

# Herbals, Supplements, and Dementia

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**Laura Hart, PharmD, MS, BCPS, BCGP, FASCP**  
Assistant Professor, Department of Pharmacy  
University of Washington School of Pharmacy

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## Learning Objectives

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- > Summarize efficacy and safety data regarding herbals and supplements for dementia and cognitive health
- > Describe ways to ensure optimal and safe supplement use in older adults with dementia or cognitive impairment
- > Apply the above to a patient case



# Abbreviations Used in Presentation

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- > AD = Alzheimer's disease
- > DHA = docosahexaenoic acid
- > EPA = eicosapentaenoic acid
- > HR = hazard ratio
- > IU = international units
- > MCI = mild cognitive impairment
- > NMDA = N-methyl-D-aspartate
- > RCT = randomized controlled trial



# Outline

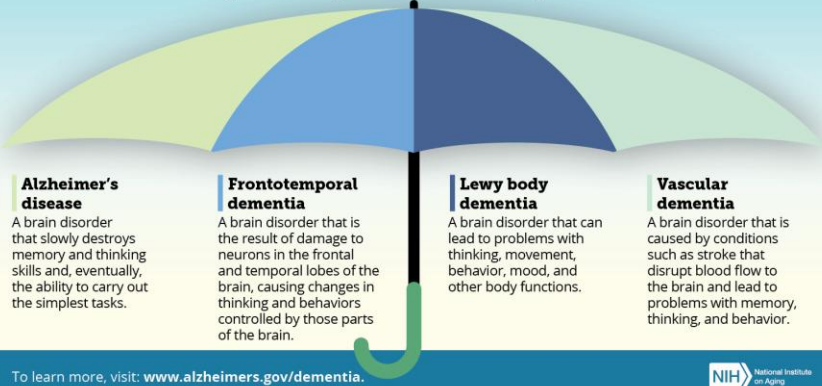
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- > Background
- > Herbal/Supplement Data for Dementia and Cognition
- > Other Considerations for Supplement Use
- > Supplement Use Through the 4 Ms Framework
- > Patient Case



# Dementia

**Dementia Is an Umbrella Term**  
It is used to describe a range of neurological conditions affecting the brain that worsen over time.




**Alzheimer's disease**  
A brain disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks.

**Frontotemporal dementia**  
A brain disorder that is the result of damage to neurons in the frontal and temporal lobes of the brain, causing changes in thinking and behaviors controlled by those parts of the brain.

**Lewy body dementia**  
A brain disorder that can lead to problems with thinking, movement, behavior, mood, and other body functions.

**Vascular dementia**  
A brain disorder that is caused by conditions such as stroke that disrupt blood flow to the brain and lead to problems with memory, thinking, and behavior.

To learn more, visit: [www.alzheimers.gov/dementia](http://www.alzheimers.gov/dementia).



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## Pharmacologic Therapies for Dementia (Cognitive Symptoms)

- > **Cholinesterase Inhibitors**
  - Donepezil (Aricept®)
  - Rivastigmine (Exelon®)
  - Galantamine (Razadyne®)
  - Benzgalantamine (Zunveyl™)
- > **NMDA Receptor Antagonist**
  - Memantine (Namenda®)
- > **Monoclonal Antibodies**
  - Lecanemab (Leqembi®)
  - Donanemab (Kisunla™)

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Donepezil (Aricept®)  
Rivastigmine (Exelon®)  
Galantamine (Razadyne®)  
Etidonate (Zunveyl™)

## Cholinesterase Inhibitors

- > **Approved for:** Mild to moderate AD<sup>1</sup>
- > **Mechanism:** Inhibit acetylcholinesterase, the enzyme that breaks down acetylcholine
- > **Adverse effects:** Nausea/vomiting/diarrhea, anorexia, weight loss, dyspepsia, bradycardia

<sup>1</sup>Donepezil also approved for severe AD; rivastigmine also approved for mild to moderate Parkinson disease dementia



Memantine (Namenda®)

## NMDA Receptor Antagonist

- > **Approved for:** Moderate to severe AD
- > **Mechanism:** Unclear; may reduce glutamatergic overstimulation of the NMDA receptor
- > **Adverse effects:** Confusion, headache, constipation, dizziness



Lecanemab (Leqembi®)  
Donanemab (Kisunla™)

## Monoclonal Antibodies

- > **Approved for:** MCI and mild AD
- > **Mechanism:** Target and clear beta-amyloid plaques in brain
- > **Adverse effects:** Infusion-related reactions, amyloid-related imaging abnormalities (ARIA) – *boxed warning*

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## Herbals/Supplements Evaluated for Dementia & Cognition

- > Ginkgo biloba
- > Omega-3 fatty acids
- > Vitamin E
- > Curcumin
- > Saffron
- > Bacopa monnieri
- > Folic acid and vitamin B12

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# Ginkgo Biloba – Efficacy in Dementia

- > Most studied herbal product for dementia
  - Dose studied: 240 mg/day
- > Cochrane review of ginkgo use in dementia (35 RCTs, 5,222 participants) concluded that it may lead to improved global clinical status, cognitive function, and activities of daily living at 6 months
  - High heterogeneity and low-certainty evidence



Wieland et al. Cochrane Database. 2026.

# Ginkgo Biloba – Efficacy in MCI and Dementia Prevention

- > Landmark trial Ginkgo Evaluation of Memory (GEM) (n = 3,069) did not find benefit in dementia prevention (HR 1.12, 95% CI 0.94-1.33)
  - Also showed little to no difference in clinical status at 12 months in patients with MCI



DeKrosky et al. JAMA. 2008.

## **Ginkgo Biloba – Safety**

- > Greatest concern is bleeding risk
  - Especially in patients taking anticoagulants or antiplatelet agents
  - Case reports have described major bleeding events with concurrent use of anticoagulants or antiplatelet agents



Liperoti et al. JACC. 2017.

## **Omega-3 Fatty Acids – Efficacy in Observational Studies**

- > Observational studies and meta-analyses suggest that higher dietary intake of DHA and EPA associated with ~20% reduced risk of cognitive decline
  - Strongest evidence for DHA
- > Long-term supplementation with omega-3 fatty acids has shown reduced risk of AD (HR 0.36, p=0.004)



Wei et al. Am J Clin Nutr. 2023.

# Omega-3 Fatty Acids – Efficacy in RCTs

- > Benefit shown for omega-3 fatty acid supplementation (particularly DHA) in slowing cognitive decline in patients with MCI
- > No benefit shown in cognitively healthy individuals or patients with AD
- > Response may be affected by dose, length of supplementation, APOE genotype, stage of cognitive decline

Butler et al. Ann Intern Med. 2018.  
Scarmeas et al. Lancet Neurol. 2018.  
Wood et al. Eur J Nutr. 2022.  
Welty. Curr Opin Lipidol. 2023.



# Omega-3 Fatty Acids – Safety

- > High-dose purified EPA associated with increased bleeding risk
  - FDA suggests intake of EPA + DHA up to 3 g/day unlikely to increase risk for significant bleeding
- > REDUCE-IT and STRENGTH trials showed significantly higher incidence of atrial fibrillation
  - Risk appears to be dose-dependent

Javaid et al. J Am Heart Assoc. 2023.  
Weinberg et al. JACC. 2021.



## **Vitamin E – Efficacy in AD**

- > TEAM-AD VA trial (n=613) found that 2,000 IU/day of alpha-tocopherol slowed functional decline by 19%/year in patients with mild to moderate AD
  - No significant cognitive benefit
- > Cochrane review also found functional benefit with no benefit for cognition or neuropsychiatric symptoms

Dysken et al. JAMA. 2014.

Farina et al. Cochrane Database. 2017.



## **Vitamin E – Efficacy in Patients Without Dementia**

- > Vitamin E has shown no benefit in preventing cognitive decline in cognitively intact adults
- > No benefit shown in preventing progression of MCI to dementia

Butler et al. Ann Intern Med. 2018.

Farina et al. Cochrane Database. 2017.

Andrieu et al. Lancet Neurol. 2015.



## Vitamin E – Mortality Risk

- > Meta-analysis of 19 RCTs (135,965 participants) showed dose-dependent increase in all-cause mortality at doses  $\geq 400$  IU/day
- > Cochrane meta-analysis also showed that vitamin E (alone or with other antioxidants) significantly increased all-cause mortality

Miller et al. Ann Intern Med. 2005.  
Bjelakovic et al. Cochrane Database. 2018.



## Vitamin E – Other Safety Concerns

- > Bleeding risk, especially at high doses or in patients taking anticoagulant or antiplatelet agents
  - Cochrane review showed increased risk of hemorrhagic stroke (by 22%)
- > HOPE trial showed increased risk of heart failure and hospitalization in individuals  $> 55$  years with diabetes or vascular disease
- > TEAM VA-AD trial showed loss of benefit and increase in adverse effects when combined with memantine

Farina et al. Cochrane Database. 2017.



## Curcumin – Efficacy

- > Robust pre-clinical data
- > Limited and inconsistent clinical evidence
- > Meta-analysis of 8 RCTs (389 participants) showed modest improvement in working memory
  - No significant improvement in episodic memory, language, or cognitive function



Tsai et al. Pharmaceuticals. 2021.

## Curcumin – Safety

- > Gastrointestinal adverse effects (nausea/vomiting/diarrhea) most common
  - Considered dose-dependent
- > Reports of hepatotoxicity
  - Linked to HLA-B35:01 allele carrier status
  - Associated with high doses
- > Inhibits CYP2D6/3A4
  - Metabolic pathway for donepezil, galantamine
  - Unclear clinical significance



Ayati et al. BMC Complement Med Ther. 2020.

## **Saffron – Efficacy**

- > Systematic review and meta-analysis of 4 RCTs in patients with MCI or AD showed significant improvement of cognitive function compared to placebo, as well as non-inferiority to donepezil
  - Small sample sizes
  - Insufficient evidence to make clinical recommendations



Ayati et al. BMC Complement Med Ther. 2020.

## **Saffron – Safety**

- > May cause nausea, dry mouth, headache
- > Dose-dependent toxicity: hematological and hepatorenal toxicities at suprathreshold doses



Butnariu et al. Oxid Med Cell Longev. 2021.

## **Bacopa Monnieri – Efficacy**

- > Limited clinical data
- > Meta-analysis found inconsistent improvements in various cognitive tests
- > Insufficient evidence to support use for dementia treatment



Brimson et al. Scientific Reports. 2021.

## **Bacopa Monnieri – Safety**

- > Doses >600 mg daily may increase risk for adverse effects such as gastrointestinal intolerance (nausea, diarrhea, cramping)



Morgan et al. J Altern Complement Med. 2010.

# **Folic Acid and Vitamin B12 – Efficacy**

- > Supplementation with folic acid plus vitamin B12 associated with improvement on certain memory tests
  - Clinical significance unclear
- > No benefit found for preventing MCI or dementia



Butler et al. Ann Intern Med. 2018.

# **Folic Acid and Vitamin B12 – Safety**

- > Generally well tolerated
- > At high doses, may rarely cause gastrointestinal upset or tingling in hands/feet



Supplement	Dementia Prevention	Dementia Treatment	Strength of Evidence
Ginkgo biloba	No benefit	Possible modest benefit	Moderate (prevention); low (treatment)
Omega-3 fatty acids	Benefit in observational studies; negative results from RCTs	No benefit in AD; possible benefit in MCI	Low to moderate
Vitamin E	No benefit	Slows functional but not cognitive decline in mild-moderate AD	Moderate
Curcumin	Insufficient data	Possible benefit for working memory	Low
Saffron	Insufficient data	Comparable to donepezil in small trials	Low
Bacopa monnieri	Insufficient data	Inconsistent effects	Very low
Folic acid + B12	Unclear clinical significance	Insufficient data	Low

## Other Supplement Products for Cognition

- > There are many supplements marketed for cognition and brain health, such as:
  - Prevagen®
  - Neuriva®
- > These supplements are not approved by the FDA
  - Not studied or regulated in the same way as medications



# Certain Herbals/Supplements May Negatively Impact Cognition

Effect	Herbal/Supplement Example(s)
Sedation	Melatonin, CBD, kava, valerian, passionflower
Disrupted sleep	Ginseng, caffeine, guarana
Anticholinergic effects	Jimson weed, belladonna
Drug interactions	St. John's Wort



## Bottom Line

- > There is not strong evidence to support routine use of any supplement for dementia treatment or prevention
  - Strongest evidence exists for high dose vitamin E (2,000 IU/day) to slow functional (but not cognitive) decline in mild to moderate AD
  - Ginkgo biloba (240 mg/day) may have benefit in dementia treatment (short-term) but not prevention
  - Safety risks must be taken into account



# Key Considerations for Patients

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- > Many patients/caregivers believe that supplement products are safer than prescription or over-the-counter medications
  - Supplements can still lead to adverse effects and drug interactions
  - Supplements are not regulated in the same way as medications and quality is highly variable
- > It is important for patients to report any supplement use to their healthcare team and inquire before starting a new supplement



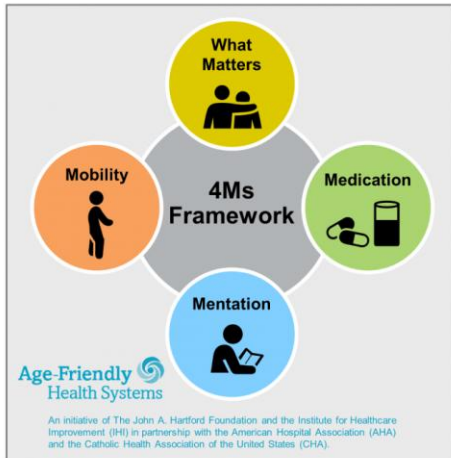
# Key Considerations for Clinicians

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- > Routinely ask about and document supplement use similar to medication use
  - Review ingredients of multi-ingredient products
- > Consider potential adverse effects alongside efficacy data
- > Always check for drug-supplement interactions



# 4 Ms Framework



## What Matters

Know and align care with each older adult's specific health outcome goals and care preferences including, but not limited to, end-of-life care, and across settings of care.

## Medication

If medication is necessary, use Age-Friendly medication that does not interfere with What Matters to the older adult, Mobility, or Mentation across settings of care.

## Mentation

Prevent, identify, treat, and manage dementia, depression, and delirium across settings of care.

## Mobility

Ensure that older adults move safely every day in order to maintain function and do What Matters.

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# Supplement Use Through the 4 Ms Framework – What Matters

- > Older adults may seek supplements for a variety of reasons, such as pursuing “natural” therapies
- > Discussions about supplements can address various elements of what matters to the patient, including treatment goals, expectations, cultural beliefs, and financial impact

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## **Supplement Use Through the 4 Ms Framework – What Matters, cont'd**

- > When discussing supplement use for dementia or cognition with patients/caregivers, it is important to:
  - Describe expectations
  - Review risks versus benefits
  - Address costs
  - Use shared decision-making

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## **Supplement Use Through the 4 Ms Framework – Medication**

- > Supplements have important potential consequences with regard to medication use, such as:
  - Increasing polypharmacy and pill burden
  - Causing adverse effects
  - Interacting with medications
- > Consider deprescribing supplements, especially if causing harm and/or benefit is low to none

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## Supplement Use Through the 4 Ms Framework – Mentation

- > Most supplements evaluated for dementia or cognition have not shown meaningful effects
  - It is important to set expectations with patients seeking to use supplements for this purpose
- > Some supplements may negatively impact cognition through direct or indirect effects

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## Supplement Use Through the 4 Ms Framework – Mobility

- > Most supplements evaluated for dementia (cognitive symptoms) or cognition have limited direct impact on mobility
  - Other supplements, such as melatonin, may have adverse effects such as sedation or balance impairment, that may affect mobility
- > Supplements may increase pill burden, which is important when considering patient's functional status

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# Patient Case

Ms. E is a 78-year-old patient with Alzheimer's disease (moderate stage) who presents to your primary care clinic today with her daughter. She lives with her daughter who assists with medication management, finances, transportation, and cooking. Ms. E recently started new supplements for memory and sleep after learning about them from a friend. She also inquires about potentially starting fish oil for further memory support. She reports new-onset daytime drowsiness and notes experiencing one fall in the last week while getting up in the middle of the night. She denies injury.

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# Patient Case, cont'd

## Past Medical History:

- > Alzheimer's disease
- > Atrial fibrillation
- > Hyperlipidemia
- > Hypertension

## Vitals/Labs:

- > BP 128/76, HR 68, Wt 62 kg
- > Labs WNL

## Medications/Supplements:

- > Apixaban 5 mg twice daily
- > Atorvastatin 20 mg daily
- > Gingko biloba 240 mg daily
- > Melatonin 10 mg nightly
- > Memantine 10 mg twice daily
- > Vitamin E 1,000 IU daily

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# Patient Case – Discussion Questions

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1. What is your assessment and plan regarding Ms. E's current supplement use?
2. What is your recommendation regarding use of fish oil for Ms. E?
3. If Ms. E feels strongly about continuing supplements, how might you approach a conversation around deprescribing?
4. What are other approaches besides supplement use that Ms. E could adopt to address memory and sleep?



## Questions?

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