

# Alzheimer's Disease

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# Disclosures

- Nothing relevant to disclose
- Principle investigator for current clinical trials for patients with Alzheimer's disease:
  - Roche Genentech - A Phase II, Multicenter, Randomized, Double-blind, Placebo-Controlled, Parallel-group, Efficacy and Safety study of MTAU99937A in Patient with Moderate Alzheimer's Disease (Lauriet)
  - Lilly AACI - Assessment of safety, tolerability and efficacy of donanemab in early symptomatic Alzheimer's disease (TRAILBLAZER)
  - Athira 201/203 - A Randomized, placebo-controlled, double-blind study of ATH-1014 in subjects with mild to moderate Alzheimer's disease, Open-label Extension of Studies ATH-1017-AD-201 and ATH-1017-AD-0202 in Subject with Mild to Moderate Alzheimer's Disease
- Past trials: Roche Genentech – A phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy, and safety study of gantenerumab in patients with prodromal to mild Alzheimer's disease (GRADUATE 1), An Open-Label, Multicenter, Rollover Study to Evaluate the Safety, Tolerability and Efficacy of Long-Term Gantenerumab Administration in Participants with Alzheimer's Disease (Post-Grad)

# Outline

- Scope
- Etiology
- Risks and protective factors
- Symptoms and expected course
- Evaluation and initial workup
- Diagnostic testing
- Treatment
- The future of AD



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# Alzheimer's Disease

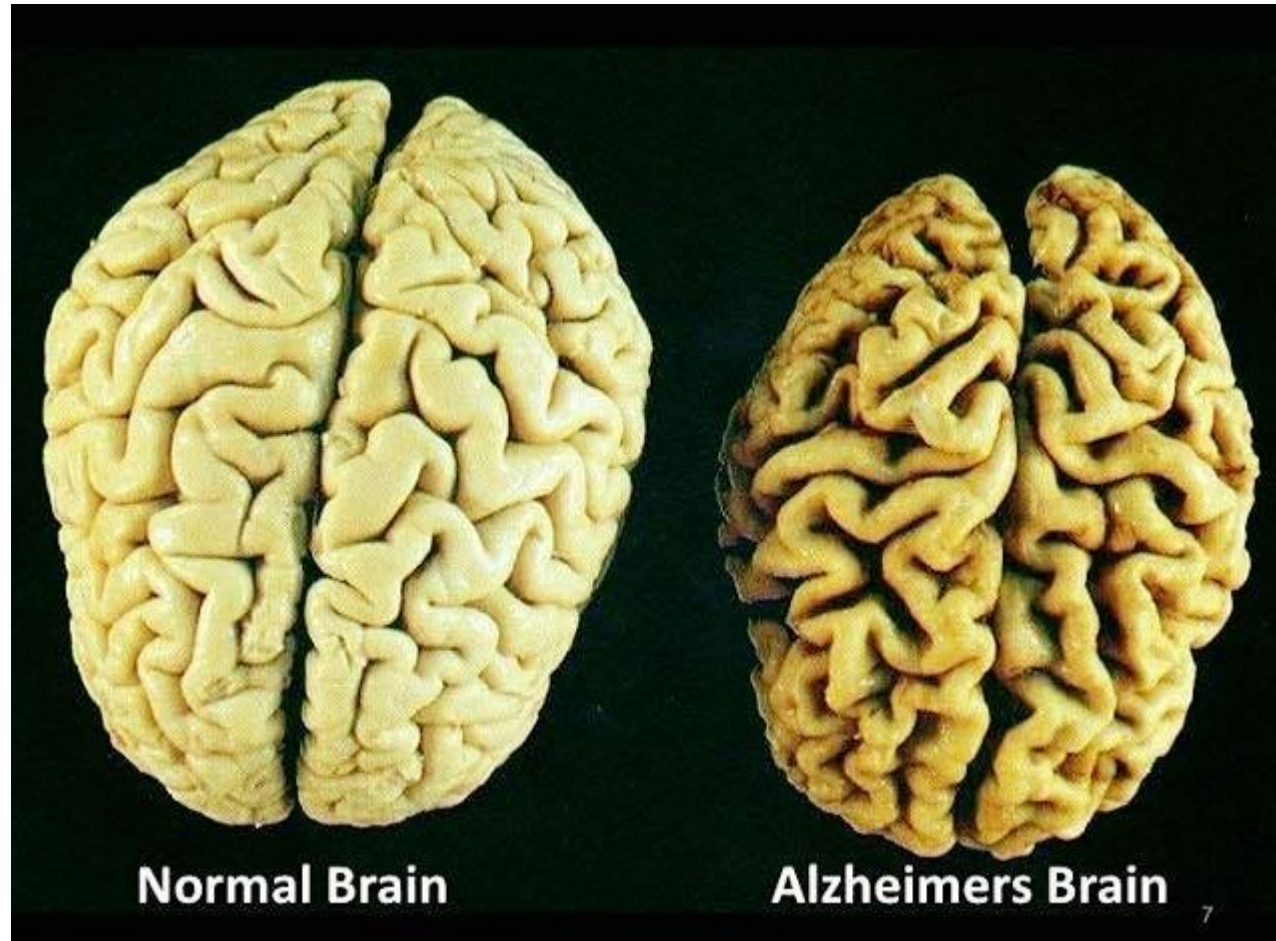
- Most common cause of dementia in the US and in the world
- Estimated prevalence of 6.5 million people over age 65 living with AD in the United States
  - 1/9 people over 65
  - 73% of these people are over age 75
- Harder to estimate in people <65, but estimated to be about 200,000 people with early-onset AD in the US
- Lifetime risk at age 45 ~1 in 5 for woman and 1 in 10 for men
- Incidence rate is decreasing
- The population of Americans age 65 and older is projected to grow from 58 million in 2021 to 88 million by 2050
  - May be 13.8 million with Alzheimer's disease by 2060



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# What causes Alzheimer's Disease?



Atrophy

Atrophy due to neuron cell loss

Loss of neurons in the brain leading to loss of function

Image courtesy of Daily Anatomy

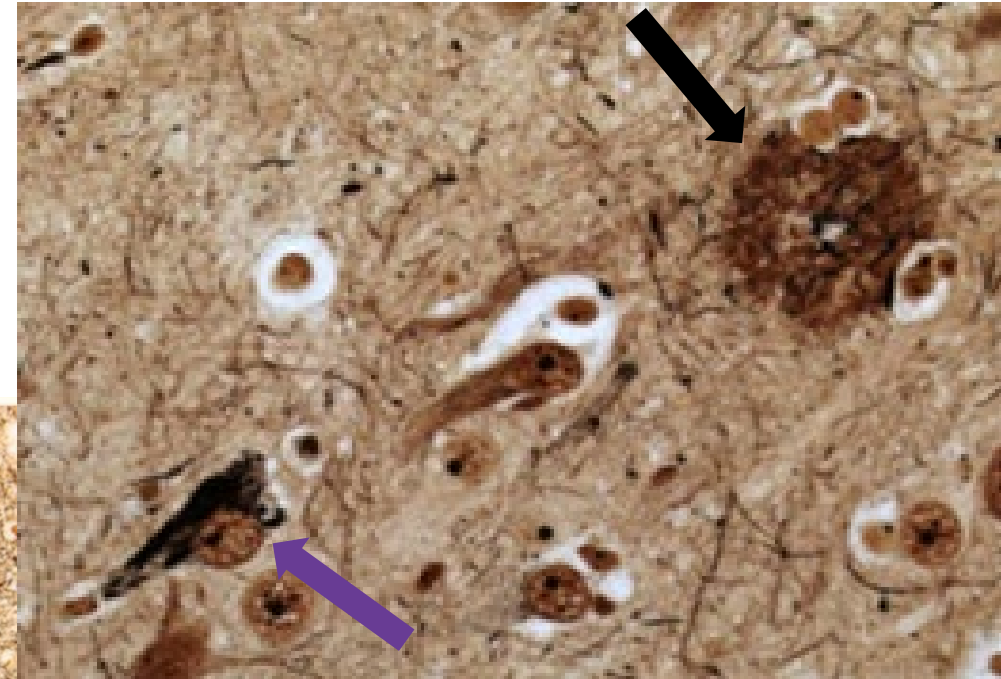
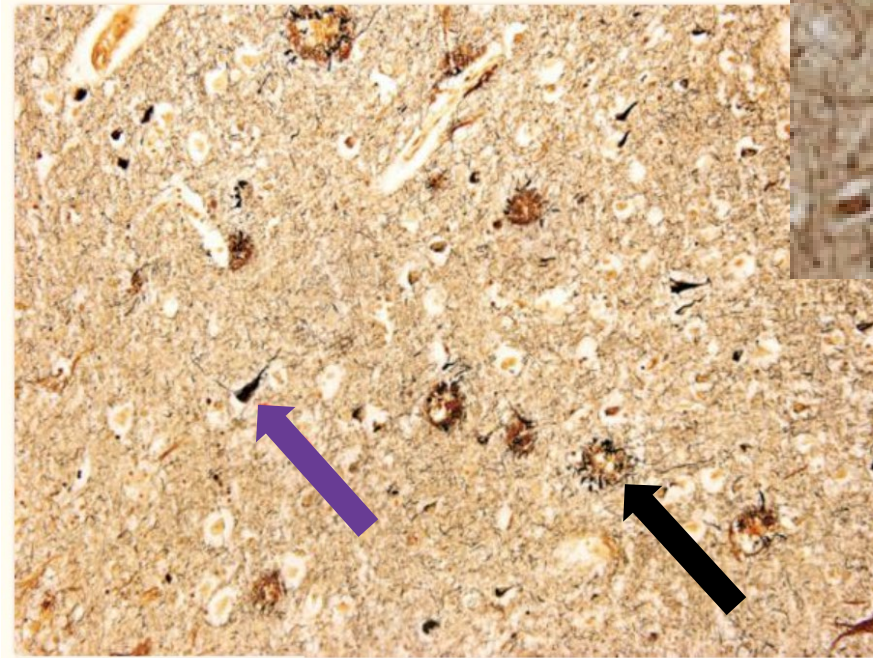


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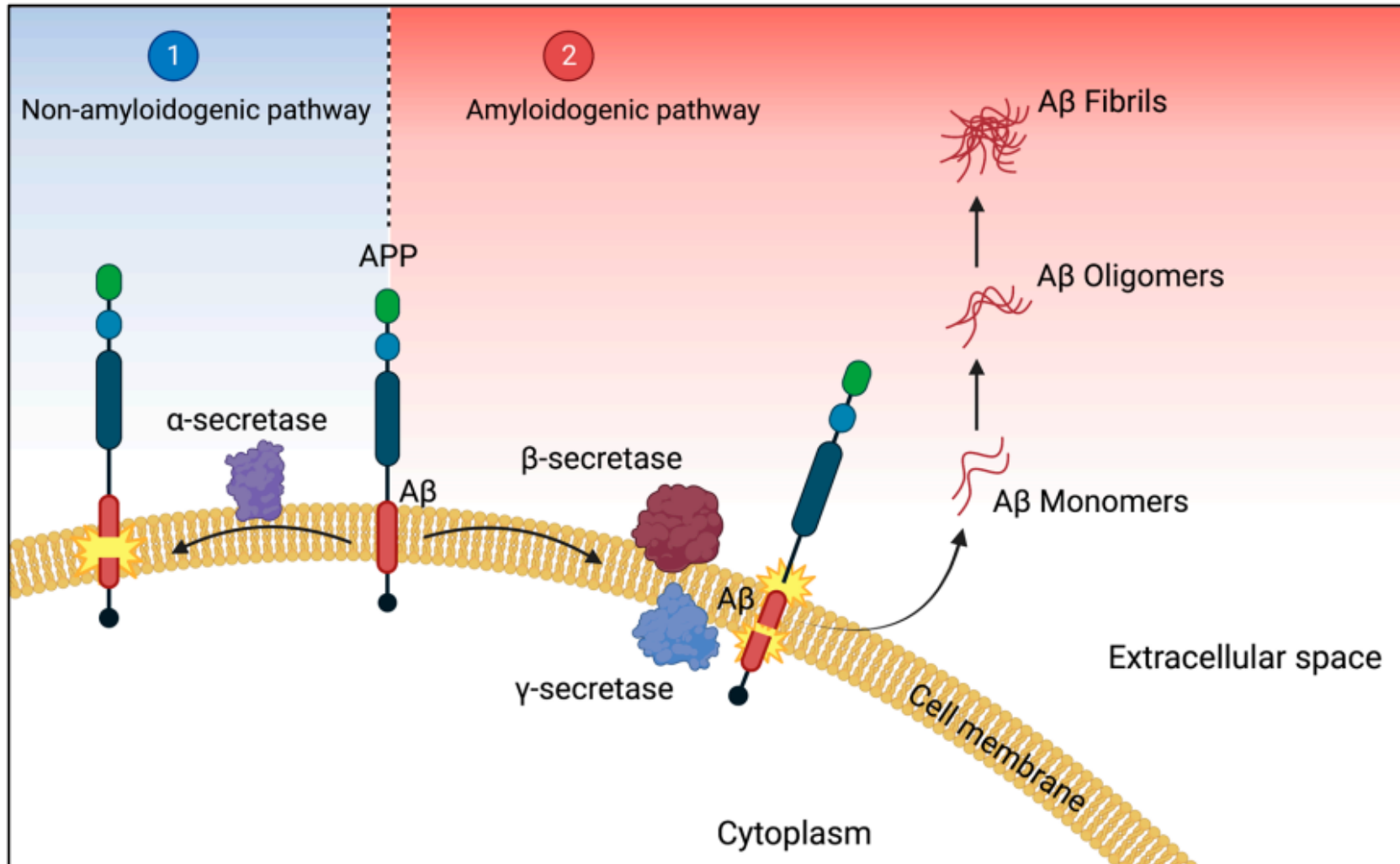
# What causes Alzheimer's disease?

Loss of neurons due to accumulation of **amyloid-beta plaques** and **neurofibrillary tangles** of p-tau



Keene CD et al. *UptoDate* 2023

# The amyloid cascade



# What causes Alzheimer's disease?

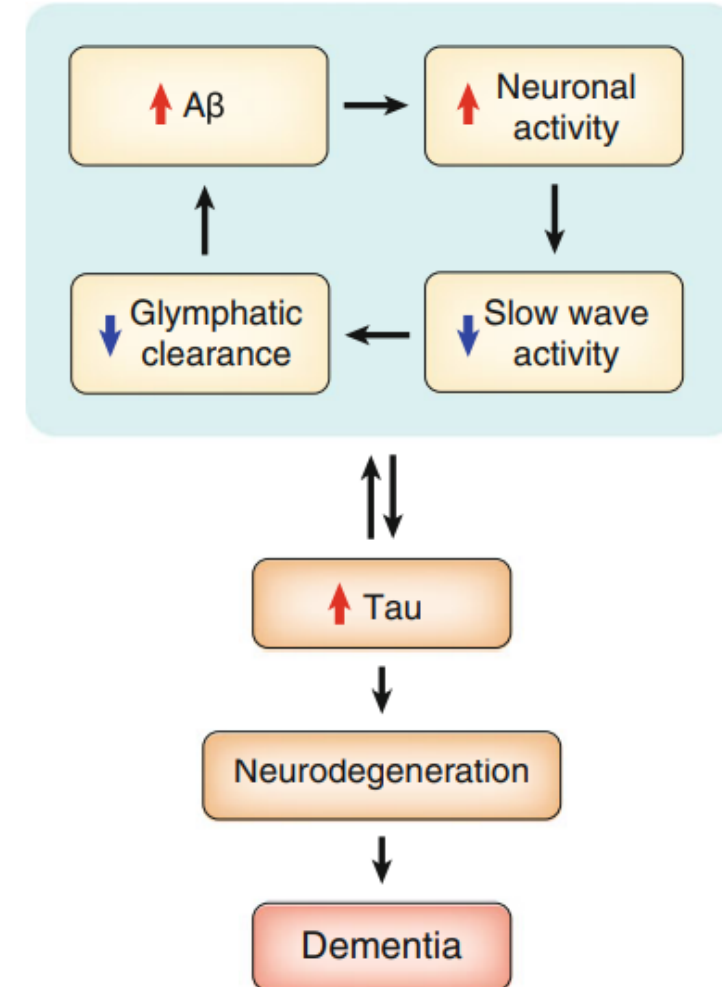
- Amyloid plaques induce abnormal tau phosphorylation
- Both amyloid and tau lead to inappropriate signaling, leading to cell dysfunction, injury and death
- This induces inflammation in the brain
  
- Inflammation from other causes worsens process
- Altered blood and CSF flow worsens process
  
- Vasculature also injured by amyloid



# What causes Alzheimer's Disease?

## Disrupted sleep and sleep apnea

- Less slow wave activity leads to less glymphatic clearance of metabolites, waste
- Less slow wave sleep leads to increased inflammation due to altered homeostasis, activation of microglia
- Less NREM sleep leads to more oxidative stress due to higher brain activity
- Sleep deprivation has been associated with increased A $\beta$  and tau levels

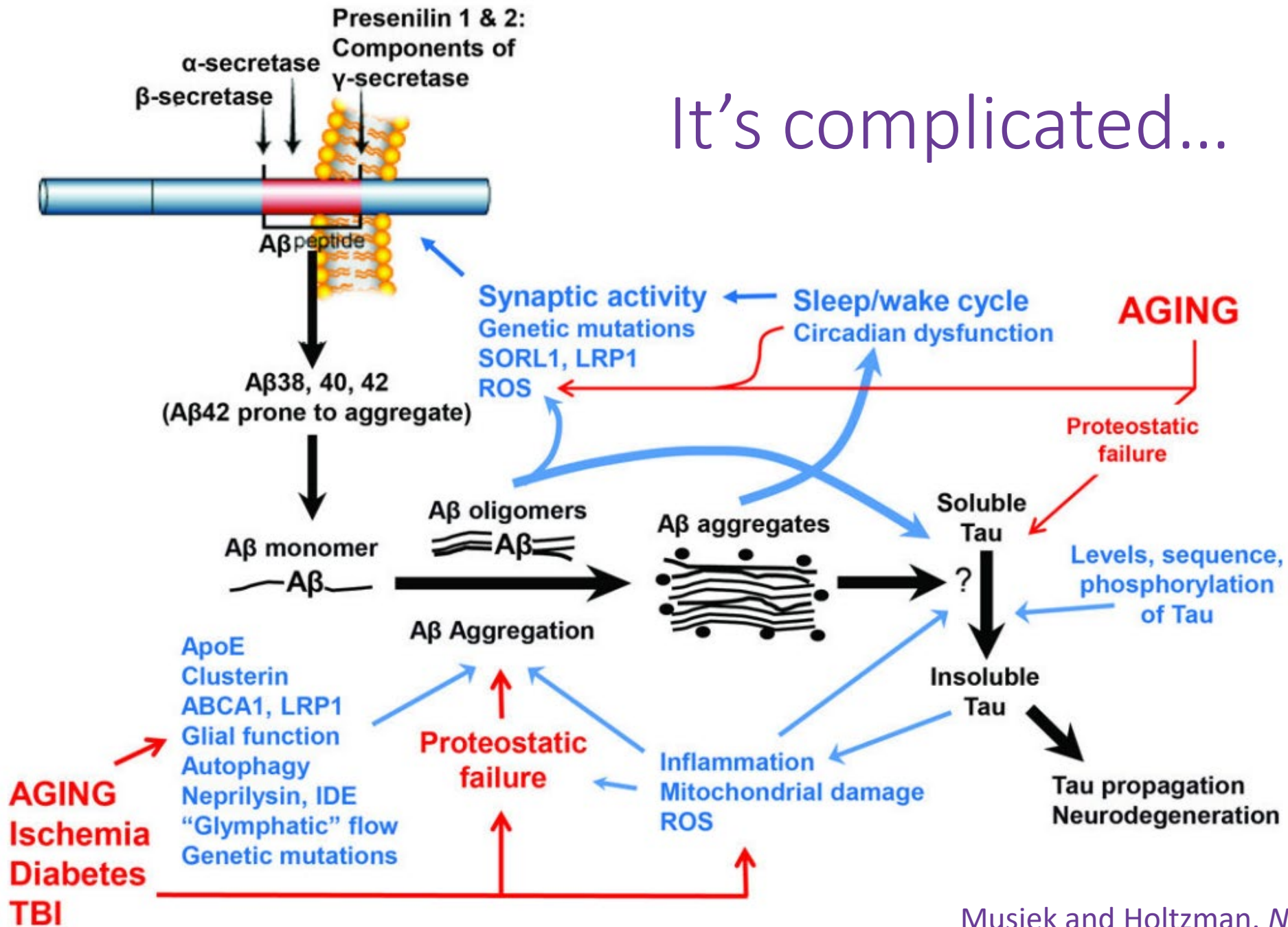




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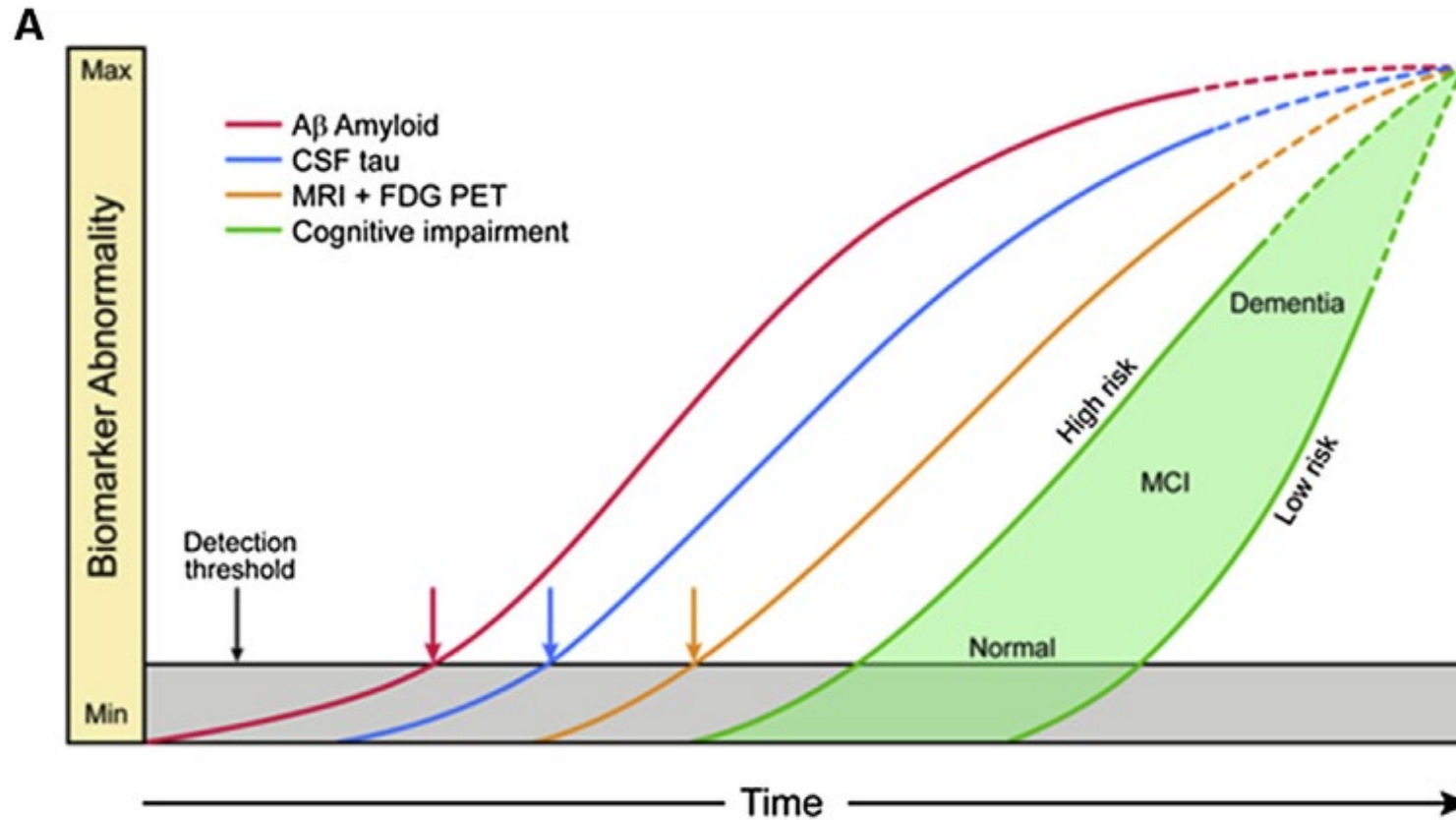
It's complicated...



... And it starts before symptoms begin



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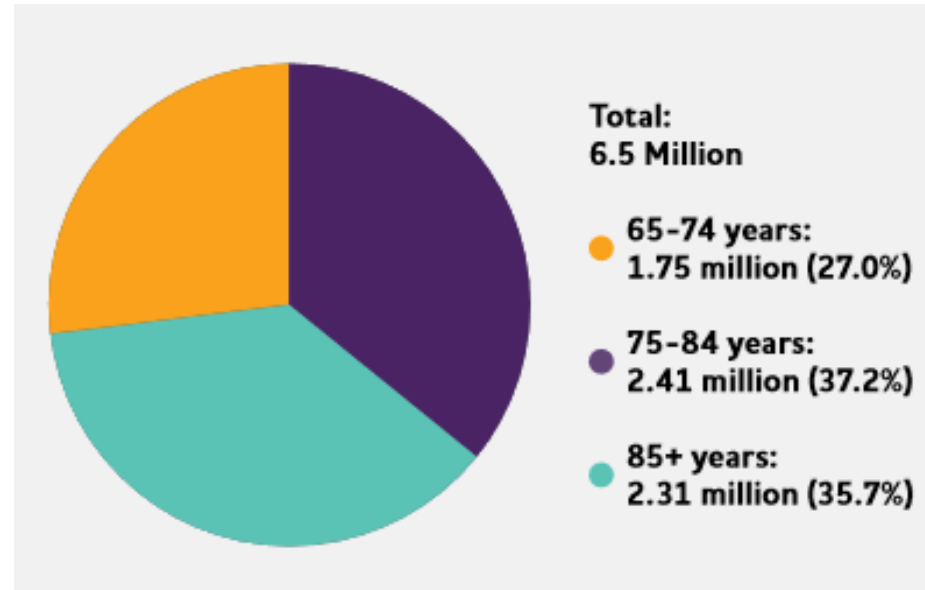


Jack and Holtzman. *Neuron* 2013 80:1347

# Risks of Alzheimer's Disease

## Non-modifiable

- Age
- Gender
- Genetics



# Risks of Alzheimer's disease

## Genetics

- <1% of patients with Alzheimer's have an inherited form
  - More common in early onset AD
- APP (Amyloid Precursor Protein)
  - On chromosome 21 - Down's syndrome patients have high risk of AD – 30% of those in their 50s, 50% in their 60s
- Presenilin 1 (PSEN1)
- Presenilin 2 (PSEN2)

# Risks of Alzheimer's disease

## Genetics

- Apolipoprotein E – involved in lipid processing
  - ApoE3 is the physiologic isoform, present in 50 to 90% of the population
  - ApoE2 may be protective for AD
  - ApoE4 increases risk
    - One allele 3x risk
    - Two alleles 8-12x risk
- Many other genes

# Risks of Alzheimer's Disease

## Modifiable risks

- Cardiovascular
  - Smoking
  - Hypertension
  - Hyperlipidemia
  - Diabetes
  - Poor diet
  - Less physical activity
- Education
  - Lower education = higher risk
- Activity
  - Physical
  - Social and cognitive
- Sleep
- Alcohol
  - Excessive – more than 7 drinks/week on average or more than 3 drinks on any day
- Hearing impairment
- Depression
- History of head injury?
- Air pollution?
- Metal exposure?
- Chronic infections?



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# Symptoms of Alzheimer's disease

- **Short term episodic memory loss**
  - Forgetting recent events, conversations, asking repetitive questions
  - Misplacing objects, forgetting to pay bills or take medications
- Executive dysfunction
  - Difficulty making decisions, multitasking
  - Driving
  - Difficulty with finances and taxes
- Difficulty completing familiar tasks
  - Hobbies
  - Household chores, cooking
  - Using technology and utilities
- Visual and spatial relationship difficulties
  - Getting lost driving in familiar places
  - Wandering
- Language difficulties
  - Word finding
- Changes in judgement, behavior, personality
  - Decision making, basic ADLs
  - Leaving the stove on, car running
  - Financial decisions
  - Worsening irritability or mood lability
  - Aggressive behaviors
  - Delusions and hallucinations



## Symptom Progression

	Mild	Moderate	Severe
Cognitive symptoms	<ul style="list-style-type: none"> <li>Misplacing items</li> <li>Forgetting appointments</li> <li>Forgetting bills/medications</li> <li>Occasional word-finding problems</li> <li>Difficulty navigating in unfamiliar areas</li> <li>More challenging hobbies/tasks abandoned</li> </ul>	<ul style="list-style-type: none"> <li>Difficulty navigating in familiar areas</li> <li>Leaving stove on</li> <li>Problems preparing meals</li> <li>Problems with simple calculations</li> <li>Difficulty with simple hobbies/chores</li> <li>Problems with utilities/mobile phone/computer</li> <li>Disoriented to date/location</li> <li>Clear word-finding difficulties</li> <li>Poor judgment (managing finances; planning activities)</li> <li>Mild apraxia</li> </ul>	<ul style="list-style-type: none"> <li>Consistent apraxia</li> <li>Poor recognition of familiar people</li> <li>Severe aphasia (global aphasia)</li> </ul>
Psychiatric symptoms	<ul style="list-style-type: none"> <li>Mild anxiety</li> <li>Mild depression</li> <li>Mild social withdrawal</li> <li>Mild irritability</li> </ul>	<ul style="list-style-type: none"> <li>Irritability/mood lability</li> <li>Aggressive behaviors</li> <li>Occasional delusions</li> <li>Increased anxiety</li> <li>Rare hallucinations</li> <li>Wandering/elopement</li> </ul>	<ul style="list-style-type: none"> <li>Hallucinations</li> <li>Apathy</li> </ul>
Non-Neuropsychiatric	<ul style="list-style-type: none"> <li>Sleep maintenance problems</li> </ul>	<ul style="list-style-type: none"> <li>Decreased appetite/weight loss</li> <li>Mild extrapyramidal symptoms (bradykinesia, gait slowing)</li> <li>Insomnia</li> <li>Incontinence (variable)</li> <li>Occasional myoclonus</li> <li>Rare seizures</li> </ul>	<ul style="list-style-type: none"> <li>Impaired gait/balance</li> <li>Rigidity (Gegenhalten)</li> <li>Incontinence</li> <li>Seizures</li> </ul>



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# Atypical Alzheimer's Disease

- Frontal variant
  - Executive dysfunction – planning, multitasking, organizing, completing projects
  - Behavioral changes – resembles FTD
    - Disinhibition, lack of empathy, disregard of societal norms, obsessive-compulsiveness, occasional hyperorality
    - Can also have delusions and hallucinations – rare in FTD
- Posterior cortical atrophy
  - Complex visuospatial abnormalities
    - Gerstmann syndrome, Balint syndrome
  - Apraxia
    - Limb apraxia
    - Dressing apraxia
    - Constructional apraxia
  - Prosopagnosia
  - Alexia
  - Vision loss, cortical blindness
- Logopenic primary progressive aphasia
  - 86-90% due to AD pathology
  - Word finding difficulties but still fluent
  - Circumlocution – talking around a subject, unable to get to the specific word or sentence
  - Phonemic paraphasias – saying “blant” for “plant”
  - Unable to repeat even simple sentences
- Corticobasal syndrome
  - Rare form of atypical parkinsonism
  - Estimates from 15-54% of cases are due to AD
  - Parkinsonism, apraxia, and cognitive impairment, plus segmental myoclonus, limb dystonia, alien limb phenomenon, cortical sensory loss, and dyscalculia

# Course of Alzheimer's disease

2021 Lancet meta-analysis of all types of dementia

- Mean age of onset of AD 68.8 years
- Mean age of diagnosis 74.2 years
- Mean age of death 78.6 years
  
- Mean survival time 7.6 years from onset, 5.8 years from diagnosis

# Initial evaluation

- Is something else causing the cognitive changes?
  - Poor sleep, OSA
  - Metabolic abnormalities – vitamins, kidney/liver, hormonal, infections, etc
  - Depression
  - Anxiety
  - Hearing loss, vision loss
  - Structural brain lesions – tumors, large strokes, MS, seizures - rare
- Is it another neurodegenerative disease?
  - Pattern of cognitive changes
  - Other neurological symptoms – parkinsonism, focal weakness or numbness, prominent behavioral symptoms, early predominant language problems

# Initial evaluation

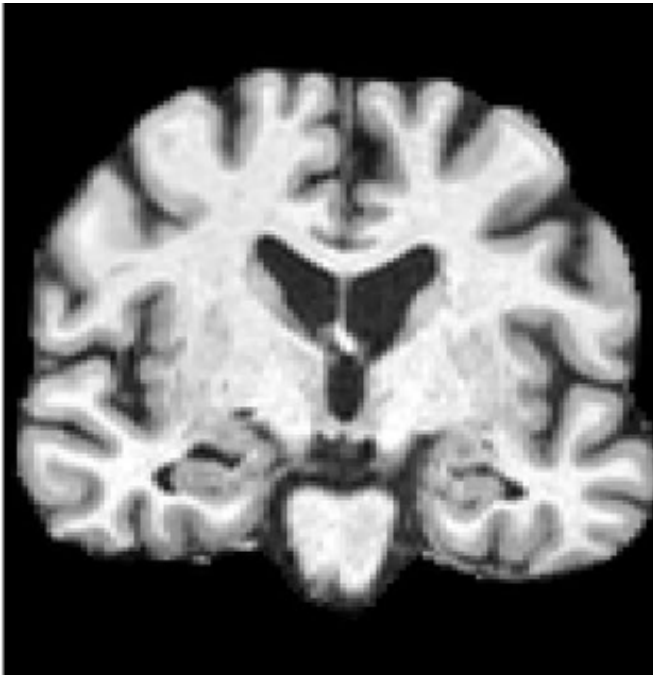
- Basic labs
  - Metabolic panel
  - CBC
  - B12, consider thiamine and folate if risks
  - TSH
  - Infections if risk – RPR, HIV, others
  
- Screen for sleep apnea
- Screen for depression, anxiety
- Head imaging – CT or MRI brain



# Diagnosis

- MRI findings

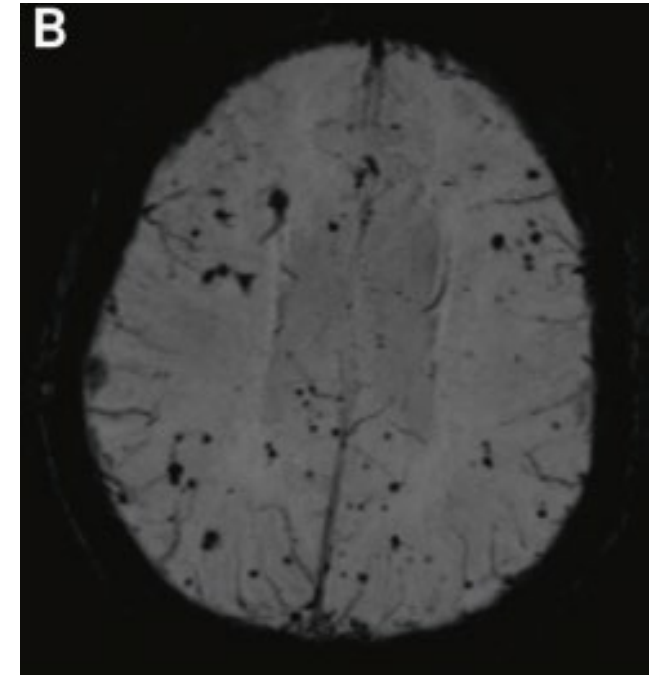
Healthy control



Alzheimer's disease



Cortical microhemorrhages





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# Initial evaluation

- Neurological exam
  - Typically normal in Alzheimer's
- In-office cognitive testing
  - MMSE
  - MoCA
  - SLUMS
  - Others – Mini-Cog, ACE-R
- Neuropsychological testing?





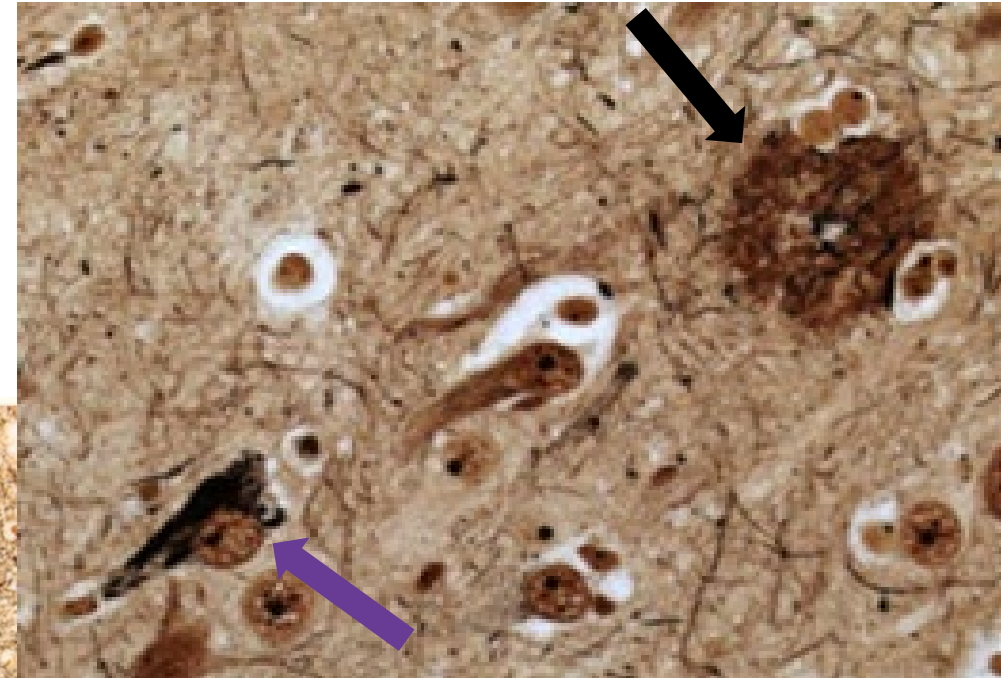
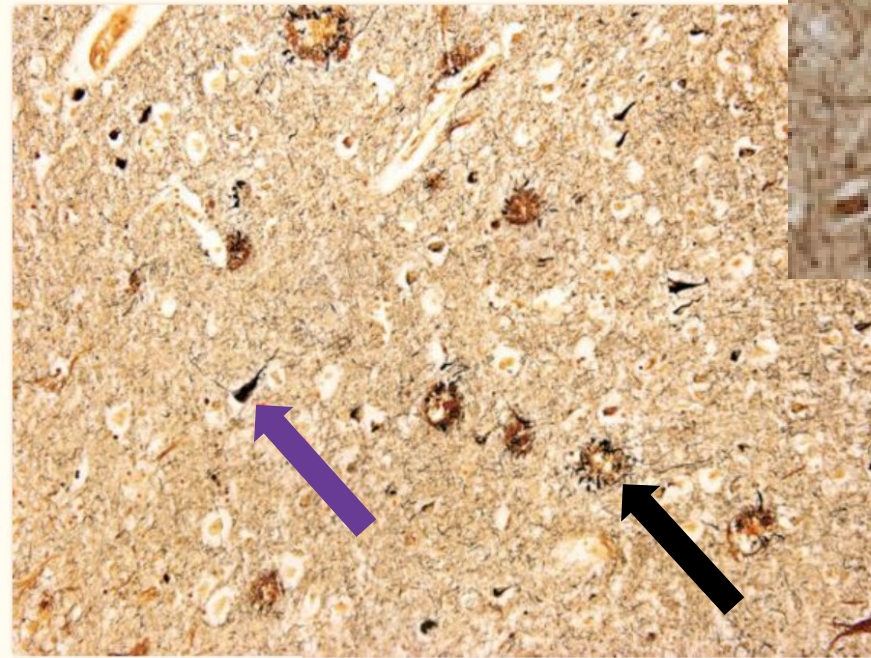
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# Diagnosis

## Definitive

- Autopsy showing amyloid and tau pathology



Keene CD et al. *UptoDate* 2023





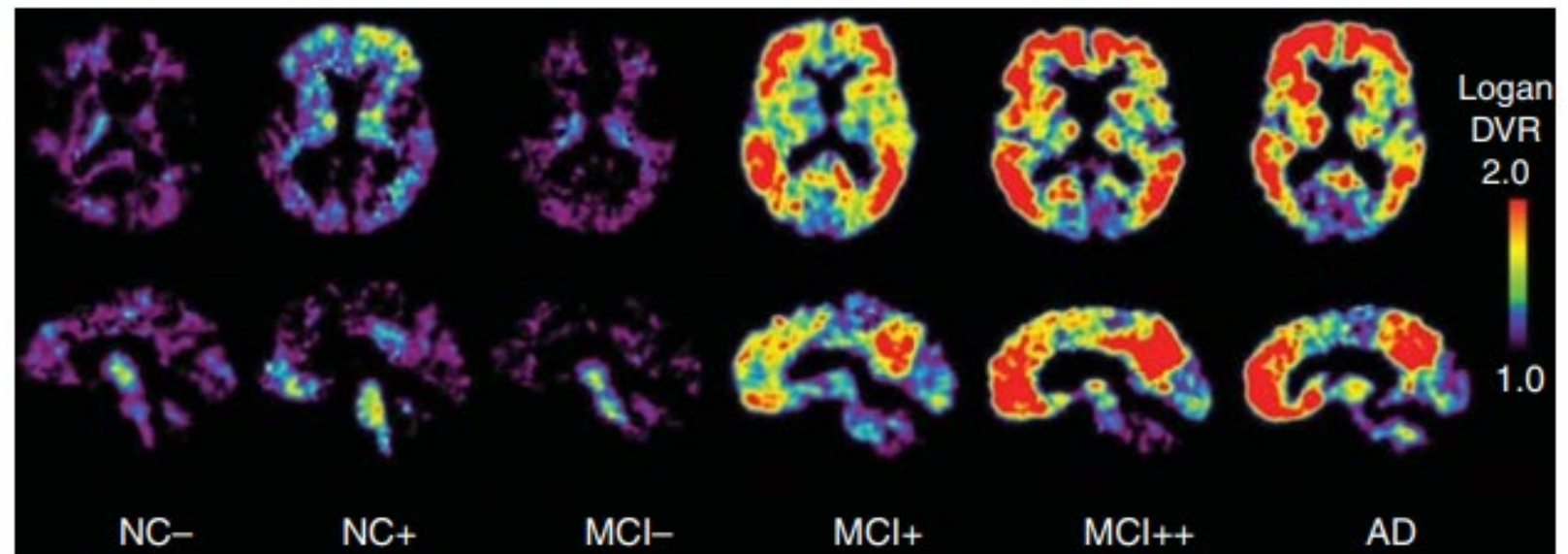
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# Diagnosis

## Biomarkers of amyloid and tau

- PET scans
  - Amyloid
  - Tau
  - FDG?



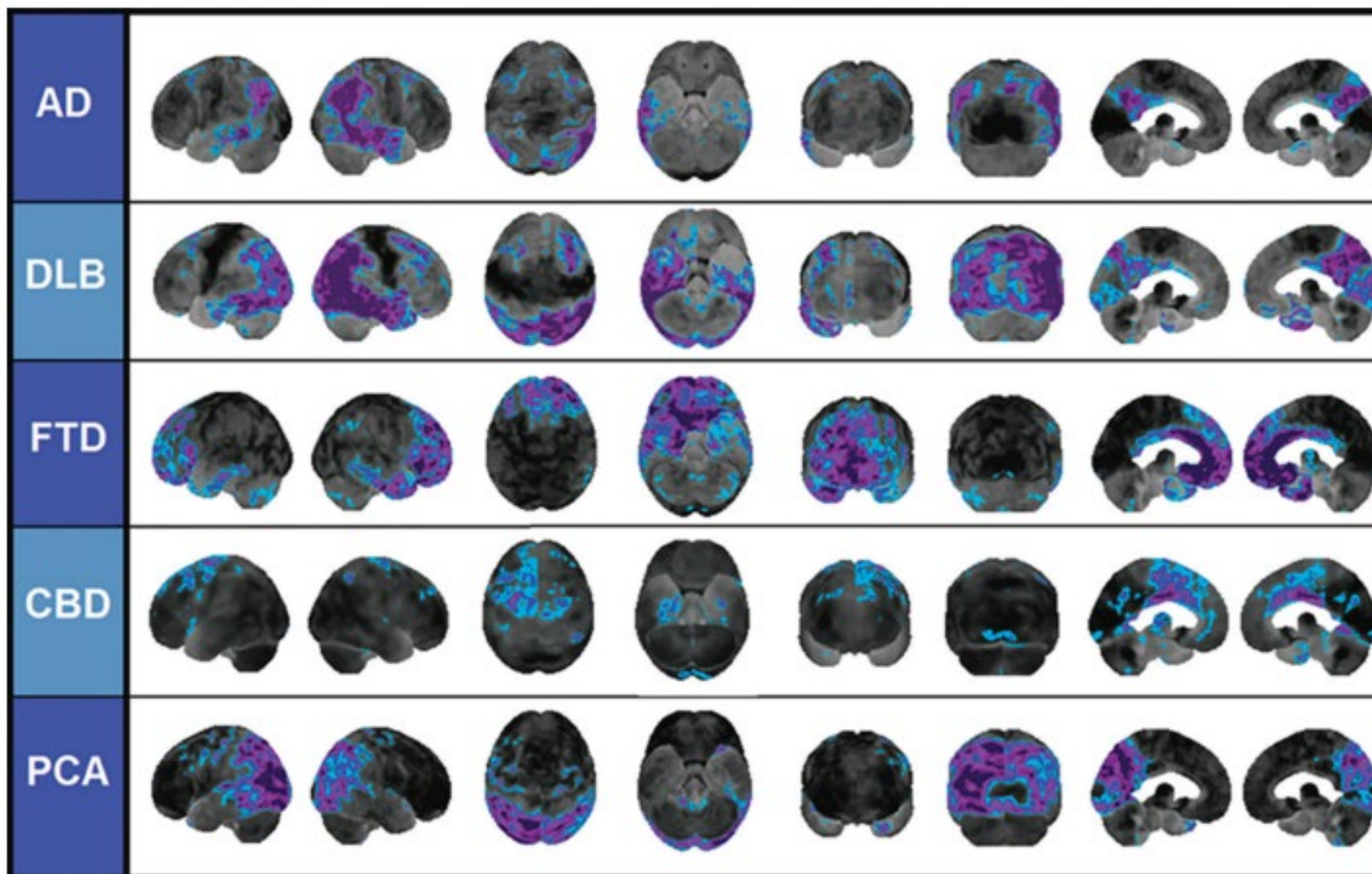
- CSF amyloid and tau, p-tau
- Serum testing

# FDG-PET (fluorodeoxyglucose)



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# Diagnosis

## Biomarkers of amyloid and tau

- PET scans
  - Amyloid
  - Tau
  - (FDG)
- CSF amyloid and tau, p-tau
  - Expect decreased Abeta42 (relative to other isoforms)
  - Expect increased total and p-tau (though this can be nonspecific)
  - Ratios often used - P-tau/Abeta42 or Abeta42/40 ratios
- Serum testing – amyloid and ?tau
  - Precivity AD – looks at Abeta42/40 ratio, as well as ApoE status and age, to generate an “amyloid probability score” – costs \$1250, financial assistance available
  - Quest-AD Detect from Quest diagnostics – also looks at Abeta42/40 ratio – costs \$500 and may be covered by insurance
  - P-tau testing – p-tau181 and p-tau217





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# Treatment of Alzheimer's disease

- Pharmacologic
  - Symptomatic
  - Disease modifying therapy
- Other pharmacologic
  - Treating mood, anxiety, behavior
  - Sleep, other symptoms
- Non-pharmacologic
  - Education
  - Assistance
  - Behavior modification



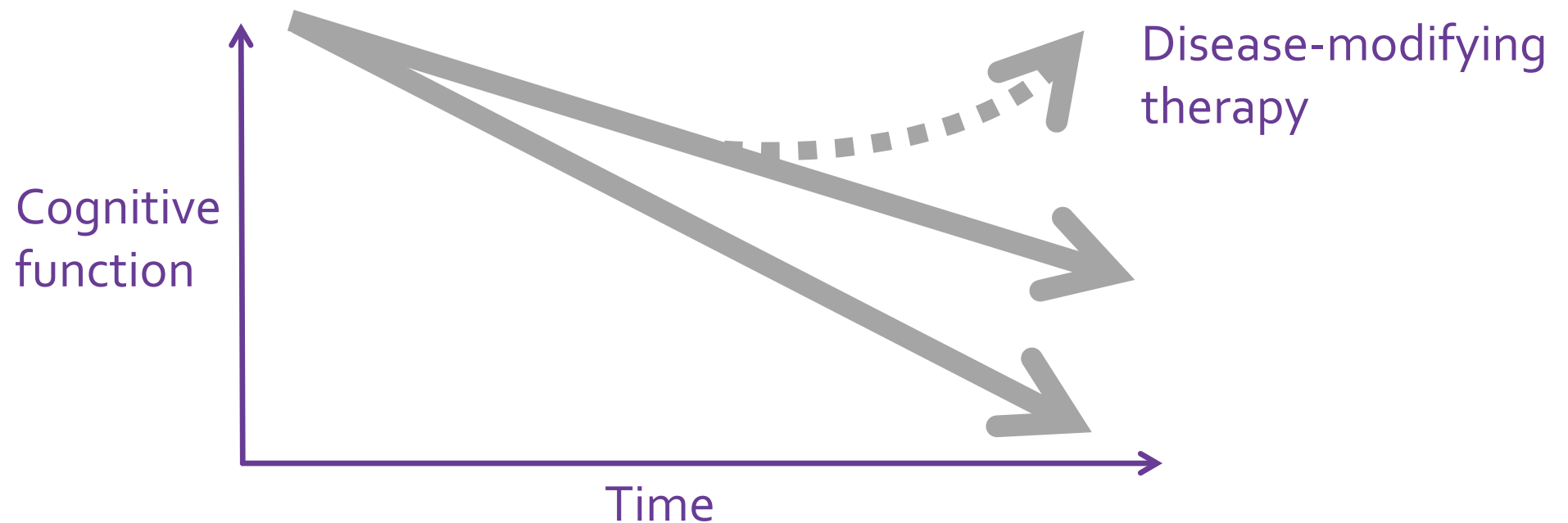


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# Treatment of Alzheimer's disease

- Current approved medications treat *symptoms*



# Current FDA-approved medications

- Cholinesterase inhibitors

- There is a loss of cholinergic neurons in the brain in Alzheimer's disease

Donepezil  
1996



Rivastigmine  
2000



Galantamine  
2001



- Memantine

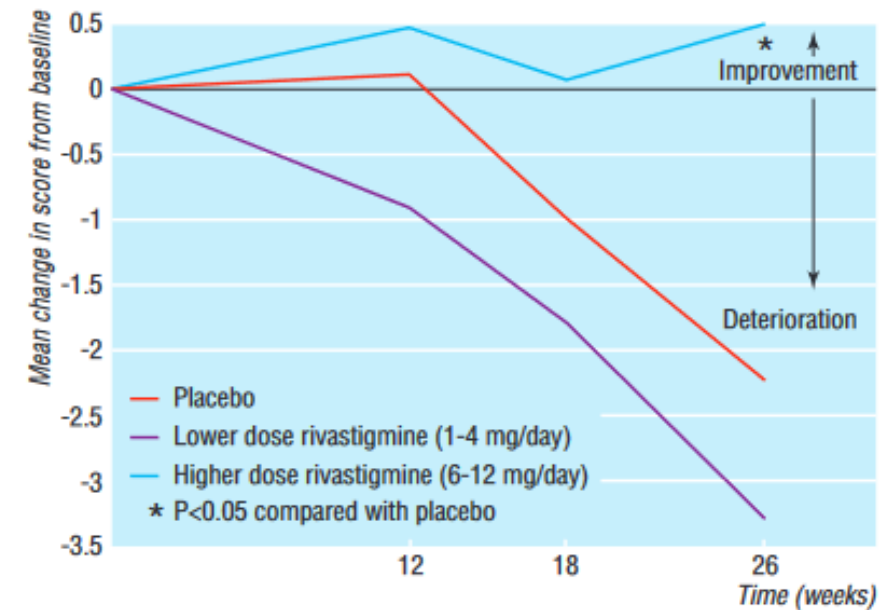
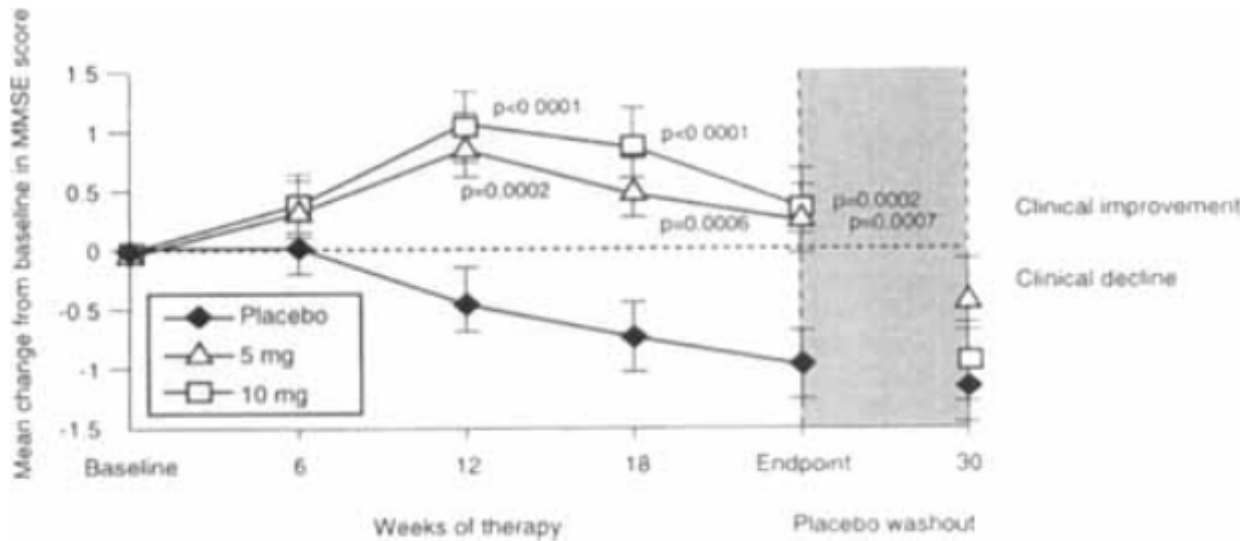
- NMDA antagonist, approved 2002
- Decreases glutamate-induced excitotoxicity
- FDA approved for moderate-severe AD dementia





# Treatment of Alzheimer's disease

Cholinesterase inhibitors improve cognitive function, slow deterioration, and improve daily function

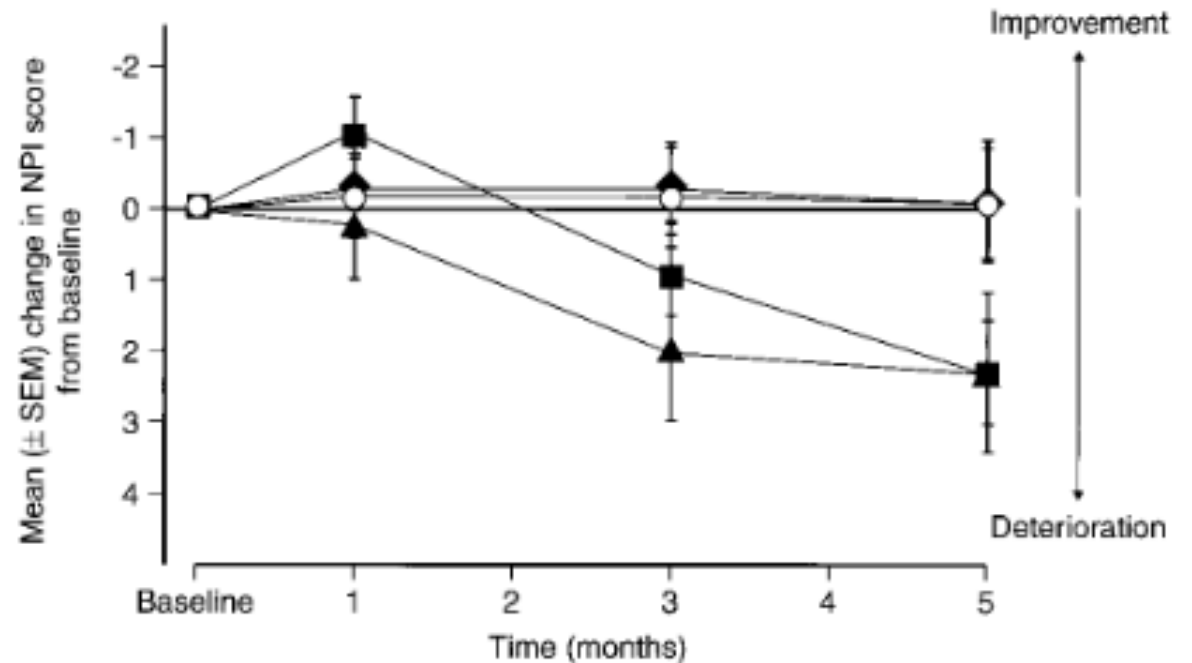


**Fig 3** Mean change in baseline scores on the progressive deterioration scale, analysis of last observation carried forward. P < 0.05 compared with placebo (two tailed pairwise Student's *t* tests using pooled error term from analysis of covariance and analysis of variance)



# Treatment of Alzheimer's disease

- Galantamine may also improve behavior and overall psychological aspects of Alzheimer's disease



*Figure 4. Mean change from baseline in total Neuropsychiatric Inventory (NPI) scores over time (observed cases analysis). ■ = placebo; ▲ = galantamine 8 mg/day; ◆ = galantamine 16 mg/day; ○ = galantamine 24 mg/day.*





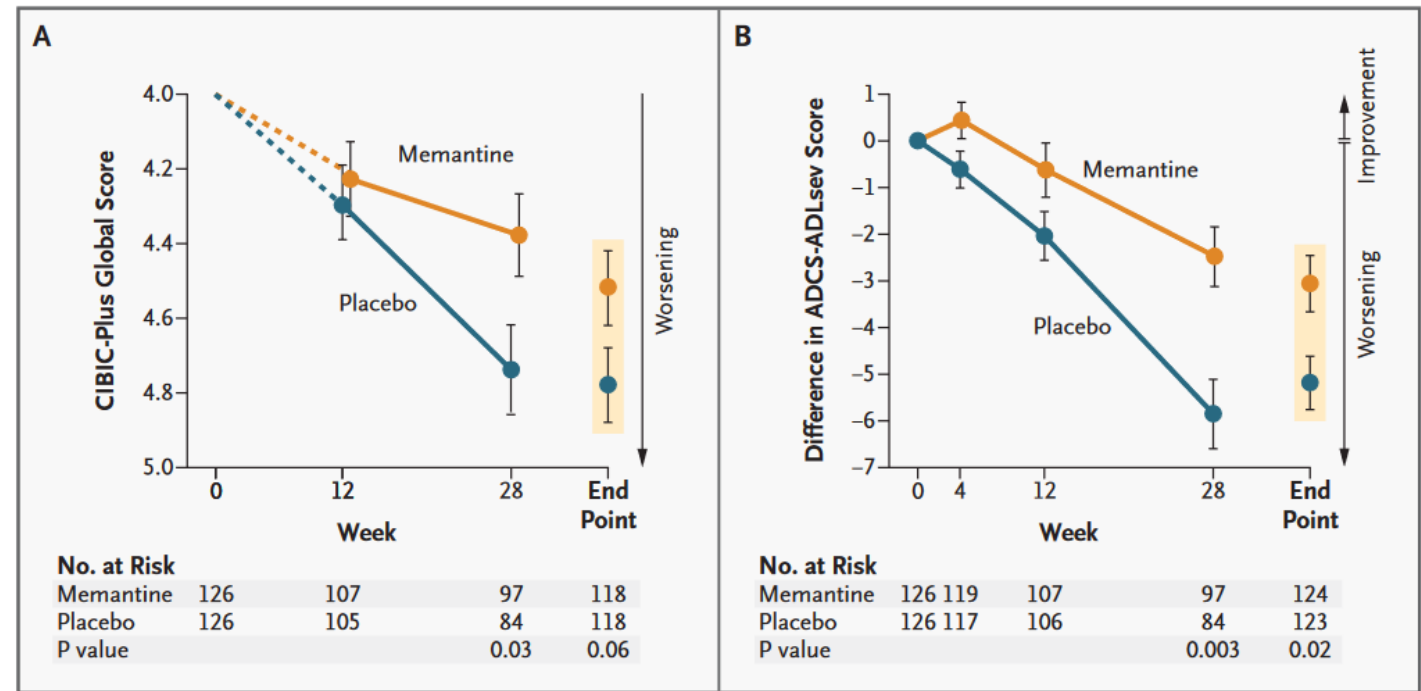
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# Treatment of Alzheimer's disease

## Memantine

- Improves cognitive scores, daily function, slows deterioration in moderate-severe AD
- Amnestic MCI and mild AD not as robust



# Side effects

## Cholinesterase inhibitors

- Nausea, vomiting
  - Diarrhea
  - Decreased appetite, weight loss
  - Insomnia, vivid dreams
- 
- Patch forms of rivastigmine and donepezil improve some side effects

## Memantine

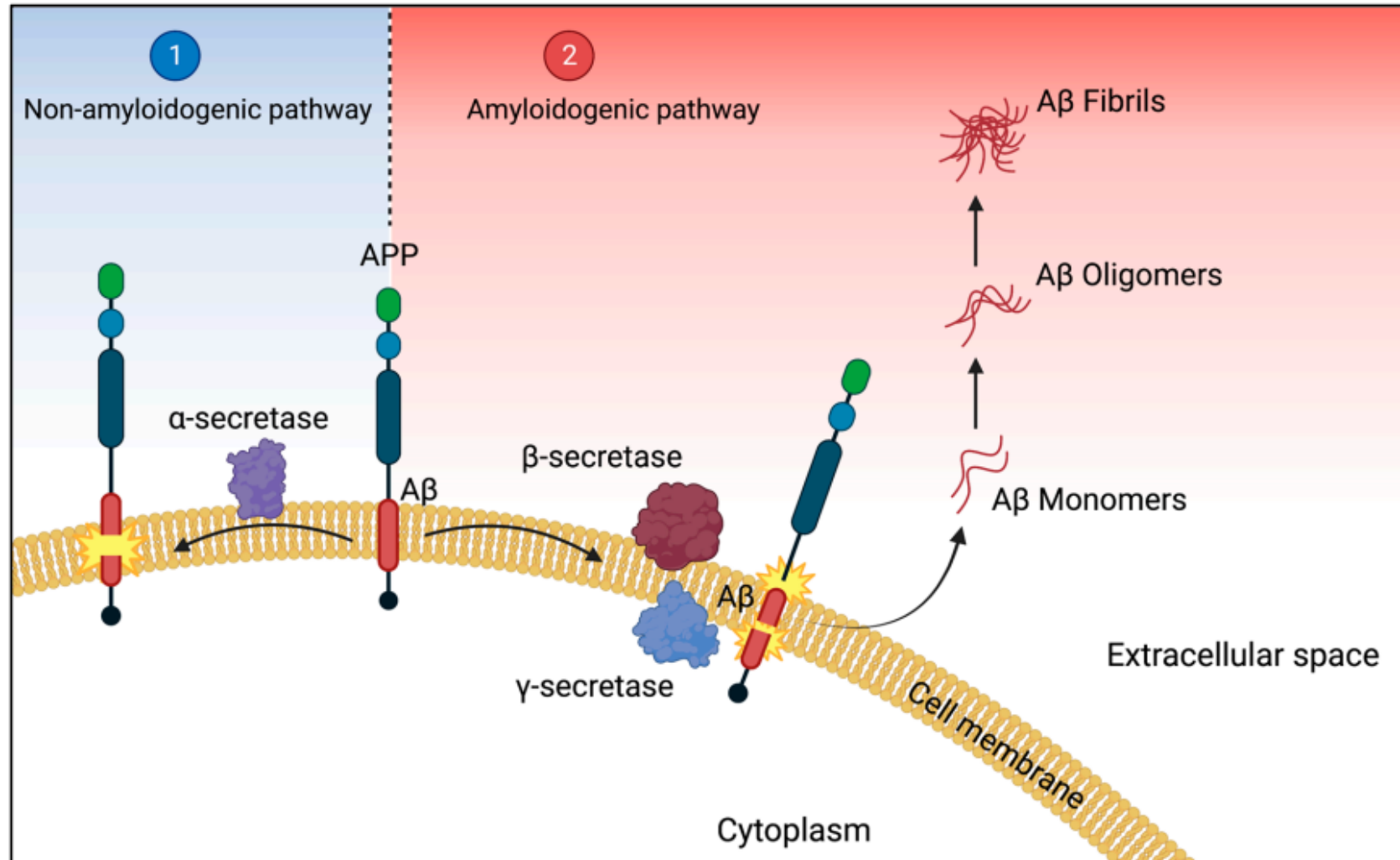
- Dizziness
- Confusion
- Headache

## Combination of donepezil and memantine

- Better outcomes vs monotherapy



# Disease-modifying therapy

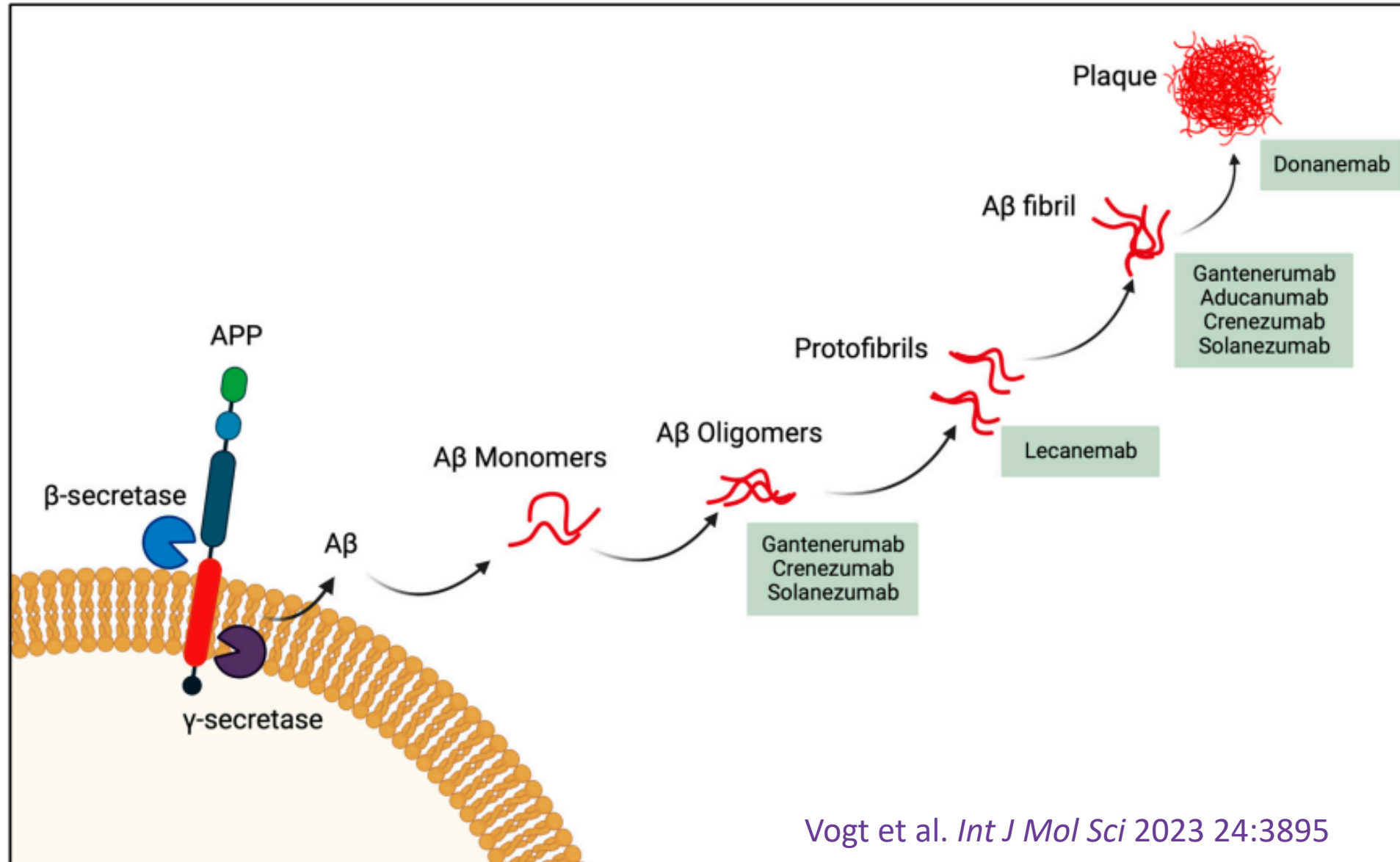


# Anti-amyloid therapies



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# Anti-amyloid antibody therapy

## Aducanumab and Lecanemab

- Very controversial – clearly remove amyloid deposits, but data does not show much improvement in memory or cognition
- Administered by monthly (aducanumab) or twice monthly (lecanemab) intravenous infusions
- Very expensive, \$28,000/\$26,500 per year for the drug itself, not including the cost of the infusions
- At present Medicare will only cover the cost if the patient is in an approved study for aducanumab, we do not know about lecanemab
- Patient must have a test that shows that amyloid is accumulating in the brain, either by a spinal tap or an amyloid PET scan. Serum testing may also be considered
- Patient must have relatively mild Alzheimer's or only significant memory impairment. MMSE  $\geq$  22 for lecanemab
- 20-43% of patients on aducanumab and 21.5% on lecanemab may experience some degree of brain swelling or microhemorrhages
- Unknown at this time how long the drug should be administered

# Treating other symptoms

- Depression and anxiety
  - SSRIs
  - SNRIs, bupropion, mirtazapine
  - Avoid benzos, tricyclics



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# Treating other symptoms

## Sleep

- Sleep apnea
- Insomnia
  - Melatonin
  - Mirtazapine
  - Trazodone
  - Ambien/others not great
  - AVOID TCAs, antihistamines, benzos, antipsychotics



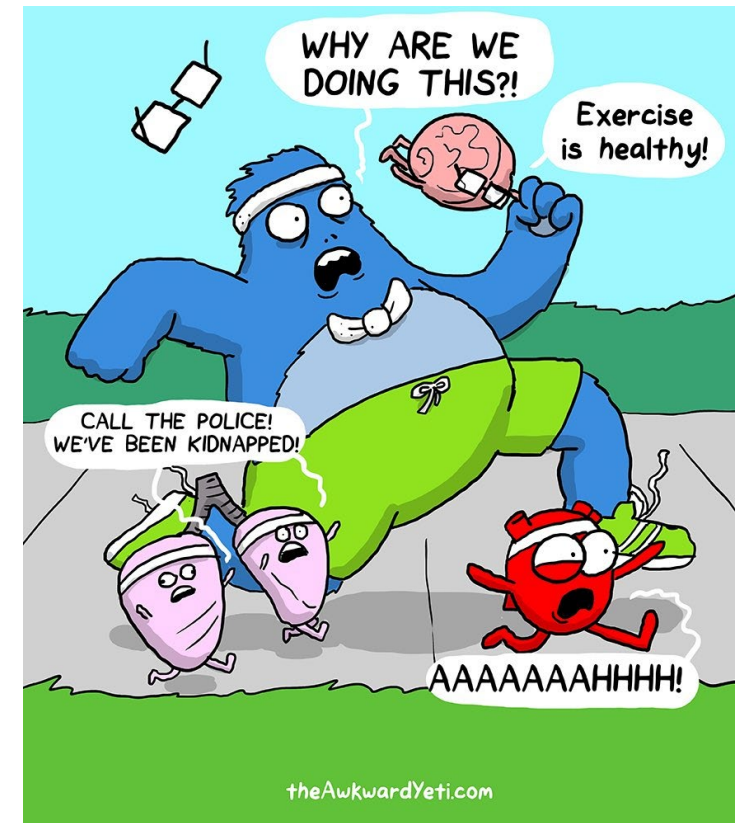


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# Non-pharmacologic treatments

- Prevention of Alzheimer's focusing on improving modifiable risks
- Improve cardiovascular health
- Exercise, maintain cognitive and social activity
- Avoid smoking, illicit drugs, limit alcohol
- Improve sleep







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# Non-pharmacologic treatments

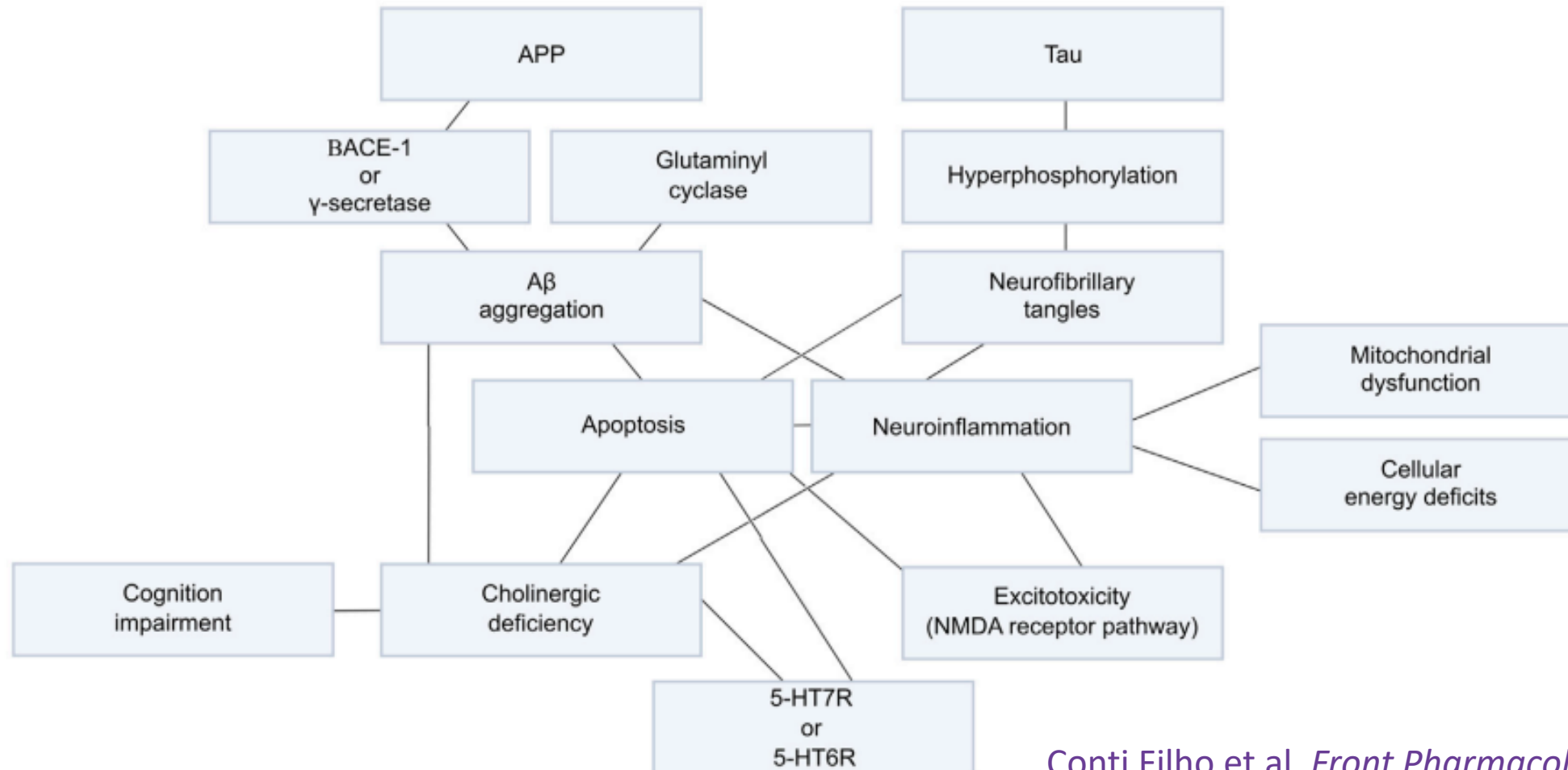
- Improving behaviors and Coping
  - Communication
  - Review photos, souvenirs, reminisce
  - Organization and routine
  - Home safety
  - Validate feelings
  - Find meaningful activities and interests
  - Senior centers and day centers
  - Music and Art – **Beyond the Medical Center**
  - Limit expectations



# The future

- What causes Alzheimer's disease?
  - Pathogenesis
  - Risks
- How do we diagnosis Alzheimer's disease?
- How do we treat Alzheimer's disease?
  - Disease modifying therapy
  - Better symptomatic medications, treatment of mood, behavior
- How else can we help our patients?
  - Changing insurance coverage/access to care
  - Better long-term care and resources
  - Education

# Potential targets for disease-modifying therapy



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Thank you!



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