Treatment of Dementia

"Has the medication had any other side effects?"

Jennifer Arnold, MD, PhD

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"Remember: medical insurance is like a hospital gown—you're never covered as much as you think you are."

Outline

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- Introduction
- Initial workup and diagnosis of dementia
- Overall goals of treatment
- Treatment of specific dementing diseases
  - Alzheimer’s disease
  - Vascular dementia
  - Lewy body dementia
  - Frontotemporal dementia
  - Others
- Other treatment considerations

Disclosures

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- Nothing relevant to disclose
- I do not receive any financial compensation for the medications discussed in this talk
- Principle investigator for current clinical trials for patients with Alzheimer's disease:

  - 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
  - ADC-061-BENFO A Seamless Phase 2A-Phase 2B Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Benfotiamine in Patients with Early Alzheimer's Disease

Introduction

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- 10% of Americans age 45 and older report subjective cognitive decline
- After 65, risk of cognitive impairment increases
  - 1 in 9 people >65 has Alzheimer's disease
- Incidence rate of Alzheimer's is decreasing (new cases per year)
  - Likely due to improvement in risk factors
- Total number of cases continues to rise, however
  - Impact of COVID-19 unknown but likely will contribute

Definitions

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- Memory changes, trouble with memory, cognitive changes, etc
  - Subjective trouble with memory or other cognitive tasks
- Mild cognitive impairment
  - Subjective complaints of cognitive changes and objective measure of cognitive impairment, but not overtly affecting daily function
  - Potentially reversible
- Dementia
  - Non-reversible process causing deterioration in cognition beyond what is expected in normal biological aging that interferes with daily living

Is it dementia?

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- Medications
  - Benzos
  - Opioids
  - Hypnotics
  - Anticholinergics
  - Barbiturates
  - Seizure meds, muscle relaxers
  - Antipsychotics
- Other medical issues, deficiencies, toxicities
  - Vitamin deficiencies – B12, B1, folate
  - Endocrine dysfunction – thyroid
  - Chronic liver or kidney disease
  - Severe lung disease, heart failure
  - Inflammatory/autoimmune disease
  - Infections
- Sleep disruption
  - Obstructive sleep apnea
  - Insomnia
- Depression, anxiety
- Other neurological causes
  - Longstanding MS
  - Epilepsy or seizures
  - Traumatic brain injury
  - Stroke
  - Tumors or other masses
- Pain
- Hearing and/or vision loss

Types of neurodegenerative dementia

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- Alzheimer's disease
- Parkinson's disease dementia and dementia with Lewy bodies
- Frontotemporal dementia
- Progressive supranuclear palsy and other parkinsonian disorders
- Chronic traumatic encephalopathy (CTE)
- Others – Huntington's disease, prion disease (CJD), LATE

- Vascular dementia

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- **Vascular dementia**

Dementia progression

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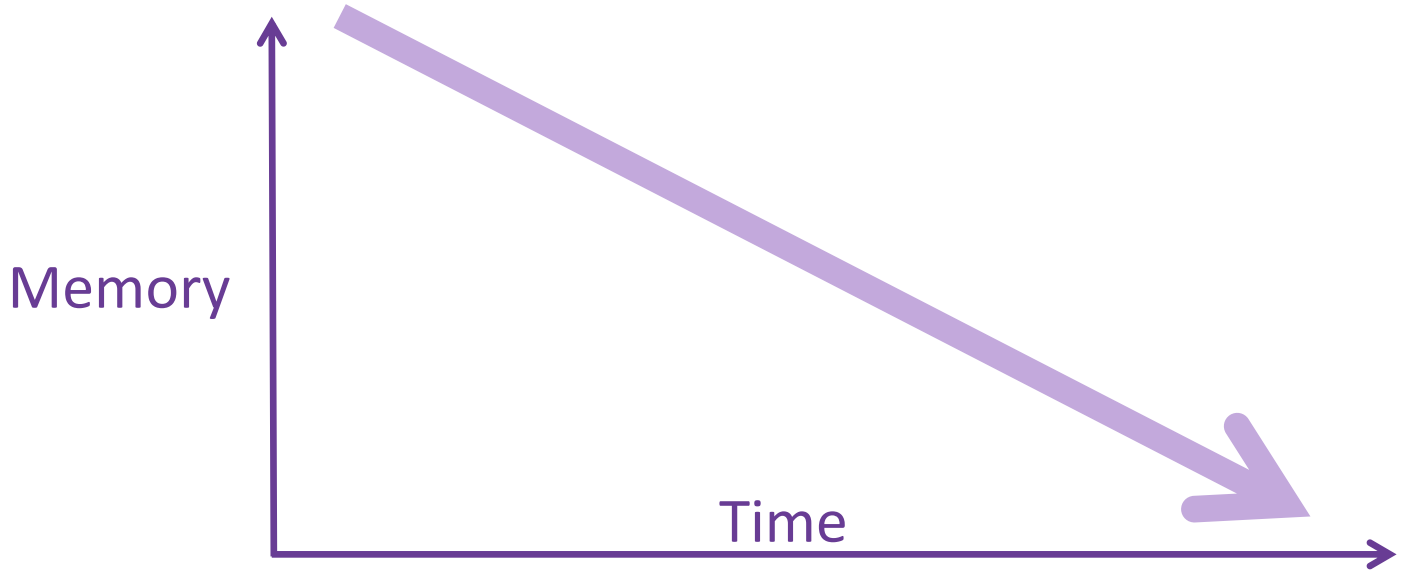

Dementia progression

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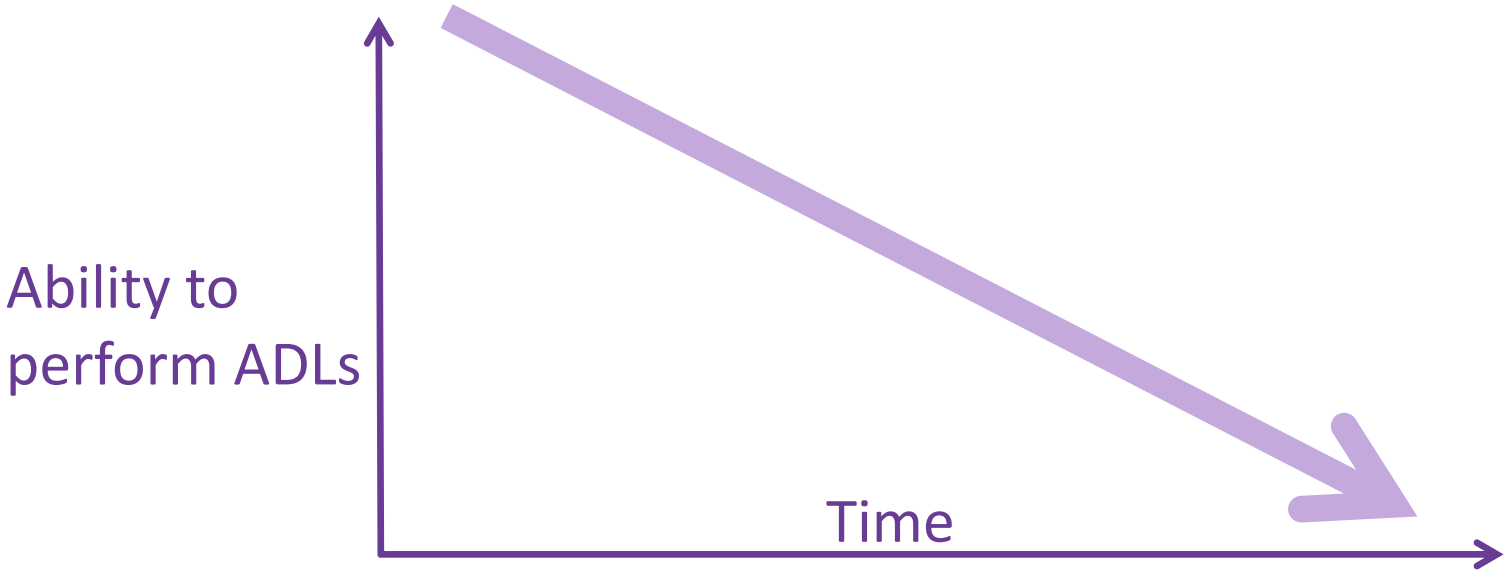

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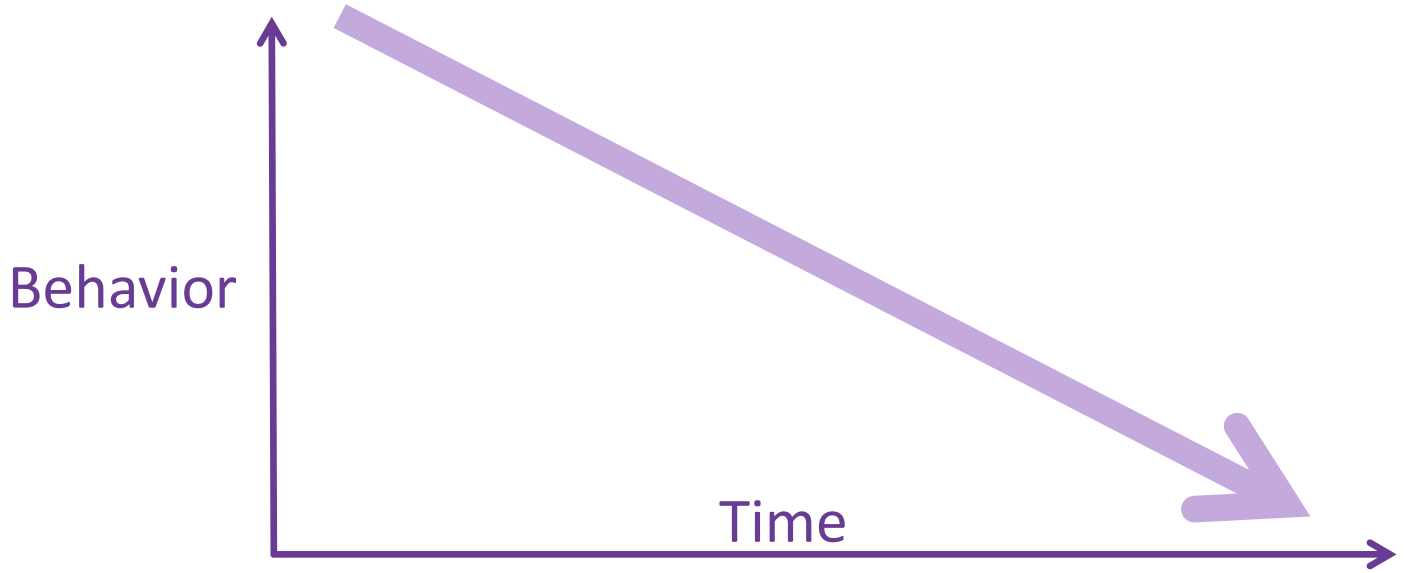

Dementia progression

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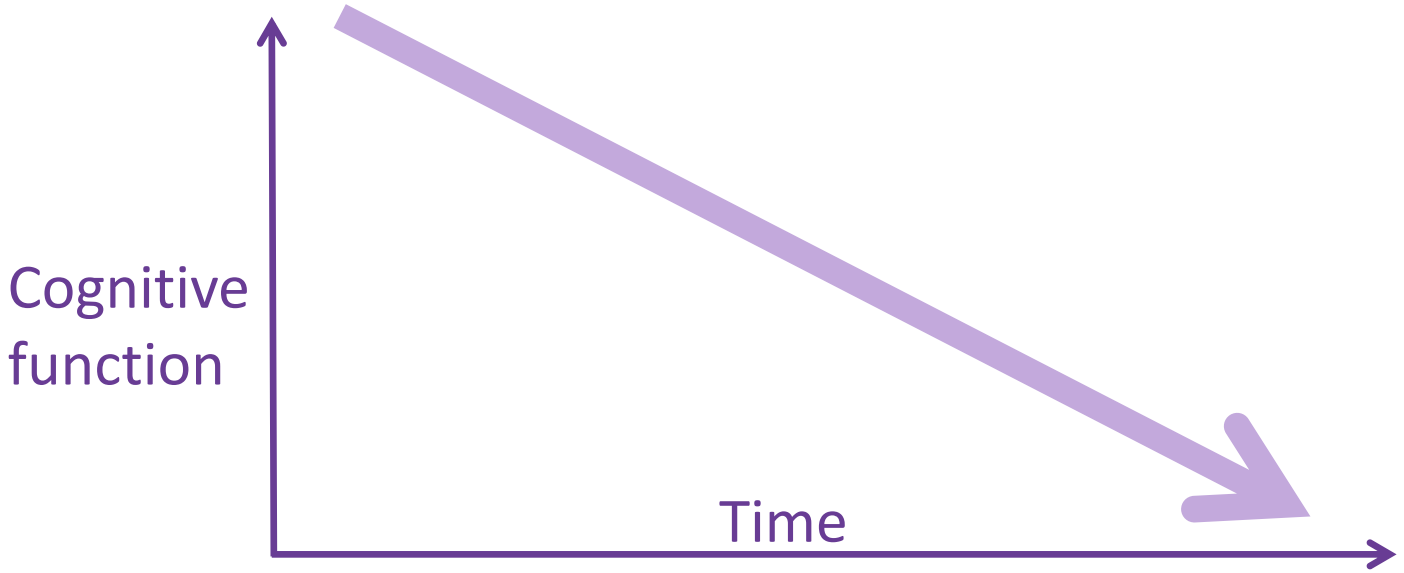

Treatment of dementia

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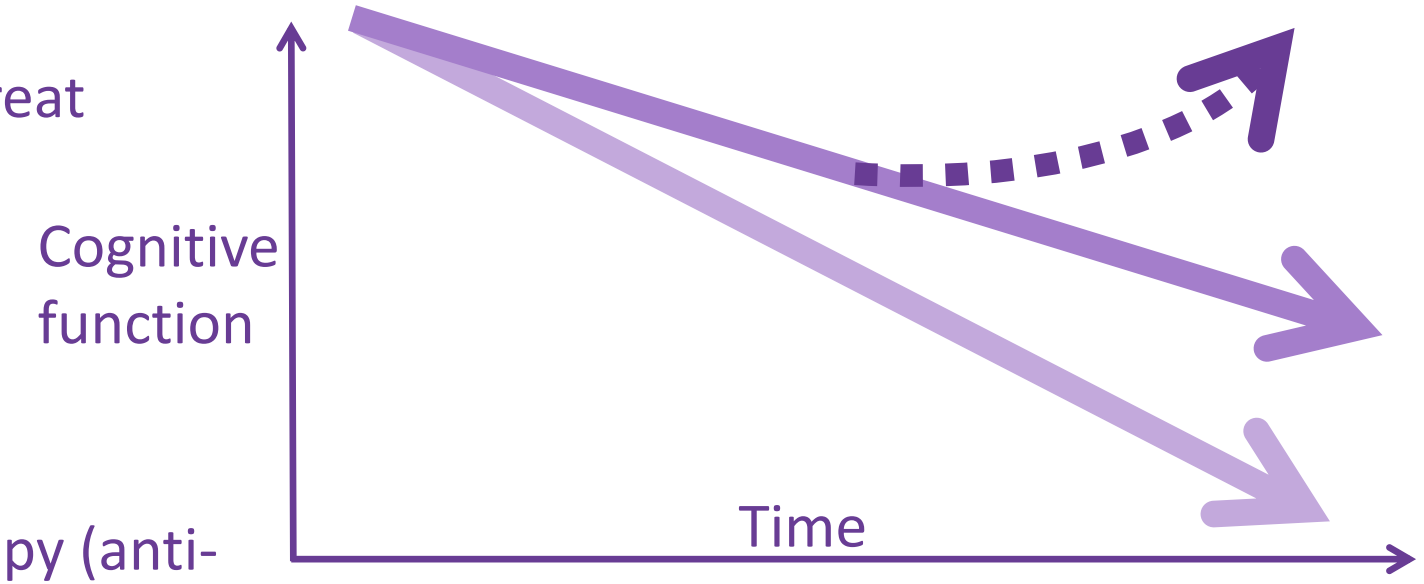
- Medications currently treat symptoms



- Disease modifying therapy (anti-amyloid antibody and medications under investigation) are trying to stop progression of disease

Treatment of dementia

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- Alzheimer’s disease
- Vascular dementia
- Lewy body dementia
- Frontotemporal dementia
- Others

Alzheimer's disease

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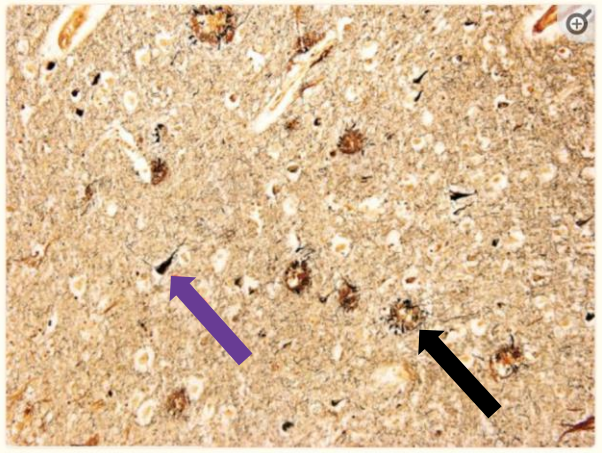
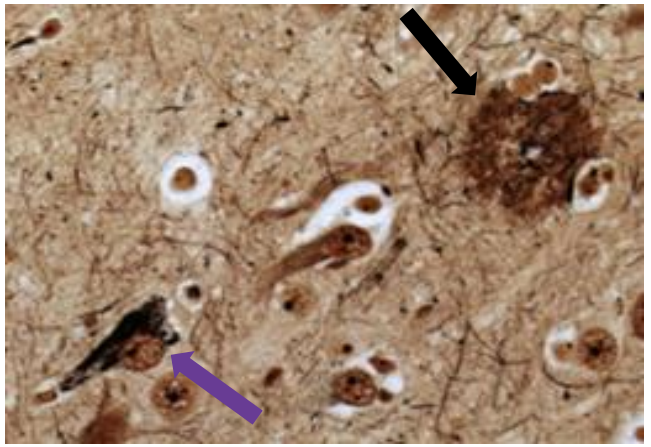
- Most common cause of dementia in the US and in the world
- Estimated prevalence of 6.5 million people over age 65 living with AD in the United States
  - 1/9 people over 65
  - 73% of these people are over age 75

- Due to accumulation of **amyloid-beta plaques** & **neurofibrillary tangles** of p-tau
- This causes cell loss and atrophy



Perl D. *Mt Sinai J Med* 2010; 77:32



Keene CD et al. *UptoDate* 2023

Alzheimer's disease symptoms

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- **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

Current FDA-approved medications For Alzheimer's disease

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

Donepezil	Rivastigmine	Galantamine
1996	2000	2001
10 mg daily	12 mg total daily, 9.5 mg patch	16 mg daily total dose

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

20 mg daily

Treatment of Alzheimer's disease

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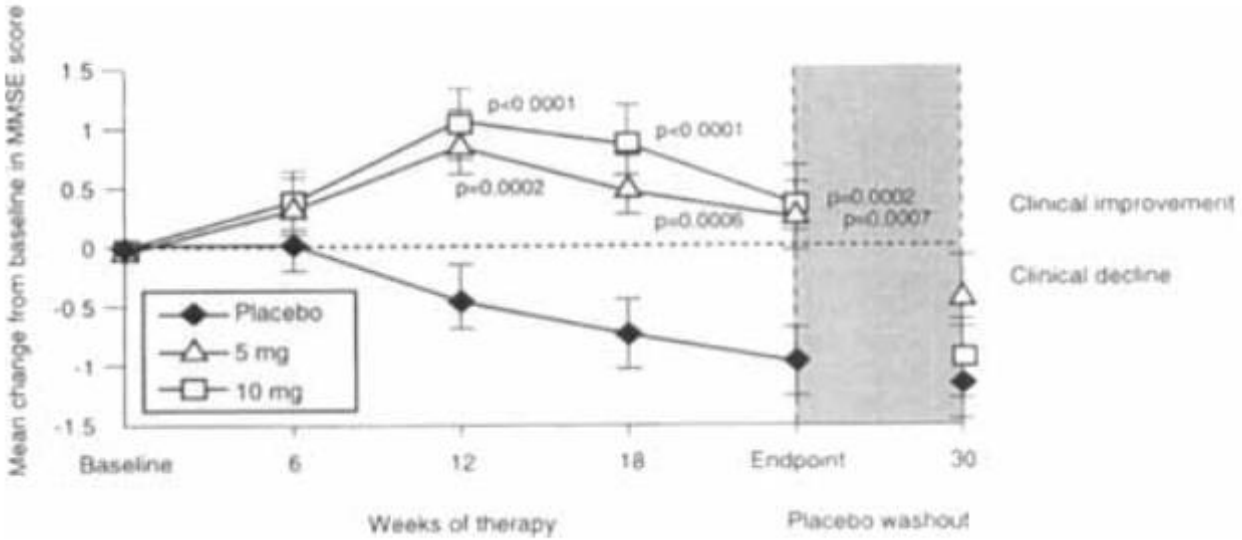
Cholinesterase inhibitors improve cognitive function, slow deterioration, and improve daily function



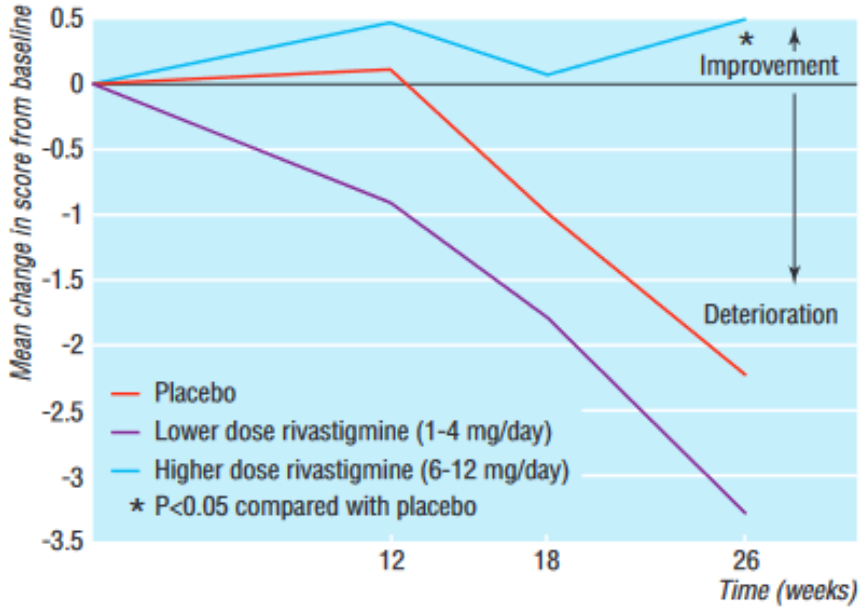


Fig 3 Mean change in baseline scores on the progressive deterioration scale, analysis of last observation carried forward. P<0.05 compared with placebo (two tailed pairwise Student's *t* tests using pooled error term from analysis of covariance and analysis of variance

Rogers et al. *Neurology* 1998 50:136

Rösler et al. *BMJ* 1999 318:633

Treatment of Alzheimer's disease

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

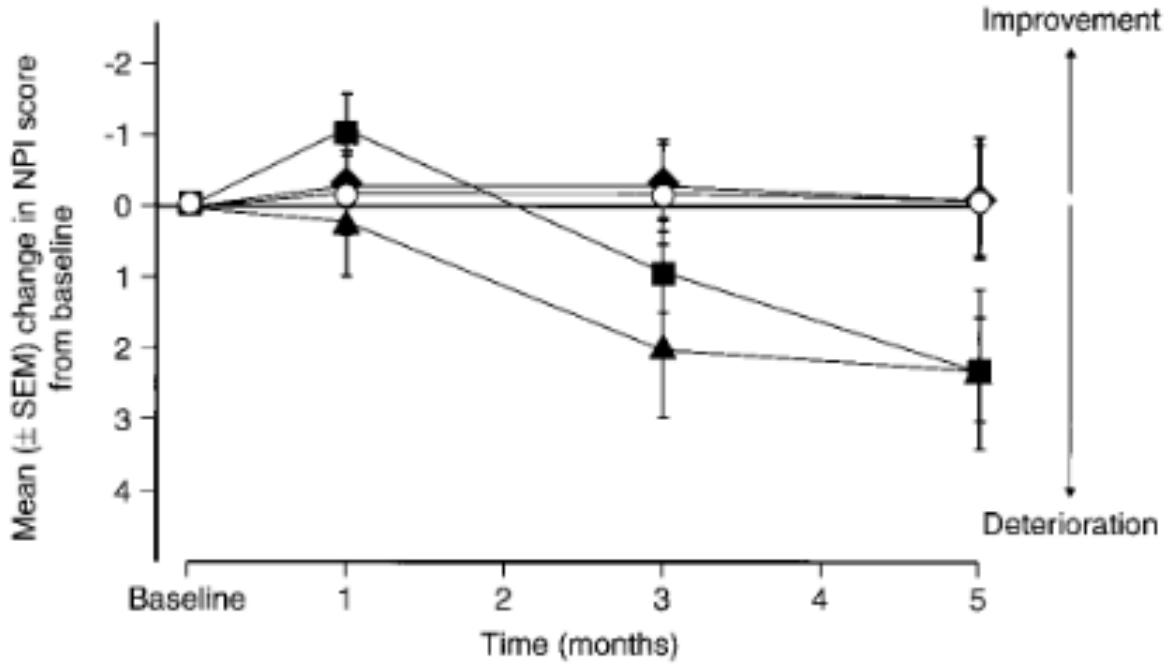

Figure 4. Mean change from baseline in total Neuropsychiatric Inventory (NPI) scores over time (observed cases analysis). ■ = placebo; ▲ = galantamine 8 mg/day; ◆ = galantamine 16 mg/day; ○ = galantamine 24 mg/day.

Tariot et al. *Neurology* 2000 54:2269

Treatment of Alzheimer's disease

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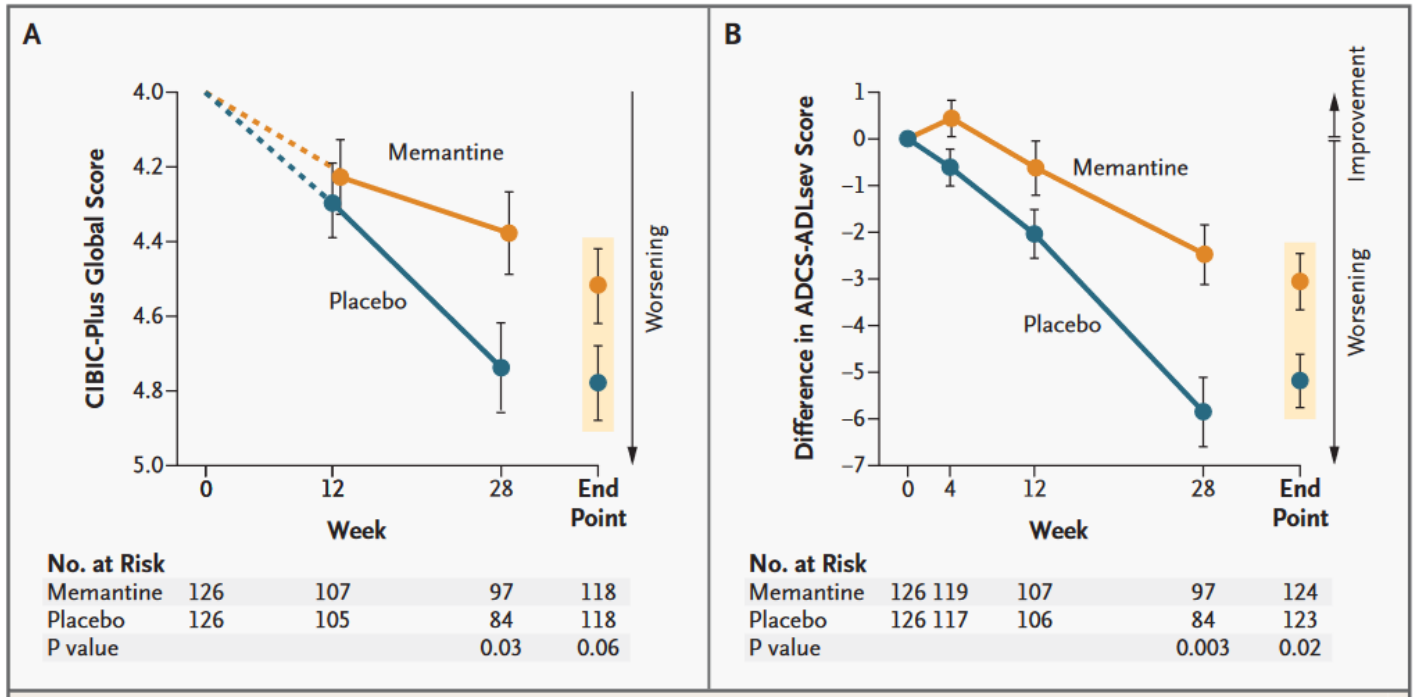
Memantine

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



Reisberg et al. *NEJM* 2003 348:1333

Side effects

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Cholinesterase inhibitors

- Nausea, vomiting
- Diarrhea
- Decreased appetite, weight loss
- Insomnia, vivid dreams
- Urinary frequency

- 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

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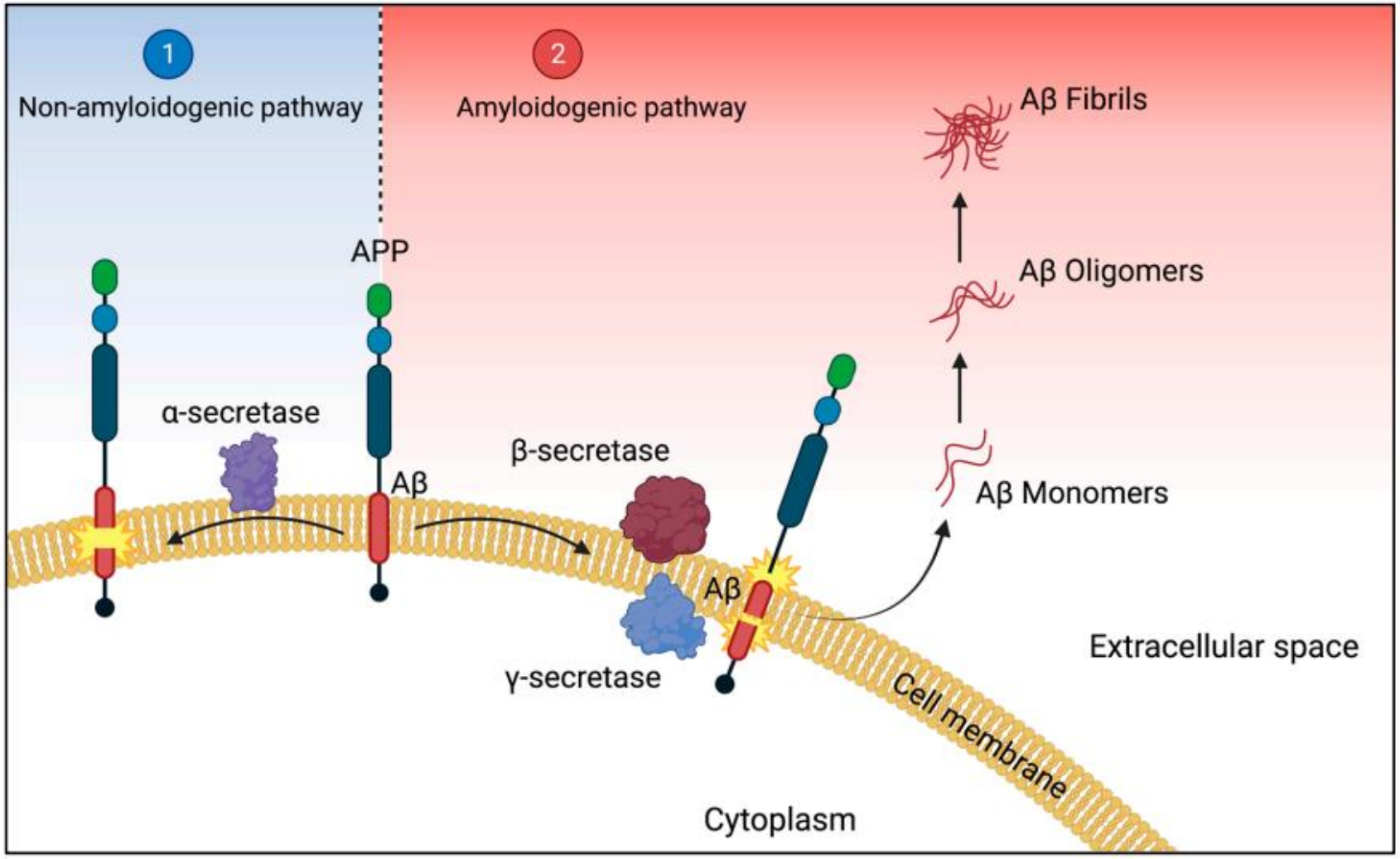

Vogt et al. *Int J Mol Sci* 2023 24:3895

Anti-amyloid therapies

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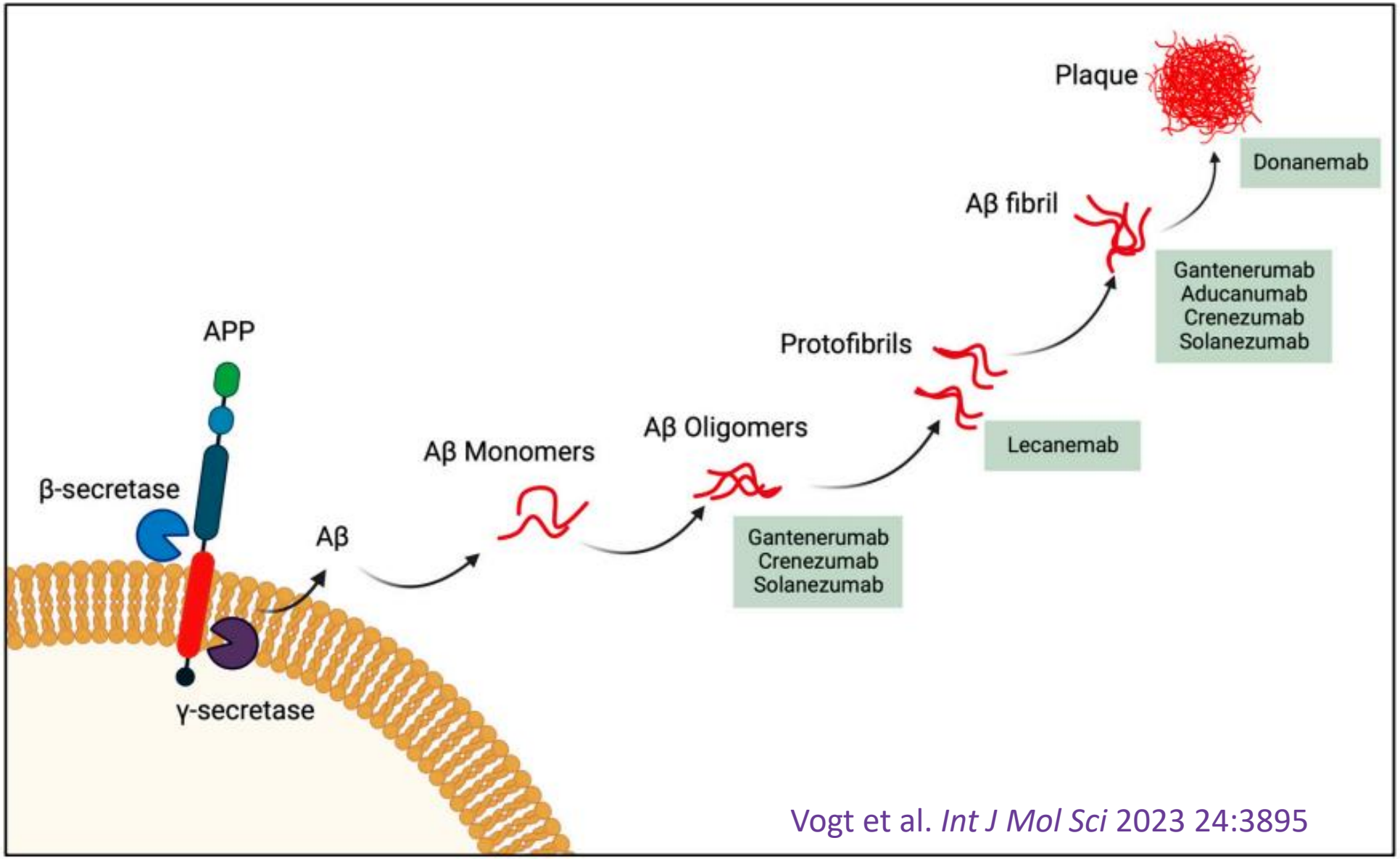

Vogt et al. *Int J Mol Sci* 2023 24:3895

Anti-amyloid antibody therapy

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(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
- Medicare covers lecanemab about 80%, other insurance companies coverage varies
- 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 but still is not accepted.
- Patient must have relatively mild Alzheimer's or only significant memory impairment. MMSE ≥ 22 for lecanemab
- 21.5% on lecanemab (and 20-43% of patients on aducanumab) may experience some degree of brain swelling or microhemorrhages
- Unknown at this time how long the drug should be administered

Vascular dementia

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- Cognitive impairment due to vascular brain injury
  - Ischemic stroke, hemorrhage, microvascular disease
- Second most common dementia type – 15-20% of diagnosed patients
- Two main types:
  - Slowly progressive over time due to microvascular disease – “Binswanger’s disease”
  - Stepwise worsening of cognition due to new strokes over time – multi-infarct dementia
  - (Post-stroke)

- Risk factors – cardiovascular
  - Hypertension
  - Hyperlipidemia
  - T2 diabetes
  - Smoking
  - Atrial fibrillation
  - Coronary artery disease

Vascular dementia

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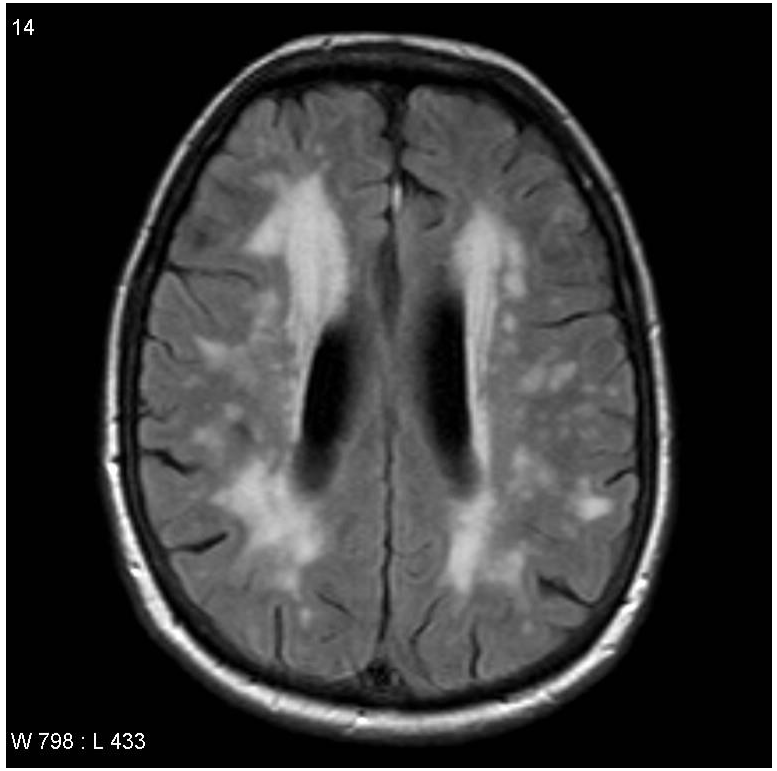
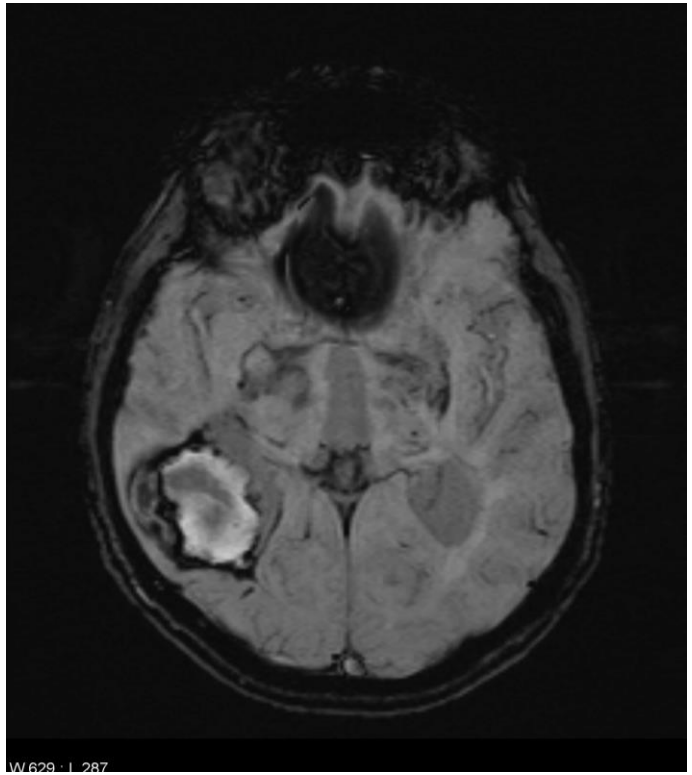
Microvascular disease



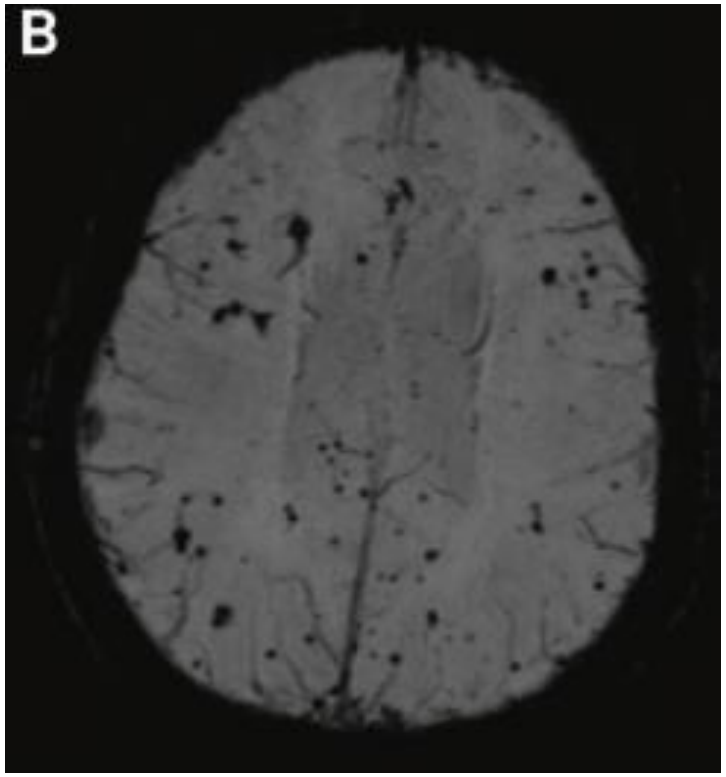
Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 10674

Intracerebral hemorrhage



Case courtesy of Charlie Chia-Tsong Hsu, Radiopaedia.org, rID: 19872

Microhemorrhages



Suppiah et al. *Diagnostics (Basel)* 2019; 9:65

Vascular dementia

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- Cardiovascular risk factor reduction
  - Blood pressure control
    - Goal of systolic BP 120-140 mm Hg range
    - Suggestion that ACE inhibitors may protect against vascular dementia
  - Lipids – complicated
    - Midlife serum cholesterol is a risk factor, later in life this is not as clear
    - Statins – overall recommended – benefits outweigh controversial risks
  - Blood sugar – goal Hgb A1c of 7.0-7.9%
    - Intensive diabetes control associated with higher rates of dementia
  - Antithrombotic medications – indicated for secondary prevention
    - Anticoagulation for patients with Afib or valvular disease
    - CAA patients should continue to use antithrombotics for secondary prevention but not primary, require discussion with stroke and cardiology specialists for anticoagulation

Vascular dementia

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- No pathological deficit in cholinergic regions
- Donepezil and galantamine have consistently shown improvement in cognitive testing
- 2022 study: donepezil 5 or 10 mg, galantamine 24 mg, memantine 20 mg, and rivastigmine 12 mg daily all exerted beneficial effects
  - Donepezil also improved executive function and global status
- Summary: vascular risk factor reduction critical, cholinesterase inhibitors are probably helpful too

Dementia with Lewy bodies and Parkinson's disease dementia

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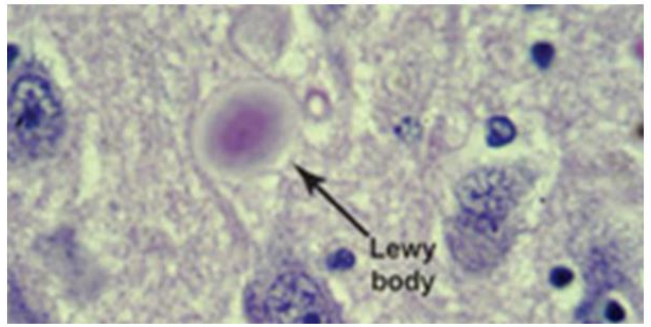
- Due to accumulation of α-synuclein – Lewy bodies = Lewy body dementia (LBD)
- Exist on a spectrum relating to timing of symptoms



https://www.alz.org

Parkinson's disease

Dementia with Lewy bodies

Motor symptoms only

Dementia only

Lewy Body Dementia and PD Dementia

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- Cognitive deficits including visuospatial and executive dysfunction, sometimes memory loss
  - DLB patients also have visual hallucinations and fluctuations
- Significant dopamine deficit leads to motor symptoms
- Likely more loss of cholinergic neurons than Alzheimer's disease
  - Trials with cholinesterase inhibitors have not shown as much improvement as expected
  - 2020 meta-analysis did not show statistically significant improvement with any treatment though donepezil had the most promising data and lowest risk

PD Dementia

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- Rivastigmine is the only medication FDA approved for PDD
  - Improved cognition, ADLs, global impression of change
  - Capsules score slight better than patches for more severe dementia
- Donepezil has more mixed data
  - Some studies show memory improvement but not global cog status, others show no improvement
- Galantamine – not much research
  - Open-label study showed improvements in cognitive testing
- Memantine – only a few studies
  - One shows improved attention and memory, but no differences in global impression of change

Lewy Body Dementia

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- Rivastigmine improves cognition, anxiety, and hallucinations
- Galantamine shows similar pattern of findings in small trials, with improvement in global impression of change, NPI (hallucinations and nighttime behavior especially)
- Donepezil – large trial with 5 mg daily dose showed improvement in MMSE, also significant changes in behavioral symptoms and caregiver burden
- Memantine – initial trials with 20 mg daily dose showed better global impression of change for both DLB and PDD, but larger trials only showed this in DLB, not PD dementia. Also showed improvement in behavior vs placebo

Lewy body dementias

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- Summary:
- Cholinesterase inhibitors likely helpful, both for cognition as well as fluctuations and visual hallucinations

- Dopamine replacement with carbidopa-levodopa (Sinemet) helpful for parkinsonism motor symptoms
  - Dopamine agonists, MAOI-Bs, COMT inhibitors not helpful
  - Avoid anticholinergics

Frontotemporal dementia

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- Most common cause of *early onset dementia* – before age 65
- Multiple causative processes, leading to frontal and/or temporal lobe predominant degeneration
  - "tauopathies" – p-tau but different isoform than that in AD
  - TDP-43, ubiquitin
- Three main subtypes
  - Semantic primary progressive aphasia (svFTD)
  - Nonfluent agrammatic primary progressive aphasia (nfvFTD)
  - Behavioral variant frontotemporal dementia (bvFTD)

Behavioral variant FTD

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- Progressive deterioration of behavior
  - Disinhibition
  - Apathy
  - Loss of empathy/sympathy
  - Oral fixations and dietary changes
  - Perseverative or ritualistic behavior
  - Cognitive testing – executive dysfunction, sparing of memory and visuospatial tasks

Behavioral variant FTD

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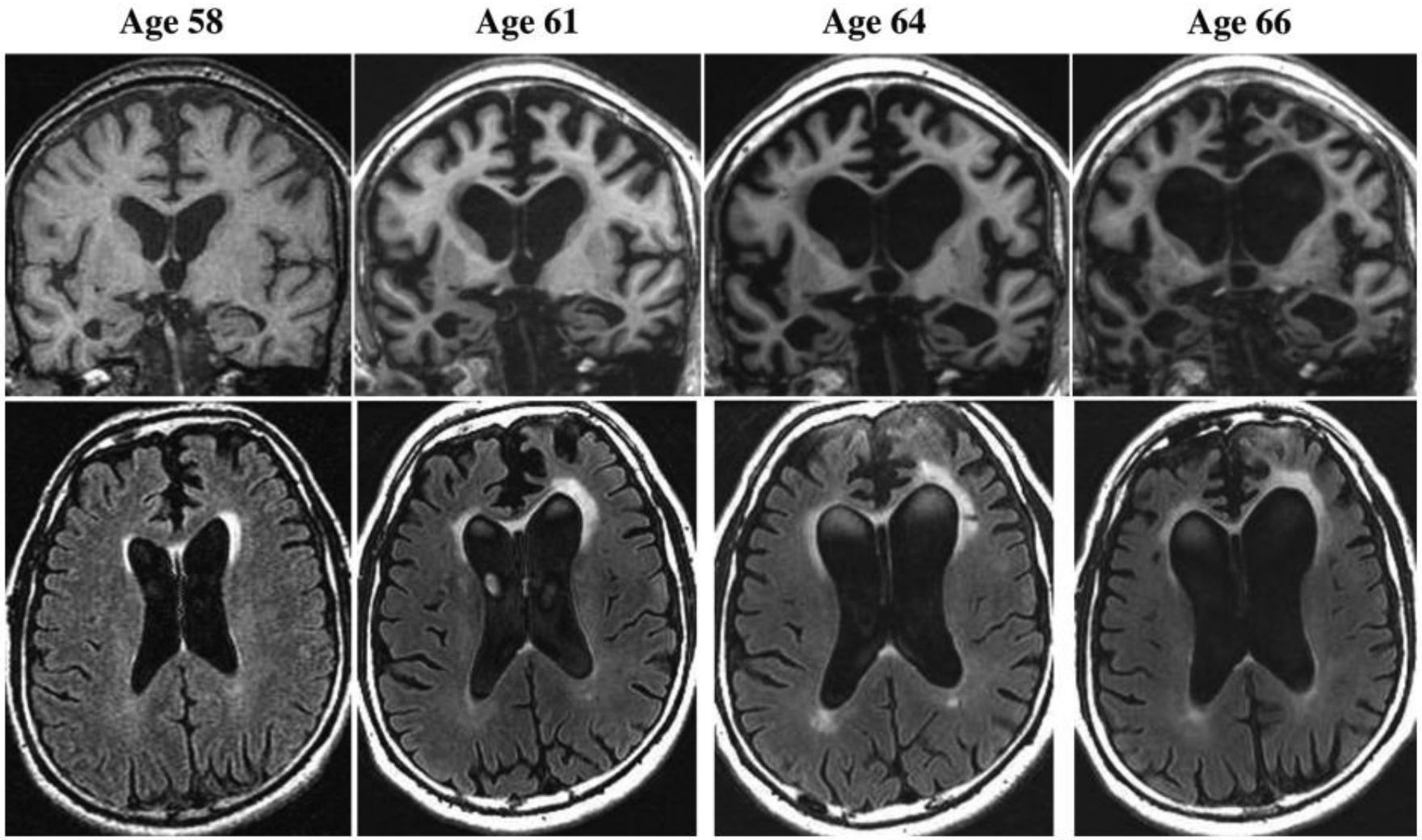

From Boeve B. *Continuum* 2022; 28:702

Frontotemporal Dementia

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- Evidence that cholinergic pathways are preserved
- Estimated that 40% of patients with FTD are treated with cholinesterase inhibitors
- Studies have failed to show a benefit from cholinesterase inhibitors, and they may actually worsen function
- Memantine shows similar findings to AChEIs – no improvement and *may worsen behavior*

- Serotonin networks appear to be disrupted – so there are multiple studies with SSRIs, suggesting some improvements in behavior
- Trazodone shown to improve some aspects of behavior, as well as sleep

Other dementias

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- Atypical parkinsonism – progressive supranuclear palsy (PSP) and corticobasal syndrome
  - Multiple causes, mostly due to tau accumulation
  - No evidence for cholinesterase inhibitors
  - Memantine may worsen behavior (similar to FTD)
  - Focus on treatment of mood disorders, maintain mobility and preventing falls, and monitoring swallowing function

Treating other symptoms

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- Depression and anxiety
- SSRIs
- SNRIs, bupropion, mirtazapine

- Avoid benzos, tricyclics

- SSRIs and trazodone may improve behavior in FTD patients

- Motor symptoms in parkinsonism
  - Dopamine replacement
    - Carbidopa-levodopa
    - Dopamine agonists
    - COMT, MAOB inhibitors
  - Anticholinergics – amantadine, Artane
    - Avoid in cognitively impaired
- Autonomic dysfunction
  - Orthostatic hypotension
  - Constipation
  - Urinary frequency/urgency
    - Avoid anticholinergic agents

Treating other symptoms

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

- Vascular risk factor reduction – also important for Alzheimer's and other dementias and overall brain health

Non-pharmacologic treatments

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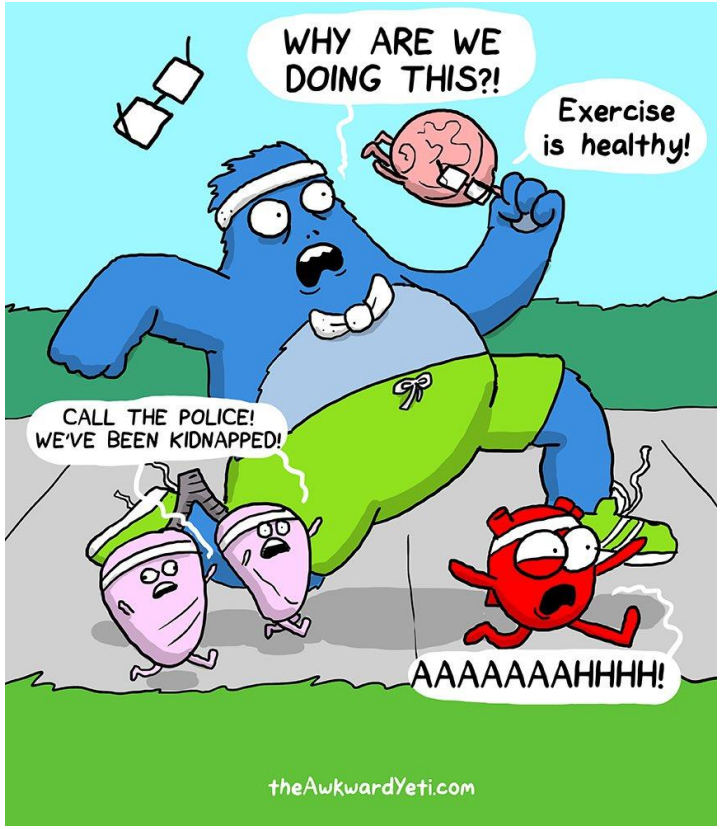
- Prevention of dementia focusing on improving modifiable risks
- Improve cardiovascular health
- Exercise, maintain cognitive and social activity
- Avoid smoking, illicit drugs, limit alcohol
- Improve sleep



Non-pharmacologic treatments

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- 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

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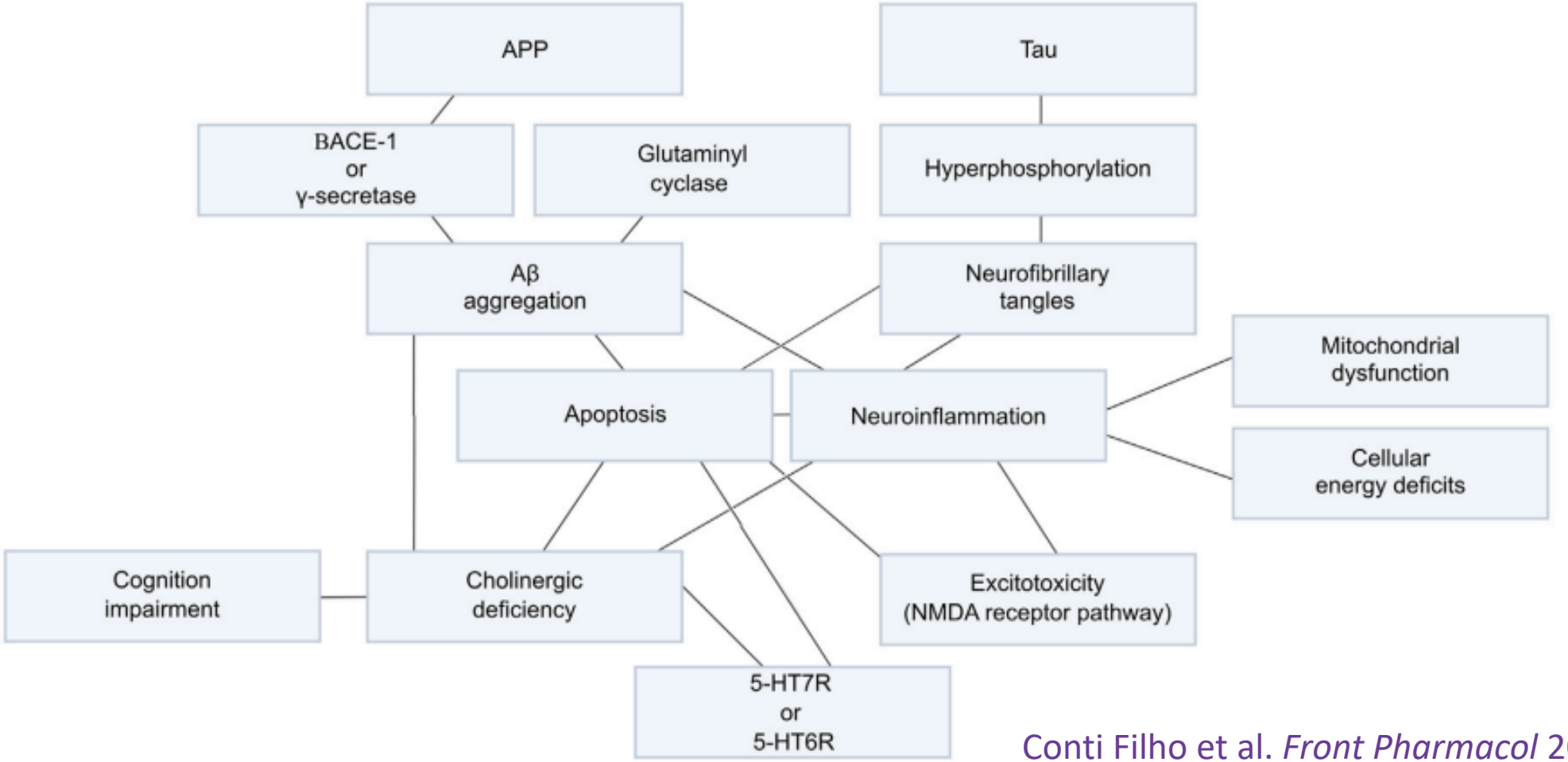
- What causes Alzheimer's disease, LBD, and frontotemporal dementia?
  - Pathogenesis
  - Risks
- How do we diagnosis these diseases?
- How do we treat dementia?
  - Disease modifying therapy
  - Better symptomatic medications, treatment of mood, behavior
- How else can we help our patients?
  - Changing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

Potential targets for disease-modifying therapy



Conti Filho et al. *Front Pharmacol* 2023 14:1101452

Summary

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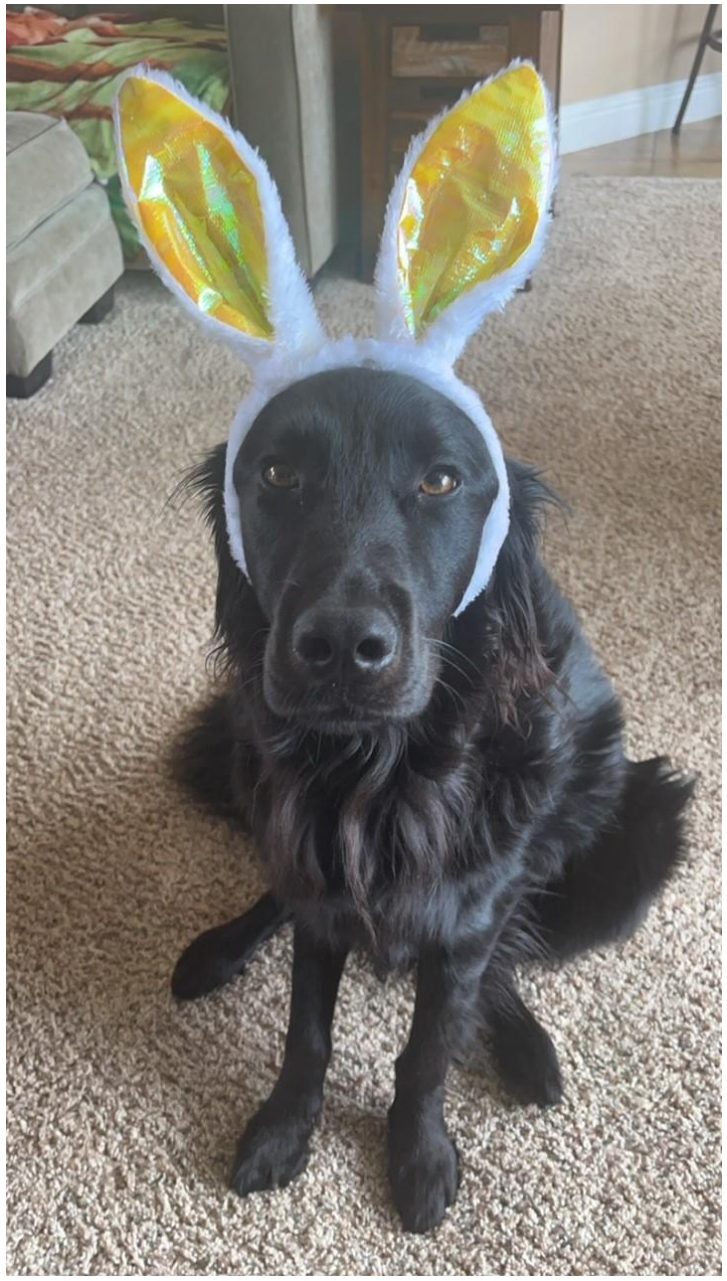
- Cholinesterase inhibitors should be considered in patients with amnestic MCI, Alzheimer's disease, and Lewy body dementia/PDD
  - No clear difference between these in efficacy, donepezil with fewest side effects though patch forms are best tolerated
  - Probably safe for vascular dementia
  - Should not be used for FTD as these may worsen cognition
- Memantine should be considered for moderate-severe AD dementia
  - No strong evidence this is helpful for DLB or PDD but probably safe
  - Should not be used for FTD as this may worsen cognition
- We need disease modifying therapies for all types of dementia
- Non-pharmacologic treatments of dementia are just as, or more, important than medications



Thank you!

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