

Alzheimer's Disease and Related Dementias

Congdon Lecture Series

Henry Ford Genesys Hospital

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MEDICINE of THE HIGHEST ORDER



Learning Objectives

By the conclusion of this presentation, attendees will...

1. Differentiate between normal cognitive aging, mild cognitive impairment, and different types of dementia based on clinical presentation and diagnostic criteria.
2. Identify appropriate evaluation strategies and tools for assessing cognitive decline, including the use of cognitive screening instruments, laboratory workups, and neuroimaging.
3. Apply current evidence to guide management of Alzheimer's disease and related dementias, including pharmacologic treatments, risk mitigation strategies, and patient/caregiver education.

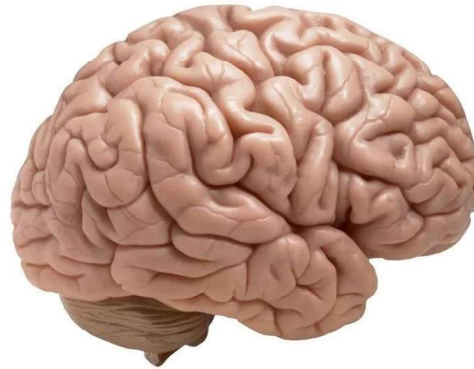
Case #1

- Susan is 72 years old, she has high blood pressure and remains physically active
- Volunteers 4 hours/week at the public library, active in her church, and cares for 6-year-old grandson after school daily
- Worried about misplacing car keys and recently saw old friend in the grocery store and could not remember friend's name

Cognitive Changes: "Normal" Aging

Common difficulties may include:

- Recall words in list
- Word-finding
- Concentration
- Process multiple tasks
- Recall visual material



Case #2

- Fred is 82 years old, retired executive, he has arthritis, diabetes, and high cholesterol
- His daughter reports short term memory problems, he is repetitive in conversation, and often gets lost while driving familiar roads of his hometown
- Fred thinks people are coming into his home and moving things so he can't find them
- He is late on several payments for gas and electric bills with 2nd or 3rd notices in the mail

Case #3

Martha is a 94-year-old female resident of an assisted living facility for the last 2 years

- Needs assistance with all activities of daily living (ADLs)
- New incontinence of bladder
- 2 hospital admissions last 6 months: following a fall and for treatment of pneumonia
- Difficulty using walker has had recurrent falls
- More confusion and some "agitation" at night

Compare "Normal" to Dementia

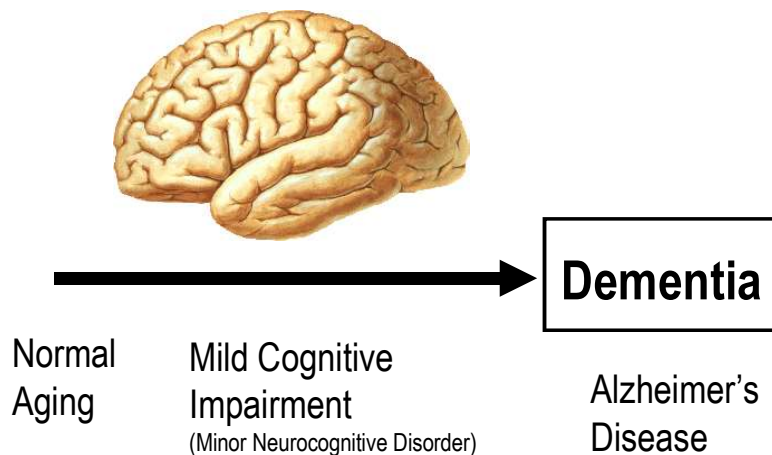
Normal Aging

- Able to remember later given time
- Able to use notes and reminders
- Able to perform daily tasks and self-care
- Medical evaluation essentially normal

Dementia

- Rarely able to recall later or with use of reminders
- Changes in memory, language, decision-making, motor skills
- Neglect in self-care, difficulties with routine daily tasks
- Abnormal neurologic findings

Cognitive Dysfunction

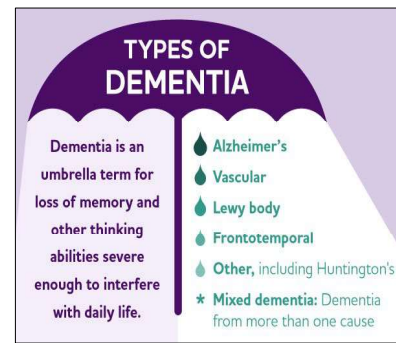


Dementia: 4 Pillars of Diagnostic Criteria

1. Progressive loss of **intellectual abilities**
2. Impairment in **memory** and at least one other **cognitive domain**
3. Interferes with daily **functioning**
4. Not due to other underlying medical disorder

Common Types of Dementia:

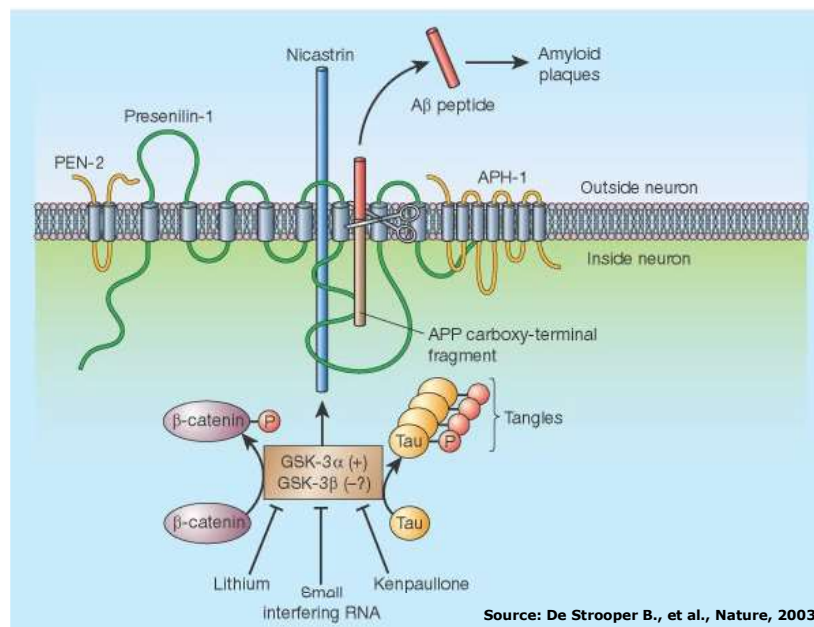
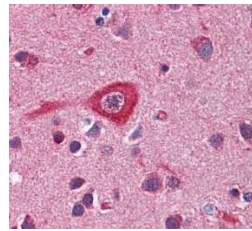
1. Alzheimer's Disease **60-80%**
2. Vascular Dementia **10-40%**
3. Dementia with Lewy Bodies **10-25%**
4. Frontotemporal Dementia **~10%**
5. Parkinsonism (subcortical dementias)



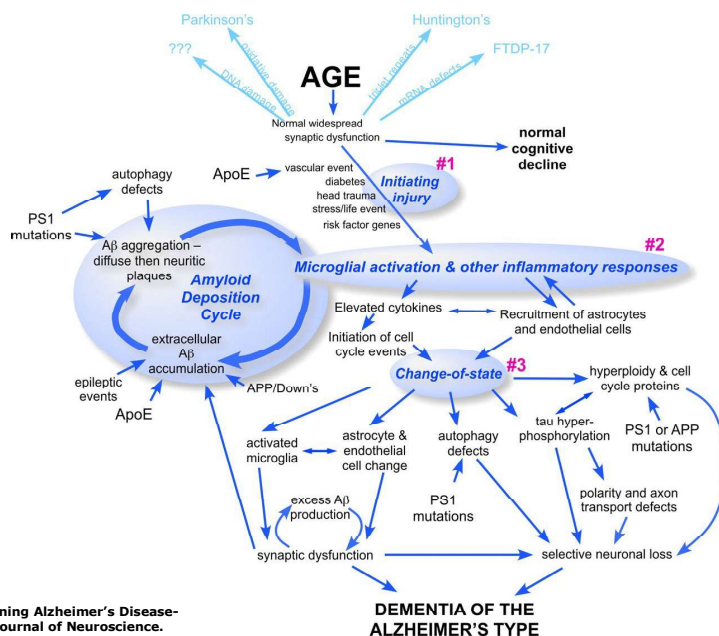
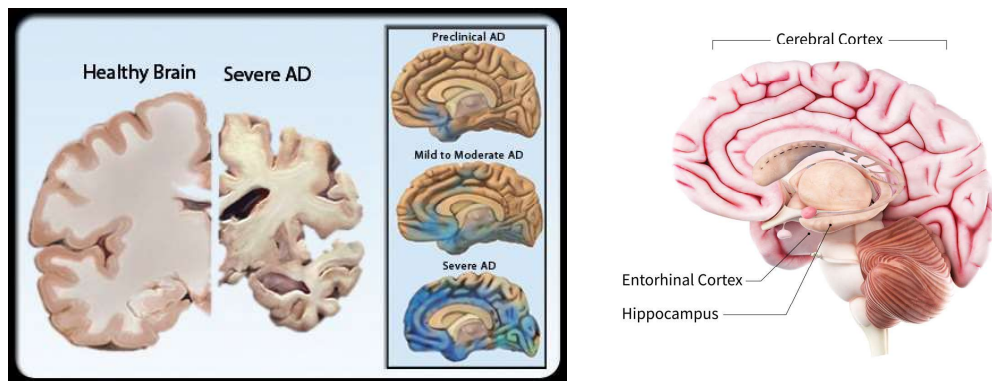
"Mixed Dementia" ~50%

Alzheimer's Disease

- Abnormality in amyloid protein metabolism in brain
- Formation of neurofibrillary tangles (dead neurons) and amyloid plaques
- Only definitive diagnosis is at autopsy
- PET scan can quantify amount of amyloid deposition, but clinical correlation is less specific



What is dementia?



Source:
Herrup, K. (2010). Reimagining Alzheimer's Disease- An Age-Based Hypothesis. Journal of Neuroscience.

Alzheimer's Disease

Facts & Figures

- **Over 7 million** Americans with Alzheimer's disease (74% age 75 or older)
- **7th Leading cause of death** among those age 65 and older
- **1 in 3 older adults will die with dementia**
- Almost two-thirds of Americans with Alzheimer's Disease are **women**
- **Racial and Ethnic Disparities:**
 - Older Black Americans are about twice as likely to have Alzheimer's or related dementias
 - Older Hispanics are about 1.5 times as likely to have Alzheimer's or related dementias
- Alzheimer's and other dementias will cost the nation \$384 billion (increase to nearly \$1 trillion by 2050)
- Deaths associated with dementia has increased 17% with COVID-19 Pandemic

Source: Alzheimer's Disease Facts and Figures 2025 (Alzheimer's Association)

Risk Factors for Alzheimer's

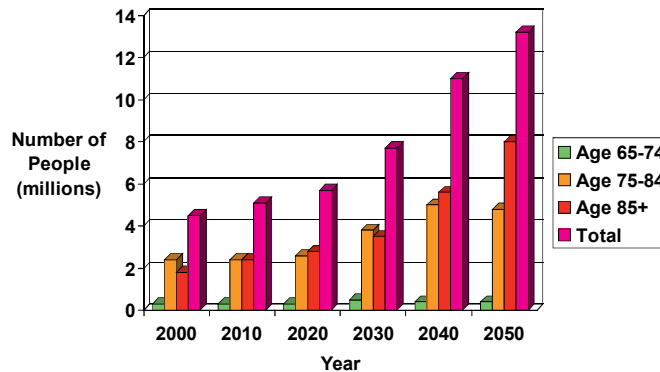


- **AGE**
- **Family History** (particularly for early onset/familial pattern)
- **Genetic Risk** (APOE-4 alleles, presenilin)
- **Cardiac Disease** and **Cerebrovascular Disease Risk Factors** (smoking, high blood pressure, cholesterol, diabetes, prior stroke, MI, atrial fibrillation, etc.)
- History of **head trauma** (concussions, traumatic brain injury, chronic traumatic encephalopathy)
- Lower **educational attainment**
- Poor **sleep** (quality/duration) and sleep disorders
- Chronic **stress**
- **Environmental Exposures?**

IMPORTANT NOTE: Changes leading to Alzheimer's disease is likely taking place in the brain 20 years prior to symptomatic memory loss

Prevalence of Alzheimer's Disease

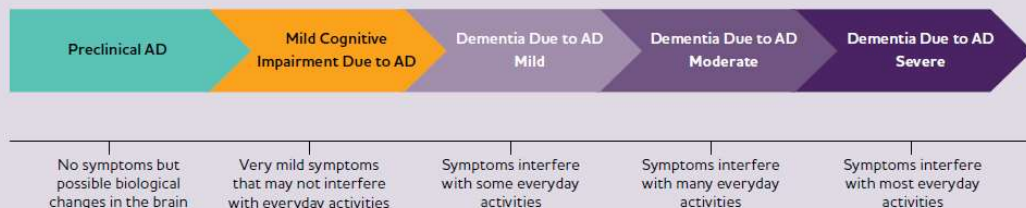
Future Projections by Age Group



Data Source: Evans, DA et al. Archives of Neurology August 2003

figure 1

Alzheimer's Disease (AD) Continuum*



*Although these arrows are of equal size, the components of the AD continuum are not equal in duration.

Alzheimer's Phenotype: Early Stages

- Memory problems frequently first reported
- Earlier changes usually evident (months to years in advance of formal diagnosis)
- Common Problems: managing finances, household chores, shopping, cooking, taking medications, driving
- Early changes attributed to aging by family
- Short term memory mostly affected and distant (remote) memory often remains intact

Alzheimer's Phenotype: Advanced Stages

Loss of ability to perform activities of daily living (ADL):

- Dressing (grooming)
- Bathing (hygiene)
- Toileting (incontinence)
- Walking (mobility)
- Eating (feeding)

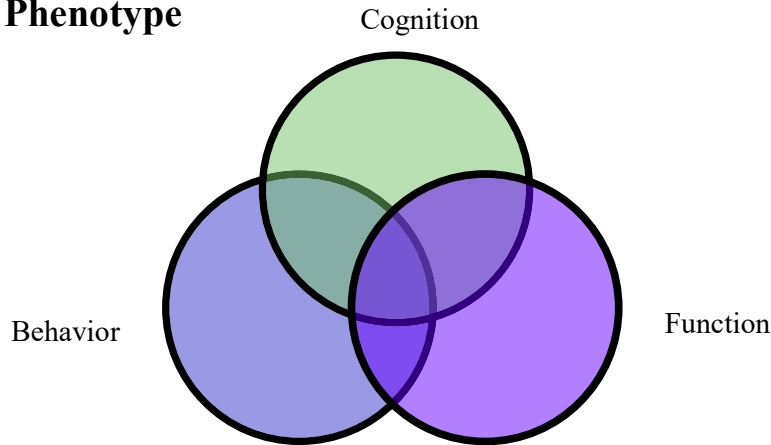


Other Common Changes

- Progressive personality change
- Behavior Changes (impulsivity, sexual disinhibition, anger, argumentative, hoarding)
- Poor judgment, insight, problem-solving
- Later stages: Agitation, Restlessness, and Wandering
- Apathy is common in early stages (social withdrawal, loss of interest)

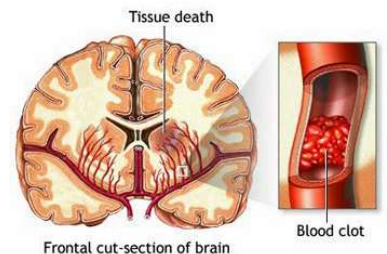
DEMENTIA

Phenotype

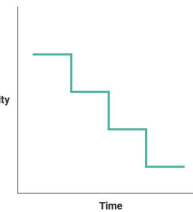


Vascular Dementia

- In contrast to Alzheimer's disease, vascular dementia is a heterogeneous disorder (usually more abrupt presentation)
- Vascular lesions from **small vessel disease** or **stroke** could affect many different brain regions (i.e. diffuse white matter changes on MRI or areas of discrete infarction)
- Often multiple cognitive domains may be affected (language, executive function, visuospatial)
- Classically described as **"stepwise" decline** in cognitive abilities and functional status
- Best way to mitigate decline is addressing cerebrovascular risk factors (but be careful not to overtreat HTN or DM)
- **"Mixed" dementia** refers to Alzheimer's type dementia with concurrent cerebrovascular disease as contributor



STEPWISE DECLINE
(DUE TO STROKES)



Dementia with Lewy Bodies

- Lewy Body Dementia (LBD) hallmark degeneration is the "Lewy Body" which is composed of **Alpha-synuclein protein**
- Classic Triad: **cognitive decline, parkinsonism, and psychosis**
- Clinical hallmarks: fluctuation of symptoms ("good and bad days"), prominent visual hallucinations, and autonomic dysfunction (orthostatic hypotension)
- Memory loss less prominent compared to Alzheimer's disease
- Parkinsonism is manifest by gait imbalance, slowness of movement (bradykinesia), and rigidity - less prominent is tremor
- Sleep disturbances common (REM sleep disorder history often predating other symptoms)
- Caution: Patients extraordinarily sensitive to antipsychotic medications

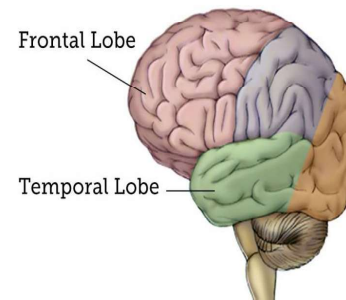


Parkinsonism



Frontotemporal Dementia (FTD)

- Primary areas of degeneration occurs in the **frontal** and **temporal** lobes (ideally preferential volume loss in these areas on MRI)
- Usually manifests with prominent behavioral changes including personality changes, disinhibition, and language abnormalities
- Complex classification of related disorders:
 1. Behavior variant (including Pick's disease)
 2. Primary Progressive Aphasia (semantic and nonfluent)
 3. Motor variants: Amyotrophic lateral sclerosis, Corticobasal syndrome, Progressive Supranuclear Palsy
- Highest prevalence in younger patients (ages 45 to 65 years old) compared to Alzheimer's Disease



Subcortical Dementia

- Can be due to underlying **vascular etiology** (Binswanger's disease/vascular parkinsonism) or due to advanced idiopathic **Parkinson's disease** – primary affecting basal ganglia
- Clinical manifestations: impaired cognition (memory), slowness of mental processing or speech (bradyphrenia), depressive symptoms (apathy and anhedonia), extrapyramidal symptoms (tremors, bradykinesia), and some cases with psychosis.
- Parkinsonism symptoms usually present and cognitive testing usually shows prominent deficits in speed and efficiency of memory recall and cognitive processing
- Memory can often be facilitated in early stages with trials/repetition and reminders (different from Alzheimer's Disease)
- Variable response to dopaminergic therapy (more likely benefit in Parkinson's disease)
- Can be difficult to distinguish from Lewy Body Dementia (generally subcortical dementia psychosis is in later stages of disease)

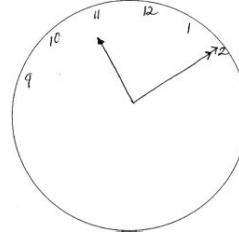
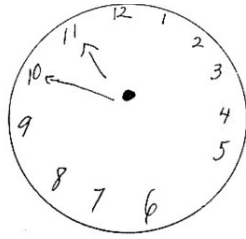
Medical Evaluation


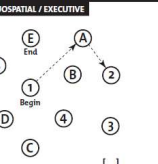



- A neurologic exam including a cognitive assessment can positively identify the presence of dementia
- No single "gold standard" test to diagnose the specific type of dementia
- **Blood and CSF tests** and specialized brain (PET) imaging are now becoming standard for evaluation of early clinical Alzheimer's disease
 - Guide disease directed therapy (required for most treatment protocols)
 - Not indicated for general screening or to exclude Non-Alzheimer's dementia
 - Cognitive Assessment is still standard of care for evaluating patients

Mini-Cog Assessment

1. 3 Item (word recall)

2. Clock-Drawing – “ten minutes after eleven”



MONTREAL COGNITIVE ASSESSMENT (MOCA)		NAME :	Education :	Date of birth :			
		Sex :	DATE :				
VISUOSPATIAL / EXECUTIVE	 Copy cube  Draw CLOCK (Ten past eleven) (10 min)						
NAMING	 []  []  []						
MEMORY	Read list of words, subject must repeat them, then a fifth, do a recall after 5 minutes. List read: [] [] [] [] [] 2nd read: [] [] [] [] []	FACE	VELVET	CHURCH	DAISY	RED	No points
ATTENTION	Read list of digits (4 digit/ sec). Subject has to repeat them in the forward order [] [] 2 1 8 5 4 Subject has to repeat them in the backward order [] [] 7 4 2 Read list of letters. The subject must tap with his hand at each letter A. No points if a 2 error [] F B A C M N A A I K L B A F A K D E A A A J A M O F A A B						
LANGUAGE	Repeat: I only know that John is the one to help today. [] The cat always hid under the couch when dogs were in the room. [] Fluency / Name maximum number of words in one minute that begin with the letter F [] (N = 11 words)						
ABSTRACTION	Similarity between e.g. banana - orange - fruit [] train - bicycle [] watch - roller						
DELAYED RECALL	Has to recall words: FACE [] VELVET [] CHURCH [] DAISY [] RED [] WITH NO CLUE [] [] [] [] [] Optional: Category cue [] [] [] [] [] Multiple choice cue [] [] [] [] []						Points for UNLUID recall only
ORIENTATION	[] Date [] Month [] Year [] Day [] Place [] City						
© L.Rosewood MD Version 7.0 www.mocatest.org Normal 2 26 / 30		TOTAL		Add 5 points if < 12 yr edu		/30	

Montreal Cognitive Assessment (MoCA)

www.mocatest.org

AD8 Dementia Screening Interview		Patient ID#:	CS ID#:	Date:
Remember, "Yes, a change" indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems.	YES, A change	NO, No change	N/A, Don't know	
1. Problems with judgment (e.g., problems making decisions, bad financial decisions, problems with thinking)				
2. Less interest in hobbies/activities				
3. Repeats the same things over and over (questions, stories, or statements)				
4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)				
5. Forgets correct month or year				
6. Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills)				
7. Trouble remembering appointments				
8. Daily problems with thinking and/or memory				
TOTAL AD8 SCORE				

Informant Based Instruments for cognitive impairment:

AD8 Dementia Screening Interview

Completed by key informant (caregiver)

Medical Evaluation

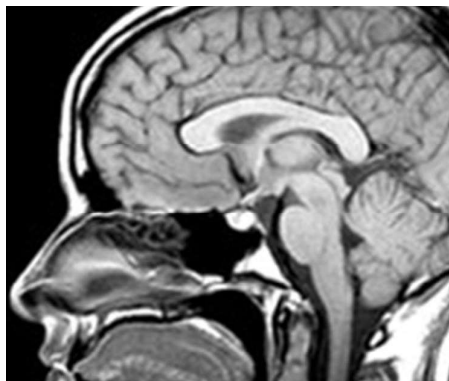
Some potentially “reversible” causes for cognitive changes should be evaluated

Some common areas includes:

- Thyroid Disorders
- B12 Deficiency
- Medication (drug levels and side-effects)
- Sensory deficits (hearing loss, vision, etc.)
- Depression

Neuroimaging: What about a “brain scan”?

- Neurologic exam remains the most important evaluation tool
- Neuroimaging is recommended at some point in the workup that some neuroimaging test be performed (CT Scan or MRI)
- Other Studies including **PET** and **Functional MRI** may play a role in specific cases (early onset dementia) or enrollment in clinical trials but not standard currently for screening



Dementia: Cognitive Treatment

- No “cure” exists for Alzheimer’s disease
- Medications may improve some symptoms of the disease
- Advertising suggest greater benefit than likely exists for most patients
- Side Effects are REAL and potentially life-threatening
- Duration of treatment is unknown, limited benefit at advanced stages of the disease

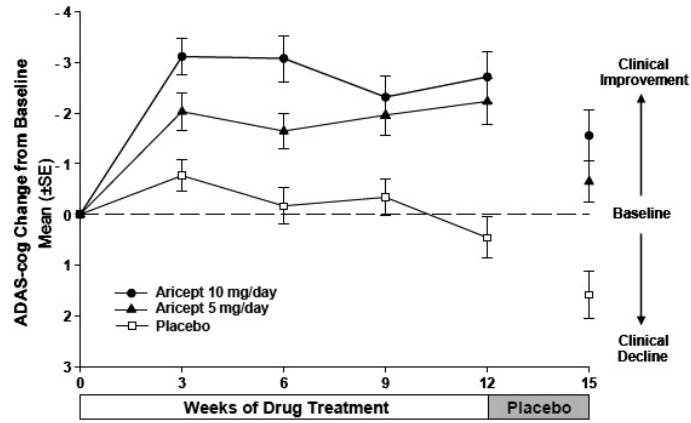
Two most commonly used medication classes:

1) **Acetylcholinesterase inhibitors**

- Donepezil
- Rivastigmine
- Galantamine

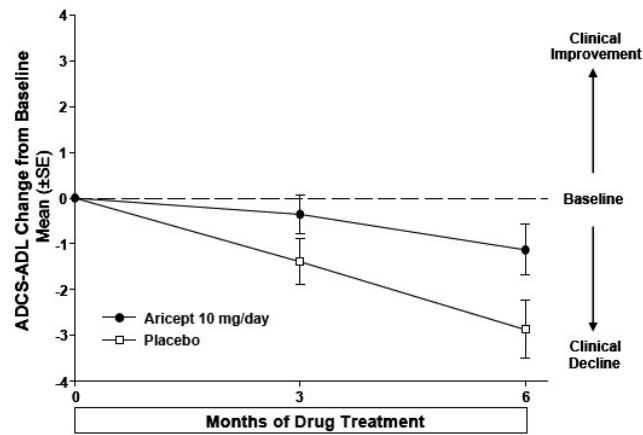
2) **Memantine** – targets NMDA receptor hyperactivity by blocking glutamate

Donepezil



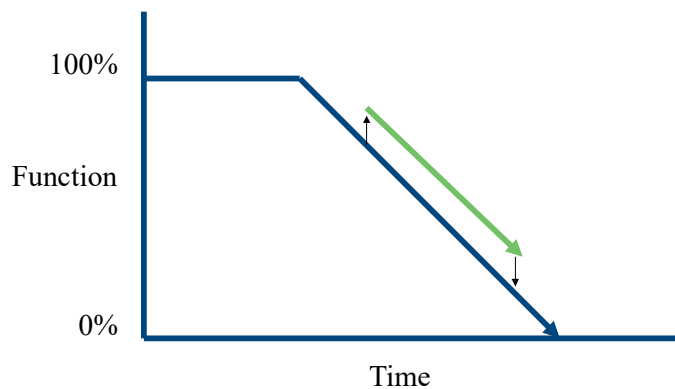
Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment. Alzheimer's Disease Assessment Scale for Cognition (ADAS-Cog)

Donepezil



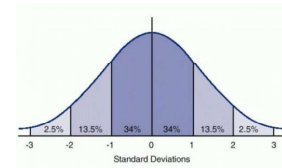
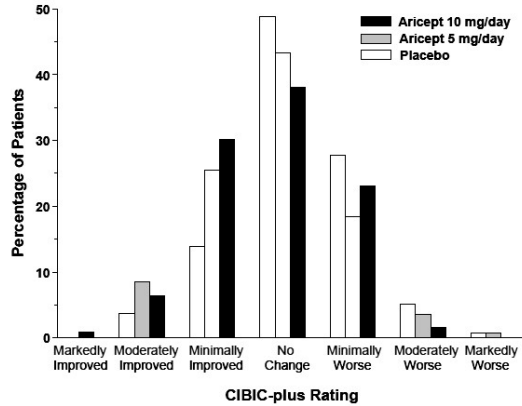
Time Course of the Change from Baseline in ADCS-ADL-Severe Score for Patients Completing 6 Months of Treatment

Current Treatment: Symptom Management



Courtesy: Frederick J. Marshall, M.D.

Donepezil



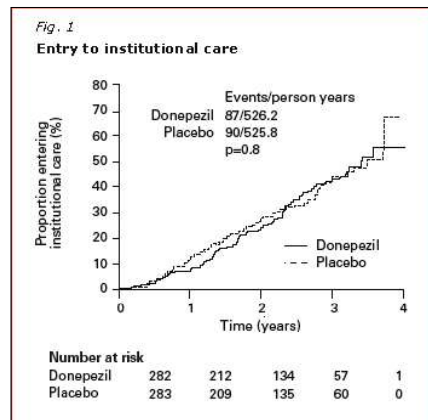
Standard Distribution or Bell Curve????

Frequency Distribution of CIBIC plus Scores at Week 12. (Clinician's Interview Based Impression of Change plus caregiver input scale)

Long term donepezil did not delay institutionalisation or progression to disability in patients with Alzheimer's disease

AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet* 2004;363:2105-15.

- 3 years
- 566 subjects
- Double blinded RCT
- Intention to treat analysis
- No delay in nursing home placement with donepezil**



Potential Side Effects: Acetylcholinesterase Inhibitors

- Nausea/Vomiting
- Obstructive uropathy
- Weight loss
- Seizures
- Peptic Ulcer/GI bleed
- Asthma exacerbation
- Dizziness/falls
- Cardiac (heart block)

Anti-Amyloid Monoclonal Antibodies

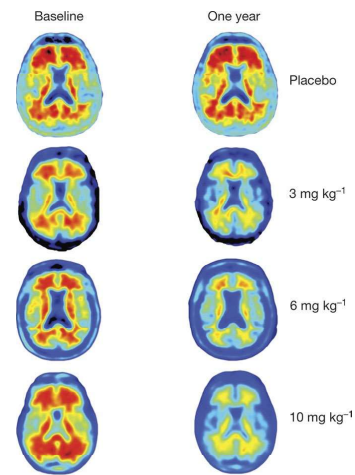
- **First new medication class approved for Alzheimer's disease since 2003 and first true disease modifying therapy**
- Indicated for treatment in **early Alzheimer's disease** patients who have proven β -amyloid pathology ($A\beta$)
- Specifically target removal of aggregated beta amyloid protein accumulation in the brain
- **Monoclonal antibody therapies** approved by FDA:
 - **Aducanumab** (Aduhelm) – approved in 2021; withdrawn in 2024
 - **Lecanemab** (Leqembi) - 2023
 - **Donanemab** (Kinsunla) - 2024
- **Significant Risks:**
 - Aducanumab trials (EMERGE and ENGAGE) found **amyloid-related imaging abnormalities (ARIA)** – both microhemorrhage and edema
 - Patients symptomatic with headache, confusion, dizziness, and nausea
 - Approach was to hold doses or dose reduction and scheduled neuroimaging to monitor

Anti-Amyloid Monoclonal Antibodies

Aducanumab Clinical trials

- <85 years old, confirmed MCI, and evidence of beta amyloid by PET scan
- Dose dependent removal of amyloid plaques was observed
- Modest/questionable clinical benefit and risk for microhemorrhages and edema is limitations on therapy
- Required IV dosing every 4 weeks and frequent MRI assessments
- Discontinuation of treatment associated with deaccumulation of amyloid

Aducanumab PET Imaging for β -amyloid



Anti-Amyloid Monoclonal Antibodies

- No longer restricted to patients enrolled in clinical trials for Medicare Coverage
- Patients need to be enrolled in a **CMS-approved patient registry** in order to receive payment coverage for the treatment

Future Direction

Dosing Frequency

- *Lecanemab dosing q2 weeks initial and q4 weeks maintenance*
- *Donanemab dosing q4weeks (monthly)*

Administration

- *Subcutaneous route of administration and autoinjector will increase the ease and availability/accessibility of these medications*

Reducing Risk of Dementia: Some Rules of Thumb

All of us at risk for dementia as we get older...but there are things we can do

1. Brain "fitness" and physical activity (exercise/fitness) are key
2. Mitigate **cerebrovascular risk factors**: smoking, blood pressure, cholesterol, diabetes
3. Diet may play an important role:
 - best evidence for **DASH** and **MIND**
 - poor evidence for omega-3 fatty acids, antioxidants, supplements
4. Stress Reduction is important (along with sleep, treating depression)
5. Social Engagement/Connectedness

Questions?

Thank you for attending today!

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