia

- ▶ Alzheimer's Disease
- ▶ Fronto temporal dementia
- ▶ Multi infarct dementia
- ▶ Dementia with Lewy Bodies
- ▶ Parkinson's dementia
- ▶ Drugs, depression, delerium
- ▶ Alcohol

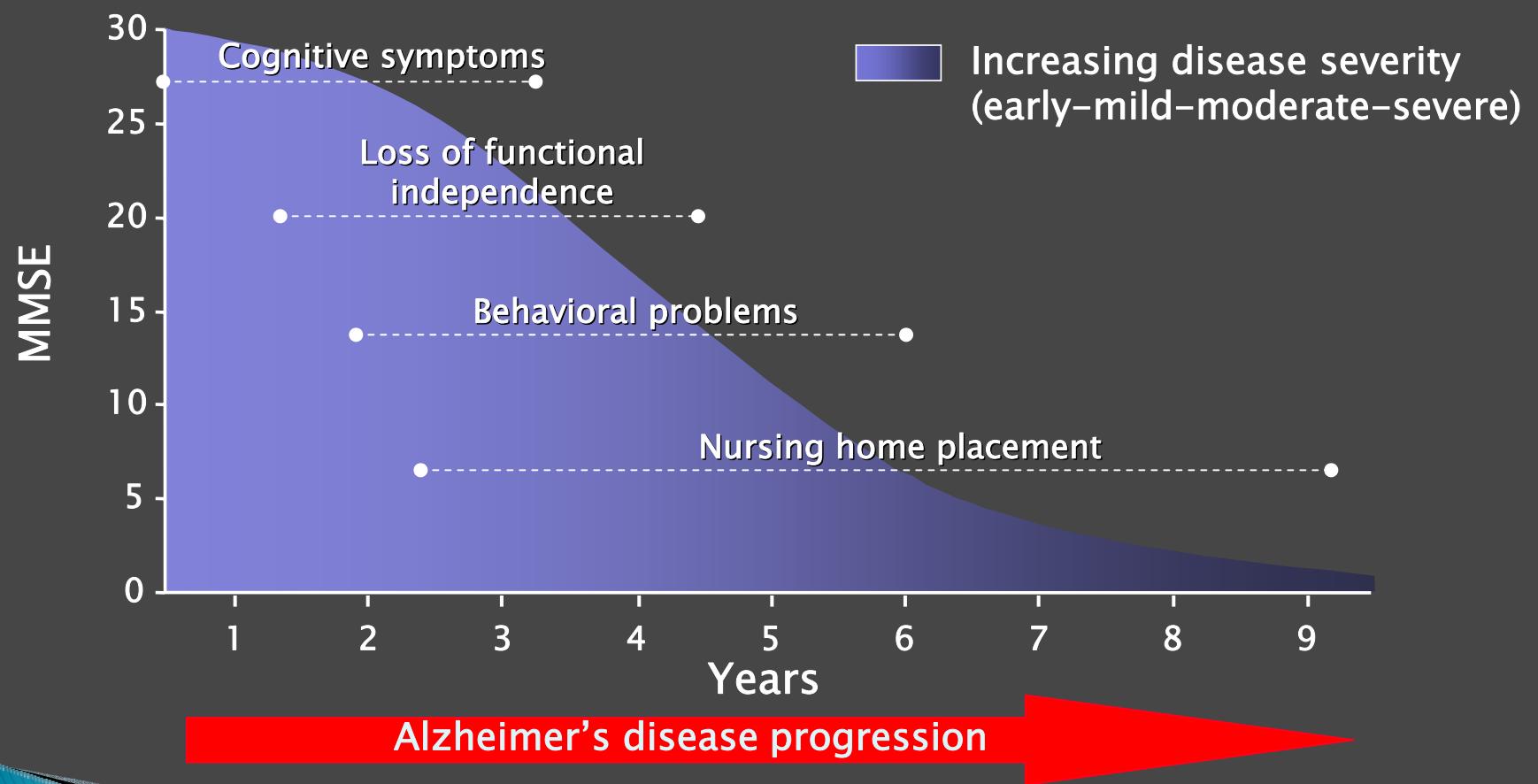
# Alzheimer Warning Signs

## Top Ten

Alzheimer Association

1. Recent memory loss affecting job
2. Difficulty performing familiar tasks
3. Problems with language
4. Disorientation to time or place
5. Poor or decreased judgment
6. Problems with abstract thinking
7. Misplacing things
8. Changes in mood or behavior
9. Changes in personality
10. Loss of initiative

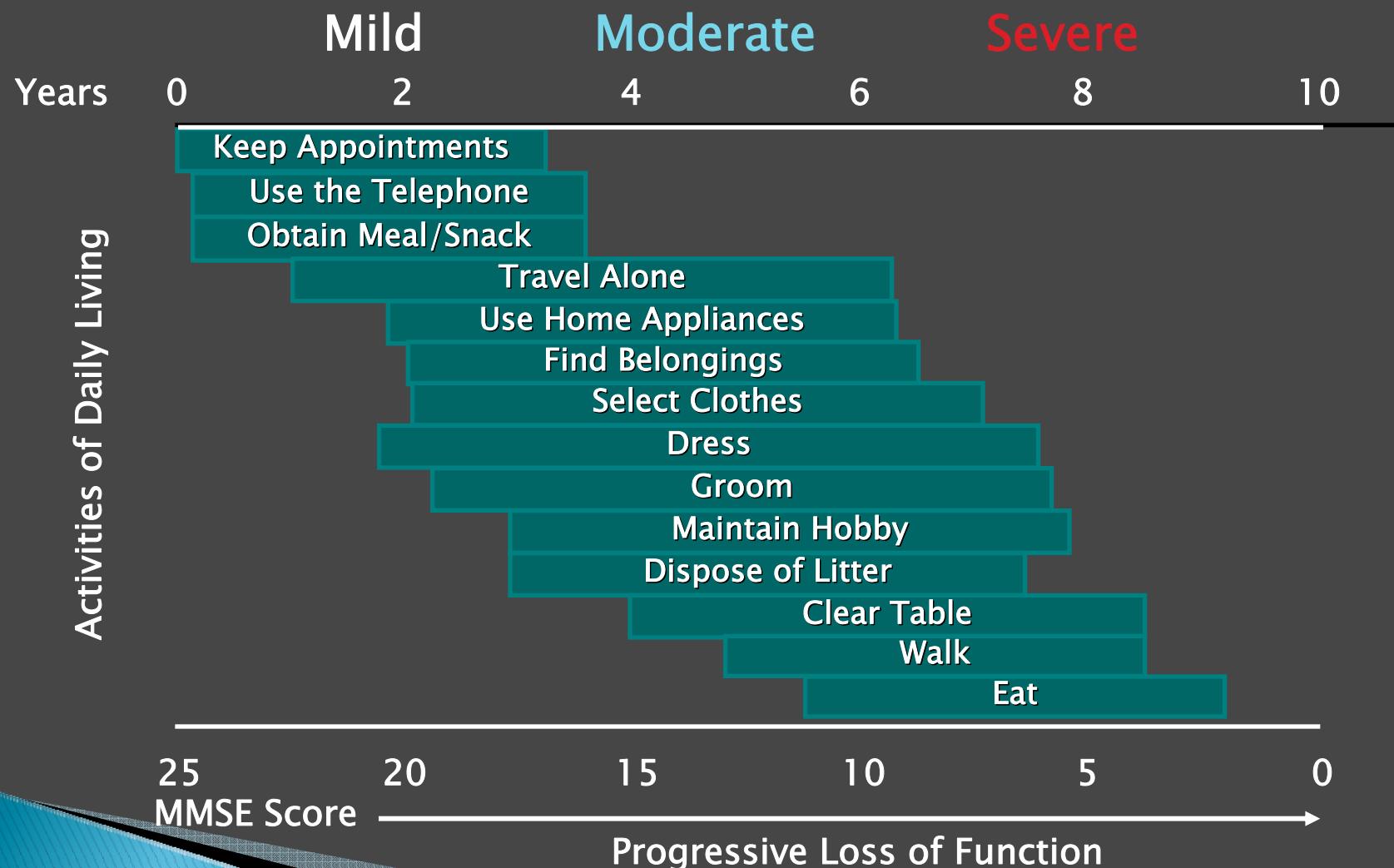
# Symptomatic Course and Progression of AD



MMSE = Mini-Mental State Examination

Adapted with permission from Feldman et al. *Clinical Diagnosis and Management of Alzheimer's Disease*. 1999:249–268.

# Progressive Loss of Activities of Daily Living



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

# Stage 1

- ▶ No impairment (normal function)
- ▶ Unimpaired individuals experience no memory problems and none are evident to a health care professional during a medical interview.

# Stage 2

- ▶ Very mild cognitive decline (may be normal age-related changes or earliest signs of Alzheimer's disease)
- ▶ Individuals may feel as if they have memory lapses, especially in forgetting familiar words or names or the location of keys, eyeglasses or other everyday objects. But these problems are not evident during a medical examination or apparent to friends, family or co-workers.



# Stage 3

- ▶ Mild cognitive decline
- ▶ Friends, family or co-workers begin to notice deficiencies. Problems with memory or concentration may be measurable in clinical testing or discernible during a detailed medical interview. Common difficulties include:
- ▶ Word- or name-finding problems noticeable to family or close associates

# Stage 3

- ▶ Decreased ability to remember names when introduced to new people
- ▶ Performance issues in social or work settings noticeable to family, friends or co-workers
- ▶ Reading a passage and retaining little material
- ▶ Losing or misplacing a valuable object
- ▶ Decline in ability to plan or organize

# Stage 4

- ▶ Moderate cognitive decline  
(Mild or early-stage Alzheimer's disease)
- ▶ Decreased knowledge of recent occasions or current events
- ▶ Impaired ability to perform challenging mental arithmetic—for example, to count backward from 75 by 7s

# Stage 4

- ▶ Decreased capacity to perform complex tasks, such as planning dinner for guests, paying bills and managing finances
- ▶ Reduced memory of personal history
- ▶ The affected individual may seem subdued and withdrawn, especially in socially or mentally challenging situations

# Stage 5

- ▶ **Moderately severe cognitive decline  
(Moderate or mid-stage Alzheimer's disease)**
- ▶ Major gaps in memory and deficits in cognitive function emerge. Some assistance with day-to-day activities becomes essential. At this stage, individuals may:
  - ▶ Be unable during a medical interview to recall such important details as their current address, their telephone number or the name of the college or high school from which they graduated
  - ▶ Become confused about where they are or about the date, day of the week or season

# Stage 5

- ▶ Have trouble with less challenging mental arithmetic; for example, counting backward from 40 by 4s or from 20 by 2s
- ▶ Need help choosing proper clothing for the season or the occasion
- ▶ Usually retain substantial knowledge about themselves and know their own name and the names of their spouse or children
- ▶ Usually require no assistance with eating or using the toilet

# Stage 6

- ▶ Severe cognitive decline  
(Moderately severe or mid-stage Alzheimer's disease)
- ▶ Memory difficulties continue to worsen, significant personality changes may emerge and affected individuals need extensive help with customary daily activities.
- ▶ Lose most awareness of recent experiences and events as well as of their surroundings

# Stage 6

- ▶ Occasionally forget the name of their spouse or primary caregiver but generally can distinguish familiar from unfamiliar faces
- ▶ Need help getting dressed properly; without supervision, may make such errors as putting pajamas over daytime clothes or shoes on wrong feet
- ▶ Experience disruption of their normal sleep/waking cycle

# Stage 6

- ▶ Need help with handling details of toileting (flushing toilet, wiping and disposing of tissue properly)
  - ▶ Have increasing episodes of urinary or fecal incontinence
  - ▶ Experience significant personality changes and behavioral symptoms, including suspiciousness and delusions, hallucinations or compulsive, repetitive behaviors such as hand-wringing or tissue shredding
- ▶ Tend to wander and become lost

# Stage 7

- ▶ **Very severe cognitive decline**  
(Severe or late-stage Alzheimer's disease)
- ▶ This is the final stage of the disease when individuals lose the ability to respond to their environment, the ability to speak and, ultimately, the ability to control movement.
- ▶ Frequently individuals lose their capacity for recognizable speech, although words or phrases may occasionally be uttered

# Stage 7

- ▶ Individuals need help with eating and toileting and there is general incontinence of urine
- ▶ Individuals lose the ability to walk without assistance, then the ability to sit without support, the ability to smile, and the ability to hold their head up. Reflexes become abnormal and muscles grow rigid. Swallowing is impaired.

# FDA Approved Treatments for Alzheimer's Disease

Agent	Donepezil (Aricept)	Rivastigmine (Exelon)	Galantamine (Razadyne)	Memantine (Namenda)
Mechanism	AChEI	AChEI, BuChEI	AChEI, NRM	NMDA antagonist
Dose Range	5-10mg/d	3-12mg/d	8-24mg/d	5-20mg/d
Target Dose	5-10mg/d	6-12mg/d	16-24mg/d	10-20mg/d
Serum Half Life	70 hours	10 hours	6-8 hours	60-80 hours
Dose Frequency	QD	BID/Patch	QD	BID
Dose Titration	4 weeks	2-4 weeks	4 weeks	1 week
Metabolism	CYP2D6, 3A4	Non-Hepatic	CYP2D6, 3A4	Non-Hepatic
Protein Binding	96%	40%	19%	45%
Most Common Adverse Events (Drug-Placebo)	Nausea (13%) Diarrhea (10%) Insomnia (8%)	Nausea (35%) Vomiting (25%) Dizziness (10%)	Nausea (12%) Vomiting (9%) Anorexia (6%)	Headaches (3%) Dizziness (2%) Constipation (2%)

# Does the Stage of the Disease Matter

- ▶ Cannot be answered definitively
- ▶ Mod-Severe Aricept study lends support to notion that AChEI may be more efficacious in later stages vs earlier stages.
- ▶ The net difference between Aricept and Memantine in mod-severe disease as compared to placebo controls is comparable.

# Research Studies

- ▶ Passive antibody therapy – *Bapineuzumab*
- ▶ RAGE – blocking the interaction of amyloid beta protein and a receptor called Receptor for Advanced Glycation Endproducts (RAGE)
- ▶ Dimebon – inhibit brain cell death

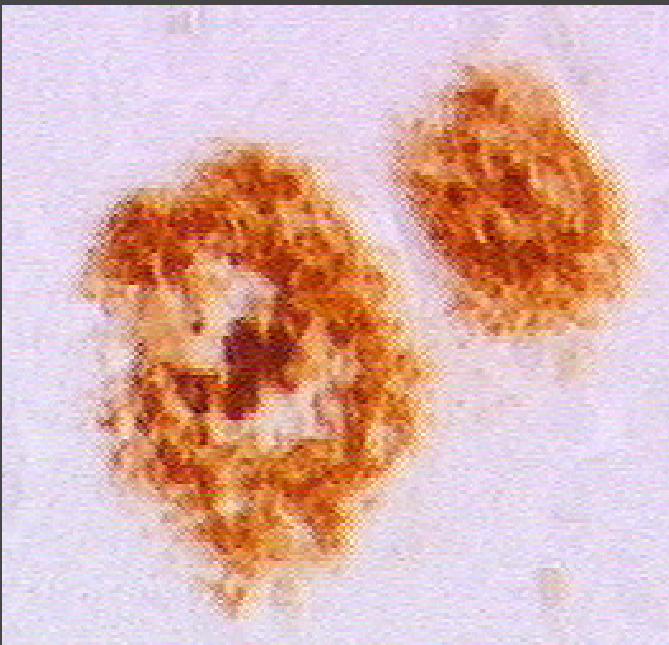
# Research Studies

- ▶ Docosahexaenoic acid (DHA) -Omega3 fatty acid
- ▶ LY-450139 - gamma secretase inhibitor
- ▶ Resveratrol - phytoalexin produced by several plants (red grapes)

# Research

- ▶ Rosiglitazone – antidiabetic drug
- ▶ *scyllo*-inositol – amyloid peptide binding agents
- ▶ ELND005 – preventing and reversing the fibrilization of beta-amyloid

# $\beta$ -amyloid Plaques



Immunocytochemical staining of senile plaques in the isocortex of a brain of a patient with AD.  
Contain A $\beta$  peptide, a fragment of amyloid precursor protein APP.

# Passive Immunization

- ▶ Phase 3 study to evaluate the safety and effectiveness of an investigational drug, *Bapineuzumab*, for controlling progression of AD.
- ▶ *Bapineuzumab* is an antibody (a type of protein usually produced by white blood cells to destroy other substances) that may help to clear beta amyloid from the brain.
- ▶ Beta amyloid is a protein that accumulates in brain tissue to form plaques, which are believed to play a major role in the development of AD.

# Thank You!!

- ▶ Michael A. Lobatz MD
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