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# Examining Emerging Therapies and Care Management Interventions for **Alzheimer's Disease**

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MEDICAL EDUCATION RESOURCES

This activity is supported by independent educational grants from Avanir Pharmaceuticals and Lilly USA, LLC. For further information concerning Lilly grant funding visit www.LillyGrantOffice.com.

AMCP Academy of Managed Care Pharmacy®

Held in conjunction with AMCP Managed Care & Specialty Pharmacy Annual Meeting 2017.

# Educational Objectives

- Describe various diagnostic tools for Alzheimer's Disease (AD) and evaluate their respective benefits and disadvantages for standardized use among network providers
- Describe the impact of care coordination in AD in terms of patient quality of life and disease outcomes
- Implement plan-wide initiatives to better coordinate care for AD among primary and ancillary providers in acute and long-term settings
- Appraise the novel mechanisms of action (MOAs) and clinical benefits of emerging disease-modifying agents for the management of AD
- Recommend benefit design strategies for emerging biologic and small-molecule AD therapies that encourage appropriate utilization while facilitating patient access and adherence
- Outline the components and benefits of an effective medication therapy management (MTM) program for AD
- Characterize the role of specialty pharmacy in supporting appropriate utilization and administration of emerging therapies for AD

# Assessing the Clinical Potential and MOAs of Emerging Therapies

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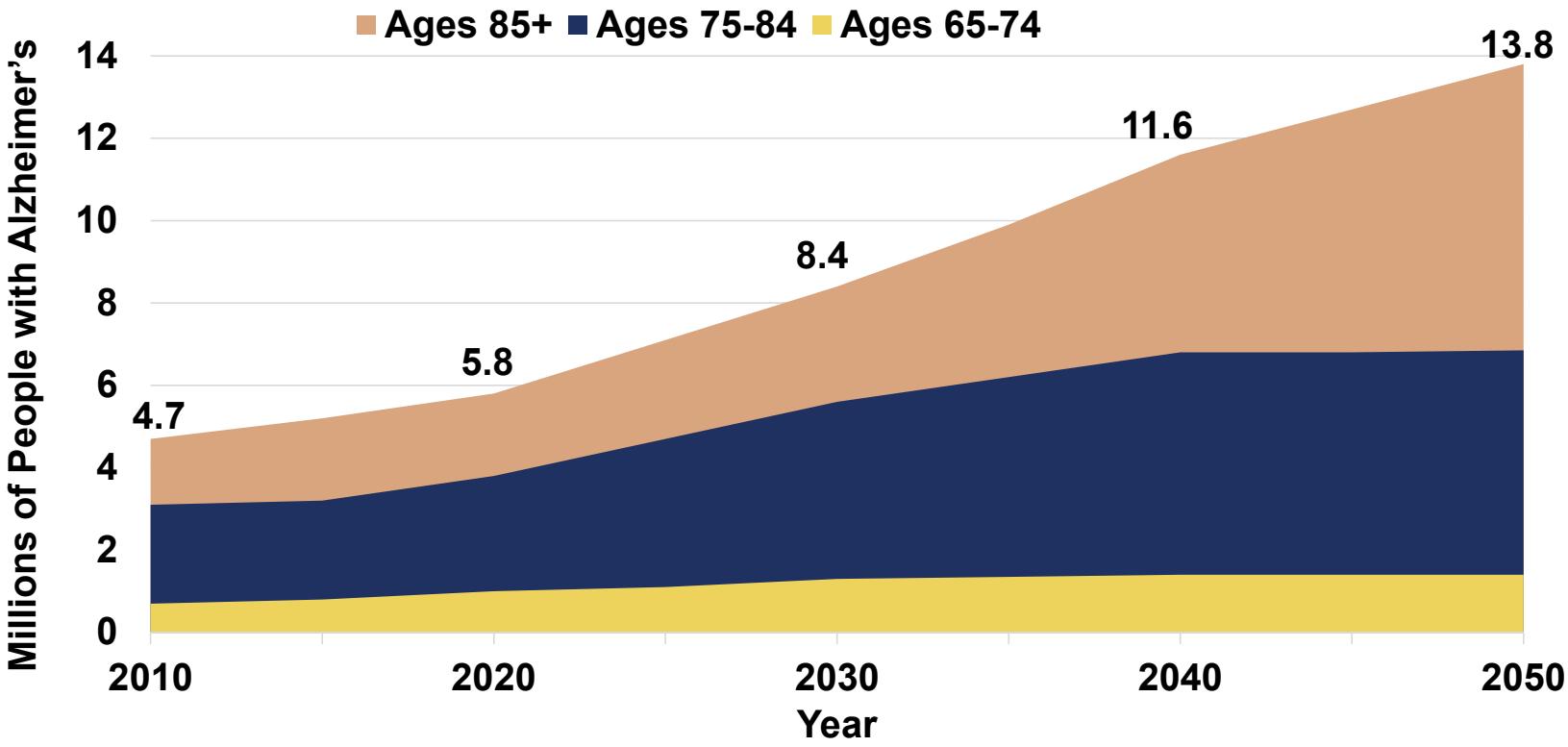
# Disease Overview

- Dementia represents a disease category, and the current parlance involves assigning its cause, ie, “dementia due to Alzheimer’s disease”
  - Alzheimer’s disease (AD) is the most common type of dementia
    - Occurs in 60%-80% of dementia diagnoses
    - Affects ~5.3 million US adults
    - Incidence is estimated to be increasing at a rate of 4% per year
- AD is a progressive neurodegenerative disorder with no cure
  - Uncertain cause and pathogenesis
  - Majority of cases occur after age 65
    - Incidence & prevalence increase exponentially with age
- Selective memory impairment is the most essential and often earliest clinical manifestation

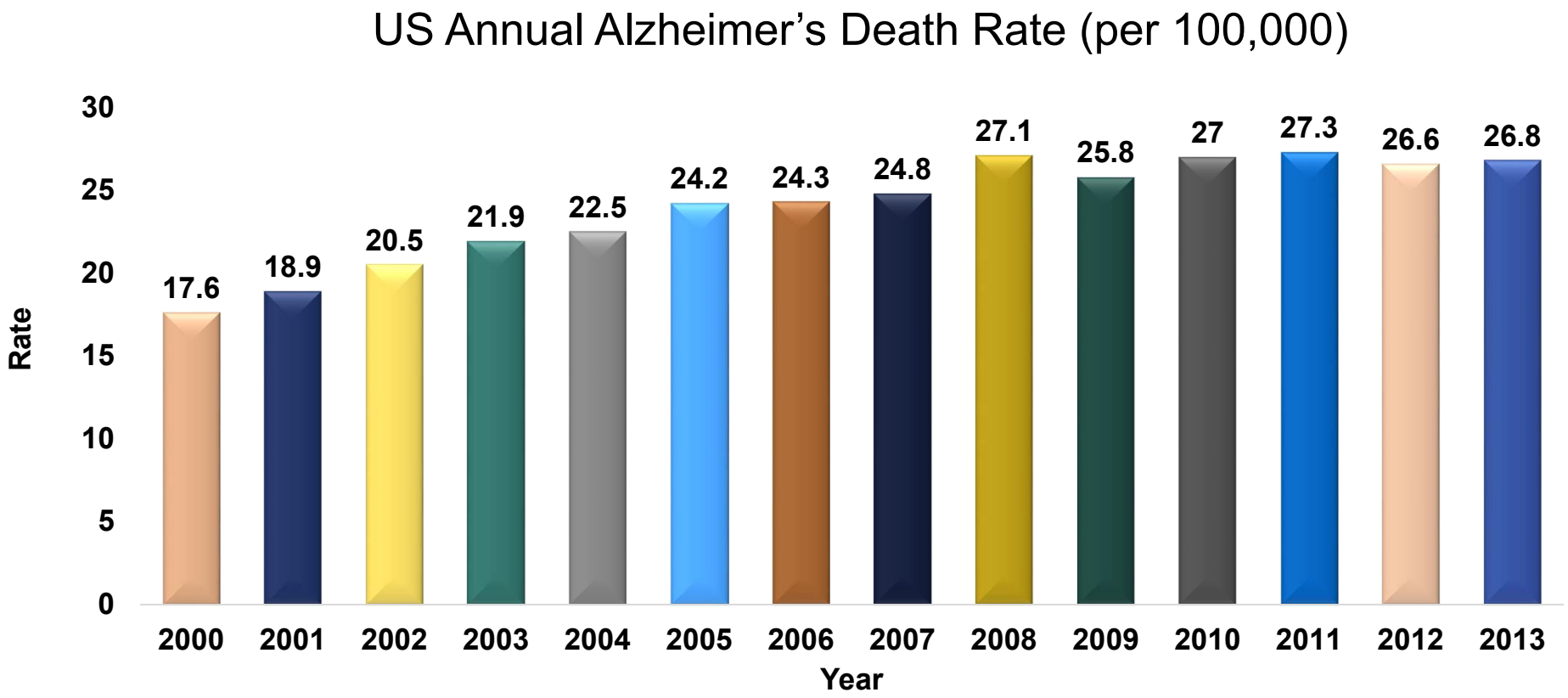
Alzheimer’s Association. Facts & Figures 2016. https://www.alz.org/documents_custom/2016-facts-and-figures.pdf. Accessed March 2017.
Wolk, DA, et al. Clinical features and diagnosis of Alzheimer disease. In: UpToDate, Eichler, AF (Ed), UpToDate, Waltham, MA. http://www.uptodate.com/contents/clinical-features-and-diagnosis-of-alzheimer-disease

# The Prevalence of AD is Rising and Expected to Reach 13.8 Million by 2050



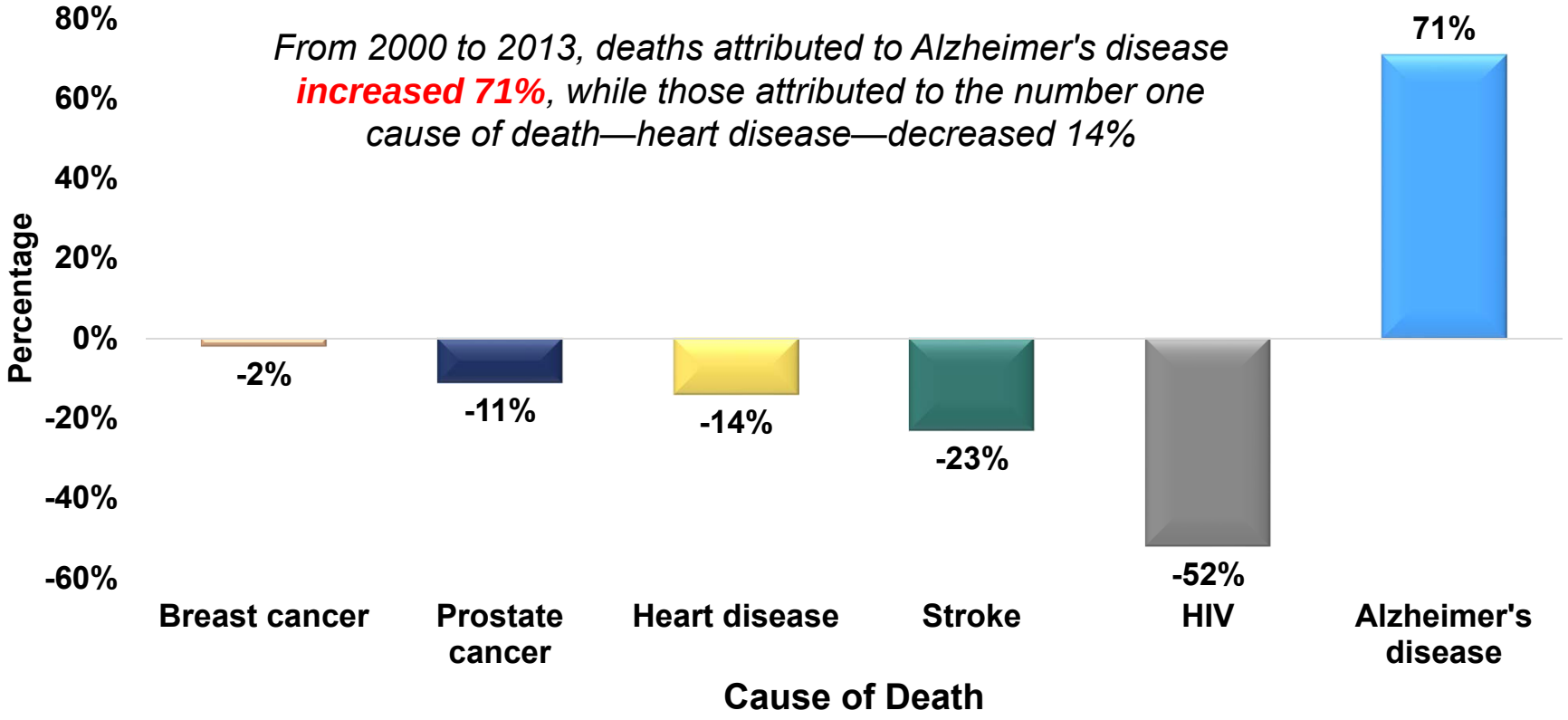

Hebert LE, et al. *Neurology*. 2013;80:1778-1783.

# Mortality Associated with the Disease is Significant




Alzheimer's Association. Facts & Figures 2016. https://www.alz.org/documents_custom/2016-facts-and-figures.pdf. Accessed March 2017.

# In Recent Years, AD-related Mortality Has Increased Dramatically




Xu JQ, et al. National Vital Statistics Reports. 2016;64. http://www.cdc.gov/nchs/data/nvsr/nvsr64/. Accessed March 2017.

# In the Absence of Disease-modifying Therapy, AD and its Morbidity/Mortality Remain Unchecked

*AD is the only top-10 leading cause of death in America that can't be prevented, delayed, or cured*

| Rank[1] | Cause of death | (based on ICD-10) | Number | Percent of total deaths |
|---|---|---|---|---|
| … | All causes | | 2,626,418 | 100.0 |
| 1 | Diseases of heart | (100-109, I11, I13, I20-I51) | 614,348 | 23.4 |
| 2 | Malignant neoplasms | (C00-C97) | 591,699 | 22.5 |
| 3 | Chronic lower respiratory diseases | (J40-J47) | 147,101 | 5.6 |
| 4 | Accidents (unintentional injuries) | (V01-X59, Y85-Y86) | 136,053 | 5.2 |
| 5 | Cerebrovascular diseases | (I60-I69) | 133,103 | 5.1 |
| 6 | Alzheimer's disease | (G30) | 93,541 | 3.6 |
| 7 | Diabetes mellitus | (E10-E14) | 76,488 | 2.9 |
| 8 | Influenza and pneumonia | (J09-J18) | 55,227 | 2.1 |
| 9 | Nephritis, nephrotic syndrome and nephrosis | (N00-N07, N17-N19, N25-N27) | 48,146 | 1.8 |
| 10 | Intentional self-harm (suicide) | (*U03, X60-X84, Y87.0) | 42,773 | 1.6 |

Kochanek KD, et al. *National Vital Statistics Reports*. 2014

# Disease Severity, Progression, and Associated Symptomology

## Mild

- Primary early symptom is forgetfulness (e.g., names/words, addresses, shopping items)
- Main deficit is in recent memory
- Intellectual deficits confirmed by neuropsychological testing
- Some awareness of their symptoms, so the person may become anxious, depressed and may be in denial
- No distinguishing features on physical examination

## Moderate

- Significant memory loss (e.g., close family members, well known routes/places)
- Personality and behavioral changes
- Self-neglect
- Disorientation in time and space
- Inability to undertake simple tasks (e.g., getting dressed)
- Reduced range of thinking (intellectual deficits)
- Initial language problems
- Aggression, restlessness, and wandering

## Severe

- Dysphasia with disordered and fragmented speech
- Increased aggression, restlessness, and wandering
- Delusions
- Incontinence
- Immobility, rigidity, and recurrent falls
- General physical deterioration

# Disease Pathophysiology

- AD affects the three processes crucial for neuronal vitality: communication, metabolism, and repair
- As the disease progresses, specific neurons in the brain stop working, lose connections (synapses) with other neurons, and subsequently die
- The destruction and death of these neurons result in the memory failure, personality changes, problems carrying out daily activities, and other features characteristic of the disease

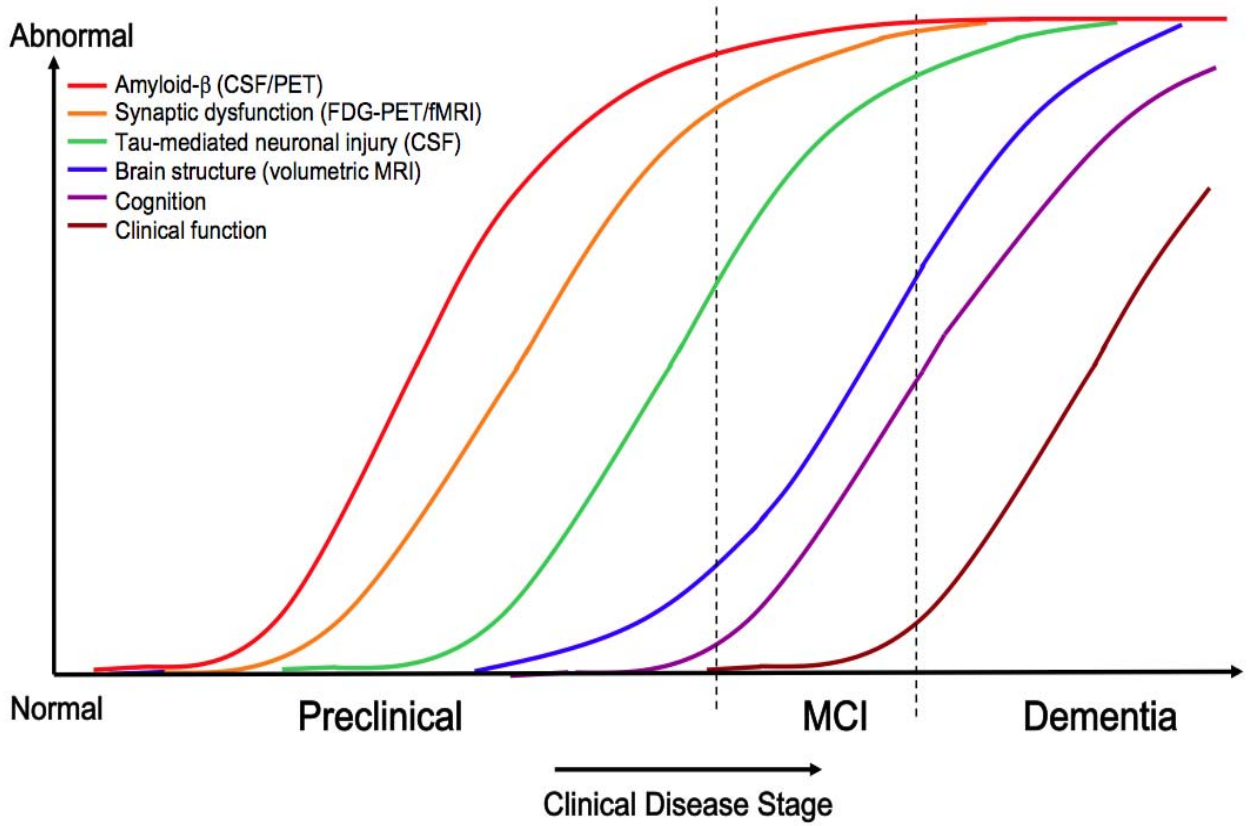
# Neuronal Structure and Dysfunction

- Healthy neurons have an internal transport system composed of microtubules with tau protein binding and stabilizing the microtubules
- This tau protein is chemically altered in AD and begins to pair with other threads of tau
- The resulting neurofibrillary tangles (NFTs) lead to the disintegration of the microtubules, causing a collapse of the neuron's transport system
- In addition to NFTs, the anatomic pathology of AD includes β-amyloid or senile plaques at the microscopic level and cerebrocortical atrophy at the macroscopic level
- The accumulation of β-amyloid plaques primarily precedes the clinical onset of AD, while the formation of NFTs, loss of neurons, and loss of synapses accompany the progression of cognitive decline

**However, it is not known whether β-amyloid plaques are a CAUSE or a CONSEQUENCE of neural dysfunction**

# Biomarkers for AD Highlight the Role of β-amyloid and Tau Protein in AD Pathophysiology

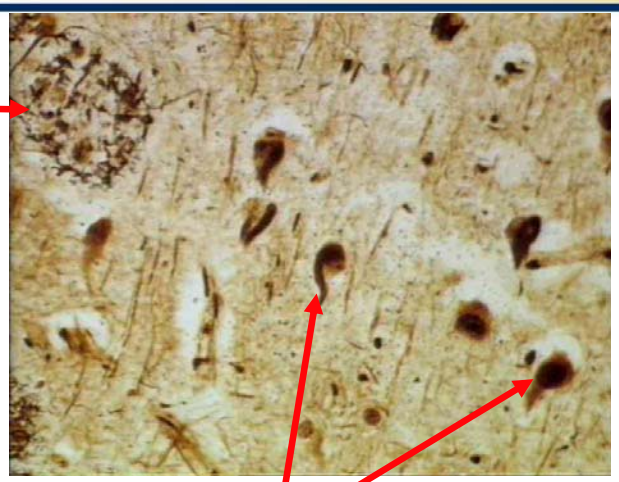
- Biomarkers demonstrate promise for early detection of AD
- However, associated tests can be costly and invasive

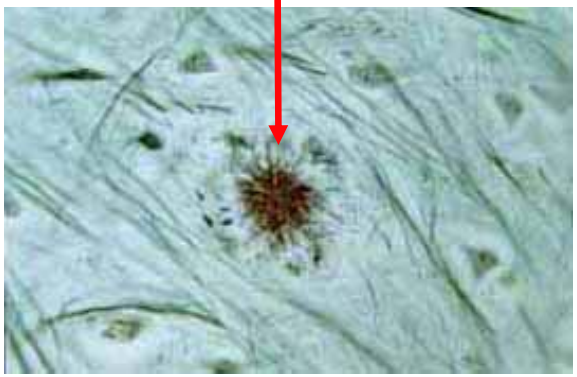



National Institute on Aging/Alzheimer's Association Diagnostic Guidelines for Alzheimer's Disease: Criteria for preclinical Alzheimer's Disease. Sperling et al., 2011 (Adapted from Jack et al., 2010)

# AD Pathology: Amyloid Plaques and Neurofibrillary Tangles in the Brain

**Amyloid plaques contain large amounts of a 42 amino acid peptide β-amyloid or Aβ42**



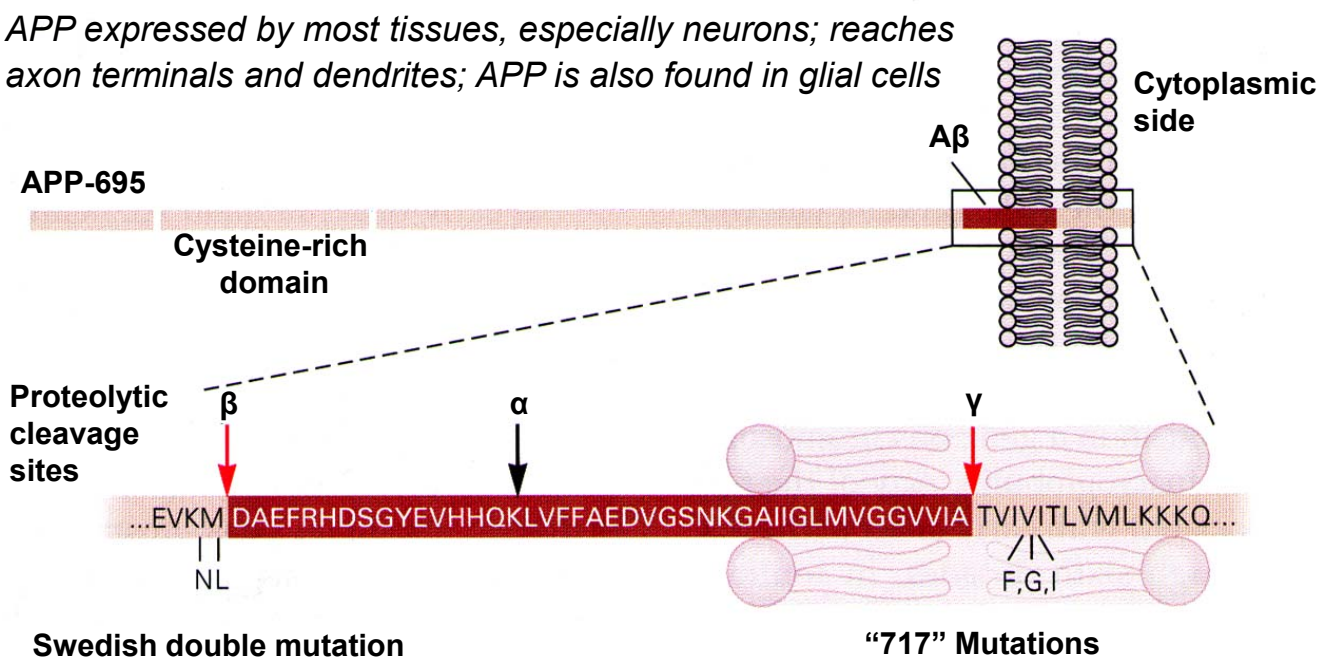


**Neurofibrillary tangles: rich in cytoskeletal proteins, especially the microtubule-associated protein, tau. In the tangles: heavily phosphorylated proteins, which may cause aggregation and precipitation of the cytoskeleton.**

**Also noted is generally reduced brain volume, especially in entorhinal cortex and hippocampus**

Kandel ER, et al. *Principles of Neural Science*. 5th ed. New York:McGraw-Hill; 2012.

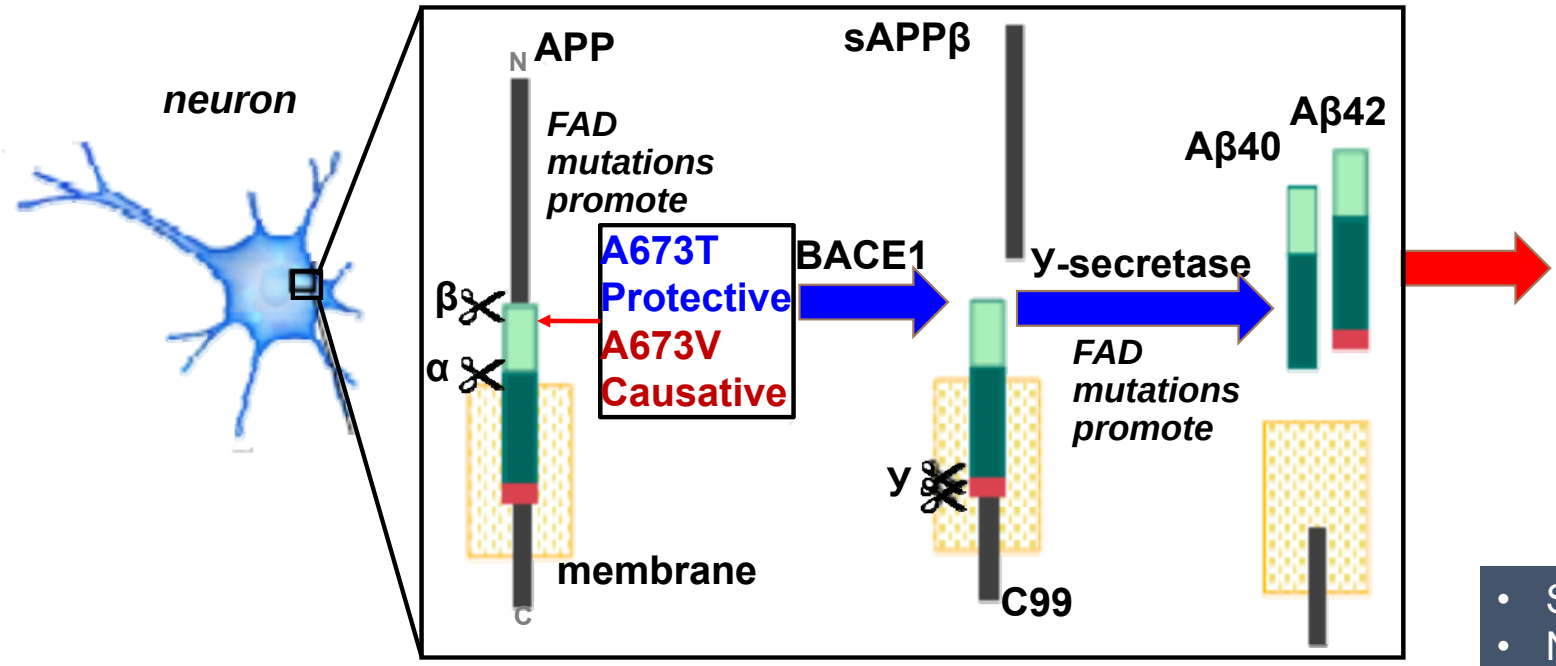
# Aβ40 and Aβ42 are Proteolytic Products Formed from Amyloid Precursor Protein (APP)

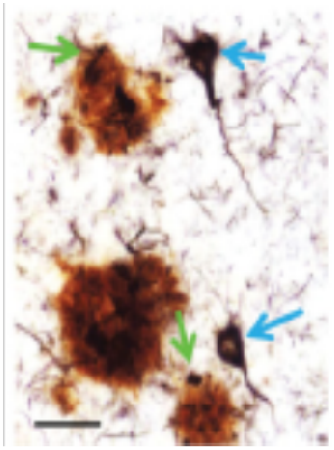



Overproduction of βb40 and βb42 results from an altered ratio of proteolytic cleavages at sites termed α, β, and γ

Selkoe DJ, et al. *EMB Molecular Med*. 2016;8:595-608.

# These Components Comprise the "Amyloid Hypothesis" of AD Pathogenesis



Immunohistochemistry:
Aβ (brown) and Tau (black)

- Synaptic dysfunction
- Neuronal cell death
- Neuroinflammation


Jonsson, et al. *Nature*. 2012;488:96-99.
Karran et al. *Nat. Rev. Drug. Disc*. 2011,10:698.

# All Known Genetic Risk Factors Predisposing to Alzheimer's Disease Increase Accumulation of Aβ Peptides

| Chromosome | Gene defect | Phenotype |
|---|---|---|
| 21 | β-APP mutations | ↑All Aβ peptides, or Aβ40 peptides<br>A673T↓ Aβ peptides, AD, cognitive decline |
| 19 | ApoE4 polymorphism (ε4 allele) | ↑Density of Aβ plaques & vascular deposits |
| 14 | Presenilin 1 mutation | ↑Production of Aβ42 peptides |
| 1 | Presenilin 2 mutation | ↑Production of Aβ42 peptides |
| 6 | TREM2 | ↑Density of Aβ plaques |

**Abnormal states of tau mediate some effects of β-amyloid. This stage may be distal to the more toxic dimers and oligomers.**

Sheng et al. *Cold Spring Harb Perspect Biol.* 2012;4(5):a005777.

# Other Pathogenic Hypotheses for Primarily Synaptic Toxicity in AD

Loss of synapses correlates better than plaques or tangles with cognitive deficits

| Aβ-amyloid hypothesis | Aβ-oligomer hypothesis | Presenilin hypothesis | $Ca^{2+}$ dysregulation hypothesis | Lysosome hypothesis | Tau hypothesis |
|---|---|---|---|---|---|
| Amyloid plaque resulting from Aβ overproduction or reduced clearance | Soluble oligomers resulting from Aβ overproduction or reduced clearance | Impaired presenilin function due to mutations or Aβ | $Ca^{2+}$ dysregulation due to aging, oxidative stress, Aβ, and/or presenilin dysfunction | Lysosome/autophagy dysfunction | Aggregated hyperphosphorylated Tau |
| ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
| Aβ-amyloid-induced synapto- and neurotoxicity | Aβ-oligomer-induced synapto- and neurotoxicity | Synaptic dysfunction and neurotoxicity | $Ca^{2+}$-induced synapto- and neurotoxicity | Impaired proteostasis and axonal transport | Synaptic dysfunction and neurotoxicity |
| ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
| Neurodegeneration | Neurodegeneration | Neurodegeneration | Neurodegeneration | Neurodegeneration | Neurodegeneration |

*"Originally, it was thought that the actual amyloid is pathogenic—hence the term 'amyloid hypothesis.' The more current version of this hypothesis posits that Aβ (especially Aβ42) microaggregates—also termed 'soluble Aβ oligomers' or 'Aβ-derived diffusible ligands' (ADDLs)—constitute the neurotoxic species that causes AD."*

Sheng et al. *Cold Spring Harb Perspect Biol.* 2012;4(5):a005777.

# Currently Available and Investigational Drug Therapies for AD Differ Significantly in Specific Effect

- While currently available pharmacotherapies for AD are aimed at improving cognitive function, investigational agents target the underlying pathophysiology

  - ***Approved therapies:*** Acetylcholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist exert their therapeutic effect by lessening cognitive decline
  - ***Investigational therapies:*** The MOAs of agents in development are generally focused on inhibiting the formation of β-amyloid, tau protein, and the resultant plaques and neurofibrillary tangles

# FDA-approved Pharmacotherapies for AD

| Drug | MOA | Indication | Approval Year |
|---|---|---|---|
| Donepezil | AChEI | All stages | 1996 |
| Rivastigmine | AChEI | All stages | 2000 |
| Galantamine | AChEI | Mild-to-moderate | 2001 |
| Memantine | NMDA antagonist | Moderate-to-severe | 2003 |
| Donepezil/ memantine | Combination AChEI/NMDA antagonist | Moderate-to-severe | 2014 |

AChEI=acetylcholinesterase inhibitor; NMDA=N-methyl-D-aspartate

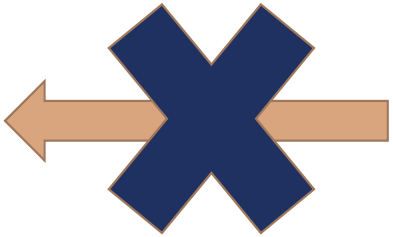
US Food & Drug Administration. FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/daf/

# Acetylcholinesterase Inhibitors (AChEIs)

- Drugs that prevent the breakdown of acetylcholine, a brain chemical involved in memory and cognition
  - ↑ acetylcholine = ↑ cognitive abilities
- FDA-approved medications
  - Donepezil
  - Galantamine
  - Rivastigmine

# Acetylcholinesterase Inhibitors (AChEIs): Mechanism of Action


By inhibiting acetylcholinesterase, these drugs allow more acetylcholine to remain activated



Increased levels of acetylcholine can help maintain or improve cognitive abilities in some people with dementia

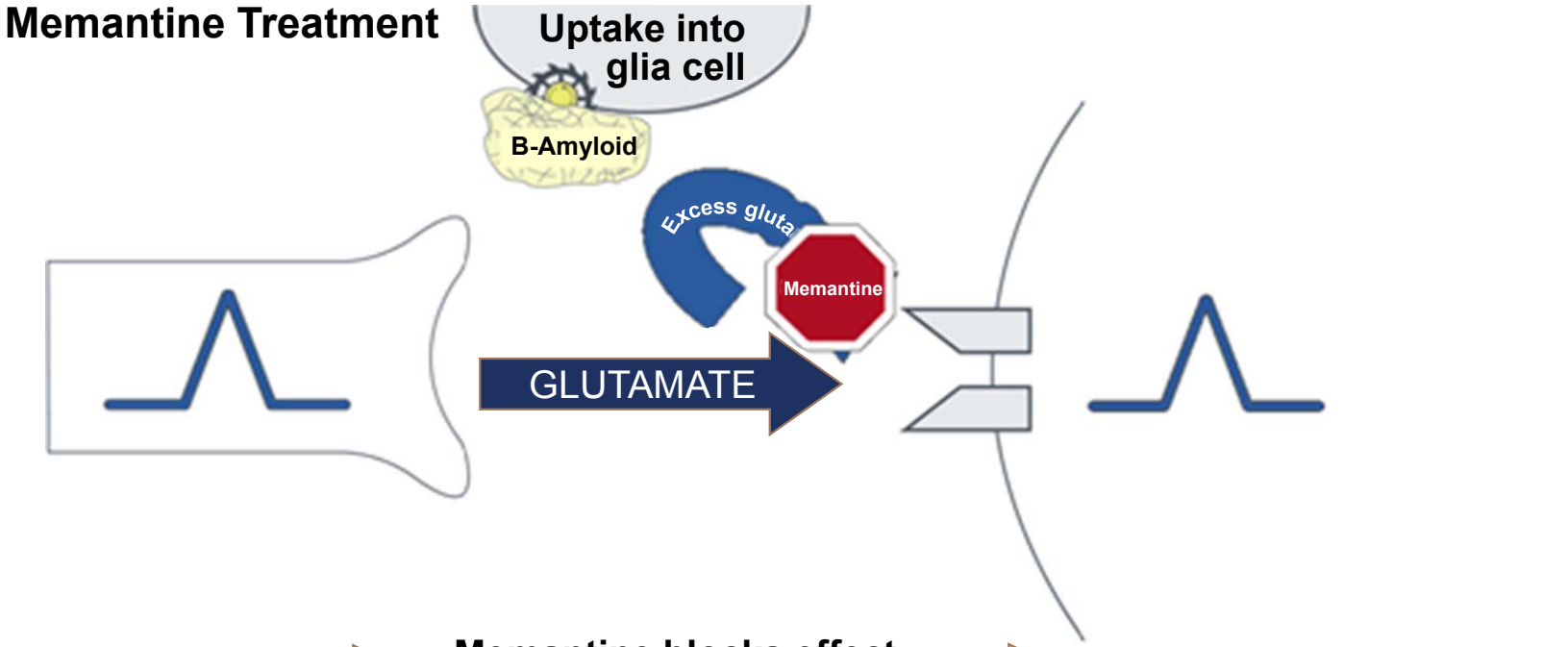
# Acetylcholinesterase Inhibitors (AChEIs): Adverse Events/Monitoring

- Most common adverse events are gastrointestinal
  - Nausea, vomiting, diarrhea, abdominal cramping
- Adverse events may become more tolerable over a few weeks; tolerability can be improved with:
  - Slow titration
  - Administration with food
- Patients should be monitored for the following:
  - Improvement in cognitive performance
    - MMSE & caregiver impression at 4 to 6 weeks then every 6 months
  - Signs and symptoms of bradycardia or AV block
  - Signs and symptoms of gastrointestinal bleeding; especially with history of ulcer disease or concomitant NSAID use
  - Hepatic and renal function
  - Body weight (rivastigmine)

# N-methyl-D-aspartate (NMDA) Receptor Antagonist

- Modifies function of NMDA brain receptor to ↓ the negative effect of having too much exposure to the brain chemical glutamate
- ↑ glutamate = ↑ death of nerve cells which can worsen memory loss
- Appears to be neuroprotective
- FDA-approved medication:
  - Memantine

# NMDA Antagonist: Mechanism of Action




Parsons CG, et al. *Neuropharmacology*. 2007;53:699-723.

# NMDA Antagonist: Adverse Events/Monitoring

- Memantine appears to be associated with fewer adverse events than AChEIs
  - Dizziness is the most common adverse event
  - Confusion and hallucinations have been reported in a small number of patients
- Patients should be monitored for improvement in cognitive function and activities of daily living as indicators of clinical response

# Combination AChEI and NMDA Antagonist

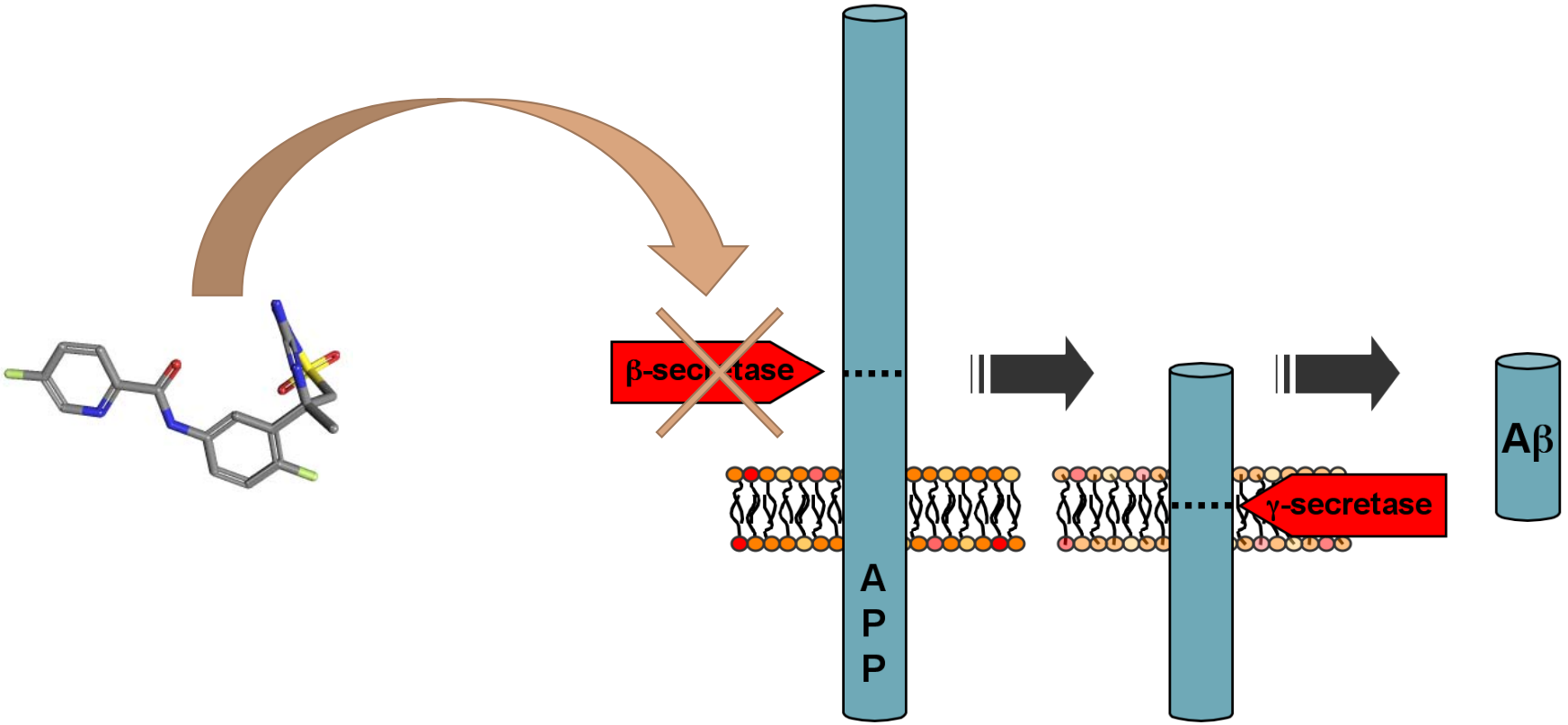
- The combination of an AChEI and memantine can be used in advanced disease or if the person does not respond to an AChEI alone
  - Evidence (and its interpretation) of adding memantine to AChEIs is mixed
- A fixed-dose combination of extended-release memantine and donepezil approved in December 2014
  - Indicated for treatment of mild to moderate AD in patients who have already taken one of the two drugs as monotherapy

# Based on What is Known of AD Pathophysiology, Amyloid Plaques and Tau Protein Remain the Leading Targets for Investigational Therapies

| Biomarker | % of Trials | |
|---|---|---|
| | Phase 3 | Phase 2 |
| 1. CSF amyloid | 27.7 | 25 |
| 2. CSF tau | 22.2 | 21.1 |
| 3. FDG-PET | 19.4 | 11.5 |
| 4. vMRI | 25 | 15.3 |
| 5. Plasma amyloid | 8.3 | 5.7 |
| 6. Plasma tau | 0 | 3.8 |
| 7. Amyloid PET | 22.2 | 9.6 |
| 8. Tau PET | 2.7 | 0 |

Cummings J. *Alzheimer Dementia*. 2016;2:222-232.

# β-secretase (BACE) Inhibitors

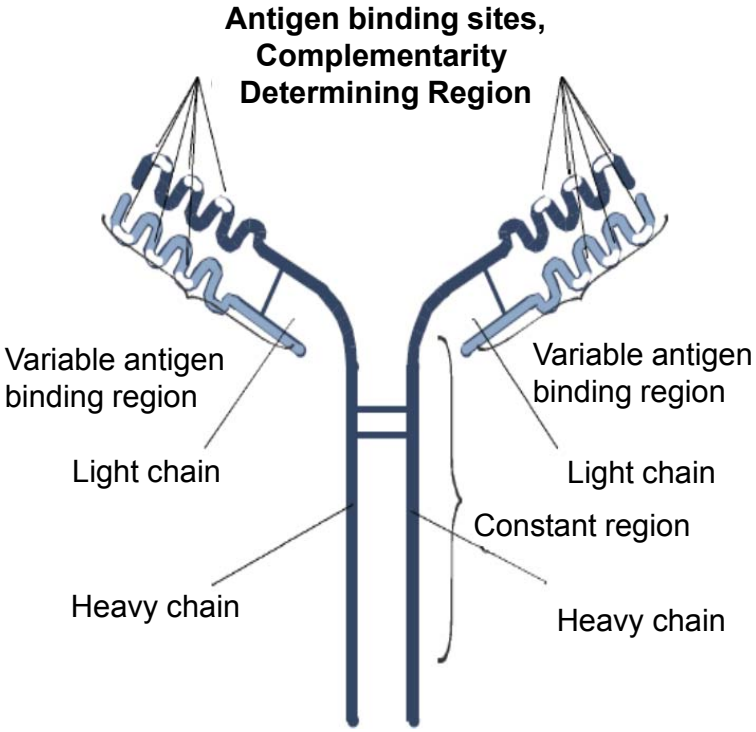


# Late-stage Investigational BACE Inhibitors

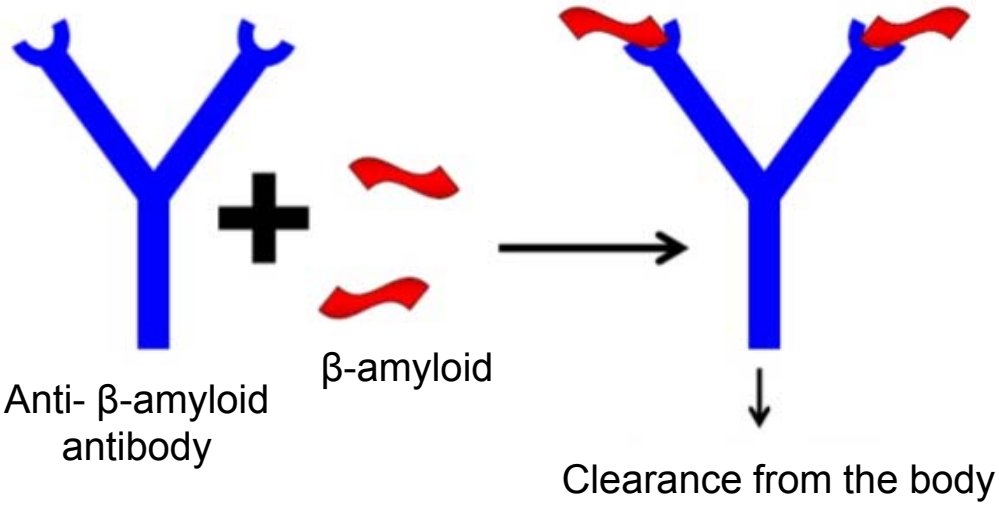
| Name | Synonyms | FDA Status | Target Type | Therapy Type |
|---|---|---|---|---|
| AZD3293 | LY3314814 | 3 | Amyloid-Related | Small Molecule |
| E2609 | | 3 | Amyloid-Related | Small Molecule |
| Verubecestat | MK-8931, MK-8931-009 | 3* | Amyloid-Related | Small Molecule |

*Trials discontinued

# Monoclonal Antibodies




***Structure***



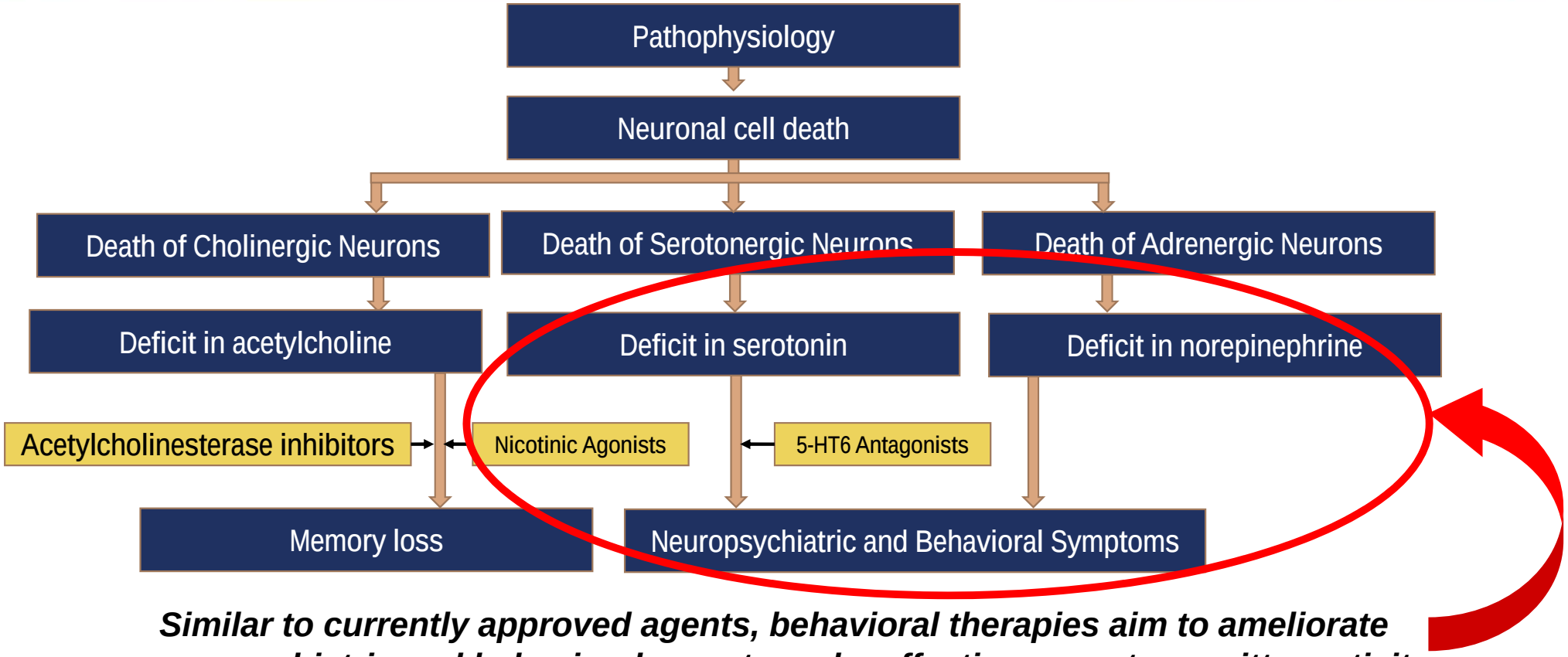

***Mechanism of Action***

# Late-stage Investigational Monoclonal Antibodies

| Name | Synonyms | FDA Status | Target Type | Therapy Type |
|---|---|---|---|---|
| Aducanumab | BIIB037 | 3 | Amyloid-Related | Immunotherapy (passive) |
| Crenezumab | MABT5102A, RG7412 | 3 | Amyloid-Related | Immunotherapy (passive) |
| Gantenerumab | RO4909832, RG1450 | 3 | Amyloid-Related | Immunotherapy (passive) |
| Solanezumab | LY2062430 | 3* | Amyloid-Related | Immunotherapy (passive) |

*Trials discontinued

# Behavioral Therapies




***Similar to currently approved agents, behavioral therapies aim to ameliorate neuropsychiatric and behavioral symptoms by affecting neurotransmitter activity***

# Late-stage Investigational Behavioral Therapies

| Name | Synonyms | FDA Status | Target Type | Therapy Type |
|---|---|---|---|---|
| AVP-786 | Deuterated (d6)-dextromethorphan and ultra-low dose quinidine | 3 | Neurotransmitter | Small Molecule |
| Aripiprazole | BMS-337039 | 3 | Neurotransmitter | Small Molecule |
| Brexpiprazole | OPC 34712 | 3 | Neurotransmitter | Small Molecule |
| ITI-007 | | 3 | Neurotransmitter | Small Molecule |
| Idalopirdine | Lu AE58054, SGS 518 | 3 | Neurotransmitter | Small Molecule |
| Intepirdine | RVT-101, SB 742457, GSK 742457 | 3 | Neurotransmitter | Small Molecule |

# Summary

- AD is a chronic, progressive neurodegenerative disorder that causes significant morbidity and mortality in the United States
- In the absence of disease-modifying therapies, AD is the only top-10 cause of death that cannot be prevented, delayed, or cured
- The pathophysiology involves the formation of β-amyloid plaques and neurofibrillary tangles of tau protein, although the exact role these features play is unclear
- A number of biologics and small-molecule drugs under clinical investigation for the treatment of AD target these two pathologies and, if approved, could dramatically shape the way the disease is managed

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AMCP Academy of Managed Care Pharmacy®

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# Care Coordination Strategies to Enhance Patient Outcomes Across the Continuum of Disease Management

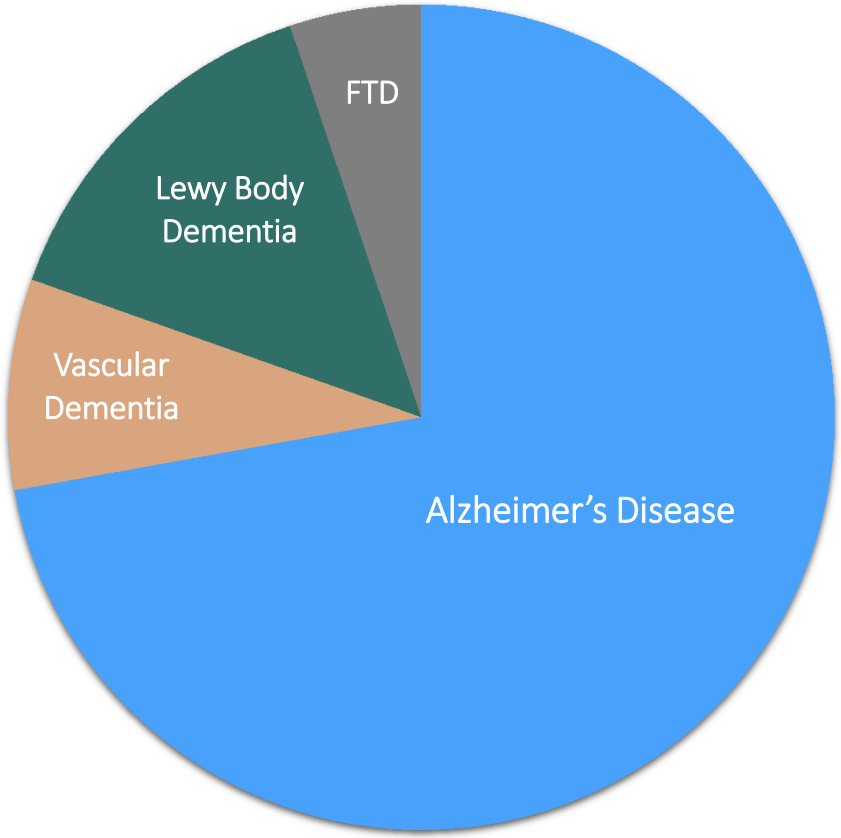
**John Fox, MD, MHA**
Senior Medical Director
Associate Vice President of Medical Affairs
Priority Health
Grand Rapids, MI

# AD is Plagued by Under-recognition and Delayed Diagnosis

- Due to the complicated etiology of the disease and the fact that primary care providers do not routinely screen for AD or related dementias, individuals with these conditions are often undiagnosed
- Recent reports indicate that the prevalence of undiagnosed AD in developed nations may be as high as 20%, with rural and/or minority populations more often remaining undiagnosed compared with urban or white demographics.
- Diagnosis is delayed on average by ≥6 years after symptom onset
- Significant impairment in function by the time it is recognized
  - Diagnosis frequently takes place at time of crises, hospitalization, failure to thrive, or an urgent need for institutionalization

World Alzheimer's Report 2016. https://www.alz.co.uk/research/WorldAlzheimerReport2016.pdf. Accessed March 2017.
Bradford A, et al. *Alzheimer Dis Dissoc Disord*. 2009;23:306-314.

# The Nuances of Dementia Diagnoses Further Complicate Accurate Disease Recognition and Management




Alzheimer's disease: 60%-80%
- Includes mixed AD + VD

Lewy Body Dementia: 10%-25%
- Parkinson spectrum

Vascular Dementia: 6%-10%
- Stroke related

Frontotemporal Dementia: 2%-5%
- Personality or language disturbance

Plassman BL, et al. *Neuroepidemiology.* 2007;29:125-32.

# Barriers to the diagnosis and treatment of persons with dementia were accentuated by specific obstacles in medical practice

- Administrative pressure to "produce" (eg, 15-minute appointments)
- Inadequate reimbursement for the time required to make a diagnosis
- Reliance on families to bring symptoms of cognitive impairment to the attention of the physician
- Lack of familiarity with different forms of dementia and appropriate screening tools in primary care
- Few geriatricians and geriatric psychiatrists practicing in the United States
- Absence of a social worker and/or supportive staff to assist families and patients with dementia

Wisconsin Alzheimer's Institute. http://www.wai.wisc.edu/resources/healthcare_providers/guide_for_physicians.html. Accessed March 2017.

# Specific Warning Signs and Dialogue with Patients Can Be Used to Identify Those Who Warrant Screening

- **Presence of Multiple Chart Review Indicators**
  - Memory concerns, forgetfulness, memory complaints
  - Missed appointments
  - Emergency contact is main contact for all communication with patient
  - Patient has been prescribed cholinesterase inhibitors but no AD diagnosis on Problem List

- **Clinical Interview Considerations**
  - Social skills remain largely intact until later stages of dementia
  - Many patients know the correct answer for the “YES” and “NO” questions
  - Intact older adult should be able to:
    - Describe at least 2 *current* events in adequate detail (who, what, when, why, how)
    - Describe events of national significance
    - Name or describe the current President and an immediate predecessor
    - Describe their own recent medical history and report the conditions for which they take medication
  - Let patient answer questions without help and then enlist the observations of family members

ACT on Alzheimer’s. http://www.actonalz.org/provider-practice-tools. Accessed March 2017.

# A Wide Array of Screening Tools are Available for Providers

- Mini-Cog™ – A 3-minute patient screening tool (3-word delayed recall and clock drawing test)
- MMSE© – A shortened version (Mini) of the Mental State Exam
- MOCA Test Mini™ – A shortened version of the Montreal Cognitive Assessment
- SLUMS™ – The 11-question St. Louis University Mental Status test used by the Department of Veteran's Affairs
- Family Questionnaire – A 5-question family/caregiver assessment of patient status from the Alzheimer's Association and National Chronic Care Consortium

Borson S, et al. *Int J Geriatr Psychiatry*. 2000;15(11):1021-1027; Folstein MF, et al. *J Psychiatr Res.* 1975;Nov 12(3):189-198; Nasreddine ZS, et al. *J Amer Ger Soc.* 2005;53(4):695-699; Tariq SH, et al. *Am J Geriatr Psychiatry.* 2006;14(11):900-910.

# Mini-Cog™

## Content

- Verbal Recall (3 points)
- Clock Draw (2 points)

## Advantages

- Quick (2-3 min)
- Easy
- Unaffected by education or language
- High yield (executive function, memory, visuospatial)

**A cut point of <3 on the Mini-Cog™ has been validated for dementia screening, but many individuals with clinically meaningful cognitive impairment will score higher. When greater sensitivity is desired, a cut point of <4 is recommended as it may indicate a need for further evaluation of cognitive status.*

Scoring*

≥4 ✔

≤3 ✖

**Mini-Cog™** — **Instructions for Administration & Scoring**

ID: _____ Date: _____

### Step 1: Three Word Registration

Look directly at person and say, "Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. The words are [select a list of words from the versions below]. Please say them for me now." If the person is unable to repeat the words after three attempts, move on to Step 2 (clock drawing).

The following and other word lists have been used in one or more clinical studies.[1-3] For repeated administrations, use of an alternative word list is recommended.

| Version 1 | Version 2 | Version 3 | Version 4 | Version 5 | Version 6 |
|---|---|---|---|---|---|
| Banana | Leader | Village | River | Captain | Daughter |
| Sunrise | Season | Kitchen | Nation | Garden | Heaven |
| Chair | Table | Baby | Finger | Picture | Mountain |

### Step 2: Clock Drawing

Say: "Next, I want you to draw a clock for me. First, put in all of the numbers where they go." When that is completed, say: "Now, set the hands to 10 past 11."

Use preprinted circle (see next page) for this exercise. Repeat instructions as needed as this is not a memory test. Move to Step 3 if the clock is not complete within three minutes.

### Step 3: Three Word Recall

Ask the person to recall the three words you stated in Step 1. Say: "What were the three words I asked you to remember?" Record the word list version number and the person's answers below.

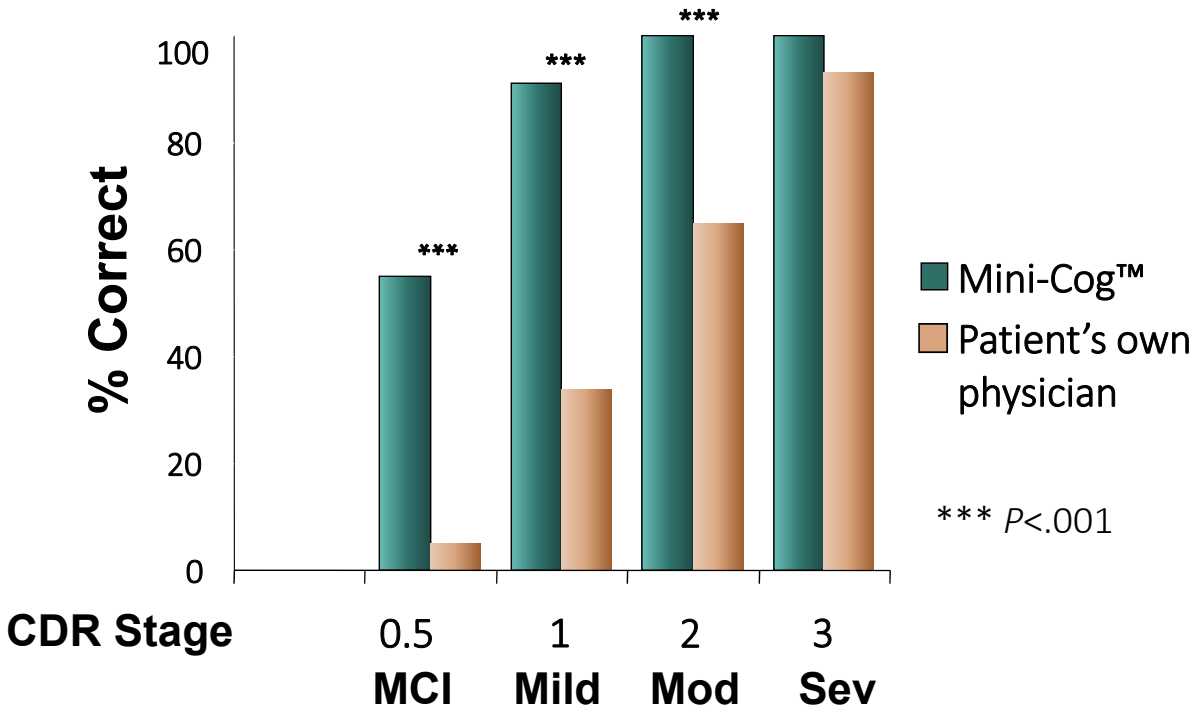
Word List Version: ____ Person's Answers: _____ _____ _____

### Scoring

| | |
|---|---|
| Word Recall: _____ (0-3 points) | 1 point for each word spontaneously recalled without cueing. |
| Clock Draw: _____ (0 or 2 points) | Normal clock = 2 points. A normal clock has all numbers placed in the correct sequence and approximately correct position (e.g., 12, 3, 6 and 9 are in anchor positions) with no missing or duplicate numbers. Hands are pointing to the 11 and 2 (11:10). Hand length is not scored.<br>Inability or refusal to draw a clock (abnormal) = 0 points. |
| Total Score: _____ (0-5 points) | Total score = Word Recall score + Clock Draw score.<br><br>A cut point of <3 on the Mini-Cog™ has been validated for dementia screening, but many individuals with clinically meaningful cognitive impairment will score higher. When greater sensitivity is desired, a cut point of <4 is recommended as it may indicate a need for further evaluation of cognitive status. |

Borson S, et al. *Int J Geriatr Psychiatry*. 2000;15(11):1021-1027; Borson S, et al. *J Am Geriatr Soc.* 2003;51(10):1451-1454; Borson S, et al. *Int J Geriatr Psychiatry*. 2006;21:349-355; Lessig MC, et al. *Int Psychogeriatr*. 2008;20(3):459-470; McCarten JR, et al. *J Am Geriatr Soc*. 2011;59(2):309-313; McCarten JR, et al. *J Am Geritr Soc.* 2012;60(2):210-217; Tsoi KK, et al. *JAMA Intern Med*. 2015;175(9):1450-1458.

# The Mini-Cog™ Improves Physician Recognition of MCI and Various Stages of AD




Borson S et al. *Int J Geriatr Psychiatry.* 2006;21:349.

CDR=clinical dementia rating; MCI=mild cognitive impairment

# Family Questionnaire

## FAMILY QUESTIONNAIRE

We are trying to improve the care of older adults. Some older adults develop problems with memory or the ability to think clearly. When this occurs, it may not come to the attention of the physician. Family members or friends of an older person may be aware of problems that should prompt further evaluation by the physician. Please answer the following questions. This information will help us to provide better care for your family member.

In your opinion does_____ have problems with any of the following?
*Please circle the answer.*

| | | | | |
|---|---|---|---|---|
| 1. Repeating or asking the same thing over and over? | *Not at all* | *Sometimes* | *Frequently* | *Does not apply* |
| 2. Remembering appointments, family occasions, holidays? | *Not at all* | *Sometimes* | *Frequently* | *Does not apply* |
| 3. Writing checks, paying bills, balancing the checkbook? | *Not at all* | *Sometimes* | *Frequently* | *Does not apply* |
| 4. Deciding what groceries or clothes to buy? | *Not at all* | *Sometimes* | *Frequently* | *Does not apply* |
| 5. Taking medications according to instructions? | *Not at all* | *Sometimes* | *Frequently* | *Does not apply* |

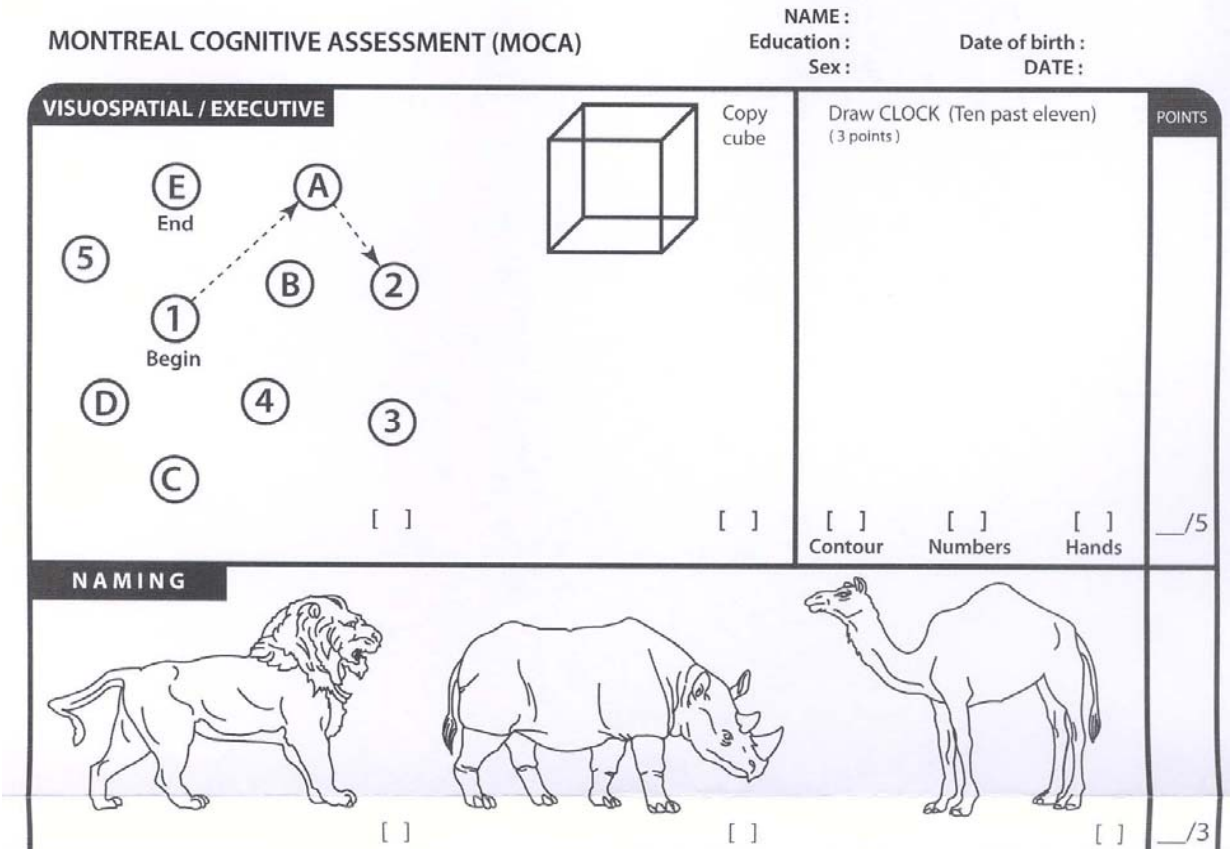
Relationship to patient _____
(spouse, son, daughter, brother, sister, grandchild, friend, etc.)

✔ <3

✖ ≥3

National Chronic Care Consortium and the Alzheimer's Associationwww.actonalz.org/pdf/Family-Questionnaire.pdf. Accessed March 2017.

# MoCA




✔ ≥26

✖ ≤25

Nasreddine ZS, et al. *J Amer Ger Soc.* 2005;53(4):695-699.

# SLUMS™

## VAMC
## SLUMS Examination

Questions about this assessment tool? E-mail aging@slu.edu.

Name _____ Age _____

Is patient alert? _____ Level of education _____

__/1 ❶ 1. What day of the week is it?

__/1 ❶ 2. What is the year?

__/1 ❶ 3. What state are we in?

4. Please remember these five objects. I will ask you what they are later.
Apple Pen Tie House Car

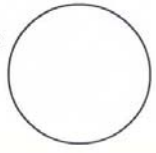
5. You have $100 and you go to the store and buy a dozen apples for $3 and a tricycle for $20.
❶ How much did you spend?
__/3 ❷ How much do you have left?

6. Please name as many animals as you can in one minute.
__/3 ❶ 0-4 animals ❶ 5-9 animals ❷ 10-14 animals ❸ 15+ animals

__/5 7. What were the five objects I asked you to remember? 1 point for each one correct.

8. I am going to give you a series of numbers and I would like you to give them to me backwards. For example, if I say 42, you would say 24.
__/2 ❶ 87 ❶ 649 ❶ 8537

9. This is a clock face. Please put in the hour markers and the time at ten minutes to eleven o'clock.
❷ Hour markers okay
__/4 ❷ Time correct









| | High School Diploma | <12 y education |
|---|---|---|
| ✔ | ≥27 | ≥25 |
| ✖ | ≤26 | ≤24 |

Tariq SH, et al. *Am J Geriatr Psychiatry*. 2006;14:900-910.

# Screening Tool Selection

## Mini-Cog™ (MC)

- Sensitivity: 76%
- Specificity: 89%

## Mini-Mental Status Exam (MMSE)

- Sensitivity: 78%
- Specificity: 88%

## Montreal Cognitive Assessment (MoCA)

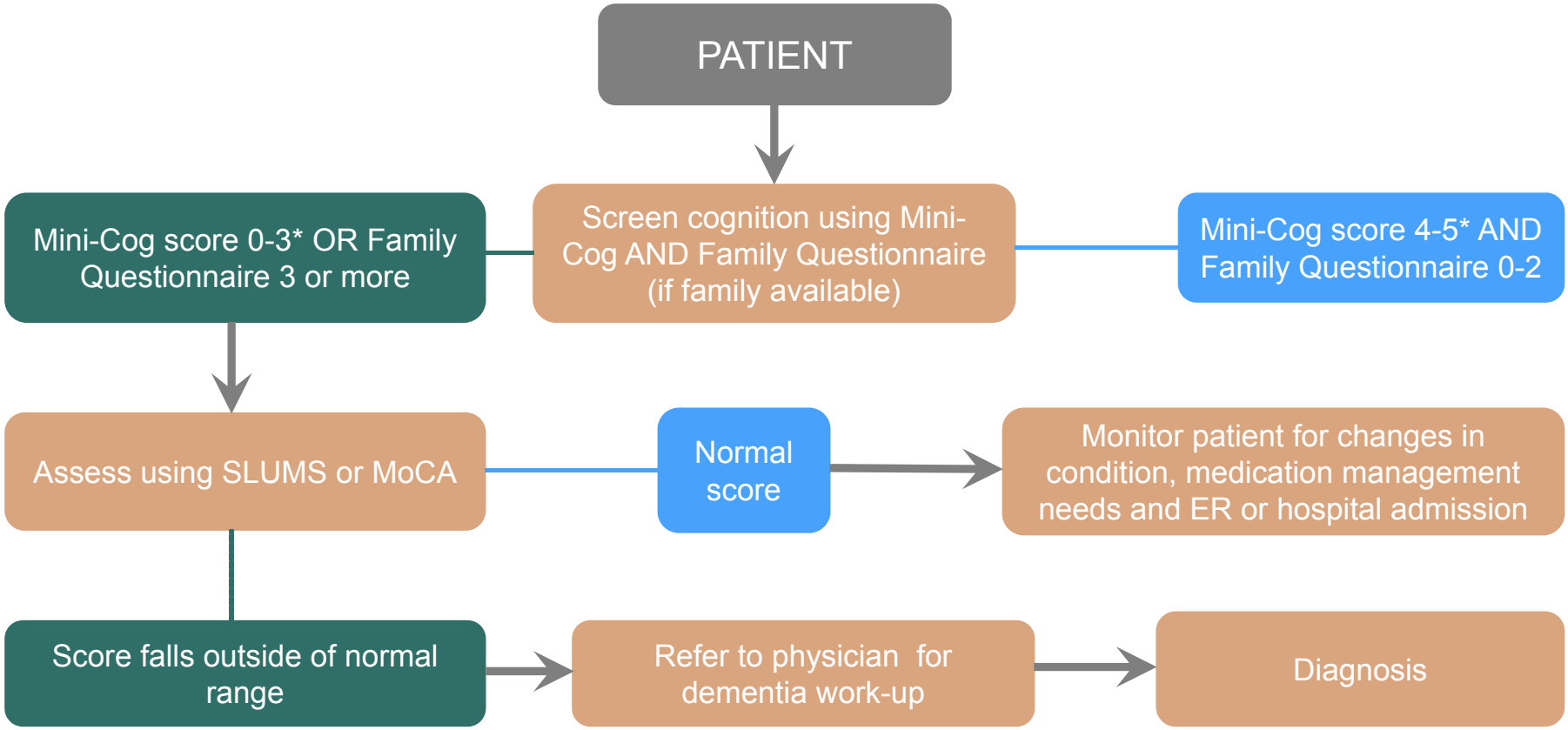
- Sensitivity: 100%
- Specificity: 87%

## St. Louis University Mental Status (SLUMS™)

- Sensitivity: 100%
- Specificity: 81%

Larner AJ. *Intern Psychogeriatrics.* 2012;24:391-396; Nasreddine ZS, et al. *J Amer Ger Soc.* 2005;53(4):695-699; Tariq SH, et al. *Am J Geriatr Psychiatry.* 2006;14(11):900-910; Ismail Z, et al. *Int J Geriatr Psychiatry.* 2010;25:111-120.

# Sample Screening/Diagnosis Scenario




ACT on Alzheimer's. http://www.actonalz.org/provider-practice-tools. Accessed March 2017.

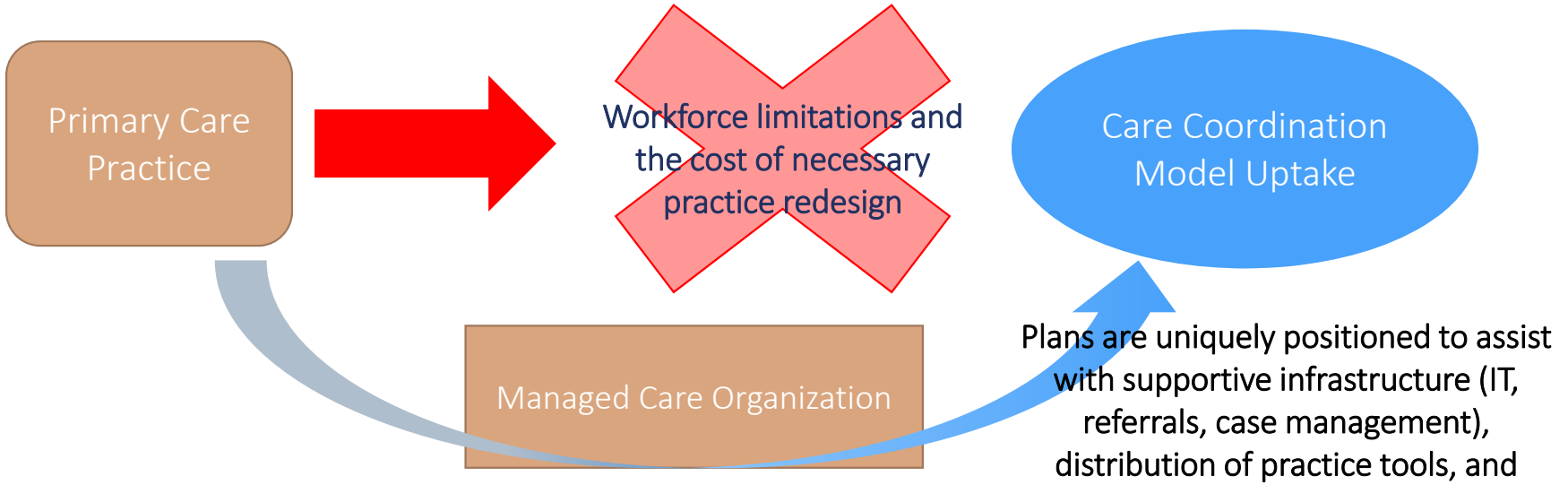
# The Potential Application of Care Coordination in the Management of AD

- Examples of successful care coordination efforts on the part of managed care organizations abound in other chronic disease states, particularly those where…
  - …multidisciplinary providers are inherently involved
  - …patients require more frequent monitoring as they migrate from one site of care to another
- AD is an ideal target for care coordination efforts due to the following characteristics:
  - The integral role that family members and other care partners play
  - The frequency of comorbid chronic conditions among elderly patients
  - The movement of patients between acute and long-term sites of care

Callahan CM, et al. *Health Aff*. 2014;33:626-632.

# Intervention on the Part of MCOs Can Facilitate the Uptake of Care Coordination Models by Network Physicians

*57% of outpatient visits for AD occur in primary care, demonstrating the need for care coordination efforts at the practice level*





Sharma MA, et al. *J Am Board Fam Med*. 2014;27:11–12.
Callahan CM, et al. *Health Aff*. 2014;33:626-632.
Lines LM, et al. *Care Coordination for People with Alzheimer's Disease and Related Dementias: Literature Review.* 2013. https://aspe.hhs.gov/care-coordination-people-alzheimers-disease-and-related-dementias-literature-review. Accessed March 2017.

# The Right Mix of Key Stakeholders in Care Coordination for AD Can Be Tailored According to Plan Resources

*Primary Care Physician*

- Most frequent medical contact for the patient/care partner(s)
- Can direct the patient to other specialists/members of the care team as necessary

*Family/Care Partner(s)*

- Can influence the patient via daily interaction
- Ideal point of contact/intermediary between the patient and various health care professionals

*Patient*

*Health Plan Case Management*

- Case managers, support with health benefits, coordination of referrals, etc

*Specialists/Allied Health Professionals*

- Neurologist, geriatric psychiatrist when available for specific components of AD
- Pharmacist for MTM
- Specialists for comorbid conditions (CVD, diabetes, etc)
- Social workers

# Steps in Care Coordination for AD

1. Identify care partner(s)
2. Conduct a comprehensive assessment
3. Provide disease education
4. Develop a care plan based on the patient's diagnosis and stage of disease, needs, and goals
5. Arrange services and support
6. Determine visit frequency
7. Develop a plan for communication
8. Monitor patient for changes in condition, medication management needs, and emergency room or hospital admission
9. Re-evaluate and modify care plan as needed

ACT on Alzheimer's. http://www.actonalz.org/provider-practice-tools. Accessed March 2017.

# Conducting a Comprehensive Assessment

## General Information

- ☐ Identify any language or cultural barriers
- ☐ Include family decision maker and emergency contact noting they may be different persons
- ☐ Identify a family/friend caregiver (might accompany the patient to primary care visits, provide medication set up, etc.)
- ☐ Identify other care coordinators involved in patient's life/care (See page 10 for definitions/descriptions and other care coordination and transition models)
- ☐ List other agencies providing service/involved in the care of the patient

## Health Assessment

- ☐ Identify other physicians involved in care
- ☐ List conditions/diagnoses
- ☐ List medications, including: OTC drugs, herbal remedies and supplements; and assess interactions (See page 20 for links and tools)
- ☐ Assess cognition (For all patients over 65 perform a Mini-Cog.) (See link on page 24 for provider best practices)
- ☐ Assess home/living environment (See page 29 for links to helpful tools)
- ☐ Assess ability to perform Activities of Daily Living (ADLs) and Instrumental ADLs in patient's home environment
- ☐ Assess who assist with the ADLs if patient is not able to perform
- ☐ Identify need for special equipment/assistive devices
- ☐ Identify medical treatments/therapies being utilized
- ☐ Assess behavioral health, including emotional health, mental health, and substance use/misuse (See page 27 for tools and links)
- ☐ Assess nutritional needs
- ☐ Identify utilization of other medical resources (frequency of hospitalizations, emergency room visits, nursing facility care)
- ☐ Assess self-preservation and safety
- ☐ Assess risk for abuse/neglect
- ☐ Assess exercise routine
- ☐ Identify hobbies and interests
- ☐ Identify any Advanced Directives in place (See page 29 for links to optional documents)

HCH Care Coordination Tool Kit. http://mn4a.org/wp-content/uploads/HCH-Clinic-Coordinator-Toolkit_3-19-15_ADA-FINAL.pdf. Accessed March 2017.

# Dementia Care Plan Process

**Conduct a comprehensive assessment of patient (include care partner)**

- Take note of cultural context
- Screening and diagnosis of diverse populations

**Educate the patient and care partner about diagnosis and disease process**

- Online resources from the Alzheimer's Association and the "Take Action" workbook

**Develop care plan based on patient's diagnosis and stage of disease, needs and goals**

- Medication therapy management, maximize abilities, care partner education, health and wellness engagement, home and personal safety, legal planning, advance care planning

**Arrange services and supports**

- Online and local chapter resources from the Alzheimer's association

**Determine visit frequency and plan for communication**

- Consider monthly face-to-face appointments until a relationship is established
- Educate patient and care partner to contact care coordinator for changes in condition, assistance with medication management, and emergency room or hospital admission

**Re-evaluate and modify care plan as needed**

ACT on Alzheimer's. http://www.actonalz.org/provider-practice-tools. Accessed March 2017.

# Care Coordination Efforts in AD Have Demonstrated Beneficial Outcomes

## Patients

- Reductions in behavioral and psychological symptoms
- Improvements associated with activities of daily living (ADL)
- Decreased difficulty dealing with memory problems
- Improved social contacts
- Increased satisfaction with their home environment
- General improvement in psychological outcomes

## Caregivers

- Reduced symptoms of depression, role captivity, and health deterioration
- Reductions in caregiving hours and burden
- Improvements in psychosocial outcomes

Lines LM, et al. *Care Coordination for People with Alzheimer's Disease and Related Dementias: Literature Review.* 2013. https://aspe.hhs.gov/care-coordination-people-alzheimers-disease-and-related-dementias-literature-review. Accessed March 2017.

# Examples of Successful and Ongoing AD Care Coordination Efforts in Managed Care

- ***Cleveland Alzheimer's Managed Care Demonstration***
  - 1-year telephone-based care coordination initiative (N=157) focusing on education and coordination community-based services
  - Representatives from the Alzheimer's Association (majority social workers) served as care consultants
  - Reduction in depression (slope=-0.12; $P \leq 0.05$) among caregivers, as measured by modification of CES-D
  - Those caregivers using other Alzheimer's Association services in combination with care coordination showed reduced health deterioration (slope = -0.33, $P = 0.03$) & role captivity (slope = -0.51, $P = 0.02$)
  - Fewer health services [Kaiser care coordination ($P \leq 0.01$, OR = 0.18) and direct care community services ($P \leq 0.10$)] used among patients in the intervention group
- ***California Coordinated Care Initiative***
  - Four-county initiative with a focus on health plan care managers who have the most direct contact with beneficiaries and their families
  - 38 care managers within HealthNet and Health Plan of San Mateo have participated in an 8-hour training session developed by the Alzheimer's Association
  - 100 family caregivers have received education and support as a result

Lines LM, et al. HHS Literature Review. 2013; Bass DM, et al. *Gerontologist*. 2003;43:73-85; Clark PA, et al. *Aging Ment Health*. 2004;8:40-51.
Alzheimer's Association. http://act.alz.org/site/DocServer/ADSSP_grant_LTSS_Collaborative_SD_summary.pdf?docID=40603. Accessed March 2017.

# Case Study #1: Sophie

***Background***

- Sophie is aged 69 years and recently retired from a position as an office manager for the family business
- She lives with her husband who is still running the family business
- Her medical history includes overactive bladder and low blood sugar

***Presentation***

- After missing her annual checkup with her primary care physician twice, Sophie's daughter escorted her to the rescheduled appointment
- Her physician noted that she was polite and affable, making several humorous remarks about her missed appointments
- During the discussion, her physician brought up a number of current events, including the most recent presidential election, and noted that Sophie was unclear and seemed somewhat confused regarding the details

***Screening***

- On the basis of the clinical interview, Sophie's physician administered the Mini-Cog™; She scored a 3 and he subsequently administered the SLUMS™ test

# Case Study #1: SLUMS™ Scoring and Subsequent Diagnosis

4/8

17

**11. I am going to tell you a story. Please listen carefully because afterwards, I'm going to ask you some questions about it.**

Jill was a very successful stockbroker. She made a lot of money on the stock market. She then met Jack, a devastatingly handsome man. She married him and had three children. They lived in Chicago. She then stopped work and stayed at home to bring up her children. When they were teenagers, she went back to work. She and Jack lived happily ever after.

✓ ❷ What was the female's name?

❷ When did she go back to work? after children born

✓ ❷ What work did she do?

❷ What state did she live in? Pennsylvania

TOTAL SCORE

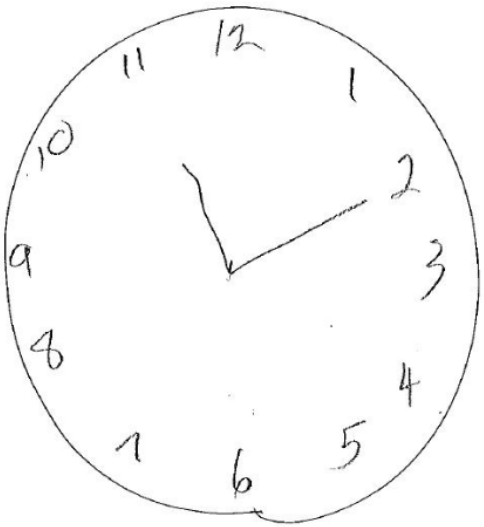
Department of Veterans Affairs

SAINT LOUIS UNIVERSITY

**SCORING**

| High School Education | | Less than High School Educatio |
|---|---|---|
| 27-30 | Normal | 25-30 |
| 21-26 | MNCD* | 20-24 |
| 1-20 | Dementia | 1-19 |

* Mild Neurocognitive Disorder



- Based on Sophie's SLUMS™ score of 17, her physician suspected a diagnosis of AD
- After referral to a specialist for neuropsychometric testing, the diagnosis was confirmed
- Sophie and her family were given educational resources on AD, in addition to scheduling monthly follow-up appointments, and she was prescribed a cholinesterase inhibitor
- Her symptoms have been stable for several months

# Case Study #2: Dean

***Background***

- Dean is aged 72 years and has been retired for 7 years
- His wife passed away 10 years ago and he lives alone, with his adult son and daughter offering assistance whenever he needs it
- In addition to a recent diagnosis of mild AD, his medical history includes hypertension (digoxin) and hyperlipidemia (atorvastatin), including close monitoring for CVD, and T2DM (rosiglitazone/metformin)

***Initial Steps in Care Coordination***

- At the time of AD diagnosis, Dean's primary care physician scheduled a follow-up and asked that both his son and daughter be present if possible
- During this follow-up visit, Dean's physician identified other members of his care team, namely his cardiologist and endocrinologist
- The physician assessed Dean's abilities to perform activities of daily living (ADL) and identified any areas where he might need assistance; he was subsequently referred to OT/PT for fall risk assessment and driving evaluation
- Dean was also referred to a geriatric psychologist for behavioral therapy in light of signs of depression upon AD diagnosis

# Case Study #2: Further Care Coordination Interventions

## Planning and Preparedness

- Dean and his children were given directions for accessing an online resource for AD-related disease information and the physician answers any questions they have; monthly appointments are scheduled with his primary care physician going forward
- The family was contacted by a case manager from Dean's health plan who assisted in coordinating appointments and put them in contract with a social worker and community resources, including the local Alzheimer's Association chapter
- The case manager encouraged the family to come up with a plan for emergencies, including contact numbers programmed into Dean's phone and the avoidance of items or scenarios in the household that may pose risks

## Maximizing Abilities

- Dean and his family were advised that glycemic control of his diabetes could prevent worsening of his symptoms, thus he should remain adherent to his medication and be reminded to take it
- Regular appointments were arranged with OT by his case manager to further simplify his home environment and facilitate independence
- His family was given information by his case manager regarding AD-related support groups and programs for Dean to maintain a routine and encourage social engagement

## Medication Therapy Management

- Upon assessing Dean's current list of prescribed medications, it was determined that he must discontinue digoxin and be prescribed a different medication for hypertension before initiating a cholinesterase inhibitor
- He and his family were counseled on any OTC medications that he may take the could also result in interactions with his cholinesterase inhibitor

***After implementing Dean's care plan, he has been able to continue living on his own and has not experienced any significant issues or setbacks***

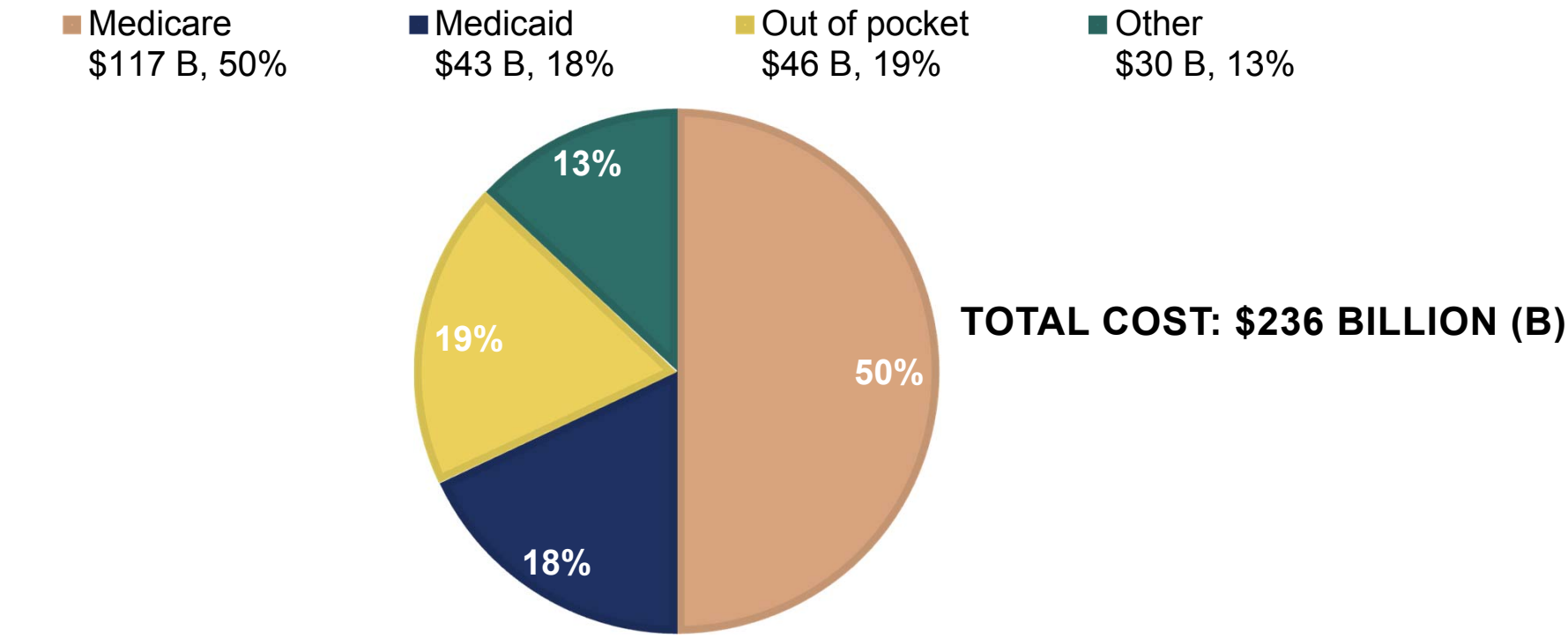
# Summary

- Diagnosis is  typically delayed in AD and related dementias due to the complicated etiology of the disease and the fact that primary care providers do not routinely screen for it
- Although a number of viable screening tools exist, they may be underused or misunderstood
- While care coordination initiatives for AD have proven effective in a number of published studies, uptake is limited in primary care due to a lack of resources
- Managed care organizations are uniquely positioned to assist network providers with care coordination via supportive infrastructure (IT, referrals, case management), distribution of practice tools, and complimentary funding in an integrated health care environment

# Medical and Pharmacy Benefit Design Strategies for Emerging Therapies

**James T. Kenney, RPh, MBA**
Manager, Specialty and Pharmacy Contracts
Harvard Pilgrim Health Care
Wellesley, MA

# Direct Costs Associated with AD Totaled $236 Billion in 2015




**TOTAL COST: $236 BILLION (B)**

Alzheimer's Association and Lewin Group. January 2015.

# Medicare- and Medicaid-related Costs

- Nearly all adults with dementia (95%) receive Medicare benefits, and some may also qualify for Medicaid through an age (65+) or disability-related pathway if they have low income and limited assets
  - About a quarter (24%) of adults with dementia living in the community have Medicaid coverage over the course of a year
- The average per-person Medicare spending for individuals aged ≥65 with AD and other dementias is 3 times higher than for seniors without dementia, while Medicaid payments are 19 times higher
- Nearly 1 in every 5 Medicare dollars is spent on individuals with AD and other dementias

Alzheimer's Association. 2016 Alzheimer's Disease Facts & Figures. https://www.alz.org/facts/downloads/facts_figures_2016.pdf. Accessed March 2017.

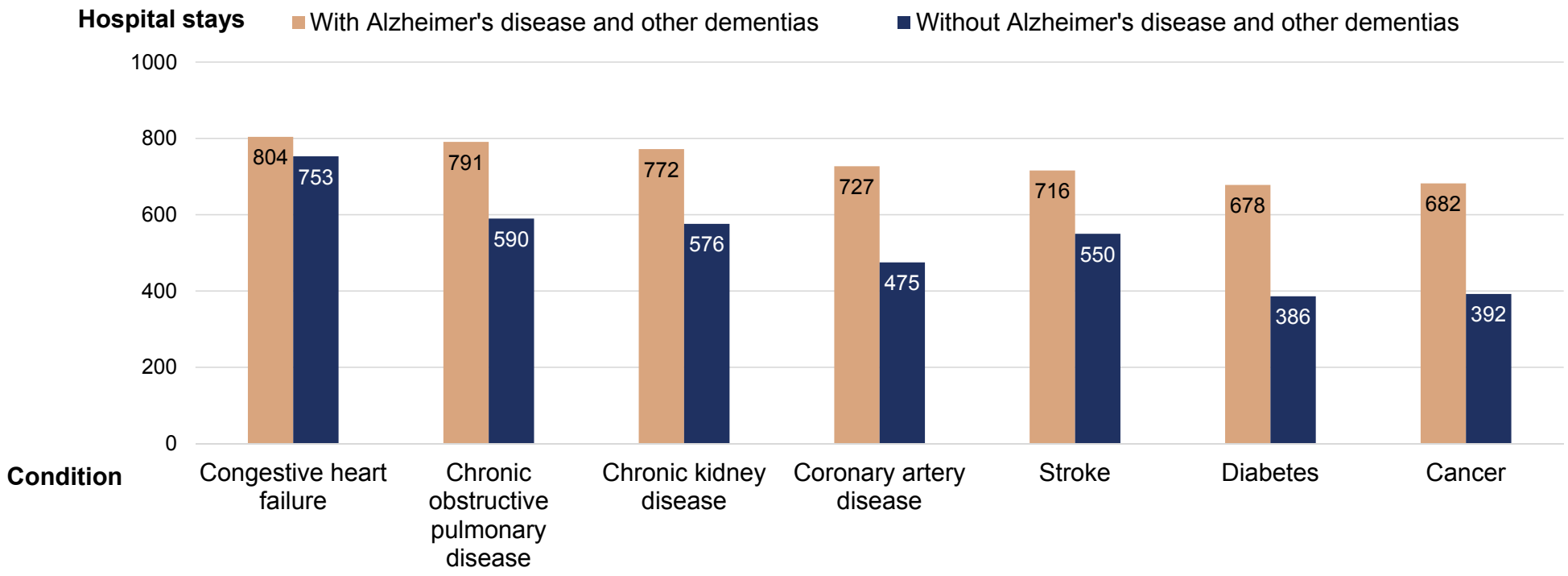
# Direct Costs for Beneficiaries with AD are Significantly Higher than Those without AD

| Service | Beneficiaries with Alzheimer's Disease and Other Dementias | Beneficiaries without Alzheimer's Disease and Other Dementias |
|---|---|---|
| Inpatient hospital | $11,834 | $4,758 |
| Medical provider* | $6,440 | $4,269 |
| Skilled nursing facility | $4,334 | $504 |
| Nursing home | $20,114 | $894 |
| Hospice | $1,976 | $193 |
| Home health | $1,583 | $511 |
| Prescription medications** | $3,037 | $3,095 |

*"Medical provider" includes physician, other medical provider and laboratory services, and medical equipment and supplies.
**Information on payments for prescription drugs is only available for people who were living in the community (i.e., not in a nursing home or assisted living facility).

Bynum J. Medicare Current Beneficiary Survey for 2008. Dartmouth School of Medicine; November 2011.

# These Costs are Characterized by Hospitalizations, Which are Invariably Greater Among Those with AD




Avalere Health. National 5% Sample Medicare Fee-for-Service Beneficiaries for 2014. January 2016

# Pharmacy Benefit Design Considerations

- Benefit design strategies should encourage the appropriate utilization of therapies while facilitating patient access and adherence
- This includes evidence-based utilization management criteria and member cost-sharing that is not prohibitive for patients in which the therapy in question is appropriate
- Increased member cost-share has gained momentum since the passage of the Affordable Care Act (ACA)
- Although effective, such interventions surrounding cost-sharing elements, such as copays and deductibles, can have a detrimental impact on adherence and, subsequently, outcomes and costs

# Utilization Management Strategies

## *Prior Authorization, Prior Approval, or Precertification*

- The result of an evidence-based decision by a health insurer or plan that a prescribed therapy is medically necessary
- Approval is not a guarantee that the insurer will cover the full cost of the therapy
- If the insurer denies the PA, an appeal for reconsideration can be filed

## *Step Therapy, Step Edits, or Fail First*

- Influences prescribers to follow an algorithm for a specific course of treatment
- Implies that plans may require a patient to try a less expensive, possibly older or unbranded therapy and “fail” on it before being able to access a newer more expensive one

## *Quantity Limits*

- Plans may set quantity limits on the amount of drugs they cover per member over a certain period of time (1 month, 3 months, etc)

# Formulary Tiering

- Number of tiers and categories vary by plan
- Copays also vary by plan, but typically copay amounts increase with each subsequent tier level
- In some cases, co-insurance may be required to access drugs on higher tiers

| | |
|---|---|
| Tier 1 | • Preferred generic or unbranded drugs |
| Tier 2 | • Non-preferred generic or unbranded drugs |
| Tier 3 | • Preferred branded drugs |
| Tier 4 | • Non-preferred branded drugs |
| Tier 5 | • Specialty drugs |

At present, only branded and unbranded *traditional* pharmacotherapies are available for the treatment of AD

# Formulary Considerations for AD

- All pharmacotherapies currently available for AD are exclusively managed under the pharmacy benefit
- Unbranded versions exist for all FDA-approved pharmacotherapies for AD, with the exception of the combination AChEI/NMDA receptor antagonist
- However, branded/unbranded versions vary in terms of dosing strengths and formulations (ie, high doses, extended-release, transdermal patch)
- Agents vary in terms of FDA indication based on disease severity, even within the AChEI class
- Flexibility should be built into formularies and benefit design strategies that takes into account several factors:
  - Therapy can and should be individualized based on tolerability, ease of use, and cost
  - The heterogeneity of treatment effects
  - Patient adherence and compatibility with different dosing schedules/formulations

# Medicare Part D Coverage for AD Pharmacotherapies

| PLANS | Aricept | Donepezil (Generic Aricept) | Exelon | Rivastigmine (Generic Exelon) | Namenda | Namenda XR | Memantine (Generic Namenda) | Razadyne | Galantamine (Generic Razadyne) | Galantamine ER (Generic Razadyne) | Namzaric (Combo Namenda ER & Donepezil) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AARP Medicare Rx Preferred | | QL | | QL – all ST - patch | | PA QL | PA QL | | QL | QL | PA QL |
| AARP Medicare Rx Saver Plus | | QL<br>1 | | QL ST – patch | | PA QL | PA QL | | | | PA QL |
| AARP Medicare Rx Walgreens | | 1 | | QL ST – patch | | | PA QL 5 | | | | |
| Aetna Medicare Rx Saver | | QL | | QL | | PA QL | PA QL | | QL | QL | PA QL |
| Envision Rx Plus | | QL | Patch only | Tartrate CAP only QL | | | | | QL | QL | |
| Express Scripts Medicare Value | | | | | 2 | PA | PA | | | | PA |
| Express Scripts Medicare Choice | | | | | PA | PA | PA | | | | PA |
| First Health Part D Plans Value Plus | | QL | | QL | | PA QL | PA QL | | QL | QL | PA QL |
| First Health Part D Plans Premier Plus | | QL | | QL | 3 | PA QL | PA QL | | QL | QL | PA QL |
| Humana Enhanced | | QL<br>1 | Patch only QL | QL<br>Patch not covered | PA, QL<br>4 | PA QL | PA QL | | QL | QL | QL ST |

Alzheimer's Association. Medicare National Plans Coverage of Alzheimer's Drugs for 2017. https://www.alz.org/care/downloads/medicarenationalplanscoverage2017.pdf. Accessed March 2017.

# Medicare Part D Coverage for AD Pharmacotherapies (cont.)

| PLANS | Aricept | Donepezil (Generic Aricept) | Exelon | Rivastigmine (Generic Exelon) | Namenda | Namenda XR | Memantine (Generic Namenda) | Razadyne | Galantamine (Generic Razadyne) | Galantamine ER (Generic Razadyne) | Namzaric (Combo Namenda ER & Donepezil) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Humana Preferred Rx/Humana Walmart Plans | | QL<br>1 | Patch only<br>QL | QL<br>Patch not covered | | PA QL | PA QL | | QL | QL | QL ST |
| SilverScript Plans (Choice, Plans) | | QL | Patch only<br>QL | Patch not covered | | PA | PA<br>5 | | QL | | |
| Symphonix Value Rx | | QL<br>1 | | QL<br>ST patch | | PA QL | PA QL<br>5 | | | | PA QL |
| WellCare Classic | | QL<br>1 | | QL | | PA | PA<br>5 | | QL | QL | |
| WellCare Extra | | QL<br>1 | | Patch only<br>QL | | PA | PA<br>5 | | QL | QL | |

| Key | | Notes | | Covered: Yes/No |
|---|---|---|---|---|
| Yes | Drugs are covered by the plan | 1 | Donepezil Hydrochloride TAB NCL 23MG | No |
| No | Drugs are not covered by the plan | 2 | Namenda Titration PAX TAB 5-10MG | Yes, PA |
| PA | Plan approval required | 3 | Namenda SOL 10MG/5MG | Yea, PA, QL |
| QL | Plan limits number of doses during a specific time period. Usually 30 days | 4 | Namenda SOL 10MG/5ML and Namenda Titration PAX TAB 5-10MG | No |
| ST | Step therapy – not covered unless another drug (usually similar but less expensive) has not worked | 5 | Memantine Hcl Titration Pak PAK 5-10mg | No |

Alzheimer's Association. Medicare National Plans Coverage of Alzheimer's Drugs for 2017. https://www.alz.org/care/downloads/medicarenationalplanscoverage2017.pdf. Accessed March 2017.

# Potential Factors in Formulary Decision Making


Comparative Effectiveness?

AMCP. *The AMCP Format for Formulary Submissions.* Version 4.0. April 2016.

# Comparative Effectiveness Research

- According to the Institute of Medicine:
  - CER is the generation and *synthesis of evidence* that *compares* the benefits and harms of *alternative methods* to prevent, diagnose, treat, and monitor a *clinical condition* or *to improve the delivery of care*
  - The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to *make informed decisions that will improve health care* at both the *individual* and *population levels*

Institute of Medicine. *Initial National Priorities for Comparative Effectiveness Research.* June 2009.

# Key Considerations for CER

- Effectiveness is better measured in real-world conditions
  - Include patients who do not meet the entry criteria for RCTs
  - Assess specific drugs after treatment failures and/or in combination with other agents (Rx and OTC)
  - Include non-adherent patients without the rigorous follow-up applied in RCTs
- CER is designed to evaluate whether products are safe and effective for use in heterogeneous patient populations ordinarily excluded from RCTs
- CER draws on existing data to describe the risks and benefits of various therapeutic choices

Kenney JT, et al. *Am J Manag Care*. 2012;18;S234-S239.

# CER in The AMCP *Format* for Formulary Submissions Version 4.0

**Section 3**

- Calls out the need for manufacturers to supply comparative effectiveness information to support an assessment of benefits and harms of their product relative to existing treatments

**Section 4**

- Discusses the need to use comparative effectiveness evidence as part of the economic evaluation

AMCP. *The AMCP Format for Formulary Submissions.* Version 4.0. April 2016.

# CER in AMCP's *Format* Version 4.0

**Formulary Monograph Template**

- Describes 5 key questions that managed care organizations and payers can use to summarize and present the evidence contained in product dossiers:

1. *What is the evidence of efficacy from clinical trials?*
2. ***Is there sufficient evidence to assess real world comparative effectiveness?***
3. *What is the evidence of safety?*
4. *What is the value proposition for this product?*
5. *Are there identifiable patient subgroups in which this treatment will be most cost-effective?*

AMCP. *The AMCP Format for Formulary Submissions.* Version 4.0. April 2016.

# Patient-Centered Comparative Effectiveness Research

- Recognizing the importance of providing guidance to researchers for improving the quality and relevance of CER, Congress issued a legislative mandate to outline these processes
- The methodology committee of the Patient-Centered Outcome Research Institute (PCORI) was charged with this task
- Such work is significant for future health services and clinical research for defining research questions and approaches to them
  - The consultation of end users (patients, providers, payers, policy-makers, etc) is crucial for this process

Tunis SR, et al. *J Compar Effect Res*. 2012;1;259-262.

# Relationship and Functions of CER, HTA, and EBM

| | Can it work (Efficacy) | Does it work? (Effectiveness) | Is it worth it? (Value) |
|---|---|---|---|
| Evidence Generation | | | |
| Evidence Synthesis | | | |
| Decision Making | | | |

CER

HTA

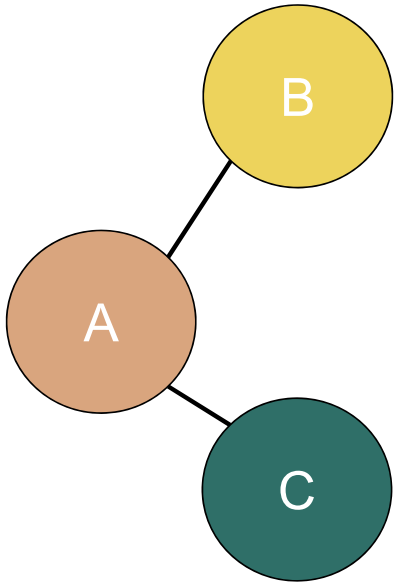
EBM

Luce BR, et al. *Milbank Q*. 2010;88;256-276.

CER=comparative effectiveness research; HTA=health technology assessment; EBM=evidence-based medicine.

# Considering a Paucity of Head-to-Head Trials, Indirect Treatment Comparisons are an Integral Component of CER

## Indirect Treatment Comparison

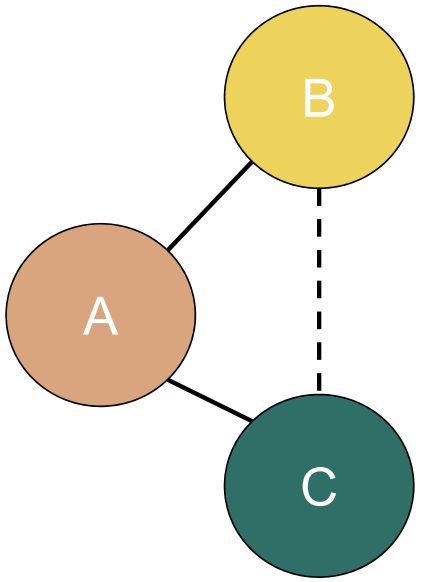



Assessing two treatments (B,C) against each other by using a common comparator (A)

Direct

Indirect

## Mixed Treatment Comparison




Combining the results of a direct comparison with indirect estimates

Jansen JP, et al. *Value Health.* 2011;14(4):417-428.

# Summary and Future Considerations

- AD is associated with a significant direct cost burden, largely owing to hospitalizations and long-term care
- Although representing a smaller portion of the total direct cost of AD, pharmacotherapies are managed with formulary tiering and traditional utilization management interventions such as PA, step-therapy, and quantity limits
- In the absence of head-to-head data, CER can serve an important role in differentiating available and emerging therapies and designing coverage strategies accordingly
- The potential approval of targeted therapies and/or biologics/injectables in the future will dramatically shape benefit design in AD and include products on the medical benefit/specialty distribution side

# Pharmacosurveillance and Patient/Caregiver Counseling Approaches to Minimize Medication Errors and Enhance Appropriate Utilization

**Steven G. Avey, MS, RPh, FAMCP**
Vice President, Specialty Clinical Programs
Medimpact Healthcare Systems Inc.
San Diego, CA

# Pharmacy Services Represent an Integral Component of Coordinated Care Management Approaches

- Industry experts estimate that 1.5 million preventable adverse events (AEs) occur annually, resulting in $177 billion in injury and death
- Medication therapy management (MTM) and similar pharmacosurveillance interventions represent a valuable instrument employed by managed care organizations to protect their sizeable investment in drug therapies and improve patient outcomes
- These services, overseen and managed by clinical pharmacists within health plans, include assessment, counseling, and surveillance activities directly related to pharmacotherapy

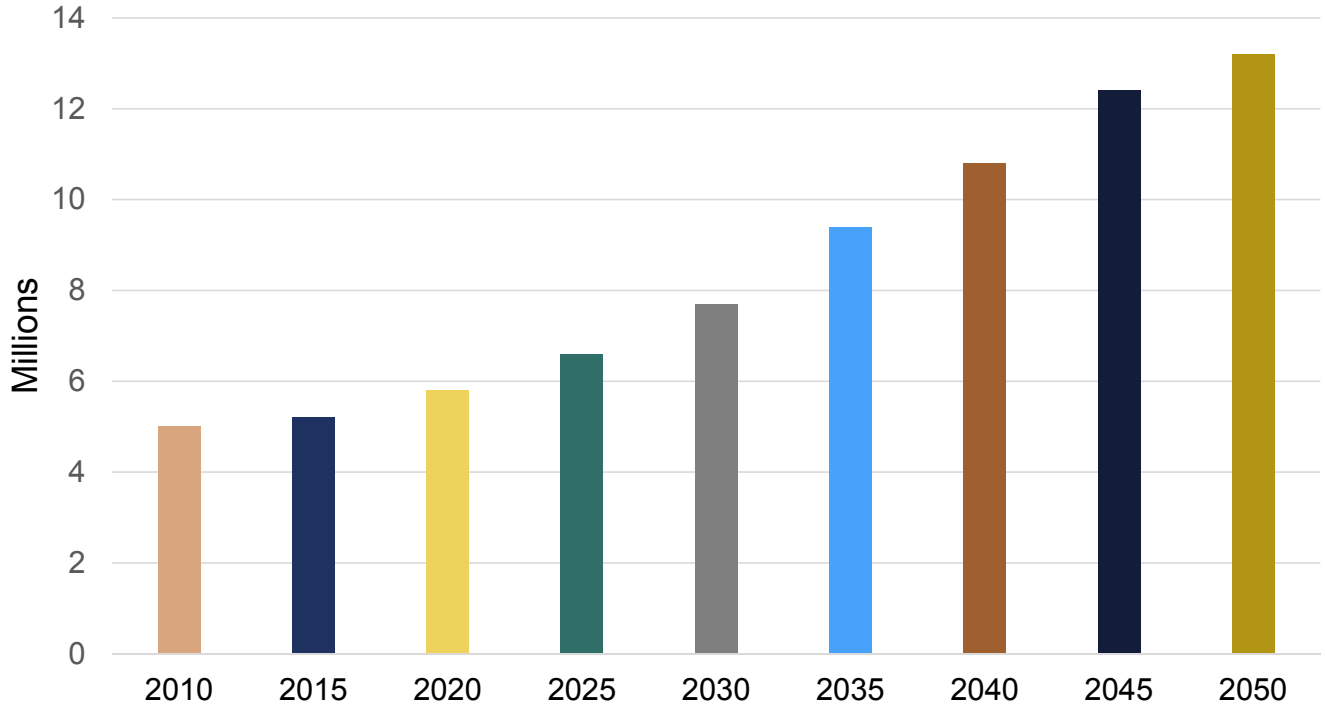
American Pharmacists Association. APhA MTM Central. What is Medication Therapy Management? http://www.pharmacist.com/mtm. Accessed March 2017.

# Key Issues and Challenges to Solve

- Who will provide the pharmacovigilance?
- Who will provide the care management?
- Who will pay for it?
- What is the cost/benefit?

# Number of People with AD

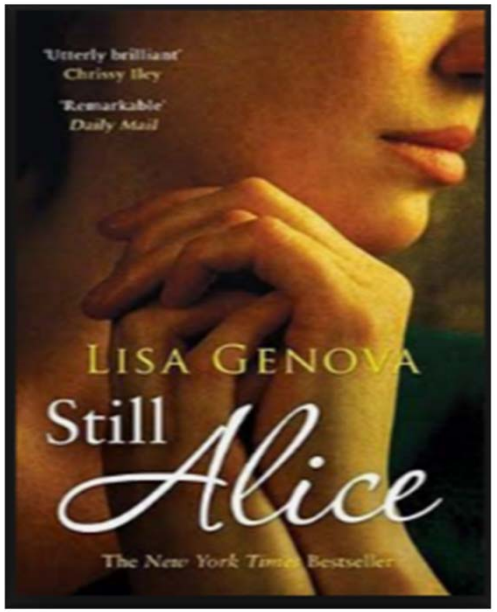
## 5.4 Million Americans Currently Suffer From AD in the US




Source: US Against Alzheimer's Disease http://www.usagainstalzheimers.org/crisis?gclid. Accessed March 2017.

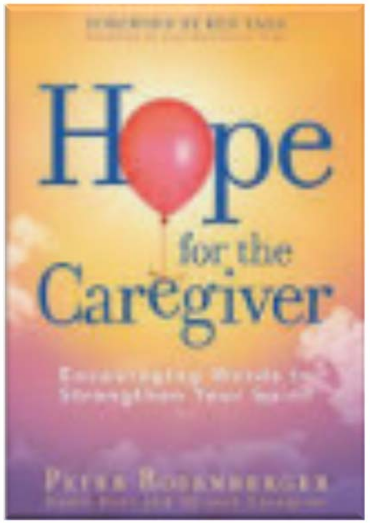
# Impact of Disease

- Everyone knows a person or family affected by AD
- Suggested reading
  - *Still Alice*
- Family burdens
  - Quality of life
  - Caregiving
  - Oversight
- Pharmacy responsibilities
  - Monitoring
  - Coaching
  - Adherence
  - Reporting



# Challenges Facing Care Managers

- Different model than traditional retail or specialty pharmacy
  - Over time less interaction with actual patient
  - More attention is given to the caregiver
  - Who will provide that care and attention?
  - What can the pharmacy channel provide?
    - Consistent information
    - Coaching
    - Great support
    - Empathy
    - Guidance



# Current Care Management Issues

- Where are Alzheimer's Disease prescriptions being filled today?
  - Traditionally filled at retail pharmacies
  - Are we getting the care management we need?
  - What is missing?

# We Need Services Similar To Specialty Care Management

- With new Alzheimer's Disease biologic agents would they be dispensed by specialty pharmacies?

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# Persistence and Adherence with Dementia Pharmacotherapy: Relevance of Patient, Provider, and System Factors

*"In light of the modest clinical benefits observed with the available drugs for dementia, poor persistence or adherence may undermine any economic advantage arising from therapy"*

*"Estimates of adherence and 1-year persistence to these drugs have ranged from 34% to 94% and 35% to 60%, respectively"*

Maxwell CJ, et al. *Can J Psychiatry.* 2014;59(12): 624-631.

# Adherence Can Be Different by Channel

| Drug Class | Proportion of Members Adherent | | | |
|---|---|---|---|---|
| | Specialty Pharmacy Provider | Other | Relative Difference | *P* Value |
| Anti-retroviral | 88.9% | 75.5% | +15.0% | 0.009 |
| Multiple Sclerosis | 74.7% | 69.0% | +7.6% | <.001 |
| Autoimmune-related | 60.3% | 55.3% | +8.4% | <.001 |
| **Average Total** | **74.6%** | **66.6%** | **+10.7%** | **<.001** |

**Members filling HIV, MS, and autoimmune-related medications are over 10% more likely to be adherent to their specialty medication regimen.**

Wang SM, et al. Presented at the AMCP 26th Annual Meeting & Expo; Tampa, FL; April 1-4, 2014.

# Adherence

- Who is monitoring the medication usage?
- What is the level of communication to patient or caregiver?
- Is there a consistent level of monitoring and coaching?

# Monitoring for AEs

- Who is monitoring for adverse events?
- Who is monitoring the patient status and collaborating with the prescriber?
- Are we providing special care for the caregiver
  - Empathy for emotional burden
  - Patience and kindness

# Consistency of Care and Monitoring

- Is the patient properly on-boarded with good education materials?
- Is there consistent adherence coaching?
- Is there ongoing monitoring for adverse events?
- Is there 24 X 7 X 365 day support for patient of caregiver?
- Is there good reporting on costs, encounters, and outcomes?

# Ongoing Patient Assessment

- Is the medication having positive effects on the AD patient?
- What criteria will be utilized?
- Will there be a point at which the medication will be withdrawn due to lack of efficacy?

# We Need MTM Services

- With non-biologic therapies an MTM program would be warranted
  - Similar outreach from a specialty pharmacy
  - Clinicians that are specifically trained in AD care management
  - Ongoing assessments and coordinated care
  - Better caregiver assistance

# The Purpose of MTM

- To optimize therapeutic outcomes
- To decrease the likelihood of adverse events
- To enhance patient understanding and adherence
- To reduce overall healthcare spending

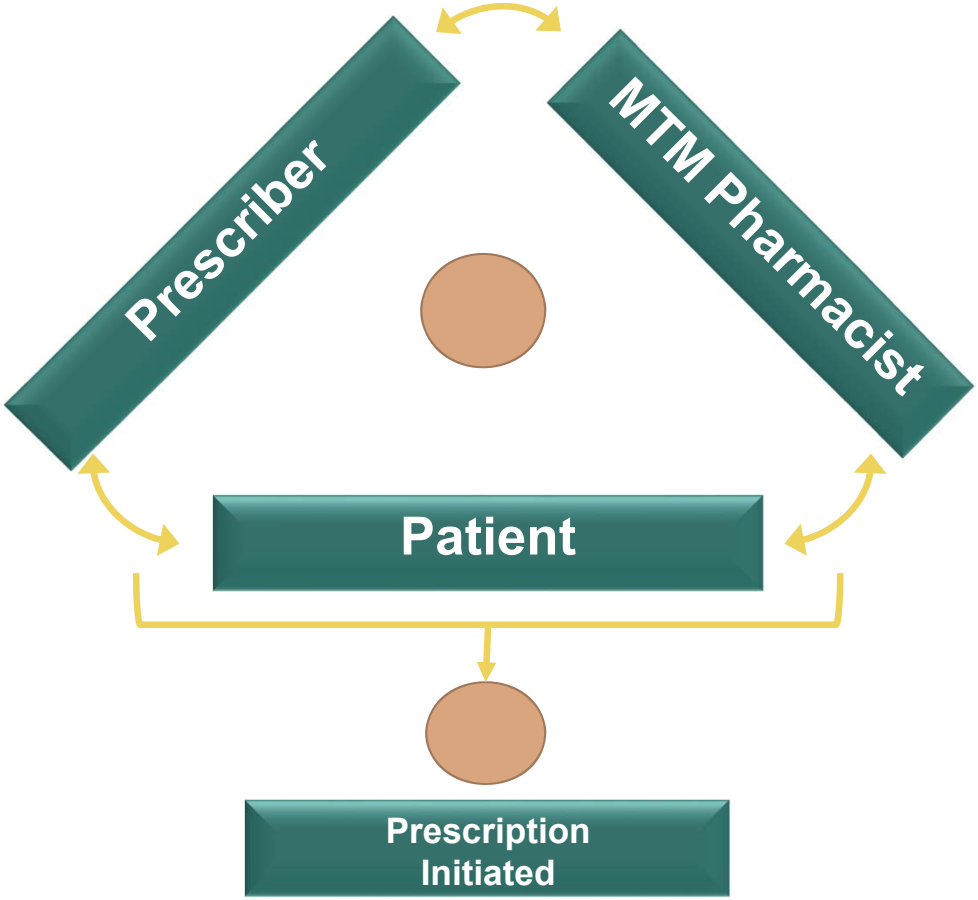
American Pharmacists Association. APhA MTM Central. What is Medication Therapy Management? http://www.pharmacist.com/mtm. Accessed March 2017.

# Medication Therapy Management Services

- Assess patients' health status
- Devise medication treatment plan
- Select, modify, and administer medications
- Review current medications and identify drug-related problems
- Communicate care to other providers
- Provide patient education
- Refer patients for broader disease management services

APhA. Pharmacists Improving Care and Reducing Costs for Your Plan Participants. www.pharmacist.com. Accessed March 2017.

# MTM Pharmacist/Prescriber Relationship



# Medication Recommendations

MTM pharmacists may make recommendations in a number of ways:

| Directly to the patient | Through the prescriber | Directly to the patient under a collaborative practice agreements |
|---|---|---|
| • Over-the-counter changes, general adherence tips, managing side effects | • Changes in prescription medications | • Allows pharmacists to make adjustments to prescription medications via protocol |

# The Value of MTM: Summary of Evidence

- Economic
  - Multiple studies have shown positive results on total health care costs, creating a positive return on investment
- Clinical
  - Multiple studies have indicated improvements in clinical outcomes, specifically in diabetes, asthma, hypertension and dyslipidemia
- Humanistic
  - The Asheville project has demonstrated reduced employee sick days and increased productivity.

Fera T, Bluml BM, Ellis WM. *JAPhA*. 2009;49(3):383-391; Isetts BJ, et al. *J Am Pharm Assoc*. 2008;48(2):203-211; Bunting BA, Cranor CW. *JAPhA*. 2006;46:133-147; Cranor CW, Bunting BA, Christensen DB. *J Am Pharm Assoc.* 2003;43:173-84.

# The Value of MTM to the Patient

- MTMS provides patients with improved health outcomes from optimizing medication use
  - In studied therapy classes MTM programs decreased emergency department visits and hospitalizations
  - But in AD will this really play out the same given AD patients do not typically have a lot of either one?
  - Even with the new therapies, will the outcomes be different and will MTM programs improve them?
- Increased understanding of medications and disease management
  - With patients in outpatient settings, this will definitely be critical
- Improved quality of life
  - This remains to be seen with the new therapies
  - The quality of life for the caregiver could be improved through MTM services

# MTM Implications for AD

- Patients taking AChEIs have a decreased cholinergic reserve and are therefore particularly susceptible to the risk of anticholinergic side effects with certain medications
- Potentially severe drug-drug interactions among prescribed therapies:
  - Antidepressants
  - Antipsychotics
  - Digoxin
  - Anti-emetics
- Over-the-counter drug interactions with prescribed therapies:
  - Scopolamine patches for motion sickness
  - Antihistamines
  - Antacids

# Concluding Questions

- What will the new therapies offer in terms of disease progression?
- What will their cost be?
- Will they be biologics or small molecules?
- How will MTM services by provided?
- Who will pay for them?
- Can we justify the cost of MTM programs long term by showing positive outcomes?