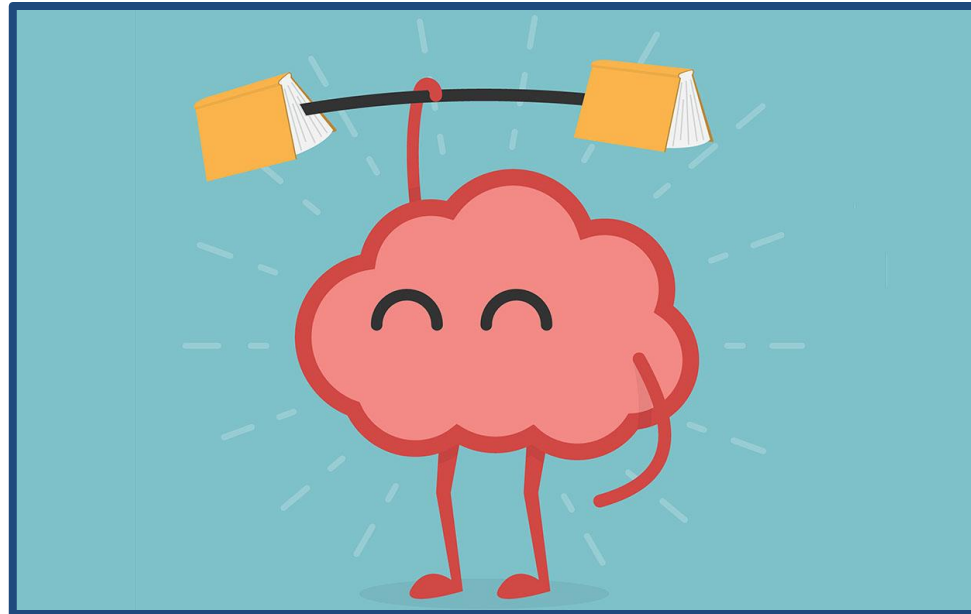


Pharmaceutical Use and Brain Health:

Magical Thinking and Practical Solutions



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Assistant Professor

University of Washington

Disclosures

- No potential conflicts of interest

Poll Everywhere

- Go to Pollev.com/marcum
- We will use it for 2 questions during today's webinar

W Drop a pin on your location today



Overview



- ✓ Background
- ✓ Prescription & OTC medications
- ✓ Herbal supplements and vitamins

****Caveat:** I will not be discussing a comprehensive list of all medications and supplements.*

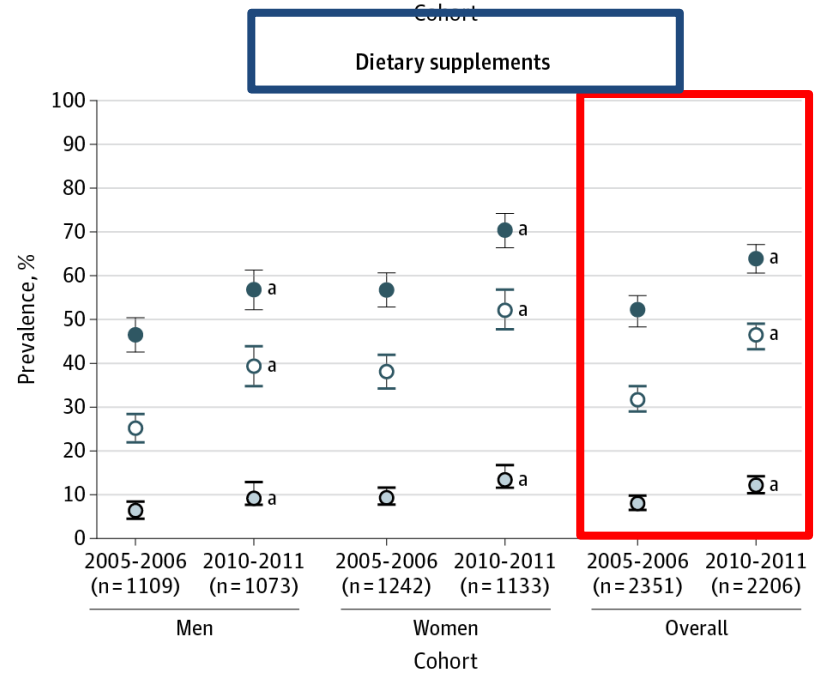
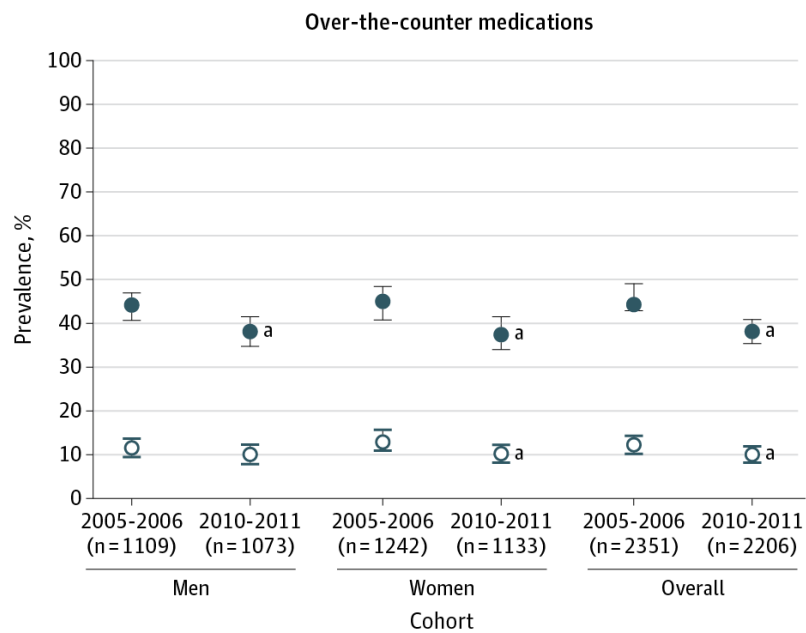
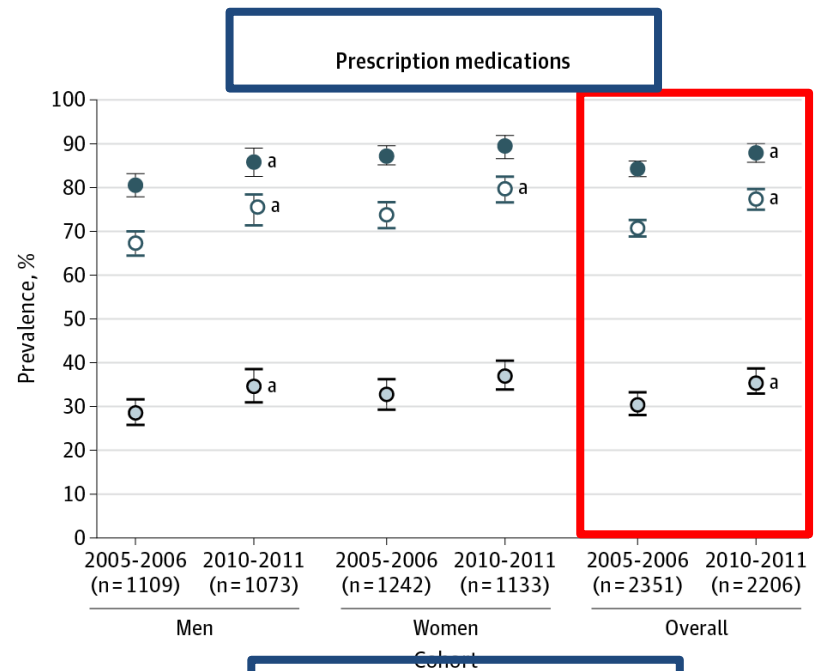
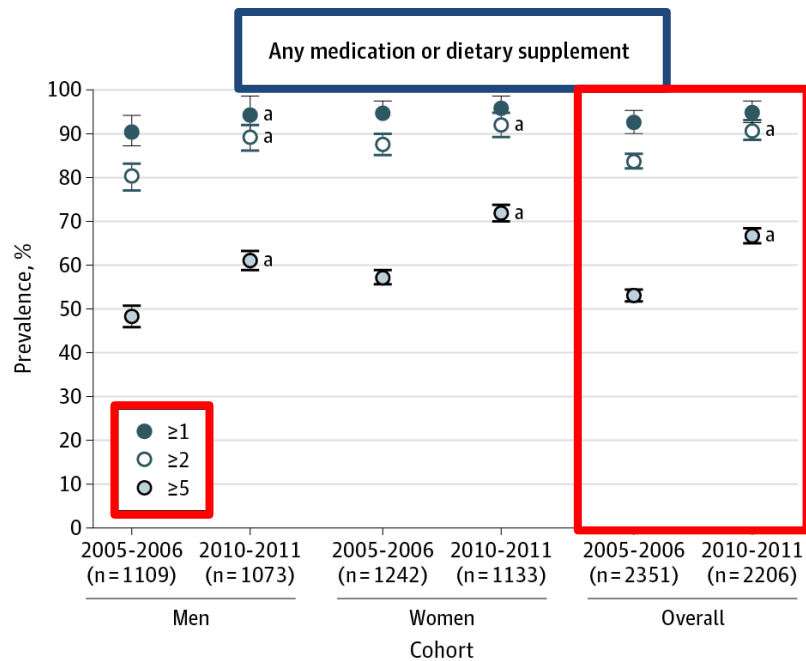
Older Adults & Medication Use

- The use of prescription medications and dietary supplements in older adults is **high** and **increasing** over time

Original Investigation

Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs 2011

Dima M. Qato, PharmD, MPH, PhD; Jocelyn Wilder, MPH; L. Philip Schumm, MA;
Victoria Gillet, BS; G. Caleb Alexander, MD, MS



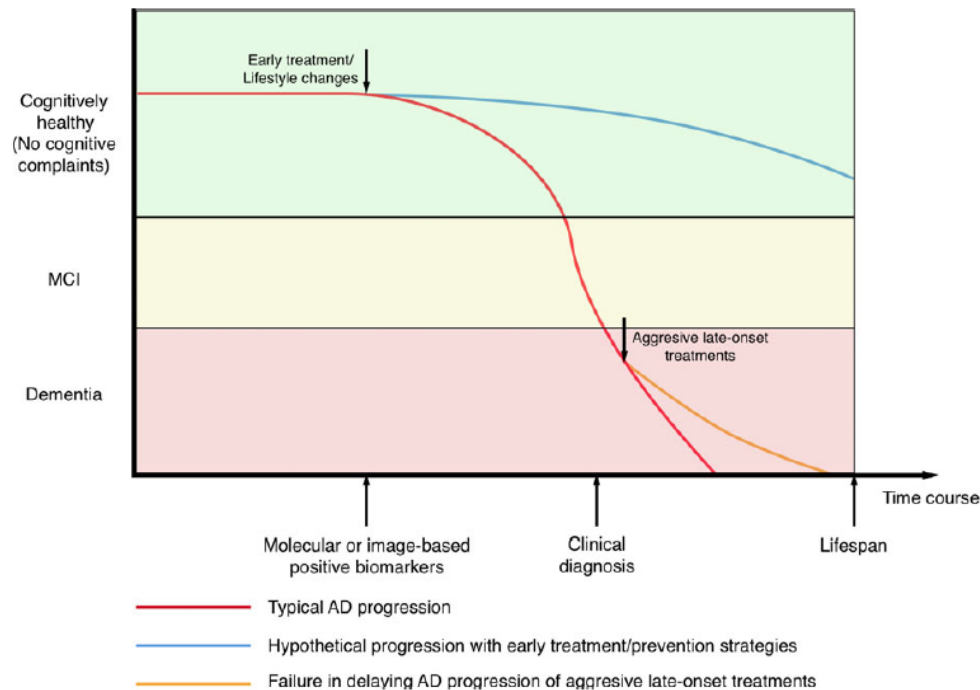
Pharmaceutical Use & Brain Health

- Role of pharmaceuticals for dementia prevention:
 - Avoiding harmful medications or supplements
 - Taking medications or supplements that are thought to improve brain health



When to Treat in Dementia Disease Process

- In the absence of a cure or disease-modifying treatment for late-life dementia, much of the current focus is on prevention



Overview



- ✓ Background
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Medications / Risk

Original Investigation

Cumulative Use of Strong Anticholinergics and Incident Dementia A Prospective Cohort Study

Shelly L. Gray, PharmD, MS; Melissa L. Anderson, MS; Sascha Dublin, MD, PhD; Joseph T. Hanlon, PharmD, MS; Rebecca Hubbard, PhD; Rod Walker, MS; Onchee Yu, MS; Paul K. Crane, MD, MPH; Eric B. Larson, MD, MPH

- Most common AC classes used were TCAs, first-generation antihistamines, and bladder antimuscarinics
- Adjusted HR for cumulative AC use (vs. nonuse):
 - TSDD > 1095: **1.54** (95% CI 1.21-1.96)

Medications / Risk

Anticholinergic drugs and risk of dementia: case-control study

Kathryn Richardson,¹ Chris Fox,² Ian Maidment,³ Nicholas Steel,² Yoon K Loke,² Antony Arthur,¹ Phyo K Myint,⁴ Carlota M Grossi,¹ Katharina Mattishent,² Kathleen Bennett,⁵ Noll L Campbell,⁶ Malaz Boustani,⁷ Louise Robinson,⁸ Carol Brayne,⁹ Fiona E Matthews,¹⁰ George M Savva¹

- Adjusted OR for any AC drug (ACB=3):
 - **1.11** (95% CI 1.08-1.14)
- Result was observed for exposure 15-20 years before a dementia diagnosis

Medications / Risk

- **Reducing Risk of Dementia Through Deprescribing (R2D2)**
 - Cluster, randomized controlled trial (ongoing)
 - Pharmacist-based deprescribing intervention for older adults within primary care practices
 - Target population: older adults with subjective cognitive decline but without dementia and currently using a strong AC medication
 - 24 month follow up
 - Cognition (primary) + safety (secondary) outcomes

Beliefs about benefits and harms of medications and supplements for brain health

Zachary A. Marcum^{a,*}, Sarah D. Hohl^b, Douglas Barthold^a, Oleg Zaslavsky^c, Eric B. Larson^d, Shelly L. Gray^a

^a School of Pharmacy, University of Washington, Seattle, WA, USA

^b School of Public Health, University of Washington, Seattle, WA, USA

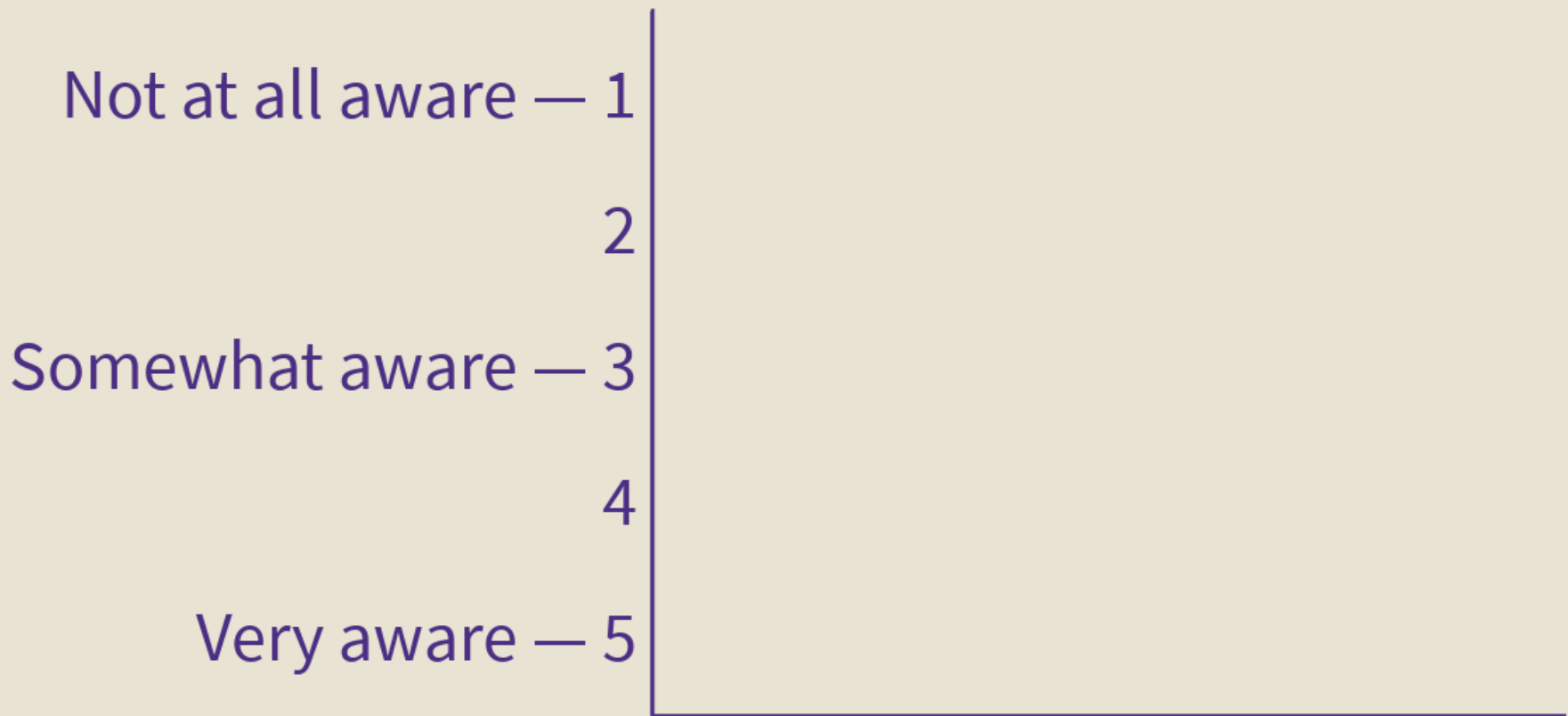
^c School of Nursing, University of Washington, Seattle, WA, USA

^d Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA

- N=1661
- Convenience sample of Kaiser Permanente WA members
- 77% female, 64% aged 51-70 years, 89% white

- **~1 out of 3** respondents reported OTC sleep aids such as Benadryl to be very/somewhat harmful to brain health
 - **~2 out of 3** respondents reported not knowing

Among your patients (and their caregivers),
W how aware are they of the potential risks of AC
medications related to brain health?



AC Take-Home Points

- Minimize exposure to AC medications to the greatest extent possible
- Among older adults receiving AC medications, consider dose reduction or discontinuation, if appropriate
- Stay tuned for trial data on deprescribing AC medications
- Consistent patient (and caregiver) education is needed on medication risks

Medications / Risk

Proton Pump Inhibitor Therapy and Dementia: What Is the Evidence?

- PPIs thought to possibly affect amyloid-beta metabolism
- Initial epidemiological studies (in Germany and Taiwan) found PPI use to be associated with increased risk of dementia
- Two main issues with studies:
 - Unmeasured and residual confounding
 - Defining etiologically relevant exposure window

Medications / Risk

Proton Pump Inhibitor Use and Dementia Risk: Prospective Population-Based Study

Shelly L. Gray, PharmD, MS, Rod L. Walker, MS,[†] Sascha Dublin, MD, PhD,^{††} Onchee Yu, MS,[†] Erin J. Aiello Bowles, MPH,[†] Melissa L. Anderson, MS,[†] Paul K. Crane, MD, MPH,[§] and Eric B. Larson, MD, MPH^{†§}*

- PPI use, whether measured by cumulative dose or duration, was **not associated** with risk of dementia

Beliefs about benefits and harms of medications and supplements for brain health

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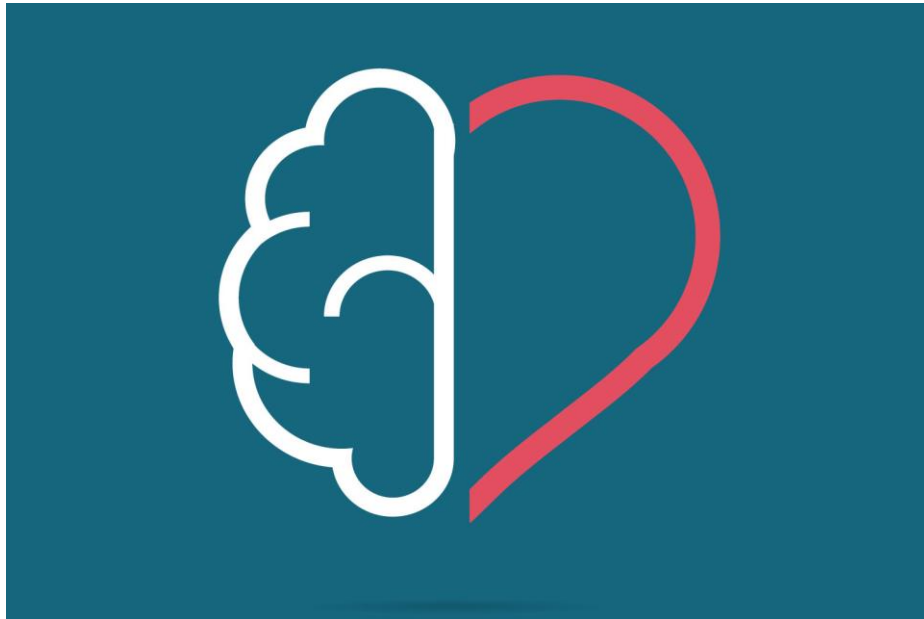
- **~1 out of 5** respondents reported PPIs such as Prilosec to be very/somewhat harmful to brain health
 - **~4 out of 5** respondents reported not knowing

PPI Take-Home Points

- No one with proper indications for PPI therapy should be deprived of these medications because of concerns of dementia risk
- In those with appropriate indications, the lowest effective dose should always be used
- Avoid unnecessary long-term or continuous therapy

Medications / Benefit

- Antihypertensives and the Aging Brain





Background (I)

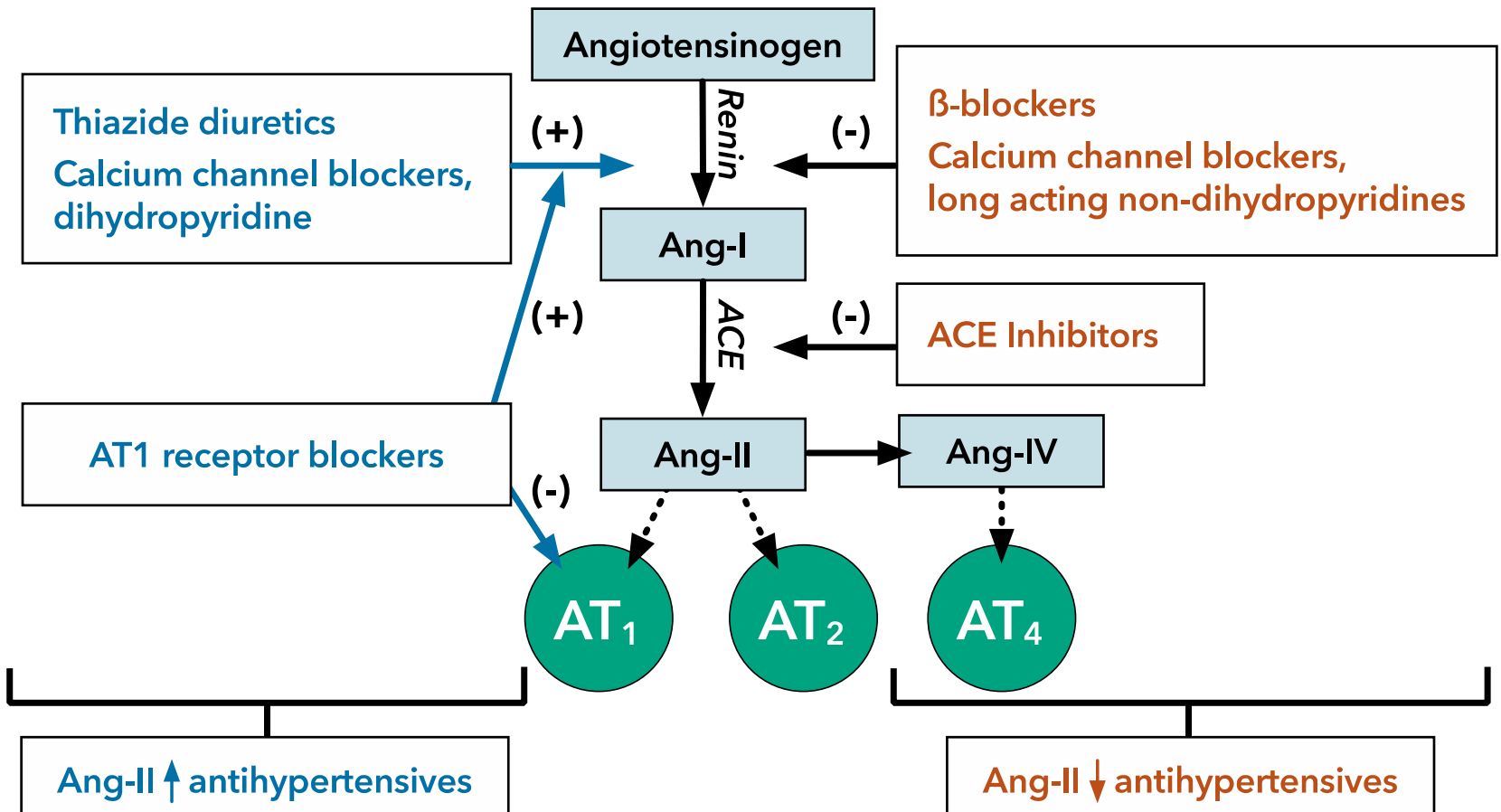
- Long-term control of cardiovascular risk factors may reduce dementia risk
- Hypertension affects 75 million (1 in 3) American adults
 - ~70% older adults (65+ years)
- Current hypertension guidelines are not informed by effects of antihypertensives on brain outcomes



Background (II)

- Delaying dementia onset for a small percentage of people would reduce overall burden
- Current evidence on long-term antihypertensive use and brain health is limited
- Antihypertensives are comprised of numerous sub-classes, each with a different mechanism
- Role of angiotensin in the brain offers a unifying hypothesis

Angiotensin Hypothesis



Preliminary Work

Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial



Eric P Moll van Charante, Edo Richard*, Lisa S Eurelings, Jan-Willem van Dalen, Suzanne A Ligthart, Emma F van Bussel, Marieke P Hoevenaar-Blom, Marinus Vermeulen, Willem A van Gool*

Lancet 2016;388:797-805.

- Post-hoc longitudinal cohort study
- Dutch general practices
- 1909 community-dwelling individuals with hypertension aged 70-78 years at baseline
- Ang-II ↑ use conveyed lower dementia risk compared to Ang-II ↓ use (HR 0.55, 95% CI 0.34-0.89)

In Press. Neurology 2021.

Preliminary Work

Journal of Alzheimer's Disease 68 (2019) 523–529
DOI 10.3233/JAD-181080
IOS Press

523

Short Communication

Patient Perceptions of Antihypertensive Use as a Dementia Prevention Strategy: A Mixed-Method Analysis of a Web-Based Survey

Zachary A. Marcum^{a,*}, Sarah D. Hohl^b, Shelly L. Gray^a, Doug Barthold^a, Paul K. Crane^c and Eric B. Larson^d

^aUniversity of Washington, School of Pharmacy, Seattle, WA, USA

^bUniversity of Washington, School of Public Health, Seattle, WA, USA

^cUniversity of Washington, School of Medicine, Seattle, WA, USA

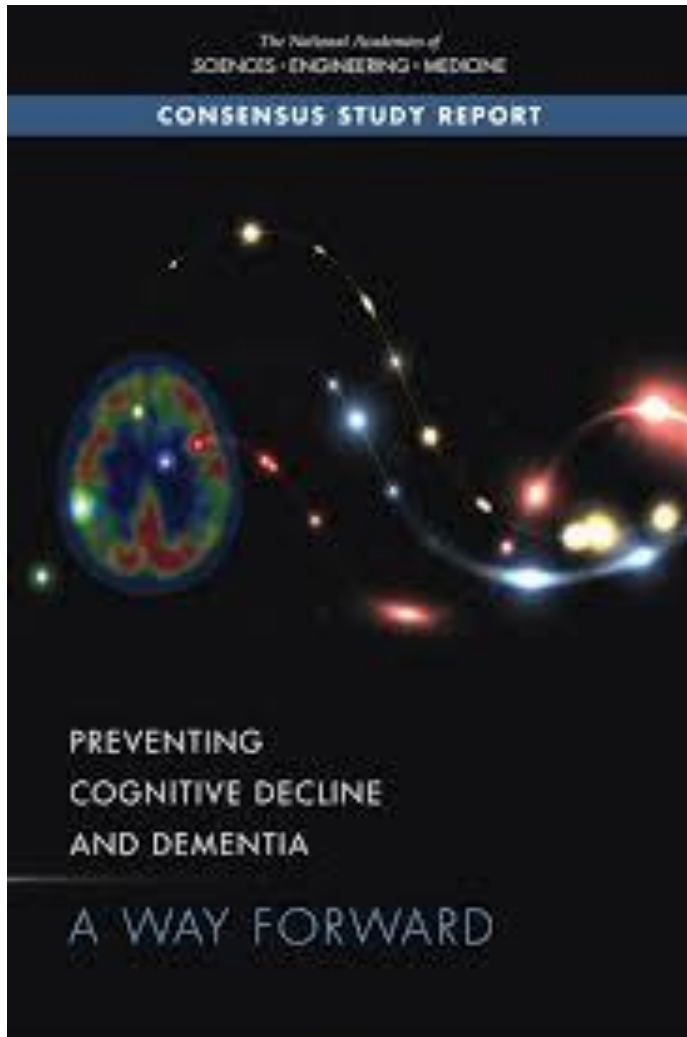
^dKaiser Permanente Washington Health Research Institute, Seattle, WA, USA

- If a specific antihypertensive medication was shown to prevent or delay dementia, the **vast majority (90%)** of respondents currently taking an antihypertensive reported that they would be willing to take that specific antihypertensive starting as early as mid-life.

Why Does This Research Matter?

- Antihypertensives are some of the most commonly used chronic medications
- There are currently no disease-modifying treatments for dementia
 - Much of the focus is on prevention
- Reducing risk of dementia even a small amount – on a population level – can have tremendous impact

NAM Report, 2017



- Priority research question:
 - *What is the comparative effectiveness of different classes of anti-hypertensive treatments (e.g., angiotensin II receptor blockers [ARBs] versus other treatments)?*

Lancet Commission, 2020

Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission

Gill Livingston, Jonathan Huntley, Andrew Sommerlad, David Ames, Clive Ballard, Sube Banerjee, Carol Brayne, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Sergi G Costafreda, Amit Dias, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Adesola Ogunniyi, Vasiliki Orgeta, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

- Specific actions for risk factors across the life course
 - Aim to maintain systolic BP of 130 mm Hg or less in midlife from around age 40 years (antihypertensive treatment for hypertension is the only known effective preventive medication for dementia).

RESEARCH ARTICLE

Drug therapies for chronic conditions and risk of Alzheimer's disease and related dementias: A scoping review

Johanna Thunell¹ | Yi Chen² | Geoffrey Joyce³ | Douglas Barthold⁴ |
Paul G. Shekelle⁵ | Roberta Diaz Brinton⁶ | Julie Zissimopoulos⁷

- **GREAT RESOURCE:**
 - Scoping review to identify drug classes associated with increasing or decreasing ADRD risk
 - 29 drug classes across 11 therapeutic areas, and 404 human studies
 - Drugs for treating hypertension and hyperlipidemia most common

Overview



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- ✓ Herbal supplements and vitamins

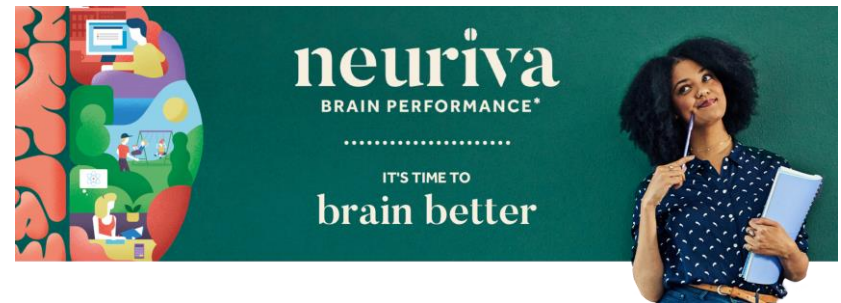
****Caveat:** I will not be discussing a comprehensive list of all medications and supplements.*



"...in clinical trials, it has been shown to improve short term memory..."

"...breakthrough..."

"...the secret is an ingredient originally discovered in jellyfish..."



W Have you had patients or caregivers (or family members) ask about these products? How do you respond?

Google Search Term Trend: “prevagen”

Interest over time



Numbers represent search interest relative to the highest point on the chart for the given region and time. A value of 100 is the peak popularity for the term. A value of 50 means that the term is half as popular. A score of 0 means there was not enough data for this term.

● prevagen
Search term

+ Compare

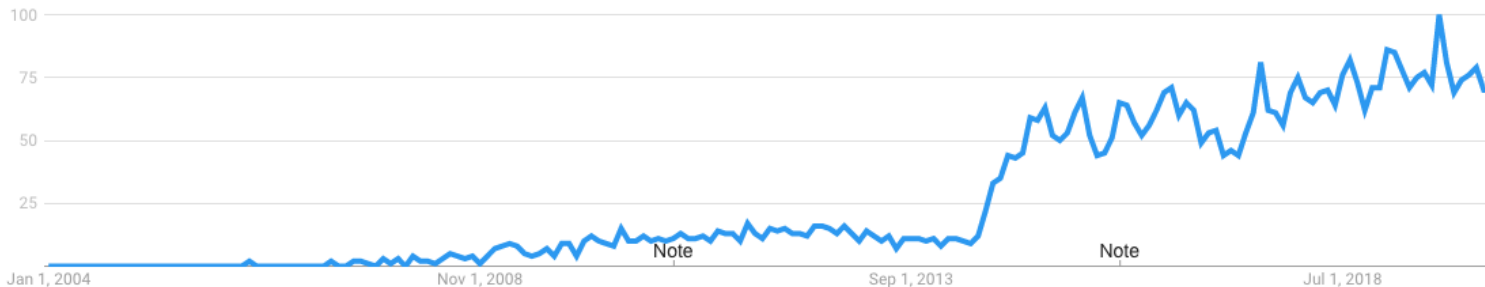
United States ▼

2004 - present ▼

All categories ▼

Web Search ▼

Interest over time ?





Be Sure to Take Your Vitamins and Memory-Specific Nutrients

If you're serious about the prevention of Alzheimer's and improving memory loss, you should definitely take a high potency multiple vitamin and mineral capsule. Be sure the vitamin formula you choose contains folic acid and vitamin C. Folic acid reduces homocysteine levels—high homocysteine levels put you at risk for both heart disease and memory loss. Vitamin C has been shown to reduce your risk of Alzheimer's disease by 20% when taken with vitamin E. To take advantage of its fullest benefits, you should take a dose of 2,000 mg of vitamin C per day.

When you create a balanced diet that puts your overall wellbeing at the forefront, you're not only doing good for your body, but you're also supporting and enhancing your memory as well.

Consider including the following memory-specific nutrients in your daily vitamin plan:

- coenzyme Q10
- alpha lipoic acid
- ginkgo biloba
- phosphatidylserine
- Omega-3's
- acetyl-L-carnitine

Two additional nutrients are recommended only for people who have moderate to severe memory loss:

- huperzine-A
- vinpocetine

<https://alzheimersprevention.org/4-pillars-of-prevention/pillar-1-diet-supplements/>

Evidence

REVIEW

Annals of Internal Medicine

Over-the-Counter Supplement Interventions to Prevent Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer-Type Dementia

A Systematic Review

Mary Butler, PhD, MBA; Victoria A. Nelson, MSc; Heather Davila, MPA; Edward Ratner, MD; Howard A. Fink, MD, MPH; Laura S. Hemmy, PhD; J. Riley McCarten, MD; Terry R. Barclay, PhD; Michelle Brasure, PhD, MSPH, MLIS; and Robert L. Kane, MD†

- Evidence is **insufficient** to recommend any OTC supplement for cognitive protection in adults with normal cognition or MCI.

The Real Deal on Brain Health Supplements:

GCBH Recommendations on Vitamins,
Minerals, and Other Dietary Supplements

Global Council on
Brain HealthSM
A COLLABORATIVE FROM AARP

2019

Available at: www.GlobalCouncilOnBrainHealth.org

DOI: <https://doi.org/10.26419/pia.00094.001>

Dietary Supplements

- Products taken by mouth that contain a dietary ingredient
 - Vitamins, minerals, amino acids, botanicals (including herbs) and enzymes
 - Many formulations, including pills, capsules, tablets, powders, food bars, and liquids
- How many dietary-supplement products are sold in the U.S.? (2018)
 - 85,000
- >\$40 billion in retail sales in the U.S. (2018)

Manufacturing & Approval

- Around the world, manufacturers are generally prohibited from selling unsafe ingredients, but **none** regulates or evaluates dietary supplements for **effectiveness** before they are permitted to be sold
- FDA does not determine whether dietary supplements are both safe and effective

Older Adults' Views

- Among adults age 50 and older, 81% believe that supplements are at least somewhat important for over health
 - 69% are currently taking a dietary supplement at least 3 times a week

Memory Supplements

- Growing portion of overall market for dietary supplements
 - Sales nearly doubled from 2006 to 2015, increasing to \$643 million
- >25% of Americans age 50 and older regularly take supplements for their brain health
- 11% report currently taking a supplement to delay the onset of dementia
- 8% report currently taking a supplement to reverse dementia

Beliefs about benefits and harms of medications and supplements for brain health

Zachary A. Marcum^{a,*}, Sarah D. Hohl^b, Douglas Barthold^a, Oleg Zaslavsky^c, Eric B. Larson^d, Shelly L. Gray^a

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- N=1661
- Convenience sample of Kaiser Permanente WA members
- 77% female, 64% aged 51-70 years, 89% white

1 out of 4 respondents reported benefits of vitamin E and **nearly half** reported benefits of fish oil on brain health

Apoaequorin (jellyfish)



- Protein isolated from the Aequorea Victoria jellyfish
- Main clinical trial used for claims of benefit did not have a control arm
- Second clinical trial failed to show improvement in treatment vs. placebo
- Likely broken down in the gut before reaching the brain

GCBH Consensus Statements

- For most people, the best way to get your nutrients for brain health is from a healthy diet.
- We do not endorse any ingredient, product or supplement formulation specifically for brain health, unless your health care provider has identified that you have a specific nutrient deficiency.
- Consumption of fatty fish, as well as other types of seafood, may benefit cognitive function. This may be due to their omega-3 fatty acid content, in particular DHA, but this is not proven. Overall, there is insufficient evidence to recommend taking a fish oil-derived omega-3 supplement for brain health.
- Supplement manufacturers and distributors often make vague or exaggerated claims about brain health. Because dietary supplements are marketed without premarket governmental review of their safety and efficacy or the truthfulness of their claims, consumers should approach claims made on supplement packaging and in marketing materials with skepticism.
- The quality of ingredients in supplements can vary widely. The ingredients in supplements are not generally reviewed for purity and content by government agencies before they are allowed to be sold.

Supplements and Deprescribing

- Providers should initiate discussions about dietary supplements with older patients
- Anchoring topics can include:
 - Effectiveness, interactions, and safety
- Strive for an open, respectful, and non-judgmental discussion through shared decision making
- Little empirical evidence on strategies for deprescribing supplements in older adults

Cognitive Vitality



- Evaluate the available evidence on strategies to promote brain health and prevent dementia—such as FDA-approved drugs, herbal supplements, and vitamins—and summarize findings in ratings



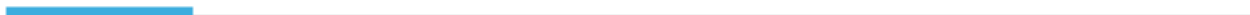
EVIDENCE



POTENTIAL BENEFIT



SAFETY





EVIDENCE



POTENTIAL BENEFIT



SAFETY



There is evidence from multiple randomized controlled trials or from a randomized trial in combination with a systematic review of observational studies, all in humans. A biological rationale for the treatment has been developed from preclinical studies.



Evidence includes at least one appropriately designed randomized controlled trial or a systematic review of observational studies, all in humans. A biological rationale for the treatment has been developed from preclinical studies.



There is some evidence on the use of the therapy from human studies (e.g., randomized trials, open or uncontrolled trials, or observational studies). A biological rationale for the treatment has been developed from preclinical studies.



Preclinical studies in animals and test tubes have evaluated its potential for biological effects, but there is no information on its effects on brain health in humans.



No human clinical studies have been conducted on brain health and no preclinical studies have developed a biological rationale for the treatment.



EVIDENCE



POTENTIAL BENEFIT



SAFETY



Research suggests a clinically meaningful benefit for long-term brain health.



Research suggests a noticeable benefit to short-term brain health or a small benefit for long-term brain health.



Research suggests a small benefit to short-term or long-term brain health but the clinical evidence is uncertain (i.e., it is unlikely to be noticeable in daily life).



Research to-date suggests that benefit to brain health is unlikely.



No research evidence is available to estimate potential benefit to brain health.



EVIDENCE



POTENTIAL BENEFIT



SAFETY



Very low risk. Extensive clinical research suggests that side effects or adverse events are very rare or mild for most people. This research could include several high-quality long-term randomized trials or rigorous post-marketing surveillance of consumer use.



Low risk. Limited clinical research suggests that side effects or adverse events are rare or mild for most people. This research could include one or two high-quality long-term randomized trials, limited post-marketing surveillance of consumer use, or widespread consumer use that has not identified health risks yet have not been monitored for long-term use in scientific studies.



Moderate Risk. Extensive clinical research has raised concerns for significant side effects or adverse events. Or, the clinical research does not predict significant risks but is extremely limited with no long-term randomized trials or long-term widespread consumer use.



High risk. Clinical research indicates serious side effects or adverse events. Or, the clinical research is completely inadequate to gauge safety, with no relevant randomized trials and no reliable information from long-term consumer use.



No clinical research evidence or use by consumers/patients exists.



ANGIOTENSIN II RECEPTOR BLOCKERS

Updated Apr 12, 2019

Evidence



Potential Benefit



Safety



TINOSPORA CORDIFOLIA

Updated Mar 22, 2019

Evidence

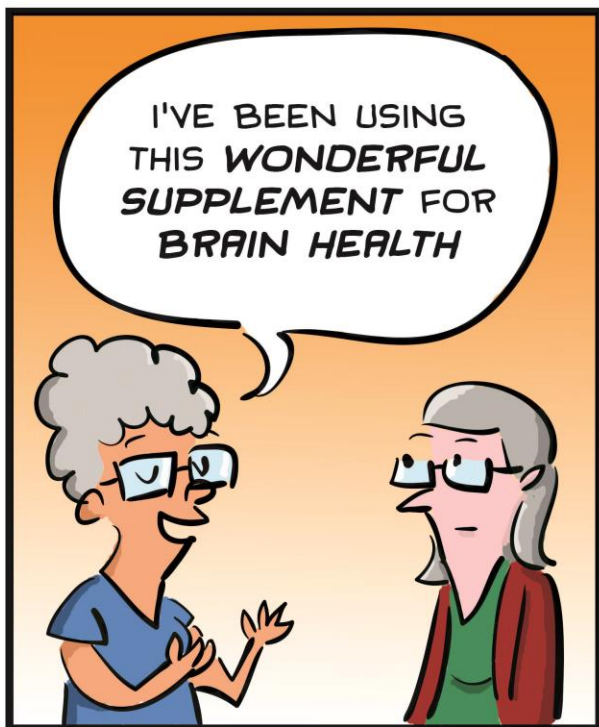


Potential Benefit



Safety





Summary

- Background
 - Medication and supplement use is **common** and **increasing**
- Prescription & OTC medications
 - ACs: *General consensus* is that they ↑ risk of dementia
 - PPIs: *Unlikely* to ↑ risk of dementia
 - Antihypertensives: TBD
- Herbal supplements and vitamins
 - **No evidence** to support their use for dementia prevention in the absence of a specific indication

Discussion

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