Improving Outcomes for an Aging Population: ALZHEIMER'S TREATMENT IN LONG TERM CARE

Cosponsored by Indiana University School of Medicine and The Academy for Continued Healthcare Learning

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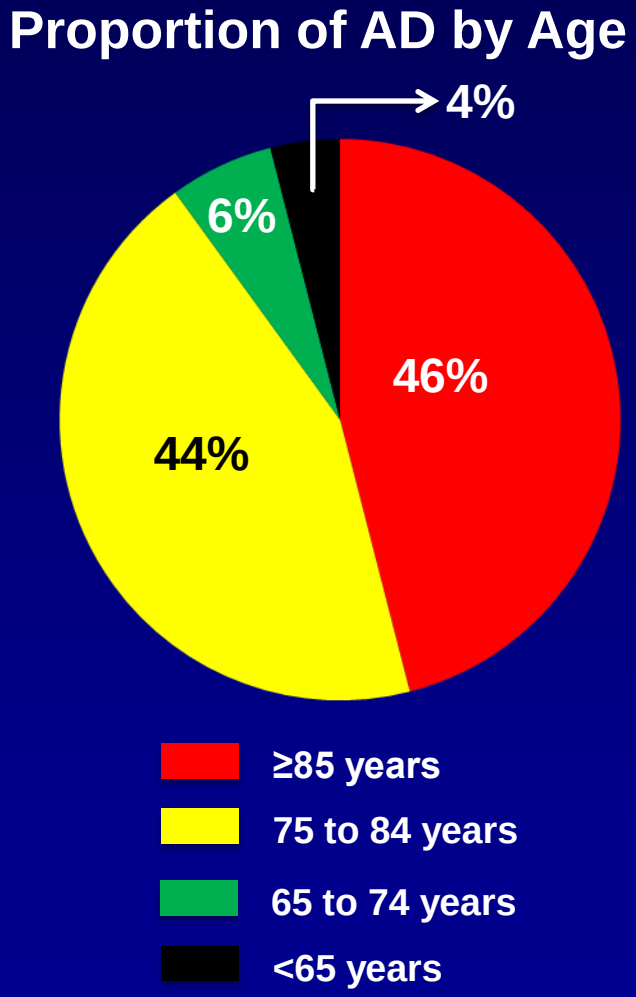
Slides developed for quality improvement toolkit; available at www.achlqicme.org/alzheimers/toolkit

Outline

- Epidemiology
  - Prevalence
  - Financial impact
  - The AD continuum
- Diagnosis
  - Differentiating between dementias and AD
  - Pathophysiology
  - Biomarkers
  - Common comorbidities
  - Cognitive assessments
- Treatment
  - Pharmacologic therapies and imaging
  - Side effect management
  - Non-pharmacologic interventions
  - Care delivery methodologies
  - National needs/future directions
- Case Studies

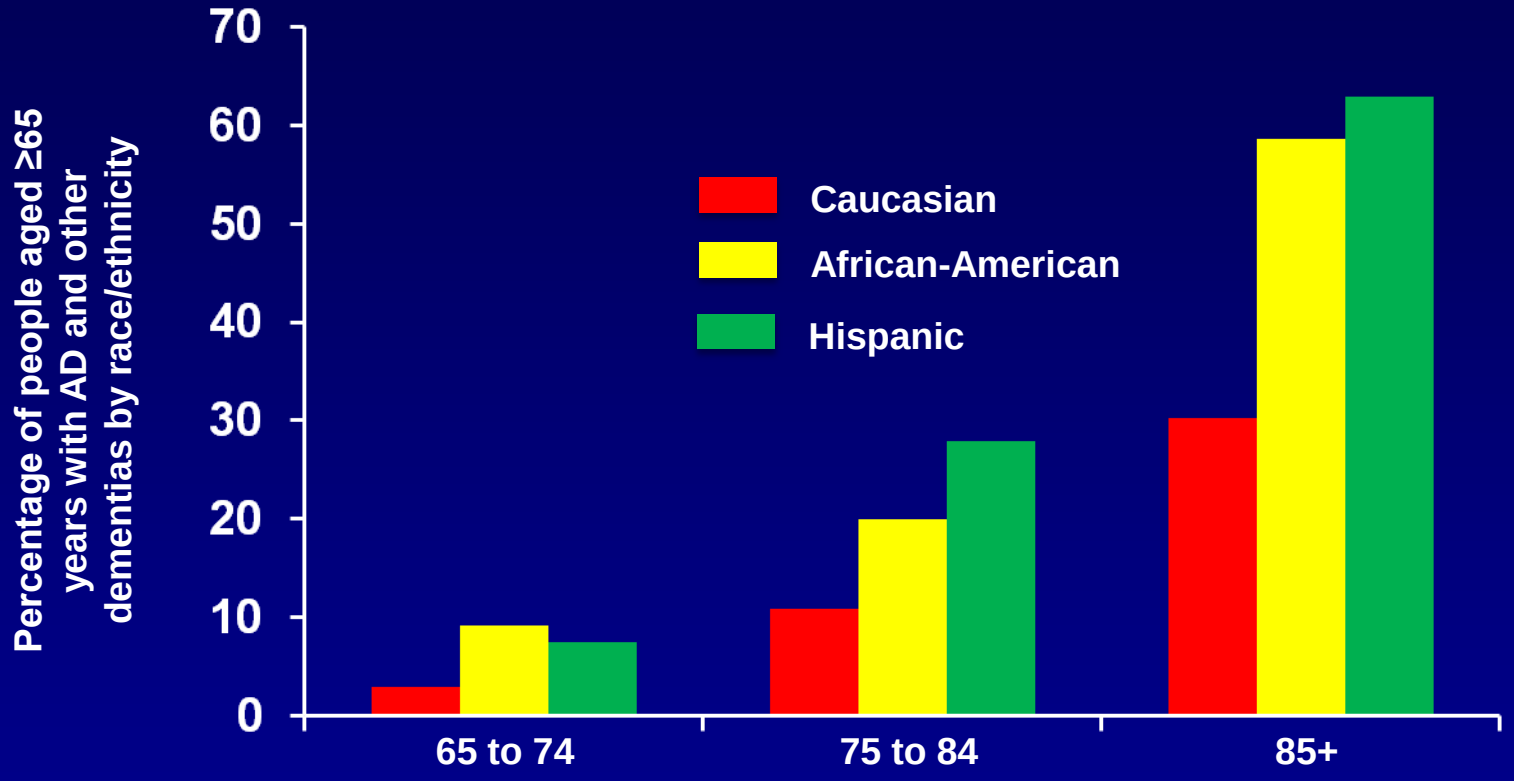
AD: Current Statistics

- Prevalence and Incidence
  - 6th leading cause of death in the U.S.
  - Estimated 5.4 million Americans with AD in 2012
  - 1 in 8 people aged ≥65 years has AD
  - Incidence increased by 66% between 2000–2008



Alzheimer's Association. *Alzheimers Dement*. 2011;7:208-211.

AD Prevalence by Age and Ethnicity



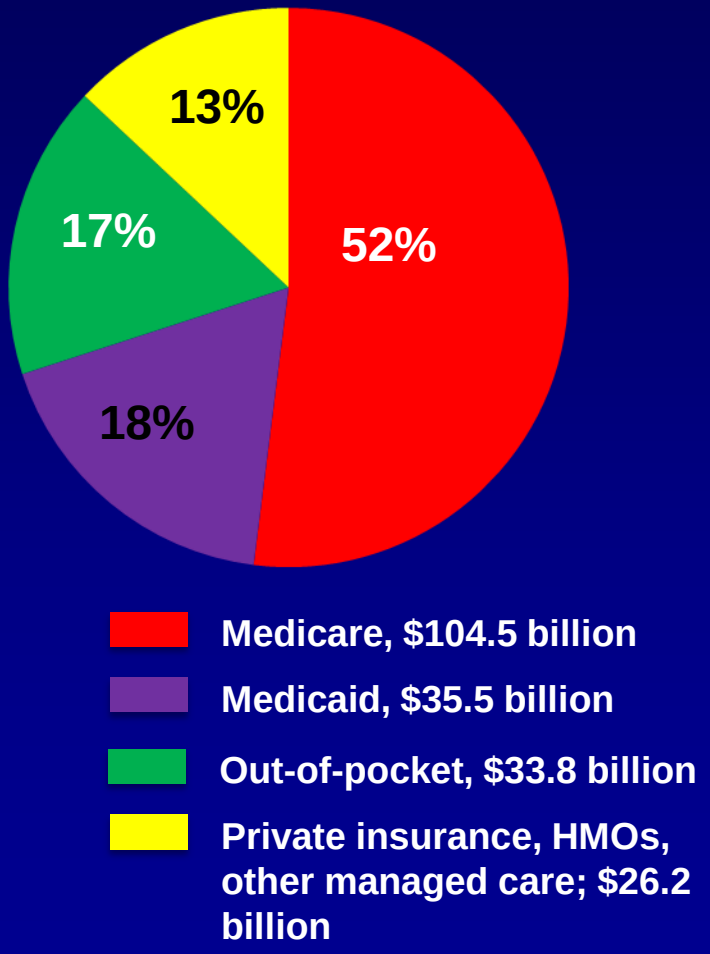
- Sample from north Manhattan circa 1999 (North Manhattan Aging Project) includes individuals living in nursing homes as well as independently
- No difference in proportion of diagnosis of AD
- When education and age are controlled, ethnic differences are not significant

Alzheimer's Association. *Alzheimers Dement*. 2011;7:208-211.
Adapted from Gurland B, et al. *Int J Geriatr Psychiatry*. 1999;14:481-493.

The Cost of AD

- $183 billion spent in 2011 on healthcare, long-term care and hospice services for people aged ≥ 65 years with AD and dementias
- Caregivers (including unpaid family members) contributed ~$202 billion in services in 2010
- Because AD is a progressively worsening disease, the cost per person increases as time passes

Aggregate Cost of Care for Individuals ≥65 years with AD and Other Dementias



Alzheimer's Association. *Alzheimers Dement*. 2011;7:208-211.
Adapted from Bynum J. Medicare Current Beneficiary Survey for 2008. Dartmouth Medical School; 2011.

Ten Warning Signs of AD

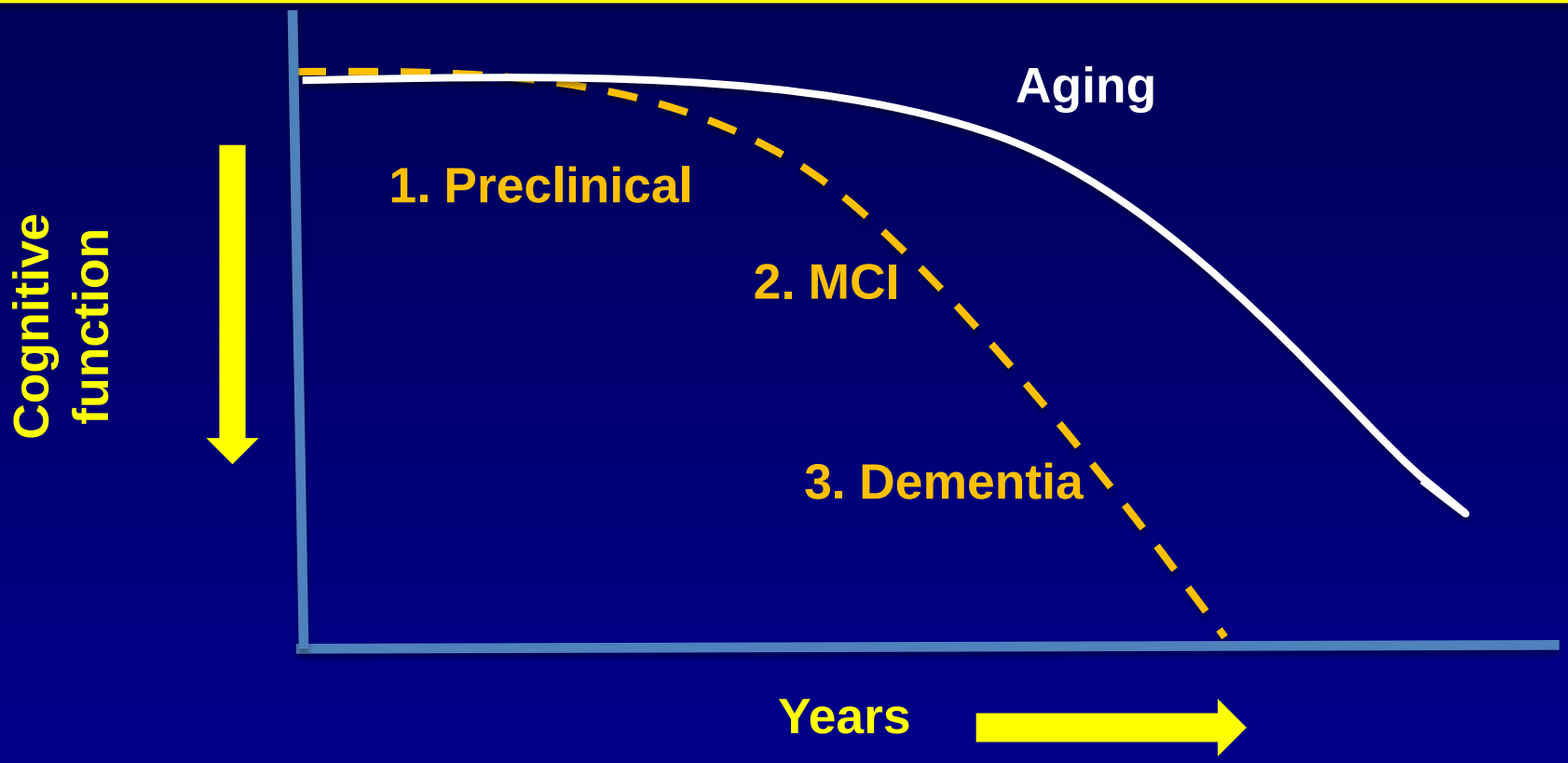
- Memory Loss
- Challenges in planning or solving problems
- Difficulty completing familiar tasks
- Withdrawal from work or social activities
- Decreased or poor judgment
- Confusion with time or place
- Problems with speaking or writing
- Misplace things/loss of ability to retrace steps
- Trouble with spatial relationships/visual images
- Mood or personality changes

The ten signs and symptoms can be grouped into 2 major categories:

1. Loss of abilities
   - Memory
   - Activities of daily living
   - Communication
2. Behavioral Symptoms
   - Depression, agitation or psychosis (mood or personality changes)

Alzheimer's Association. 10 signs of Alzheimer's. http://www.alz.org/alzheimers_disease_10_signs_of_alzheimers.asp. Accessed March 2012.

The AD Continuum

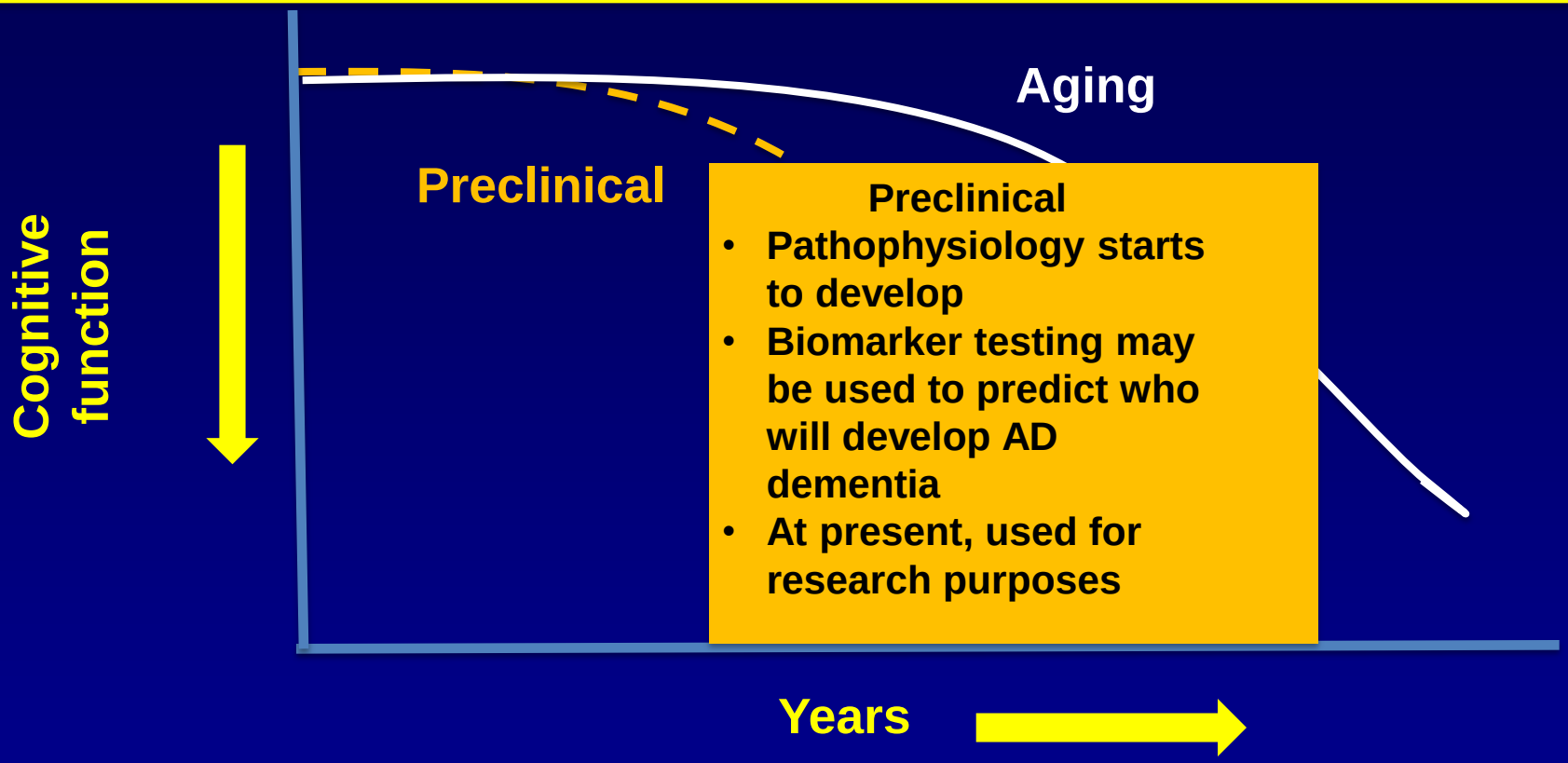


- AD encompasses all 3 stages

MCI = Mild Cognitive Impairment

Adapted from Sperling RA, et al. *Alzheimers Dement.* 2011;7:280-292.

The AD Continuum



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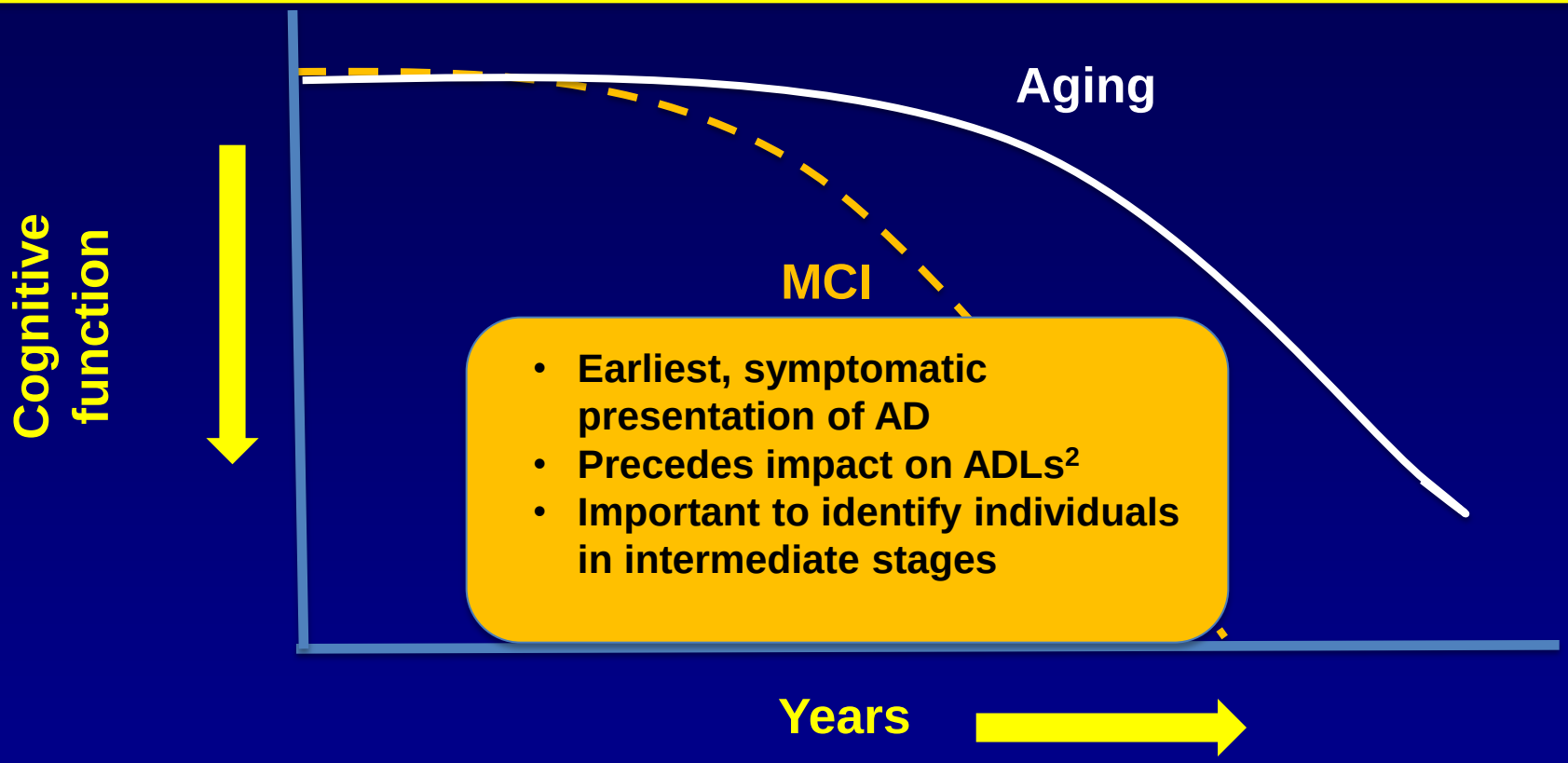
Adapted from Sperling RA, et al. *Alzheimers Dement.* 2011;7:280-292.

The AD Continuum[1]



- AD encompasses all 3 stages

MCI = Mild Cognitive Impairment

1. Adapted from Sperling RA, et al. *Alzheimers Dement.* 2011;7:280-292.
2. Jack CR, et al. *Alzheimers Dement*. 2011;7:257-262.

Revised Guidance

- The 2011 diagnostic guidelines for AD were revised from the 1984 version by NIA workgroups
- The 2011 recommendations attempt to delineate/clarify the differences between the stages:
  - Asymptomatic, preclinical phase
    - More for research purposes and can be identified by use of biomarker assays
  - Symptomatic, predementia phase
  - Dementia phase

Jack CR, et al. *Alzheimers Dement*. 2011;7:257-262.

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Core Clinical Criteria

All-cause Dementia

- Interference with the ability to function at work or at home
- Decline from a previous level of functioning
- Not explained by delirium or other major psychiatric disorder
- Cognitive or behavioral impairment involving at least 2 of the following:
  - Impaired ability to acquire and remember new information
  - Impaired reasoning and handling of complex tasks and/or poor judgment
  - Impaired visuospatial abilities
  - Language functions (speaking, reading, writing)
  - Changes in personality, behavior or comportment

Probable AD Dementia

- Meets criteria for all-cause dementia AND
  - Has an insiduous/gradual onset over months to years
  - History of worsening cognition (either by observation or report)
- Cognitive deficits in 1 of the following:
  - Amnestic presentation: impairment in learning and recall of recently learned information
  - Nonamnestic presentation:
    - Language: deficits in word-finding
    - Visuospatial: spatial cognition, impaired facial recognition, alexia, simultanagnosia, object agnosia
    - Executive dysfunction: impairments in reasoning, judgment, problem solving

McKhann GM, et al. *Alzheimers Dement*. 2011;7:263-269.

Core Clinical Criteria (cont'd)

Probable AD Dementia

- Meets criteria for all-cause dementia AND
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      - Executive dysfunction: impairments in reasoning, judgment, problem solving

Possible AD Dementia

- Meets clinical criteria for AD dementia AND has either:
  - Sudden onset (ie, lack of progressive decline) and/or there is a lack of a reliable patient history or any of the following
    - Has CVD (stroke, infarcts)
    - Dementia with Lewy bodies
    - Medication or a neurological or non-neurological condition impacting cognition

McKhann GM, et al. *Alzheimers Dement*. 2011;7:263-269.

Differentiating Between AD and Other Dementia Types[1]

	AD	Lewy Body Dementia	Vascular Dementia	Mixed Dementia
Prevalence	• Most common • Accounts for 60%-80% of cases	• Considered the 2nd most common type of dementia, along with vascular dementia[2]	• Considered the 2nd most common type of dementia, along with Lewy Body dementia	• More common than previously thought
Behavioral characteristics	PROGRESSIVE Early: • Difficulty remembering names, events • Apathy, "low mood" Late: • Confusion • Behavioral changes	• More likely to have sleep disturbances, visual hallucinations, muscle rigidity or other Parkinsonian movement features	• Memory not as seriously impacted as in AD; high degree of overlap with AD symptoma-tology	• Symptoms of both AD and vascular dementia
Physiological markers	• Beta-amyloid plaques • Tau protein tangles	• Oftentimes the formation of abnormal aggregates of α-synuclein in cortex	• Decreased blood flow to the brain; caused by strokes	• Lewy bodies • Beta-amyloid plaques • Tau protein tangles

1. Alzheimer's Association. *Alzheimers Dement*. 2011;7:208-211.
2. Lewy Body Dementia Assoc. Description of LBD. Available at http://community.lbda.org/forum/viewtopic.php?f=1&t=2524

Compare and Contrast: FTD and AD[1]

	FTD	AD
Similarities	Both disease states can be characterized by : • Brain atrophy • Progressive loss of brain function	
Differences	• Disease of behavior and language dysfunction • 60% of the time, FTD occurs in those 45-64 years of age • More likely to display motor abnormalities or muscle atrophy or weakness	• Characterized primarily by memory loss • Highest risk of death from AD occurs in those age 65 or older[2]

1. Diagnosis. AFTD. Available at http://www.theaftd.org/frontotemporal-degeneration/ftd-overview. Accessed October 2012.
2. Alzheimer's Assoc. *Alzheimers Dement*. 2012;8:131-168.

Comorbidities and AD

- Individuals with AD have more comorbidities than individuals without dementia
- Higher medical comorbidity is associated with decreased cognition, poorer self-care, decreased mobility, and increased incontinence

Vascular disease • Altered blood pressure (high blood pressure before age 65, low blood pressure in late life) • Elevated cholesterol	Osteoporosis • Low bone mineral density
Diabetes mellitus	Hyper- or hypothyroidism
Obesity	Sleep apnea

Duthie A, et al. *Q J Med*. 2011;104:913-920.

Comorbidities and Multiple Medications

- Each medication carries a risk of adverse reactions (10% for a single drug)[2]
  - Risk is increased for multiple medications (estimated 75% for ≥5 drugs)
  - Common classes of medications for comorbid conditions in people with AD include: antihypertensives, antidepressants, and chronic pain, asthma/COPD medications
- One study found that 48% of patients with AD were prescribed ≥5 drugs compared to 23% of cognitively healthy controls[2]

Andersen F, et al. *BMC Geriatrics*. 2011;11:58.

Early Detection and Diagnosis

- Check medical history thoroughly[1]
- Mental status testing[1,2]
- Physical and neurological exam[1]
- Diagnosis by exclusion; rule out and/or treat other possible diseases/comorbid conditions:[1]
- Paying attention when caregivers or family members note that a patient exceeds the thresholds of "normal aging" and has many "senior moments"[3]
  - Assign staff to residents with no family or few visitors to act as surrogate family members

Screening tools (ie, not diagnostic):

- Mini-Cog
- GP Assessment of Cognition
- Medicare's Annual Wellness Visit[2]

Other possible diseases:

- Major depressive disorder, thyroid problems, vitamin deficiencies, drug interactions, alcohol abuse
- Tests (blood, brain imaging) may rule out other causes of dementia-like symptoms

1. Alzheimer's Association. 10 signs of Alzheimer's. http://www.alz.org/alzheimers_disease_10_signs_of_alzheimers.asp. Accessed March 2012.
2. Alzheimer's Association. *Alzheimers Dement*. 2011;7:208-211.
3. Atri A. *Am J Manag Care*. 2011;17:S346-S355.

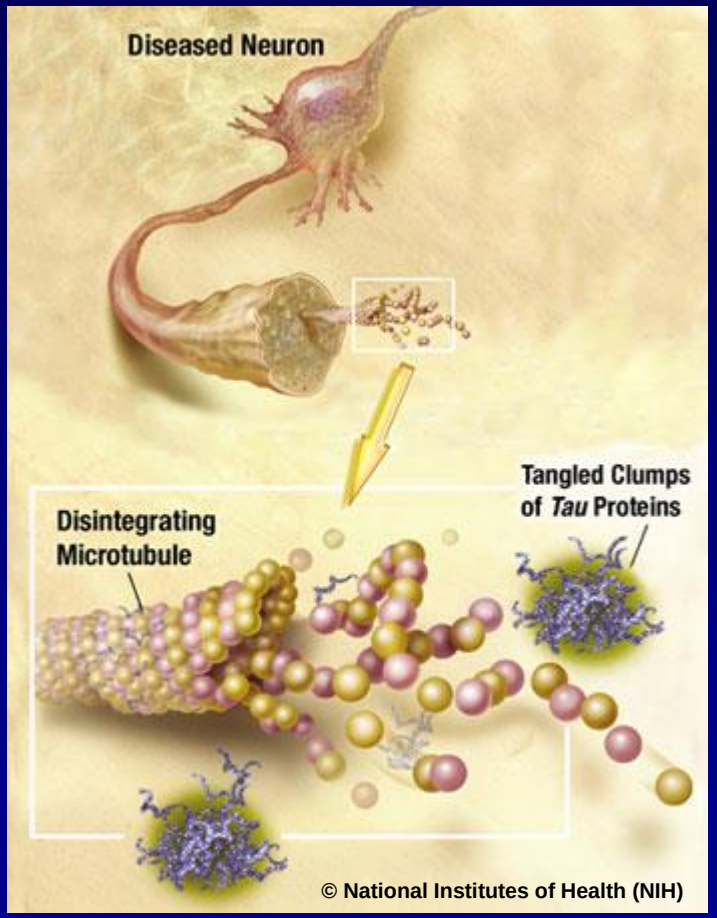
The Role of Amyloid Beta

- Amyloid plaques are found extracellularly, in the brains of AD patients
- These plaques are made up of tiny proteins called Aβ40 and Aβ42
  - Their parent protein is amyloid precursor protein
- These plaques are thought to be the primary cause of AD dementia (ie, amyloid hypothesis)
- Because of the time difference between pathology and the appearance of clinical signs there is a movement to currently accepting that multiple processes contribute to AD

Marchesi VT. *Am J Pathol*. 2012;180:1762-1767.

The Role of Tau Protein

- A microtubule-associated protein that helps to stabilize a cell's cytoskeleton
- Hyperphosphorylated form has been found in significantly higher rates in patients with AD compared with healthy, age-matched controls
- Hyperphosphorylation of this protein causes it to be misfolded—when misfolded, it can form insoluble tangles (ie, neurofibrillary tangles) found in the brain cells of patients with AD
- Type of tau protein that is phosphorylated and present in the CSF can help differentiate between AD (p-tau$_{231P}$) and frontotemporal dementia
- High concentrations of this protein are correlated with a decline in cognitive function and a transition to AD in patients with MCI



Hampel H, et al. *Alzheimers Dement*. 2008;4:38-48.

Pathophysiology

- Distinguishing characteristics: beta amyloid plaques and neurofibrillary tangles cause atrophy of the cortex[1]
- Atrophy of the nucleus basalis also impacts the functioning of cholinergic neurons, thus affecting memory[1]
- Plaque accumulation in the cortex (specifically the inferior temporal neocortex) contributes to downstream hippocampal atrophy, causing cholinergic neurons to die[2]

Image courtesy of Mayo Foundation for Medical Education and Research.

1. Harry RDJ, Zakzanis KK. *Hum Psychopharmacol Clin Exp*. 2005;20:183-187.
2. Bourgeat P, et al. *Neurology*. 2010;74:121-127.

Genetic Screens and Biomarkers May Support the Diagnosis of AD Dementia

Gene mutations[1,2,3]	Biomarkers for amyloid protein deposition[1]	Biomarkers of downstream neuronal degeneration or injury[1]
Mutations in amyloid precursor protein (APP) on chromosome 21 contribute to 10-15% of EOFAD (AD type 1)	Low CSF $A\beta_{42}$ in individuals with AD	Elevated CSF tau (including total tau and phosphorylated tau)
Mutations in presenelin 1 and/or 2 contribute to EOFAD (30-70% via PSEN1 on chromosome 14, AD type 3; 5% via PSEN2 on chromosome 1; AD type 4)	Positive PET amyloid imaging	Disproportionate atrophy as observed via MRI of the temporal, frontal lobes and medial parietal cortex

EOFAD=Early onset familial AD

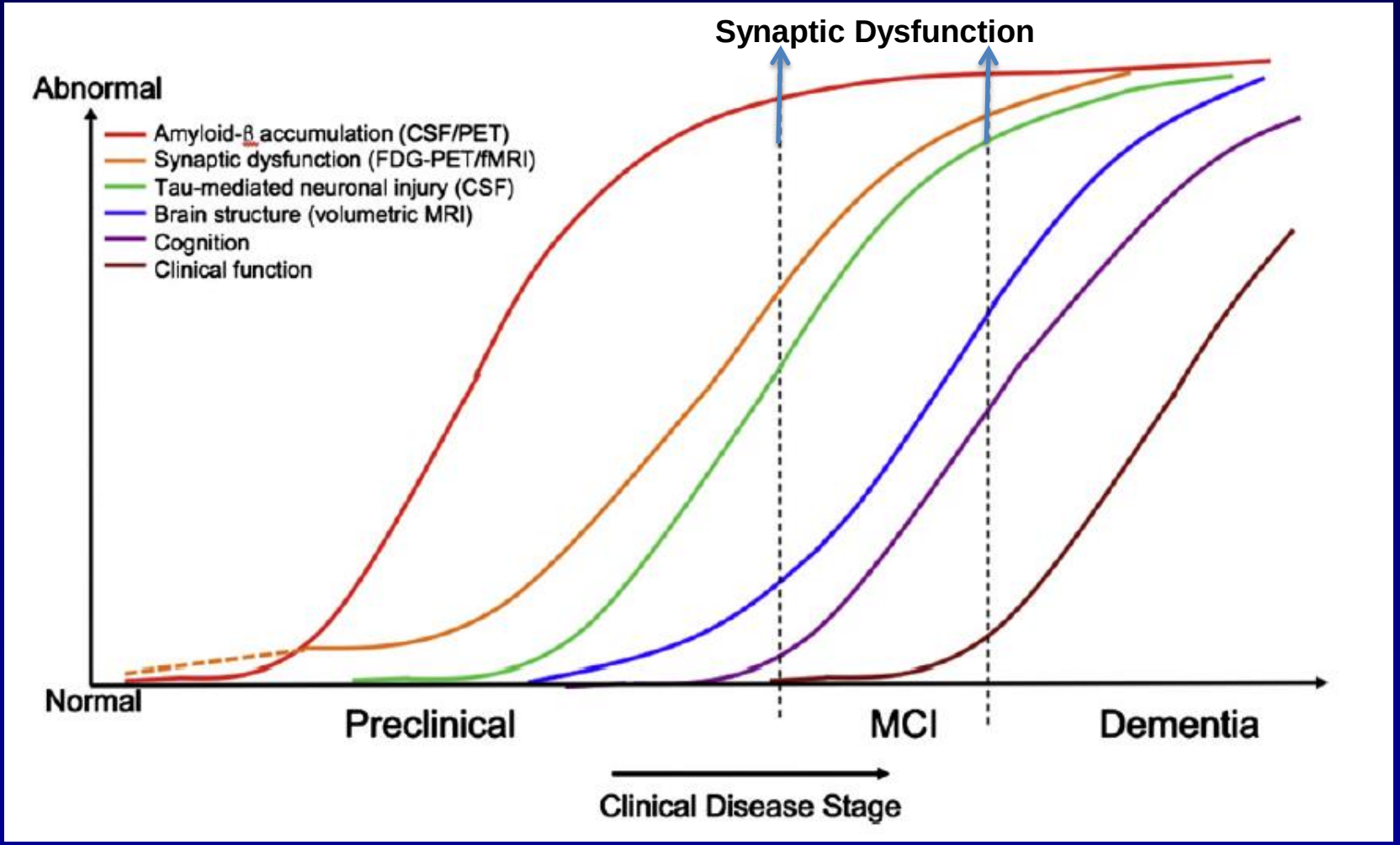
1. McKhann GM, et al. *Alzheimers Dement*. 2011;7:263–269.
2. Cummings JL. 2003. Alzheimer's Disease. Taylor and Francis Group: London, 57-116.
3. Bird TD. Early Onset Familial Alzheimer's Disease. Available at http://www.ncbi.nlm.nih.gov/books/NBK1236/. Accessed October 2012.

Genetic Screens and Biomarkers (cont'd)

- Impaired glucose metabolism or other brain-related changes (ie, biomarkers) may be present in advance of neurodegeneration and clinically apparent dementia[1,2]
- Carriers of the Apoε4 allele are also at an increased risk of developing AD[3]
- The presence of the Apoε4 allele in healthy women has shown to be associated with reduced connectivity between areas of the cortex typically affected by AD[3]
- Significant uptake of 18F-florbetaben, a beta amyloid tracer, was predictive of rapid progression to AD in patients with mild cognitive dementia[4]

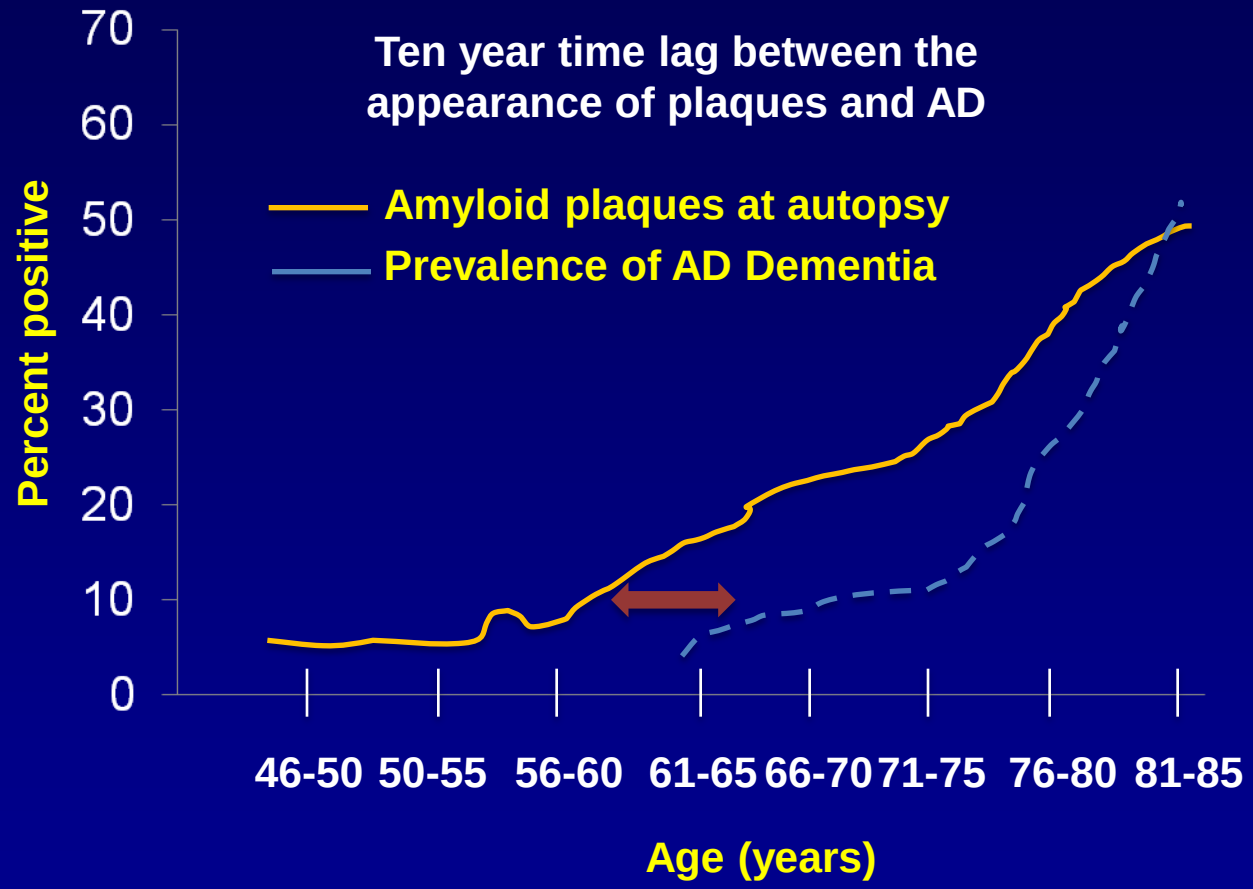
1. Cunnane S, et al. *Nutrition*. 2011;27:3-20.
2. Alzheimer's Association. 2012 Alzheimer's Disease Facts and Figures. http://www.alz.org/downloads/facts_figures_2012.pdf . Accessed June 2012.
3. Damoiseaux JS, et al. *J Neurosci*. 2012: 32:8524-8262.
4. Rowe C, et al. Annual Soc Nuclear Medicine. Abstract 299. June 12, 2012.

Structural and Functional Correlational Model by AD Phase



Sperling RA, et al. *Alzheimers Dement*. 2011;7:280-292.

The AD Confound



- Pathological changes can manifest themselves early on, however an individual may retain normal cognitive function. Thus, the majority of time the clinical symptoms of AD do not correlate with pathology.

Sperling RA, et al. *Alzheimers Dement.* 2011;7:280-292.

Clinical Dementia Rating Scale

- A research tool that reflects the patient's cognitive ability as it relates to the following 6 domains
  1. Memory
  2. Orientation
  3. Judgment and problem-solving
  4. Community affairs
  5. Home and hobbies
  6. Personal care

- ❑ **CDR-0 = none**
- ❑ **CDR-0.5 = very mild dementia**
- ❑ **CDR-1 = mild**
- ❑ **CDR-2 = moderate**
- ❑ **CDR-3 = severe**

- It is expected that a patient may rate differently in each domain (ie, some domains will be more affected than others)
- Can also be used to assess changes in CI

Morris JC. 2001. Clinical Dementia Rating (CDR) Scale. Alzheimer's Disease Research Center, Washington University: St. Louis, MO.

Clinical Global Impression

- Rating scales, used largely in research settings, to gauge symptom severity/treatment response
- Rates the resident's illness severity at the time of assessment relative to patients who have the same diagnosis
- A similar 7-point scale to assess improvement (CGI-I) relative to baseline and following an intervention also exists

Number of Points-Associated Severity
1-Normal
2-Borderline ill
3-Mildly ill
4-Moderately ill
5-Markedly ill
6-Severely ill
7-Extremely ill

Modified from https://sakai.ohsu.edu/access/content/user/brodym/.../CGI.doc. Accessed September 2012.

Additional Screening Tools: Mini-Cog

- A three-minute screen to identify early mental decline
  - Patient/resident is asked to repeat 3 unrelated words (ie, apple, quarter, house)
  - Clock drawing test (distractor task): Person is then asked to draw a clock face accurately and depict a time (ie, 10 minutes after 2). Test should take no longer than 2 minutes.
  - Three-word recall
- Scoring based on word recall:
  - 0 words recalled=dementia;
  - 1-2 words recalled=if clock is drawn correctly then probably not demented, if clock incorrect, then dementia
  - All 3 words accurately recalled=no dementia

Borson S, et al. *Int J Geriatr Pyschiatry*. 2000;15:1021-1027.

Additional Screening Tools: Mini Mental State Exam (MMSE)

- A copyrighted (ie, permission must be obtained for use), thirty point test that takes approximately 10 minutes to administer
- Screens for cognitive impairment (CI) and can be used to track CI over time
  - Focuses on simple arithmetic, memory, and orientation to time and place
- Low scores (≤20/30 points) correlate closely with the presence of dementia
- Sample and scoring instructions available:

  http://www.mhpcn.ca/uploads/MMSE.1276128605.pdf

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

St Louis University Mental Status exam, SLUMS

- Can detect both MCI and dementia[1] and has predictive validity for mortality and institutionalization (in males with dementia)[2]
- A 30-point, 11-item, clinician-administered scale that is similar in format to the MMSE.29 with the following supplements: tasks corresponding to attention, numeric calculation, immediate and delayed recall, animal naming, digit span, clock drawing, figure recognition/size differentiation, and immediate recall of facts from a paragraph[1]
- Takes into consideration a resident's educational status[1]

1. Tariq SH, et al. *Am J Geriatr Psychiatry*. 2006;14:900-910.
2. Cruz-Oliver DM, et al. *J Nutr Health Aging*. 2012;16:636-641.

FAST Staging of AD

- Functional Assessment Staging of Alzheimer's Disease (FAST)©
- The FAST scale has seven stages:
  - 1 which is normal adult
  - 2 which is normal older adult
  - 3 which is early dementia
  - 4 which is mild dementia
  - 5 which is moderate dementia
  - 6 which is moderately severe dementia
  - 7 which is severe dementia
  - FAST

 Reisberg, B. Functional Assessment Staging (FAST). *Psychopharmacology Bulletin*. 1988:24: 653-659.

FAST Stage 6

A. Difficulty putting clothing on properly without assistance
B. Unable to bathe properly (e.g., difficulty adjusting bath water temperature)
C. Inability to handle mechanics of toileting occasionally or more frequently over the past weeks
D. Urinary incontinence, occasional or more frequent
E. Fecal incontinence (occasional or more frequently over the past week)

 Reisberg, B. Functional Assessment Staging (FAST). *Psychopharmacology Bulletin*. 1988:24: 653-659.

FAST Stage 7

A. Ability to speak limited to approximately a half dozen different words or fewer, in the course of an average day or in the course of an intensive interview
B. Speech ability limited to the use of a single intelligible word in an average day or in the course of an interview (the person may repeat the word over and over.
C. Ambulatory ability lost (cannot walk without personal assistance)
D. Ability to sit up without assistance lost (e.g., the individual will fall over if there are no lateral rests [arms] on the chair)
E. Loss of the ability to smile

 Reisberg, B. Functional Assessment Staging (FAST). *Psychopharmacology Bulletin*. 1988:24: 653-659.

Pain in Older Adults

- Studies on pain in persons ≥65 years of age report 25%-50% of community dwellers have persistent pain
- 45-80% of nursing home residents report pain that is often left untreated
- Pain is strongly associated with depression and can result in
  - Decreased socialization
  - Impaired ambulation
  - Increased healthcare utilization and costs
- Older adults tend to minimize or not report their pain or are unable to due to sensory and or cognitive impairments
- Pain can often obscure other health issues

Flaherty E. Try This: Best Practices in Nursing Care to Older Adults. 2007;7.
AMDA Clinical Practice Guideline. Assisted Living Consult. 2005:28-32.

PAINAD

- Pain Assessment in Advanced Dementia
- 5 item observational tool
- Score 0-10 (based on a scale of 0-2 for 5 items)
- 5 items
  - Breathing independent of vocalization
  - Negative vocalization
  - Facial expression
  - Body language
  - Consolability

Warden V, et al. *J Am Med Dir Assoc.* 2003;4:9-15.

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Pharmacologic Management of AD

Drug	Mild-moderate dementia	Moderate-severe dementia
Cholinesterase inhibitors (ChEIs)		
Donepezil	• 5 or 10 mg OD	• 10 or 23 mg OD
Galantamine	• 4, 8, 16 or 24 mg OD (for ER preparation)	
Rivastigmine (patch)	• 4.6 mg, 9.5 mg, up to 13.3 mg/24 hrs	
N-methyl D-aspartate (NMDA) antagonist		
Memantine		• 5 mg OD up to 10 mg BID

- Starting doses are lower and should be adjusted in a step- and time-wise fashion to achieve the minimum effective dose for the individual

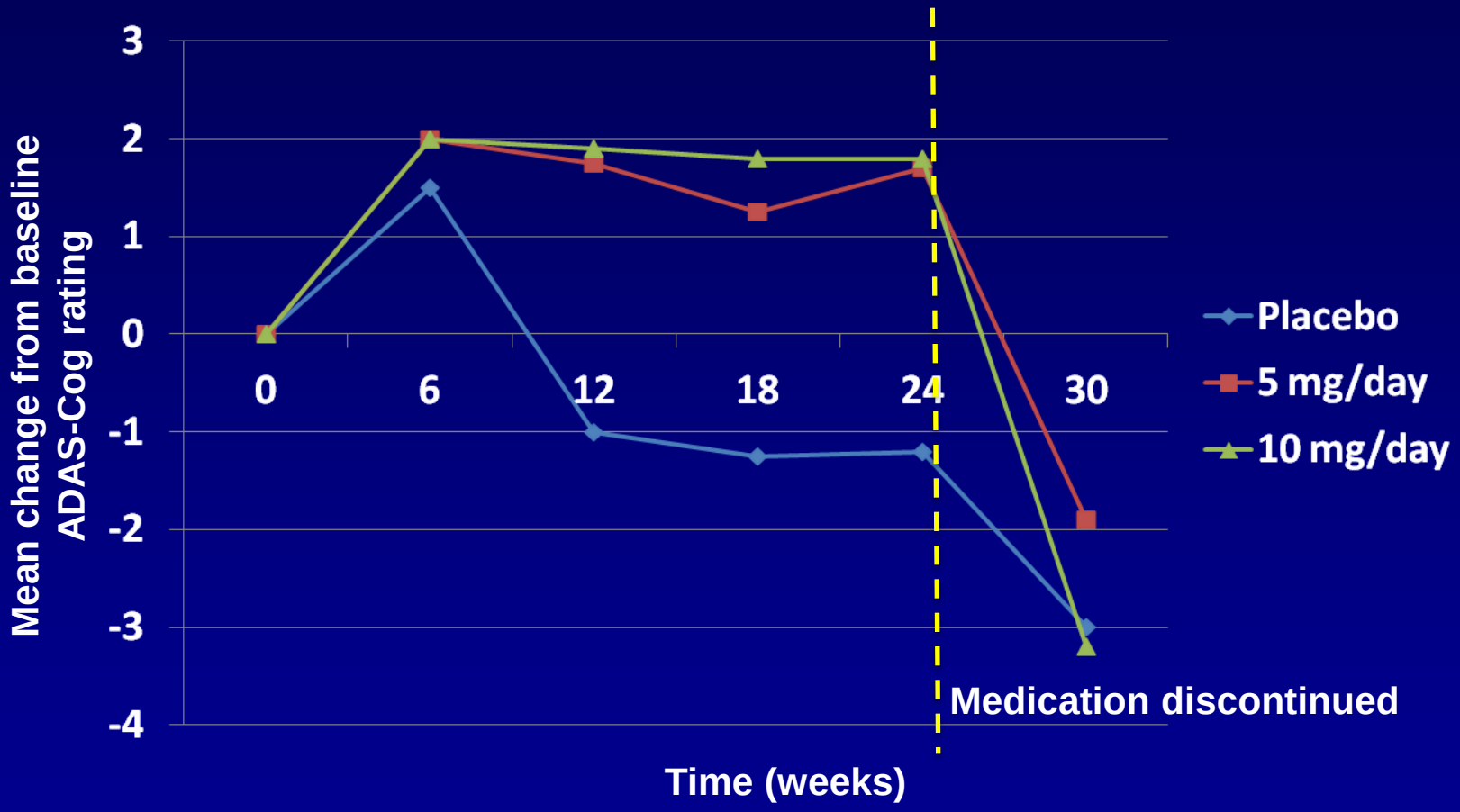
Atri A. *Am J Manag Care*. 2011;17:S346-S355.

Pharmacologic Management of AD (cont'd)

- These drugs offer symptomatic relief but do not slow the progression of AD[1]
- A meta-analysis of donepezil and galantamine found no significant difference in efficacy between the 2 drugs and both performed better than placebo in terms of cognitive improvement[1]
- Results from clinical trials showed that when compared to placebo, donepezil in combination with memantine improved outcomes in cognition, ADLs, and behavior[2]
- Although ChEIs have been shown to lessen the behavioral and psychological symptoms of dementia, it is unclear whether this results in less of a patient or caregiver burden[3]

1. Herrmann N, et al. *Drugs*. 2011;71:2031-2065
2. Tariot PN, et al. *JAMA*. 2004;291:317-324.
3. Campbell N, et al. *Clin Interv Aging*. 2008;3:719-728.

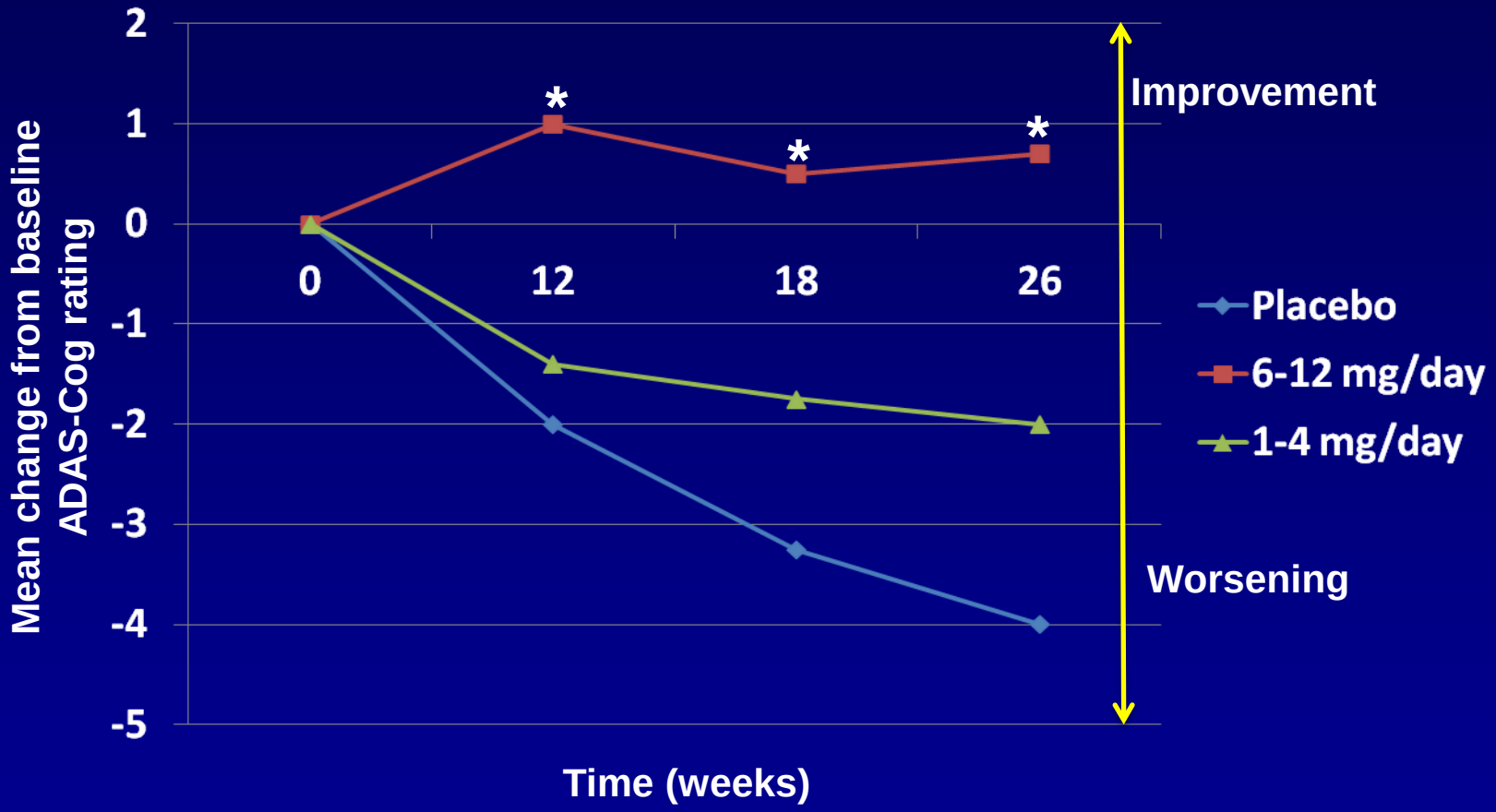
Changes in Cognition with Donepezil Therapy



- 6-month, multicenter, double-blind trial; approximately n=150 in each arm
- Patients had mild-moderate dementia and a diagnosis of uncomplicated AD
- *P*<.01 vs placebo for both drug dose groups

Adapted from Rogers SL, et al. *Neurology*. 1998;50:136-145.

Changes in Cognition with Rivastigmine Therapy



- N=699; * *P*<.001 vs placebo; study examined the effects of rivastigmine pills
- Alzheimer's disease assessment scale=ADAS; used for detailed assessments/research purposes; takes approximately 30-45 minutes to administer

Adapted from Corey-Bloom J, et al. *Int J Geriatr Psychopharmacol*. 1998;1:55-65.

Managing Side Effects of ChEIs

- Common gastrointestinal side effects include nausea/ vomiting, diarrhea, abdominal pain[1]
- Monitor rate of titration and maximum dosage to control side effects (while maintaining an effective dose)[1]
- Rivastigmine[2,3]
  - If patients are unable to tolerate rivastigmine oral therapy, they may be switched to the patch without a washout period
  - The patch (9.5mg/24hrs) has similar efficacy to the highest FDA-approved oral dose (12mg/day)
- Dizziness and/or bradycardia may also occur, so watch for falls

Good news:
ChEIs could help ease diabetic constipation[4]

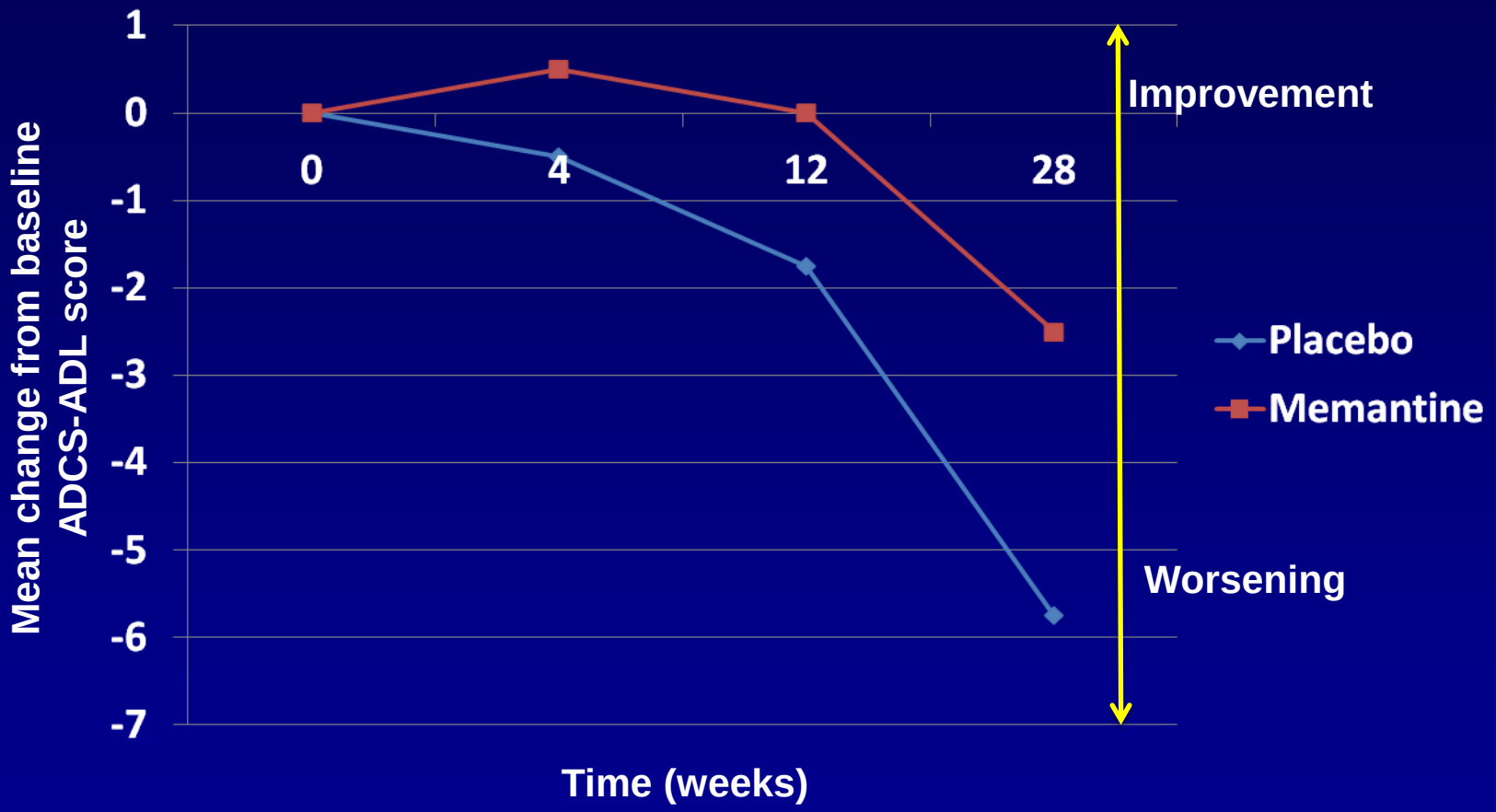
1. Imbimbo BP. *CNS Drugs*. 2011;15:375-390.
2. Articus K, et al. *Int J Clin Pract*. 2011;65:790-796.
3. Han HJ, et al. *J Clin Neurol.* 2011;7:137-142.
4. Bharucha AE, et al. *Gut*. 2012. PMID: 22677718.

Clinical Efficacy

- Patients on combination therapy (ChEIs+memantine) show slower declines in dementia and longer delays to ADL dependence[1-3]
  - Combination therapy is the standard of care for moderate-severe stages of AD[1] as is maintenance therapy (ie, discontinuing medications leads to worsening cognitive decline)[4]
- A study found that memantine (10mg BID) lowered aggression and agitation in 28 nursing home residents with AD and also lowered caregiver distress[5]

1. Atri A. *Am J Manag Care*. 2011;17:S346-S355.
2. Lopez OL, et al. *J Neurol Neurosurg Psychiatry*. 2009;80:600-607.
3. Atri A, et al. *Alzheimer Dis Assoc Discord*. 2008;22:209-221.
4. Smith DA. *Am J Health-Syst Pharm*. 2009;66:899-907.
5. Herrmann N, et al. *Drugs*. 2011;71:2031-2065.

Changes in Functioning with Memantine Therapy



- 20 mg daily (10 mg BID); N=252; LOCF analysis
- Alzheimer's disease Cooperative Study-Activities of Daily Living inventory=ADCS-ADL measures functional capability. Interviewer questions the caregiver

Adapted from Peskind ER, et al. *Am J Geriatr Psychiatry*. 2006;14:204-715.

Some Considerations for AD Therapies

	Presence of comorbidities/ chronic conditions[1]	Drug-drug interactions[2]	Cognitive decline even though taking medications
Considerations	• Multiple medications over a long duration[1]		• How rapidly was cognition deteriorating when the patient was not taking medication?

Actions	• Rational polypharmacy
	• Monitor for adverse events[2]
		• With memantine, limit carbonic anhydrase inhibitors[1]
		• Drugs that inhibit cytochrome P450 may increase circulating levels of donepezil and galantamine[1]
			• Goals
			  • Less than expected decline
			  • Slow cognitive decline

1. Smith DA. *Am J Health-Syst Pharm*. 2009;66:899-907.
2. National Committee for Quality Assurance. 2010. NQMC:006241.

Additional Therapies in Development

- IV administration of monoclonal antibodies against β amyloid
  - Phase III trials
    - Solanezumab
      - Developed by Lilly as an IV vaccine against AD
      - Preliminary analyses suggest that solanezumab slows the rate of cognitive decline by up to 30% in patients with early-stage AD[1]
    - Bapineuzumab
      - Resulted in safety signals: MRI imaging abnormalities such as vasogenic edema and sulcal effusions, have been observed with its treatment
      - These abnormalities resolved within 2 years after the first drug treatment, or after switching to a lower dose[2]
      - Pfizer and J&J halted clinical trials in August 2012 due to lack of efficacy
      - Companies may investigate whether the drug delays the start of the disease (as opposed to stopping the disease once the processes have been initiated)
- Therapies directed against pathological tau to slow the progression of neurofibrillary tangles[3]
- Intravenous immune globulin (IVIG) may bind to β amyloid plaques and is given via infusion every 2-4 weeks; may slow cognitive decline[4]

1. Norvdist C. Lilly's Solanezumab Slows Down Alzheimer's Progression. Medical News Today. Available at http://www.medicalnewstoday.com/articles/251295.php. Accessed October 2012.
2. Sperling R, et al. *Lancet Neurol*. 2012;11:241-249.
3. Delrieu J, et al. *J Neurochem*. 2012;120S1:186-193.
4. Dodel R, et al. *Drugs*. 2010;70:513-528.

Antipsychotic Drugs for Managing Behavioral Symptoms

- 14% of nursing home residents had Medicare claims for atypical antipsychotic (AP) drugs
- 83% of these claims were for off-label conditions
- 88% (of the 14%) were associated for conditions in the black-box warning
  - MDD, dementia, AD, psychosis NOS
- 89% of the residents taking atypical APs were described as being and/or having the following:
  - A danger to themselves or others
  - Inconsolable/persistent distress
  - Decline in functioning
  - Difficulty receiving needed care
- APs were also prescribed when residents experienced troublesome behaviors or emotions
  - Anxiety
  - Depression
  - Complaining
  - Mild agitation

HHS. OIE-07-08-00150. 2011.

Rationale for Nonpharmacologic Interventions for Problem Behaviors

- Pharmacologic interventions may have unwanted side effects
- Pharmacologic interventions may not address behavioral problems most upsetting to caregivers
- Pharmacologic interventions do not address all causes of problem behaviors

Possible Causes of Problem Behaviors that Can be Addressed With Non-pharmacologic Interventions

- Caregiver behavior
  - Negative communication
  - Misunderstanding patient behavior as resistance to care
- Unmet needs of person with dementia
  - Loneliness, isolation, boredom
- Environmental factors
  - Sensory deprivation
  - Overstimulation

Why Problem Behaviors Are Difficult for Family and Paid Caregivers

- Loneliness, stress, depression, fatigue
- Take behavior personally rather than attributing it to the disease process
- Behavior frequency and severity fluctuate
- More than one behavior at a time

Types of Interventions Proposed to Address Problem Behaviors

- Caregiver education, counseling, support, and training in problem solving
- Targeted therapy directed at the underlying causes for specific behaviors
- Environmental modification
- Physical exercise
- Individualized music
- Art therapy
- Social contacts
- Pet therapy
- Aromatherapy

Non-pharmacological Intervention: Habilitation

- Strategies to maximize functioning/independence and morale by altering the approach technique or the physical environment

Domain	Intervention
Physical Environment	Appropriate lighting helps to: • Improve independence • Reduce “sundowning” • Promote better sleep patterns • Help stabilize mood
Social	• Guiding or limiting choices or options so as not to overwhelm the individual • Tailoring activities to what the individual is interested in/used to doing • Having activities at dusk to reduce evening agitation
Functional	• Involve the individual in simple tasks if complex ones cannot be performed • Prioritize activities: assess whether or not it would hurt to skip occasionally

Raia, P. *Age in action*. 2011;26 (fall):1-5.

Habilitation (cont'd)

Domain	Intervention
Communication	• Avoid pointing out that individual's "reality" is not correct and instead acknowledge their emotions –As AD progresses the ability to articulate fear and to cope is lessened –Provide a safe and soothing environment • Employ distraction techniques if the individual's request is impractical –Redirect (change the topic) –Refocus (engage in conversation related to new topic) • If there are behavioral issues, assess whether there are underlying physiological causes • Maintain a sense of humor

Raia, P. *Age in action*. 2011;26 (fall):1-5.

Non-pharmacological Interventions (NPI, cont'd)

- Bathing without a battle[1]
  - Program involves caregivers accommodating resident's preferences to minimize struggle and frustration with daily activities (ie, shortened bathing sessions, bathing in bed or chair)
- MOUTh[2]
  - Strategies to reduce care-resistance with oral hygiene
    - "Guiding hands" technique: having the individual place his or her hands over the care provider's in order to guide the toothbrush or flossing procedure
- Soothing music at mealtimes decreases agitation[3]
- Family members may assist in the implementation of some of these strategies[4]

1. Bathing without a battle: person-directed care of inidviduals with dementia. http://www.bathingwithoutabattle.unc.edu/ Accessed June 2012.
2. Jablonski RA, et al. *BMC Oral Health*. 2011;11:30.
3. Ho SY, et al. *Arch Psychiatr Nurs*. 2011;25:e49-e55.
4. Raia, P. *Age in action*. 2011;26 (fall):1-5.

Non-pharmacological Interventions (NPI, cont'd)

- CARES® Activities of Daily Living™ Online Training Program
  - HealthCare Interactive, Inc. (HCI) addresses the growing national crisis of memory loss, dementia, and Alzheimer's disease by developing the most innovative set of training products for family members and professional caregivers available in the marketplace today.
  - For more information, visit www.CaresProgram.com
- Music Therapy
  - January 2008, MJHS (Metropolitan Jewish Health System) received a three-year dementia care music therapy grant from the New York State Department of Health to develop protocols that show how music interventions offer safe, non-pharmacological approaches to relieve symptoms of dementia.
  - Video http://www.youtube.com/watch?v=igWhztV2HCU
  - For more information, visit http://www.mjhs.org/

Barriers to Comprehensive Treatment of Behavior Problems in Dementia

- Physician practice constraints[1]
  - Insufficient time and low reimbursement
  - Difficulty in accessing and communicating with specialists
  - Poor connections with community social service agencies
  - Lack of interdisciplinary teams
- Low reimbursement for nonpharmacologic interventions
- Little rigorous research with well-designed randomized controlled trials (RCTs) to create an evidence base for nonpharmacologic interventions

1. Hinton L, et al. *J Gen Intern Med.* 2007;22:1487-1492.

Interventions With Evidence From RCTs

Interventions for Caregivers to Reduce Symptom Severity at Home

- Results of a meta-analysis
  - Interventions effective in reducing behavioral and psychological symptoms; effect size 0.34 (95% confidence interval [CI] = 0.20–0.48; z=4.87; *P*<0.01)
  - Interventions effective in ameliorating caregiver reactions to behaviors; effect size 0.15 (95% CI = 0.04–0.26; z=2.76; p=0.006)*

* Brodaty H, Arasaratnam C. *Am J Psychiatry.* 2012;169:946-953.

A Program for Caregiver and PWD: Reducing Disability in Alzheimer Disease

- Interventions
  - For PWD: caregiver taught how to help person with dementia with aerobic/endurance, strength, balance, flexibility exercises
  - For caregiver: behavior management
- 12 sessions in 3 months plus 3 sessions in next 3 months
- Treatment vs routine care
  - 153 patient/caregiver dyads
  - 140 (92%) completed 3-month follow-up
- Outcomes
  - Patients in the Reducing Disability in Alzheimer Disease (RDAD) group had improved Cornell Depression Scale for Depression in Dementia scores
  - 3 months: patients exercised more and better physical functioning, caregivers less depressed
  - 2 years: patients better physical functioning

PWD, person with dementia

Teri L, et al. *JAMA.* 2003;290:2015-2022.

NYU Caregiver Intervention: An Intervention Developed by Clinicians

- Intervention
  - Comprehensive assessment
  - Individual counseling
  - Family counseling
  - Ongoing counseling and support
- Participants: 406 spouse caregivers followed for up to 18 years
- Main findings of the original randomized trial
  - Improved support for spouse caregiver
  - Improved reaction to problem behaviors (Memory and Behavior Checklist)[1]
  - No effect on frequency of problem behaviors (Memory and Behavior Checklist)[1]
  - Reduced symptoms of caregiver depression
  - Improved caregiver self-rated physical health and number of illnesses
  - Delayed nursing home placement of patient = 1.5 years
  - Mediator of all other outcomes is caregiver satisfaction with social support

Mittelman MS, et al. *J Gerontol B Psychol Sci Soc Sci.* 2004;59:P27-P34.

Interventions to Reduce Symptom Severity in Nursing Homes

- Individualized intervention to address unmet needs
- Intervention for patients in groups
- Music intervention

TREA: Treatment Routes for Exploring Agitation

- Treatment designed to address unmet needs, remaining abilities, and past interests
- 125 participants: 89 in treatment group; 36 in control group
- Outcome measured by observation (Agitation Behavior Mapping Instrument)
- Results
  - Significant decline in total ($P<0.001$), physical nonaggressive ($P<0.001$), and verbal ($P<0.004$) agitation (Agitation Behavior Mapping Instrument)
  - Significant increase in pleasure ($P<0.001$) and interest ($P<0.05$) on Lawton's Modified Behavior Stream

Cohen-Mansfield J, et al. *J Clin Psychiatry.* 2012;73:1255-1261.

Multimodal Group Intervention

- Aim: preserve cognitive and practical abilities.
- Intervention
  - 6-month intervention with 3 components: motor activities, cognitive stimulation, and activities of daily living
  - Treatment in groups of 10 patients; 2 therapists; 2 hours, 6 days a week
- Participants: 139 residents of 5 nursing homes in Germany
- Results
  - Significant overall effect on behaviors (Nurses Observation Scale for Geriatric Patients; d=0.72), on social behavior (d=0.59), memory (d=0.53), challenging behaviors (d=0.44) and instrumental activities of daily living (IADLs) (d=0.41)

Luttenberger K, et al. *J Am Geriatr Soc.* 2012;60:830-840.

Music Intervention

- Pilot RCT of individualized music therapy (n=30)*
  - Intervention: music by request streamed to headphones for 16 weeks
  - Follow-up at 4, 8, 16, and 24 weeks
  - Outcome: significant improvements in anxiety (Hamilton, $P<0.01$) and depression (Geriatric Depression Scale [GDS], $P<0.01$) during 16-week intervention sustained for at least 8 weeks

Guetin S, et al. *Dement Geriatr Cogn Disord.* 2009;28:36-46.

New Interventions for People in the Early Stages of Dementia With Their Family Members

The NYU Couples Counseling Intervention

- Intervention: six couples-counseling sessions within a 2-month period; “ad hoc” counseling
- Pilot randomized wait-list control trial (All participants receive “ad hoc” counseling
  - 41 couples
  - Person with dementia in the mild stage
  - Comprehensive written assessment at baseline, 2- and 4-month follow-ups
  - Treatment had a significant effect on relationship
- Results
  - Significant effect on the Dyadic Adjustment Scale (caregiver rated) at the first follow-up (*P*=0.017), maintained at the second follow-up (*P*=0.039)
  - Goals achieved (goal-attainment scaling)
  - Improved communication observed and reported

Auclair U, et al. *Clin Gerontol.* 2009;32:130-146.

The Unforgettables: A Chorus for People With Dementia and Their Family Members

- Mary Mittelman, DrPH, director of the Psychosocial Research and Support Program at the Comprehensive Center on Brain Aging-New York University Langone Medical Center and her colleagues created a chorus named The Unforgettables, to support people with dementia as well as their family members and friends.
- For more information visit, http://aging.med.nyu.edu/research/chorus

AD 2012 Summit: Clinical Trials for Non-pharmacological Interventions

- Primarily for the research community

Suggested Methodology	Reasoning
Initiate rigorously designed clinical trials • Use –Epidemiologic information –Research from animal models –Network analysis	To establish the effectiveness of physical exercise, cognitive training, and their combination for AD treatment and prevention
Combine NPI + pharmacological therapies	Maximize possible therapeutic benefit
Develop standard outcome measures • Use ecologically valid measures of –Real-world function –QoL –Physical and cognitive function	Enable data comparisons across studies

Alzheimer's Disease Research Summit 2012 Recommendations. Available at http://www.nia.nih.gov/newsroom/alzheimers-disease-research-summit-2012-recommendations Accessed June 2012.

Additional Funding for AD

- Dominantly Inherited Alzheimer Network (DIAN)[1]
  - Purpose: Identify potential biomarkers that may predict the development of Alzheimer's disease in people who carry an Alzheimer's mutation
    - Known causative mutations for AD in the APP, PSEN1, or PSEN2 genes
  - Goals
    - Pre-symptomatic individuals: compare mutation carriers and non-carriers to determine the order in which changes in clinical, cognitive, neuroimaging, and biomarker indicators of AD occur prior to the occurrence of dementia
    - Symptomatic individuals: compare the clinical and neuropathological phenotypes of autosomal dominant AD to those of late-onset "sporadic" AD
- Anti-Amyloid Treatment in Asymptomatic (A4) Trial[2]
  - Older individuals at risk of developing AD will be screened/imaged for Aβ plaques and if positive, proactively treated with a (safe) drug to see if the trajectory of decline can be significantly impacted

1. Dominantly Inherited Alzheimer Network (DIAN). Clinicaltrials.gov. Available at http://clinicaltrials.gov/show/NCT00869817. Accessed October 2012.
2. Anti-Amyloid Treatment in Asymptomatic (A4) Trial. Alzheimer's Research Forum. Available at http://www.alzforum.org/new/detail.asp?id=3014. Accessed October 2012.

Summary

- Healthcare delivery goals[1]
  - Management of symptoms
  - Reduction of decline in the long-term
- Care management plans that foster:[2]
  - Physical well-being
  - Meaningful relationships
  - Opportunities to engage in meaningful activities
  - Discussions regarding future care decisions that will be honored

1. Atri A. *Am J Manag Care*. 2011;17:S346–S355.
2. Wisconsin Statewide Advisory Committee on Quality of Life Outcomes for People with Alzheimer's Disease and Related Dementia. Available at http://www.dhs.wisconsin.gov/aging/dementia/Dementia%20Outcomes%20Care%20Plan%20Tool.pdf. Accessed March 2012.

Outline

- Epidemiology
  - Prevalence
  - Financial impact
  - The AD continuum
- Diagnosis
  - Differentiating between dementias and AD
  - Pathophysiology
  - Biomarkers
  - Common comorbidities
  - Cognitive assessments
- Treatment
  - Pharmacologic therapies and imaging
  - Side effect management
  - Non-pharmacologic interventions
  - Care delivery methodologies
  - National needs/future directions
- Case Studies

Patient Case #1

- Presentation
  - Tom is 77 years old and lives in a LTC facility
  - The nursing staff has noticed that he has become very quiet over the past several months and also demonstrates a flattened affect
  - Has a 7-year progressive history of AD
  - Treated with rivastigmine patch

Possible Next Steps

- Reassess memory impairment
- Review medication history
  - Would combination with another AD medication be helpful?
- Screen for mood disorders
  - Would an antidepressant medication be helpful?
  - If so, are there any interactions to consider between it and rivastigmine?
- Patient/caregiver interview to find out if there have been any changes in normal routine (ie, a disruption in the 3 “R”s)
- Assess for safety concerns
- Consider transition to a more specialized unit within the LTC facility

Patient Case #2

- Elaine is an 85 year old woman residing alone in her own home
- Elaine's daughter, Corrine, lives 20 minutes away and visits her once a week in addition to chatting with her for a few minutes daily
- Lately, her daughter has noticed that her mother has become forgetful
  - She has forgotten to go to her weekly card game with her friends twice (a pastime that she regularly partakes in)
  - When Corrine has visited, she has noticed that the kitchen is disorganized (utensils are unwashed, food is not refrigerated)

Follow-up

- Medical History
  - Besides elevated blood pressure for which Elaine takes an ACE inhibitor, she does not have any other documented medical diagnoses
- Screening
  - What screening tests would you perform to differentiate between normal aging and dementia?
  - How would you progress to a diagnosis of AD?
- Treatment
  - What kinds of steps can be taken to lengthen Elaine's stay in her own house?
  - What types of factors should be considered in transitioning Elaine to either an assisted living facility or a nursing home?

Follow-up (cont'd)

- Treatment (cont'd)
  - What types of medications would you prescribe if
    - Dementia was diagnosed?
    - AD was diagnosed?