Don’t You Remember?
A Review of Dementia Treatment

Megan Hull, PharmD, BCACP

Ambulatory Care Clinical Pharmacist

OhioHealth Grant Family Medicine

OHIO PHARMACISTS ASSOCIATION

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Disclosure Statement

Name of Speaker(s) has/have no relevant financial relationship(s) with ineligible companies to disclose.

and

None of the planners for this activity have relevant financial relationships with ineligible companies to disclose.

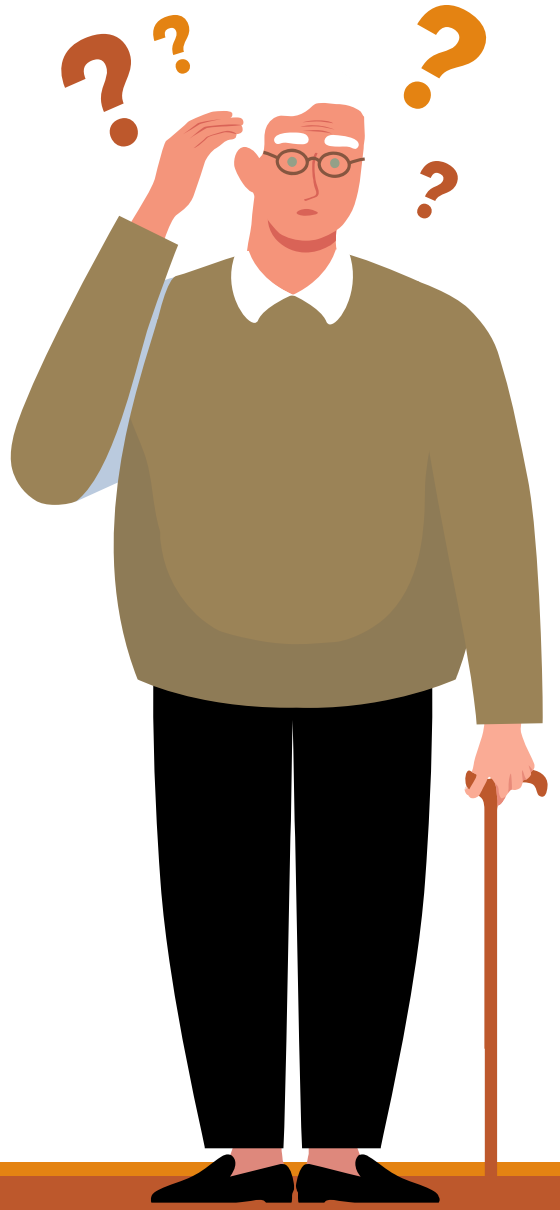
Acknowledgement goes to Dr. Megan Adelman from whom these slides were adapted

At the completion of this activity, the participant will be able to:

- **COMPARE** FDA-approved therapy options for treatment of dementia
- **IDENTIFY** treatment selection based on clinical pearls and patient-specific factors for dementia care
- **DISCUSS** novel therapies recently approved for the use of dementia

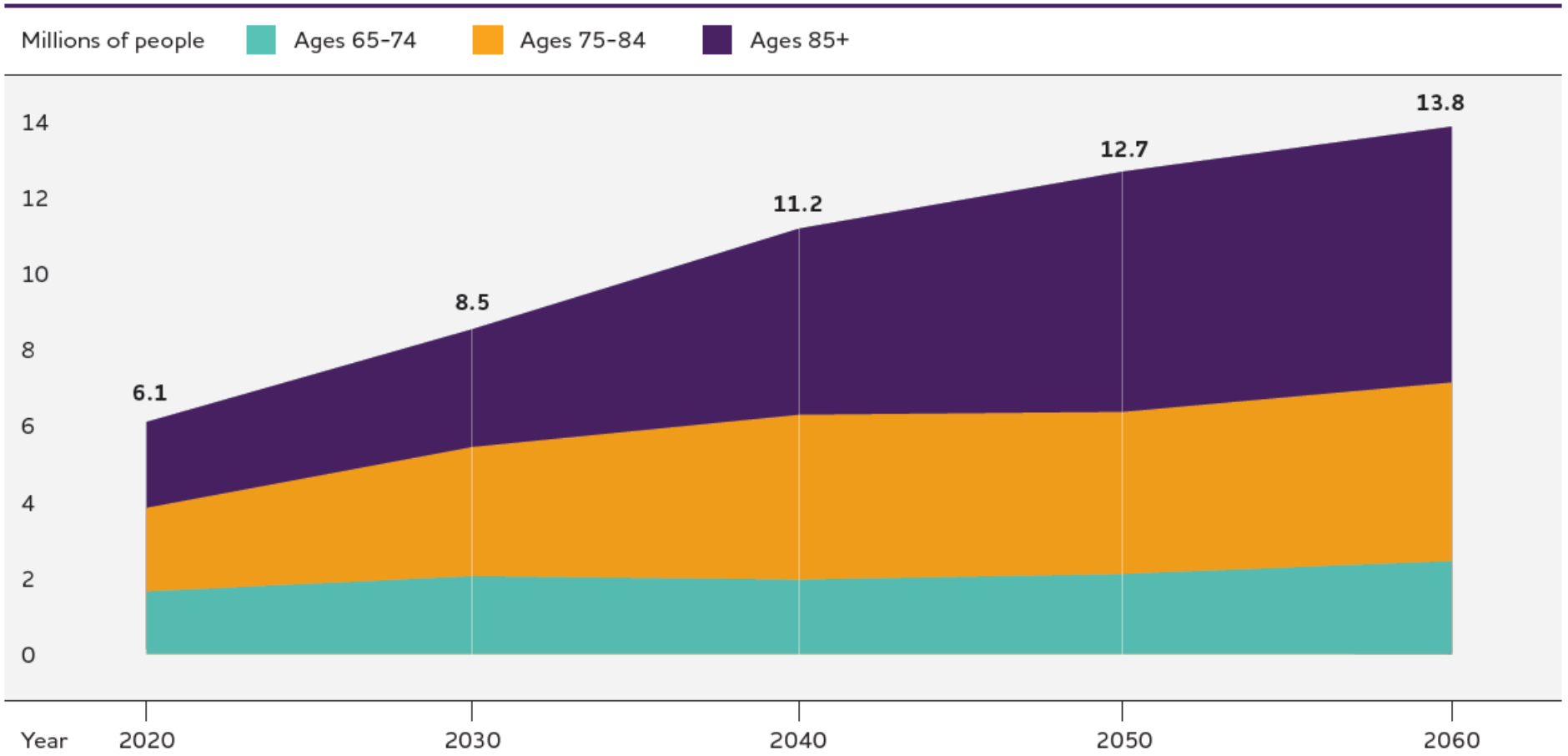
6.9 million

older adults are estimated to have Alzheimer’s dementia today and could double by 2060



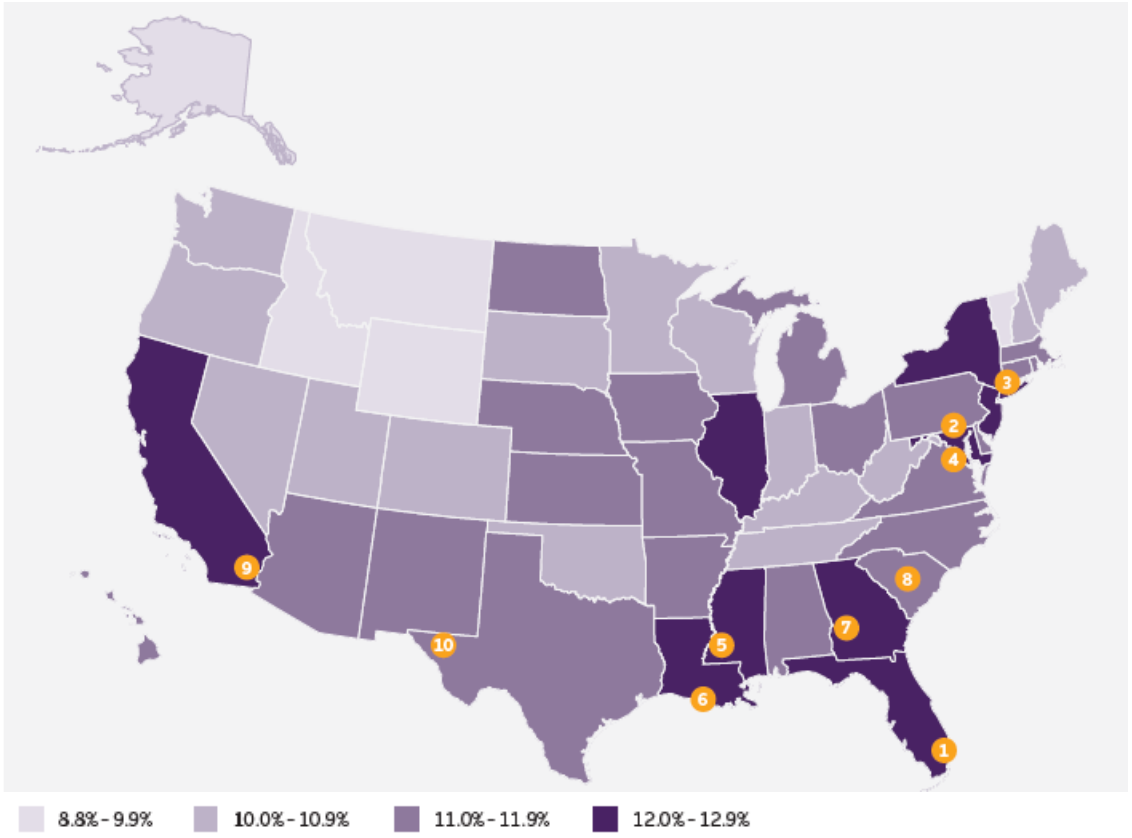
Alzheimer’s Association. 2024 Alzheimer’s Disease Facts and Figures. Alzheimers Dement 2024; 20(5)

Projected Number of People Age 65 and Older (Total and by Age) in the U.S. Population with Alzheimer's Dementia, 2020 to 2060



Alzheimer's Association. 2024 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2024; 20(5)

Prevalence of Alzheimer's Disease in the 50 U.S. States, and the 10 Counties with the Highest Prevalence, 2020*



*Only counties with 10,00 or more residents age 65 and older were included in the ranking

1. **Miami-Dade County, FL** (16.6%)
2. **Baltimore City, MD** (16.6%)
3. **Bronx County, NY** (16.6%)
4. **Prince George's County, MD** (16.1%)
5. **Hinds County, MS** (15.5.%)
6. **Orleans Parish, LA** (15.4)
7. **Dougherty County, GA** (15.3)
8. **Orangeburg County, SC** (15.2)
9. **Imperial County, CA** (15.0%)
10. **El Paso County, TX** (15.0%)

Alzheimer's Association. 2024 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2024; 20(5)

Overview

Deterioration in cognitive abilities that impairs the successful performance of activities of daily living (ADL)

Hallmark features:

- Disorders of memory, comprehension, judgement, orientation, and language
- Impaired social or occupational functioning

Overview

- Alzheimer's Disease (AD)
- Vascular Dementia (VD)
- Lewy Body Dementia (LBD)
- Frontotemporal Dementia (FD)

Alzheimer's Association. 2024 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2024; 20(5)

Pathophysiology

- Physiologic changes occur ≥ 20 years **before** symptoms begin
- Significant neuronal changes associated with Alzheimer's

Build-up of proteins beta-amyloid and tau tangle in and around neurons → Inflammation and atrophy of neurons → **Accumulation of beta-amyloid plaques**

Alzheimer's Association. 2024 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2024; 20(5)

Evaluation and Diagnosis

- Mini-Cog
- Mini-Mental Status Exam (MMSE)
- Montreal Cognitive Assessment (MOCA)

Falk N, et al. Evaluation of Suspected Dementia. Am Fam Physician. 2018; 97(6): 398-405.

Disease Continuum

PRECLINICAL

No symptoms but possible biological changes in the brain

MILD COGNITIVE IMPAIRMENT

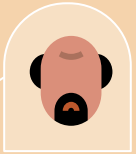
Very mild symptoms that do not interfere with everyday activities

MILD DEMENTIA

Symptoms interfere with some everyday activities

MODERATE DEMENTIA

Symptoms interefere with many everyday activities



SEVERE DEMENTIA

Symptoms interfere with most everyday activities

Alzheimer's Association. 2024 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2024; 20(5)

Dementia Prevention

- Be physically active
- Avoid smoking and excessive alcohol use
- Control weight
- Eat a healthy diet
- Maintain blood pressure, glucose, and cholesterol

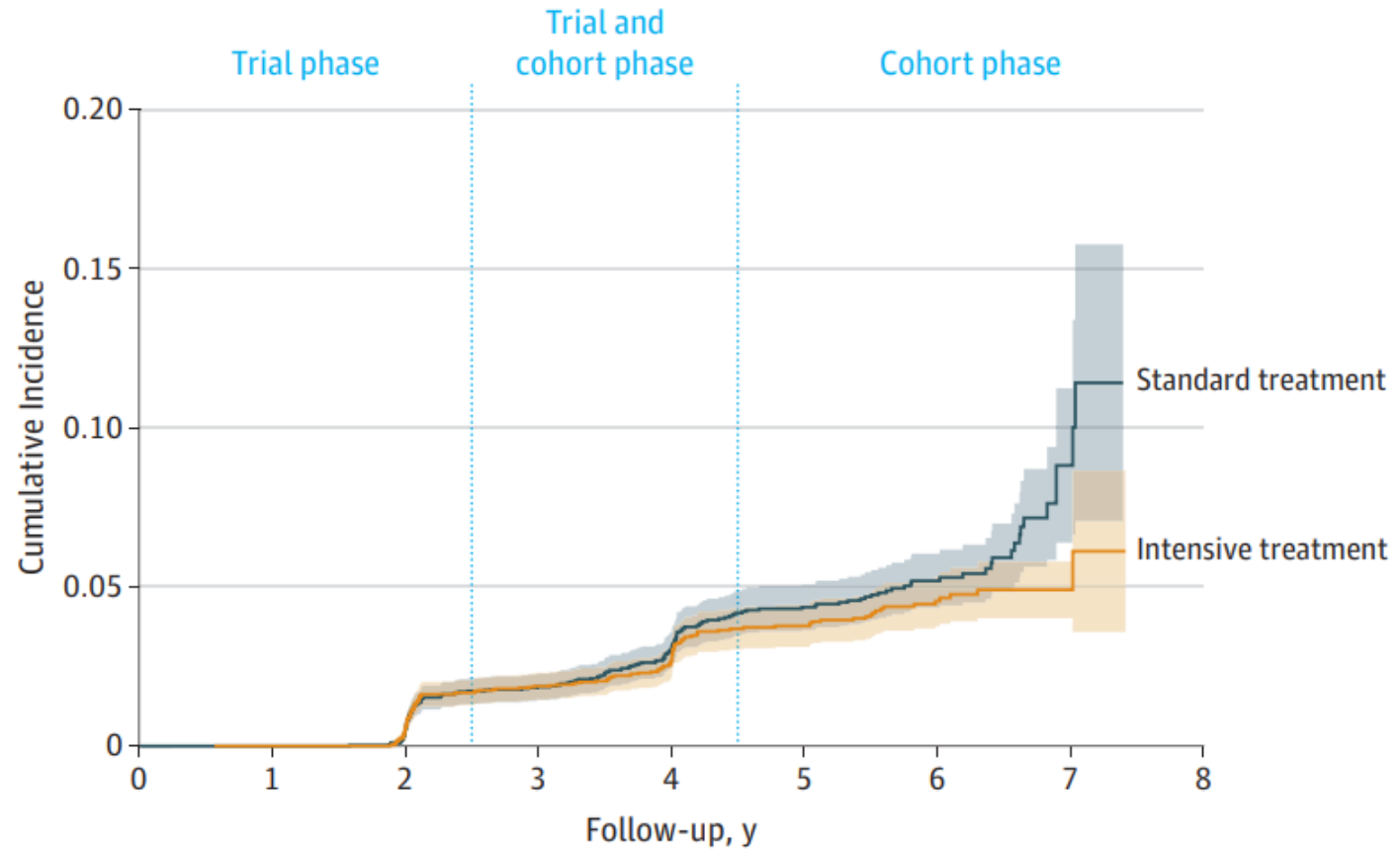
World Health Organization. Risk reduction of cognitive decline and dementia: WHO guidelines. 2019.

SPRINT-MIND Trial

Objective	Evaluate the effect of intensive blood pressure (BP) control (SBP <120 mmHg) compared to standard of care (SBP <140 mmHg) on the rates of probable dementia and mild cognitive impairment (MCI)
Outcomes	Primary: Occurrence of probable dementia Secondary: Occurrence of mild cognitive impairment (MCI) Occurrence of composite MCI and probable dementia Time to first occurrence of adjudication of MCI
Diagnosis	Scores and findings were assessed by a panel to determine cognitive status at year 2 and year 4 visit
Patient Population	Inclusion: >50 years of age; SBP >130 to 180 mmHg; One or more of the following risk factors: cardiovascular disease, kidney disease (eGFR 20-59 ml/min), Framingham risk score >15%, or age >75 years Exclusion: many!

Williamson JD, et al. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia. JAMA. 2019;321(6): 553-561.

SPRINT-MIND Trial



No. at risk

Standard treatment	4285	4282	4168	3886	2829	2107	989	87	0
Intensive treatment	4278	4277	4171	3917	2893	2189	1027	93	0

HR: 0.83
95% CI: 0.67-1.04
P-Value: 0.10

Williamson JD, et al. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia. JAMA. 2019;321(6): 553-561.

SPRINT-MIND Trial

Mild Cognitive Impairment (MCI) (# cases)

- Intensive: 287
- Standard: 353
- P-value: 0.007

Composite – MCI and Probable Dementia Impairment (# cases)

- Intensive: 402
- Standard: 469
- P-value: 0.01

Williamson JD, et al. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia. JAMA. 2019;321(6): 553-561.

TREATMENT STRATEGY

1. Assess for other causes contributing to symptoms – including medications
2. Utilize nonpharmacological treatment
3. Pharmacotherapy

Drugs with Strong Anticholinergic Properties

Antidepressants
Amitriptyline
Amoxapine
Clomipramine
Desipramine
Doxepin (>6 mg/day)
Imipramine
Nortriptyline
Paroxetine

Antimuscarinics
Darifenacin
Fesoterodine
Oxybutynin
Solifenacin
Tolterodine
Trospium

Antiemetics
Prochlorperazine
Promethazine

Antiparkinsonian agents
Benztropine
Trihexyphenidyl

Antipsychotics
Chlorpromazine
Clozapine
Olanzapine
Perphenazine

Skeletal muscle relaxants
Cyclobenzaprine
Orphenadrine

Antihistamines (first-generation)
Brompheniramine
Chlorpheniramine
Cyproheptadine
Dimenhydrinate
Diphenhydramine
Doxylamine
Hydroxyzine
Meclizine
Promethazine
Triprolidine

Antispasmodics
Atripine
Clidinium-chlordiazepoxide
Dicyclimine
Homatropine
Hyoscyamine
Scopolamine

Adapted from Table 7 in: 2023 American Geriatric Society Beers Criteria for Potentially Inappropriate Medications Use in Older Adults. JAGS. 2023:2052-81.

Clinical Considerations: Selection of Less Anticholinergic Therapies

	Highly Anticholinergic	Less Anticholinergic
Antidepressants	Amitriptyline Doxepin (>6 mg) Paroxetine	Citalopram Duloxetine Nortriptyline Sertraline
Antimuscarinics	Oxybutynin	Solifenacin Trospium
Antipsychotics	Clozapine Chlorpromazine Olanzapine	Aripiprazole Ziprasidone
Skeletal Muscle Relaxants	Cyclobenzaprine Orphenadrine	Baclofen
Gastrointestinal and Bowel Agents	Atropine Dicyclomine	Loperamide Bisacodyl

List is not exclusive

2023 American Geriatric Society Beers Criteria for Potentially Inappropriate Medications Use in Older Adults. JAGS. 2023:2052-81.

Proton Pump Inhibitors (PPIs) and Dementia

Article	Patient Population and Study Type	Intervention	Results
Torres-Bondia et al. Nature Reports. 2020;10:21046.	• Community dwelling patients >45 years who filled at least 1 prescription for PPI between 2002 to 2015 • Retrospective cohort based on prescriptions dispensed by pharmacies in Spain	PPI users (n=36,360) vs non-users (n=99,362)	**PPI use was not associated with the risk of AD (OR = 1.06, CI 0.93–1.21; p = 0.408).** A weakly but significantly increased risk of non-AD dementias was observed among PPI users (OR 1.20, CI 1.05–1.37; p = 0.007)
Cooksey et al. PLoS ONE. 2020;15(9):e0237676.	• Patients ≥55 years who were prescribed a PPI between 1999 to 2015 • Retrospective cohort based on history of prescription based on medical codes	PPI users (n=183,968) vs non-users (n=131,110)	**PPI use was associated with decreased dementia risk (HR: 0.67, CI 0.65 to 0.67, p<0.01)**
Zhang et al. BMC Medicine. 2022;20:271.	• Patients aged 40-70 years who were prescribed a PPI between 2006 and 2010 then followed until 2018 • Prospective cohort study	PPI users (n=53,735) vs non-users (n=447,267)	The incident rate of all-cause dementia among proton pump inhibitor users was 1.06 events per 1000 person-years, compared with 0.51 events per 1000 person- years among non-users. **Adjusted HR for PPI users was 1.20 (CI 1.07–1.35) for incident all-cause dementia, 1.23 (CI 1.02–1.49) for AD, and 1.32 (CI 1.05–1.67) for VD**

Statins and Dementia

Article	Patient Population and Study Type	Results
Zhang et al. Medicine. 2018;97(30):e11304.	Meta-analysis of 31 studies N=3,332,706	**Statins use was associated with decreased dementia risk (RR = 0.85, CI 0.80–0.89).** Subgroup analysis showed statins use was associated with decreased AD (RR = 0.81, CI 0.73–0.89) and non-AD dementia (RR = 0.81, CI 0.73–0.89). In addition, increased duration past 1 year (RR = 0.80, CI 0.73-0.87) and increased doses (RR = 0.89, CI 0.83-0.96) demonstrated a reduction in dementia risk.
Olmastroni et al. Eur J of Preventative Cardiology. 2022;29:804-14.	Meta-analysis of 46 studies N=5,738,737	In the pooled analyses, **statins were associated with a decreased risk of dementia** (36 studies; OR 0.80, CI 0.75–0.86) and of AD (21 studies; OR 0.68, CI 0.56–0.81). **Similar risks were observed for lipophilic and hydrophilic statins for both dementia and AD**, while high-potency statins showed a 20% reduction of dementia risk compared with a 16% risk reduction associated with low-potency statins.

AD: Alzheimer's Disease
VD: Vascular Dementia

Patient Case

MS is an 85-year-old female is seen in the family medicine office for her annual Medicare Wellness Visit. During the appointment, a MOCA was completed (score today, 18; 2 years ago, 24). The patient's daughter is with her and endorses worsening memory over the last 6-12 months. A diagnosis of AD is made. Other past medical history is significant for hypertension, diabetes with neuropathy, anxiety, and COPD. PE demonstrates normal findings and lab work is unremarkable.

While the patient's diagnosis of AD is accurate, which of the following medications could be contributing to the memory impairments?

A. Aspirin

B. Amitriptyline

C. Rosuvastatin

D. Sertraline

Medication List

metformin 1,000 mg BID
aspirin 81 mg daily
tiotropium 2 puffs daily
albuterol 1 puff Q4-6 hours PRN
amitriptyline 25 mg daily
amlodipine 10 mg daily
losartan 100 mg daily
sertraline 100 mg daily
rosuvastatin 40 mg daily

Patient Case

Amitriptyline was historically prescribed for MS 2 years ago for neuropathy. The patient endorses the therapy has helped and identifies pain levels as 0/10.

Given the patient's new diagnosis and concern with amitriptyline, what therapy alternative could be selected?

A. Duloxetine

B. Gabapentin

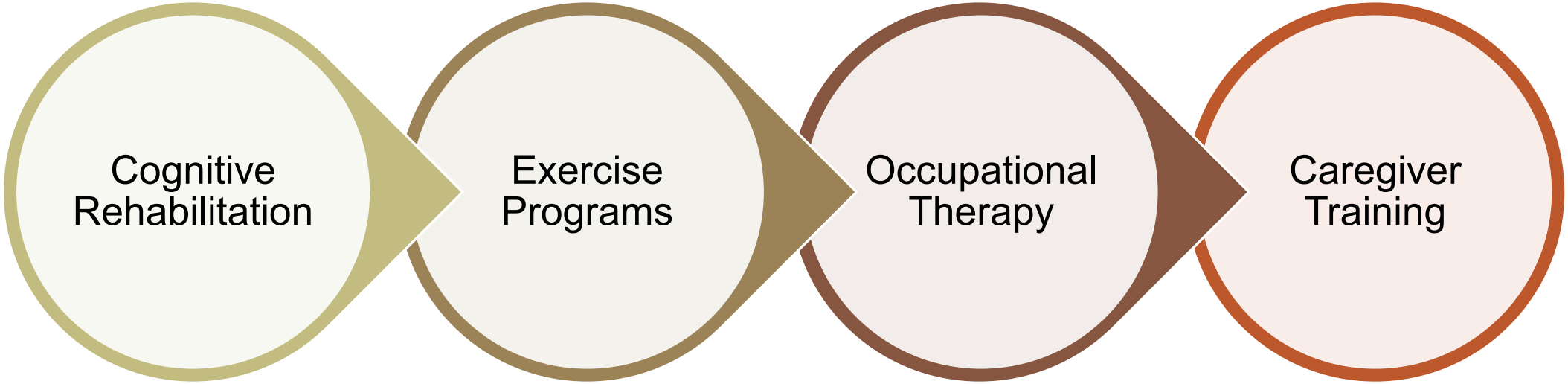
C. Nortriptyline

D. Venlafaxine

Medication List

metformin 1,000 mg BID
aspirin 81 mg daily
tiotropium 2 puffs daily
albuterol 1 puff Q4-6 hours PRN
amitriptyline 25 mg daily
amlodipine 10 mg daily
losartan 100 mg daily
sertraline 100 mg daily
rosuvastatin 40 mg daily

Nonpharmacological Treatment



Piersol CV, Jensen L, Lieberman D, et al. Am J Occup Ther. 2018 Jan/Feb; 72(1).
Clare L, Wilson BA, Carter G, et al. Aging and Mental Health. 2003;7:15-21.
Heyn P, Abreu PC, Ottenbacher KJ. Arch Phys Med Rehabil. 2004;85: 1694-704
Clare L, Linden DE, Woods RT, et al. Amer J of Geriat Psych. 2010;18:928-39.

Pharmacologic Treatment

Medications may decrease rate of progression

American Academy of Family Physicians (AAFP) and American College of Physicians (ACP) 2008 guidelines recommend the following:

- **Base start of therapy on individualized assessment**
- Base the choice of agents on tolerability, adverse effect profile, ease of use, and cost of medication

Pharmacologic Treatment

Acetylcholinesterase inhibitors

- Donepezil (Aricept®)
- Rivastigmine (Exelon®)
- Galantamine (Reminyl®)

N-methyl-D aspartate (NMDA) antagonist

- Memantine (Namenda®)

Anti-Amyloid Monoclonal Antibody

- Lecanemab (Leqembi®)
- Donanemab (Kisunla®)
- *Aducanumab (Aduhelm®)*

UpToDate Lexidrug [Internet]. Wolters Kluwer Health. Accessed October 2025.

FDA Indications

	Mild / Moderate AD	Severe AD	VD	LBD	Parkinson-Related Dementia	FD
Donanemab	✓*	X	X	X	X	X
Donepezil	✓	✓	Off Label	Off Label	Off Label	X
Galantamine	✓	Off Label	Off Label	Off Label	Off Label	X
Lecanemab	✓*	X	X	X	X	X
Memantine	X	✓	Off-Label	Off Label	Off Label	X
Rivastigmine, PO	✓	X	Off Label	Off Label	✓	X
Rivastigmine, patch	✓	✓	Off Label	Off Label	✓	X

*initiated in MCI or mild AD

AD = Alzheimer's Dementia
FD = Frontotemporal Dementia
LBD = Lewy Body Dementia
VD = Vascular Dementia

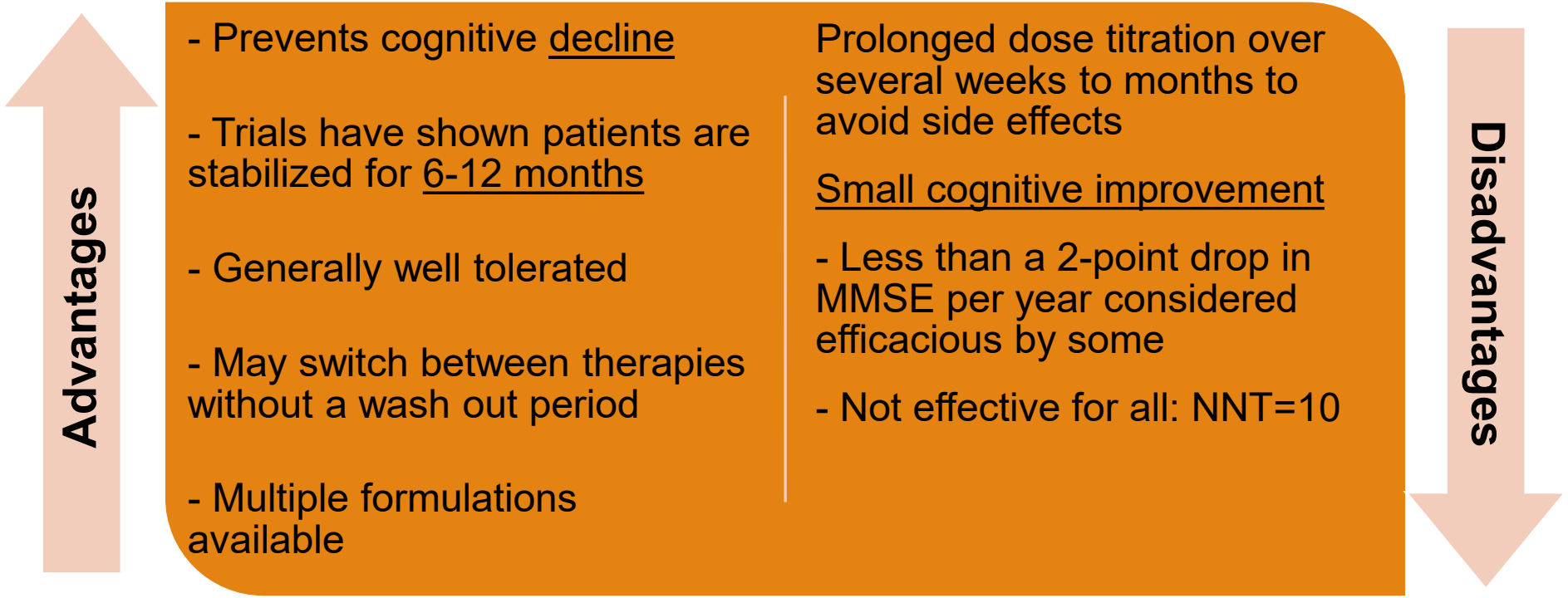
UpToDate Lexidrug [Internet]. Wolters Kluwer Health. Accessed October 2025.

Product Formulations and Dosing

Medication	Formulation and Dosing
Donanemab	Intravenous: : 700 mg every 4 weeks for 3 doses; then 1,400 mg every 4 weeks until amyloid plaques are reduced to minimal levels on amyloid PET imaging
Donepezil	Immediate Release (IR) tablet and Oral Disintegrating Tablet (ODT): 5 mg once daily; may increase to 10 mg once daily after 4 to 6 weeks Patch: 5 mg per 24-hour patch applied once weekly; may increase to 10 mg per 24-hour patch applied once weekly after 4 to 6 weeks
Galantamine	Immediate Release (IR) tablet and Solution: 4 mg twice daily for 4 weeks; if tolerated, increase to 8 mg twice daily for ≥4 weeks; if tolerated, increase to 12 mg twice daily Extended Release (ER) capsule: 8 mg once daily for 4 weeks; if tolerated, increase to 16 mg once daily for ≥4 weeks; if tolerated, increase to 24 mg once daily
Lecanemab	Intravenous: 10 mg/kg once every 2 weeks for 18 months, then may switch to 10mg/kg every 2-4 weeks IV or 360 mg subcutaneously once weekly
Memantine	Immediate Release (IR) tablet and Solution: 5 mg once daily; increase daily dose by 5 mg every week as tolerated to a target maximum dose of 20 mg/day Extended Release (XR) capsule: 7 mg once daily; increase daily dose by 7 mg every week as tolerated to a target maximum dose of 28 mg once daily
Rivastigmine	Capsule: 1.5 mg twice daily; may increase by 3 mg daily (1.5 mg/dose) every 2 weeks based on tolerability to a maximum of 6 mg twice daily Patch: 4.6 mg per 24 hours patch applied once daily; after a minimum of 4 weeks, increase as tolerated to 9.5 mg per 24 hours; continue as long as therapeutically beneficial. After a minimum of 4 weeks, may increase as tolerated to a maximum dose of 13.3 mg per 24 hours

UpToDate Lexidrug [Internet]. Wolters Kluwer Health. Accessed October 2025.

Acetylcholinesterase Inhibitors (ACh-I)



Dementia. NICE Clinical Guidelines. National Institute for Health and Clinical Excellence. 2018.
Jaqua EE, Tran MN, Hanna M. Am Fam Physician. 2024; 110(3): 281-293.
UpToDate Lexidrug [Internet]. Wolters Kluwer Health. Accessed January 2024.

Acetylcholinesterase Inhibitors (ACh-I)

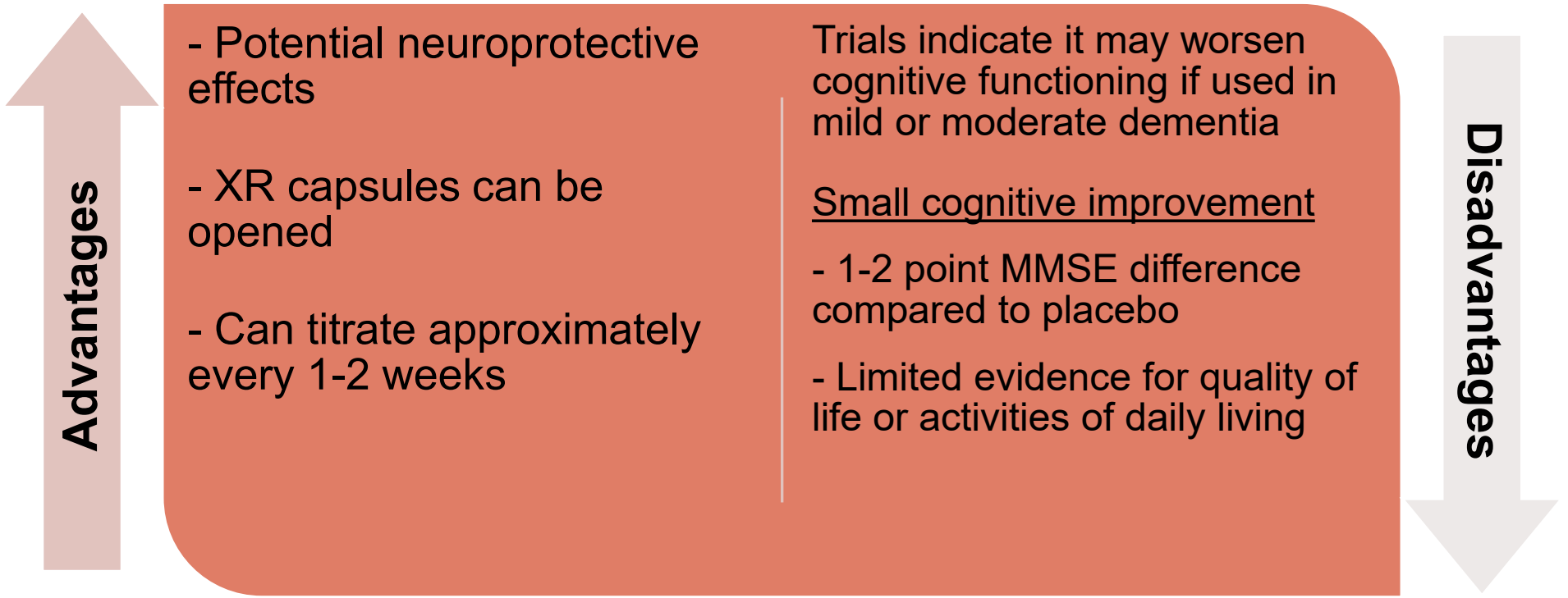
Potential Side Effects:

- GI: nausea, vomiting, diarrhea
- Anorexia, decreased appetite, and weight loss
- Syncopal related effects
- Bradycardia
- Sleep disturbances

Use with Caution: bradycardia, heart block, active peptic ulcer disease

Dementia. NICE Clinical Guidelines. National Institute for Health and Clinical Excellence. 2018.
Jaqua EE, Tran MN, Hanna M. Am Fam Physician. 2024; 110(3): 281-293.
UpToDate Lexidrug [Internet]. Wolters Kluwer Health. Accessed October 2025.

N-Methyl-D Aspartate (NMDA) Antagonist



Dementia. NICE Clinical Guidelines. National Institute for Health and Clinical Excellence. 2018.
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UpToDate Lexidrug [Internet]. Wolters Kluwer Health. Accessed January 2024.

NMDA Antagonist Clinical Pearls

Potential Side Effects:

- Constipation
- Dizziness
- Headaches
- Hallucinations/agitation – may worsen Lewy body dementia

Renal Dosing Considerations: if CrCl < 30 mL/min, use 50% of maximum dose

Dementia. NICE Clinical Guidelines. National Institute for Health and Clinical Excellence. 2018.
Jaqua EE, Tran MN, Hanna M. Am Fam Physician. 2024; 110(3): 281-293.
UpToDate Lexidrug [Internet]. Wolters Kluwer Health. Accessed January 2024.

Monitoring for Efficacy

With use of all pharmacotherapy:

- All clinical trials monitored cognition, function (ADLs), and behaviors
- All clinical trials used therapies for **at least 6 months**
- Monitoring of side effects occurred at each visit and prior to dose titration

Monitoring for Medication Use:
Crucial Conversations

Stress importance of clear expectations for medications – keep in mind goals of therapy vs. prognosis

Address and assess medication adherence

Simplify medication regimen as best as possible

Assess caregiver involvement and assistance

Jaqua EE, Tran MN, Hanna M. Am Fam Physician. 2024; 110(3): 281-293.

Monoclonal Antibodies

	Aducanumab	Lecanemab	Donanemab
Mechanism	<u>Mechanism of action:</u> human IgG1 monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta **which reduces amyloid beta plaques**		
FDA Approval	Accelerated, 2021	Full approval, 2023	Full approval, 2024
Estimated Cost Per Year	N/A	$27,000	$40,000
Supporting Literature	EMERGE, ENGAGE	Clarity AD	TRAILBLAZER-AD

Full approval trial (ENVISION) was discontinued and drug removed from market

Dyck CH et al. NEJM. 2023;388:9-21
Haeberlein SB et al. J Prev Alzheimers Dis. 2022;9(2):197-210.
Jaqua EE, Tran MN, Hanna M. Am Fam Physician. 2024; 110(3): 281-293.

Monoclonal Antibodies Clinical Considerations

- Studied in individuals in **early and mild** stages of Alzheimer disease
- Summary of efficacy results:
  - **Clarity AD:** reduction in brain amyloid burden -59.1 centiloids; Alzheimer's Disease Assessment Scale-Cognitive Subscale 14 (ADAS-cog14) score -1.44
  - **EMERGE and ENGAGE:** data primarily driven by changes in plaque; Clinical Dementia Rating Sum of Boxes (CDR-SB) improved by -0.39 in EMERGE but not in ENGAGE
  - **TRAILBLAZER-AD:** MMSE score difference 0.63 between placebo

Dyck CH et al. NEJM. 2023;388:9-21
Haeberlein SB et al. J Prev Alzheimers Dis. 2022;9(2):197-210.
Jaqua EE, Tran MN, Hanna M. Am Fam Physician. 2024; 110(3): 281-293.

Monoclonal Antibody Medicare Coverage

To receive Medicare coverage, people will need to:

1) be enrolled in Medicare,

2) be diagnosed with mild cognitive impairment or mild Alzheimer's disease dementia, with documented evidence of beta-amyloid plaque on the brain, and

3) have a physician who participates in a qualifying registry with an appropriate clinical team and follow-up care. Clinicians participating in the registry will only need to complete a short, easy-to-use data submission.

Statement: Broader Medicare Coverage of Leqembi Available Following FDA Traditional Approval. CMS (updated: 2023, accessed: 2025). Available from: https://www.cms.gov/newsroom/press-releases/statement-broader-medicare-coverage-leqembi-available-following-fda-traditional-approval

Monoclonal Antibodies ARIA Risks

Selected serious adverse drug events: hemosiderin (accumulation of iron deposits, ARIA-H; 15%), microhemorrhage of the brain (ARIA-H; 19%), brain edema (ARIA-E; <35%); **NNH ranges from 7-9 in trials**

TIMING

Varied but majority of events occur in the first 8 doses of treatment

MECHANISM

Speculated that increased clearance of amyloid from parenchymal plaques into perivascular space may result in excess fluid shifts

MANAGEMENT

Evaluate if symptoms occur and perform MRI testing if indicated; treatment continuation is dependent on severity of ARIA

RISK FACTORS

- ARIA-E may occur more frequently in apolipoprotein E ε4 carriers
- Dose-related

Jaqua EE, Tran MN, Hanna M. Am Fam Physician. 2024; 110(3): 281-293.

Alternative Therapies

Vitamin E

No evidence that vitamin E improves cognition or slows the progression of mild cognitive impairment or dementia.

Other Supplements

Gingko biloba

NSAIDs

Vitamins C, D, and V

Omega-3 fatty acids

Estrogen replacement therapy

Dysken MW, Sano M, Asthana S, et al. JAMA. 2014 Jan 1; 311(1): 33-44.
Jaqua EE, Tran MN, Hanna M. Am Fam Physician. 2024; 110(3): 281-293.
Lakhan R, Sharma M, Batra K, et al. Healthcare (Basel). 2021; 9(11): 1573.
Farina N, Llewellyn D, Isaac MGEKN, et al. Cochrane Database Syst Rev. 2017; (4): CD002854.

Over-The-Counter: Apoaequorin (Prevagen®)

- Apoaequorin was isolated from a species of jellyfish (*Aequorea victoria*) and is a bioluminescent calcium-activated photoprotein
- Launched in 2007 from Quincy Bioscience in Wisconsin
- Mechanism of Action: Calcium binding protein which blocks the rapid influx of calcium through L-type calcium channels and neurons and helps to balance intracellular calcium hemostasis
- Literature: CogState International Shopping List - 10.86% increase in the number of items correctly recalled in the intervention group compared to baseline ($p<0.001$) vs. 3.79% increase in the placebo group ($p=0.298$)
- **Lawsuit settlement: 2020**

Cangeloso L. [Internet]. Forbes. (updated: 2023; accessed: 2025). Available from: https://www.forbes.com/health/healthy-aging/prevagen-review/
Prevagen Brain Supplement. [Internet]. Top Class Actions. (updated: 2020; accessed: 2025). Available from: https://topclassactions.com/lawsuit-settlements/closed-settlements/prevagen-brain-health-supplement-class-action-settlement/

Summary

Providers should review patients' medication regimens for agents with anticholinergic activity to avoid exacerbating dementia symptoms. If able, therapies should be discontinued or changed to less anticholinergic options.

Three drug classes are currently FDA approved for dementia treatment; drug selection should be based on patient and drug characteristics, side effect profile, and cost.

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Megan Hull, PharmD, BCACP
OhioHealth Grant Family Medicine
Megan.Hull@ohiohealth.com

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