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DUBAI | UAE | 22 to 24 APRIL

DUBAI WORLD TRADE CENTRE

Dementia
Diagnosis & Treatment
What do we tell our patients ?

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Organized by
WiredIN

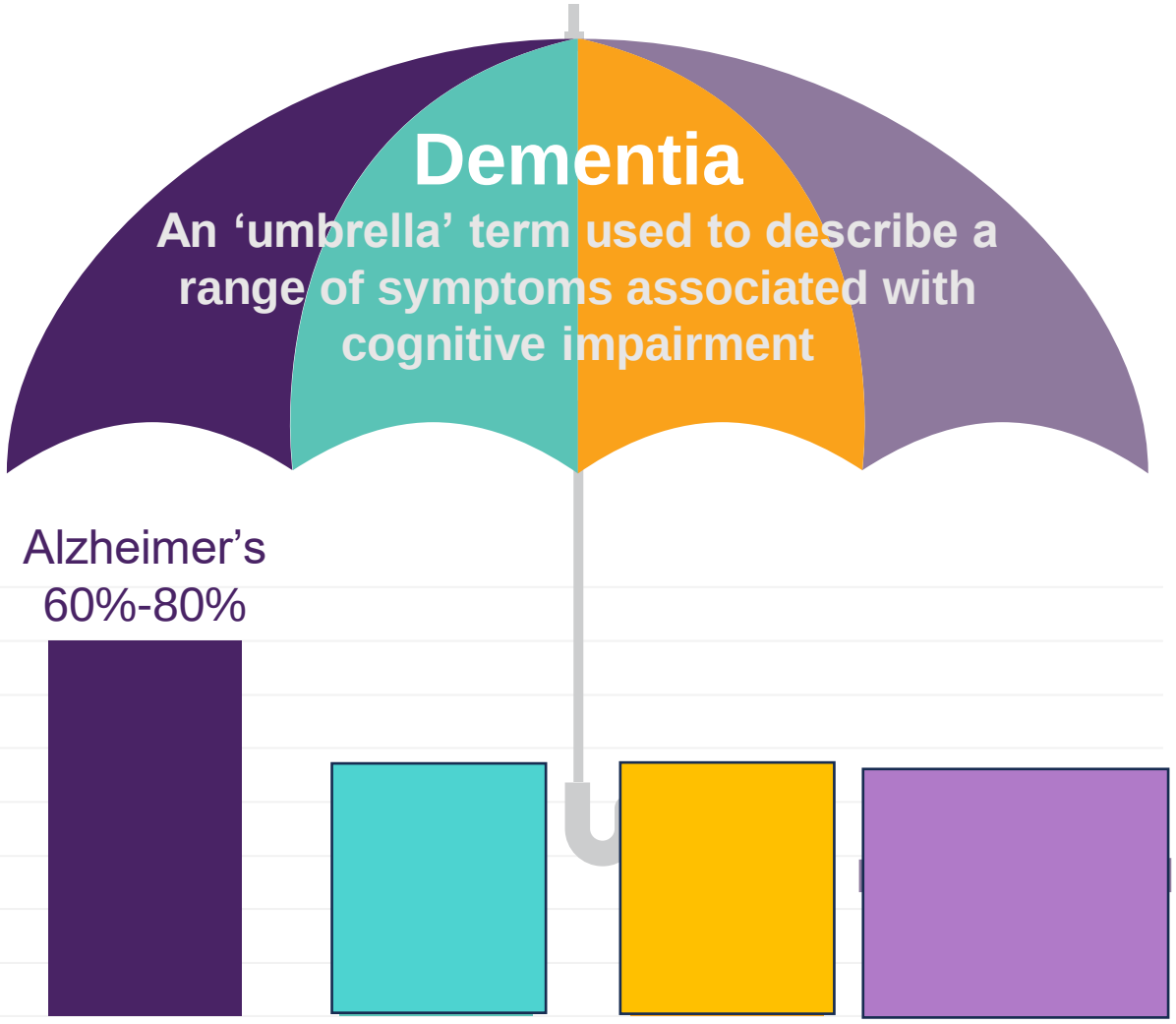
Objectives

- Understand etiology of Dementia and Alzheimer's disease
- Consider diagnostic approaches
- Recognize best strategies for prevention
- Appreciate current medications and treatments

DEMENTIA

A progressive decline in cognitive function and loss of memory

- Cognitive
- Behavioral
- Psychological



Mixed Dementia = > 1 Neuropathology Prevalence ~50%

Alzheimer's Association | Alzheimer's Disease & Dementia Help

UAE HEALTH

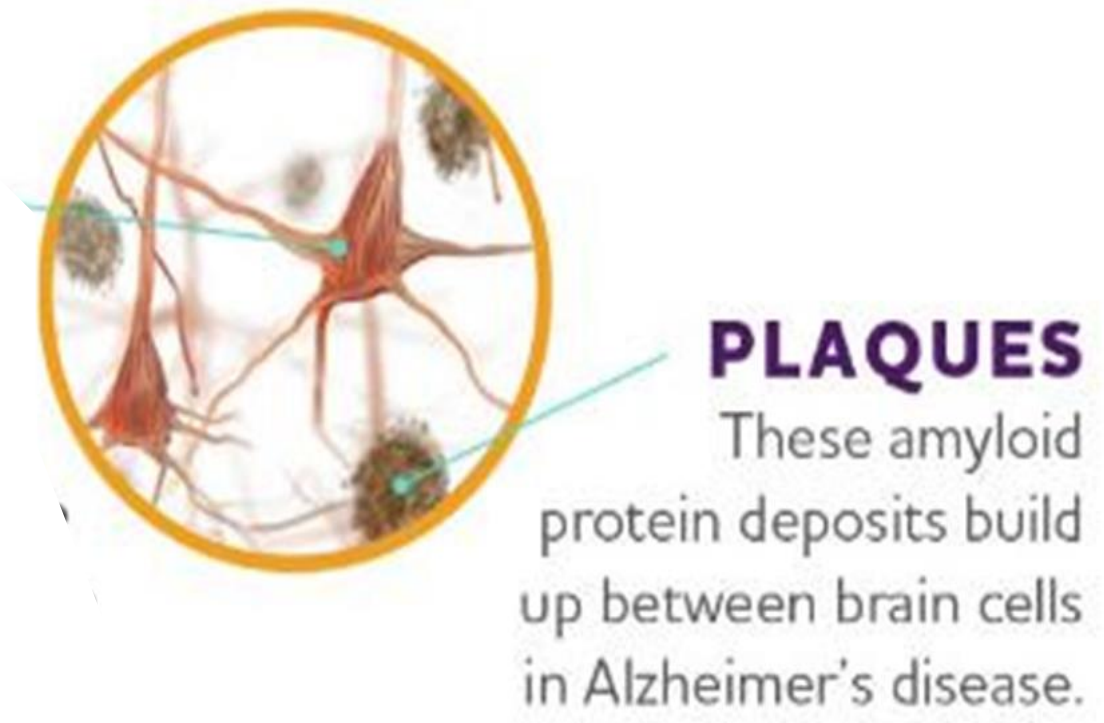
'Alzheimer’s to rise 600% by 2030 in UAE'
Medical experts call for measures against the disease to be implemented immediately

'Alzheimer’s to rise 600% by 2030 in UAE' | Health – Gulf News

Risk Factors and Protective Measures

Alzheimer's Disease

- a progressive disorder



***Amyloid plaques* and *tau tangles* damage neurons/neural connections**

Look for reversible causes…

- Hearing/vision impairments can cause confusion
- Medication side effects/polypharmacy..
- TSH, B12 levels
- Urine – UTIs associated with confusion in elderly
- MRI/CT scan – to r/o other causes (SDH, NPH, tumor)

Primary Care Dementia Screening Tools

1. Mini-Cog
2. Informant Questionnaire on Cognitive Decline in the Elderly [IQCODE]
3. Mini-Mental State Examination [MMSE]
4. Montreal Cognitive Assessment [MoCA]

Cochrane Review…

1. **2-part Mini-Cog**: 3-word recall, clock-face drawing
2. **Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE):** An acquaintance completes a questionnaire on how the patient's memory has changed over the last 10 years.
3. **Mini-Mental State Examination (MMSE):** 11-questions

The Cochrane authors did not recommend the routine use of any of these tests for dementia/AD screening….

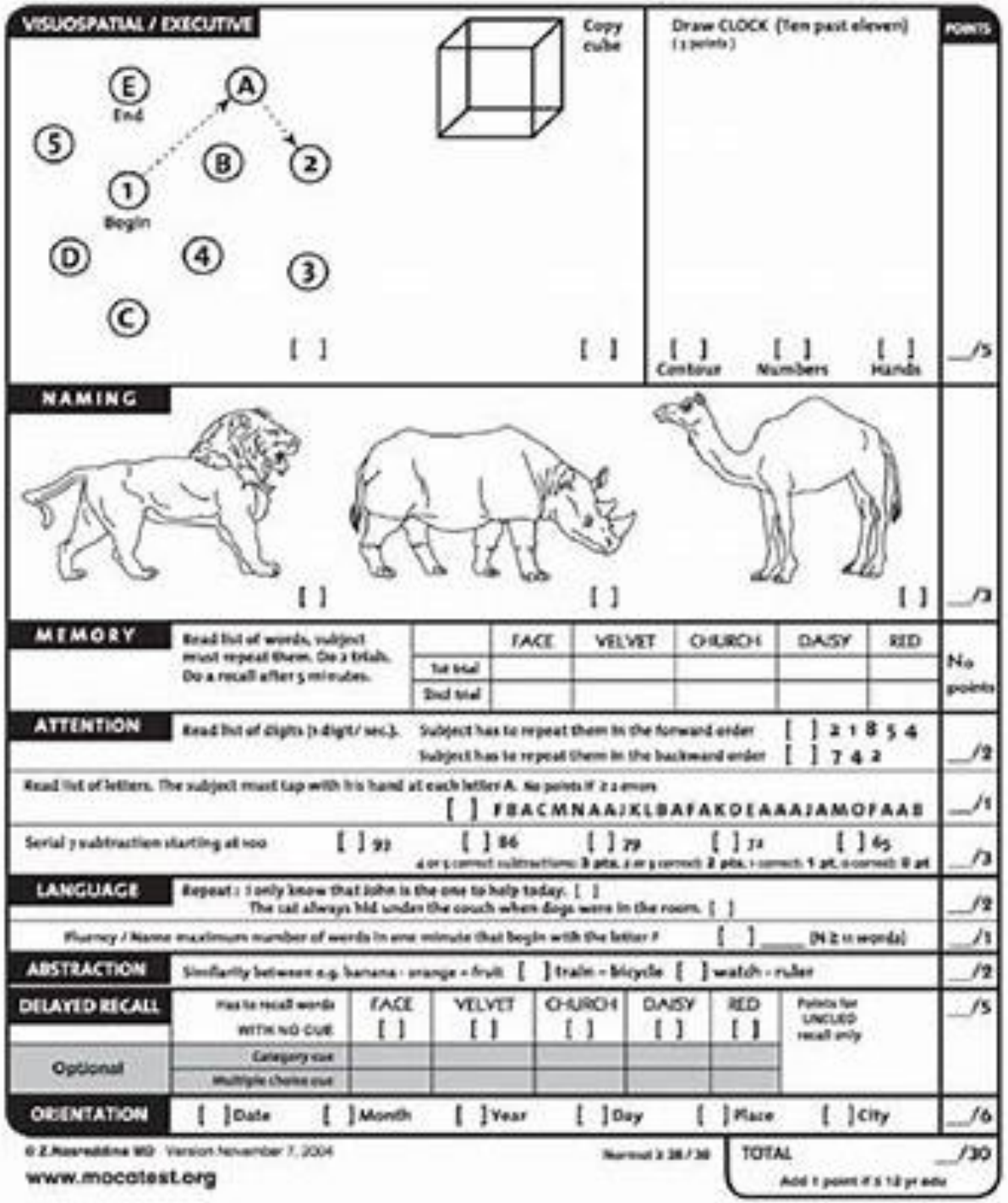
Cochrane Database Syst Rev. 2021;(7):CD011415.

Montreal Cognitive Assessment (MoCA)

A SR of 7 studies for mild cognitive impairment...

- The MoCA score of 18 considered the cutoff for AD - a standard score for Dementia has not been established.
- 4 studies (using a score < 26) found a 94% sensitivity in detecting patients with dementia; however, specificity for these diagnoses was poor (< 60%).

Cochrane Database Syst Rev. 2021;(7):CD010775; https://www.mocatest.org/faq/.



A 2020 *comparative effectiveness review* on the diagnosis and treatment of Alzheimer disease was most favorable toward use of the **MoCA** as a Screening Test…

Am Fam Physician. 2022;105(6):590-592

What about Genetic Testing???

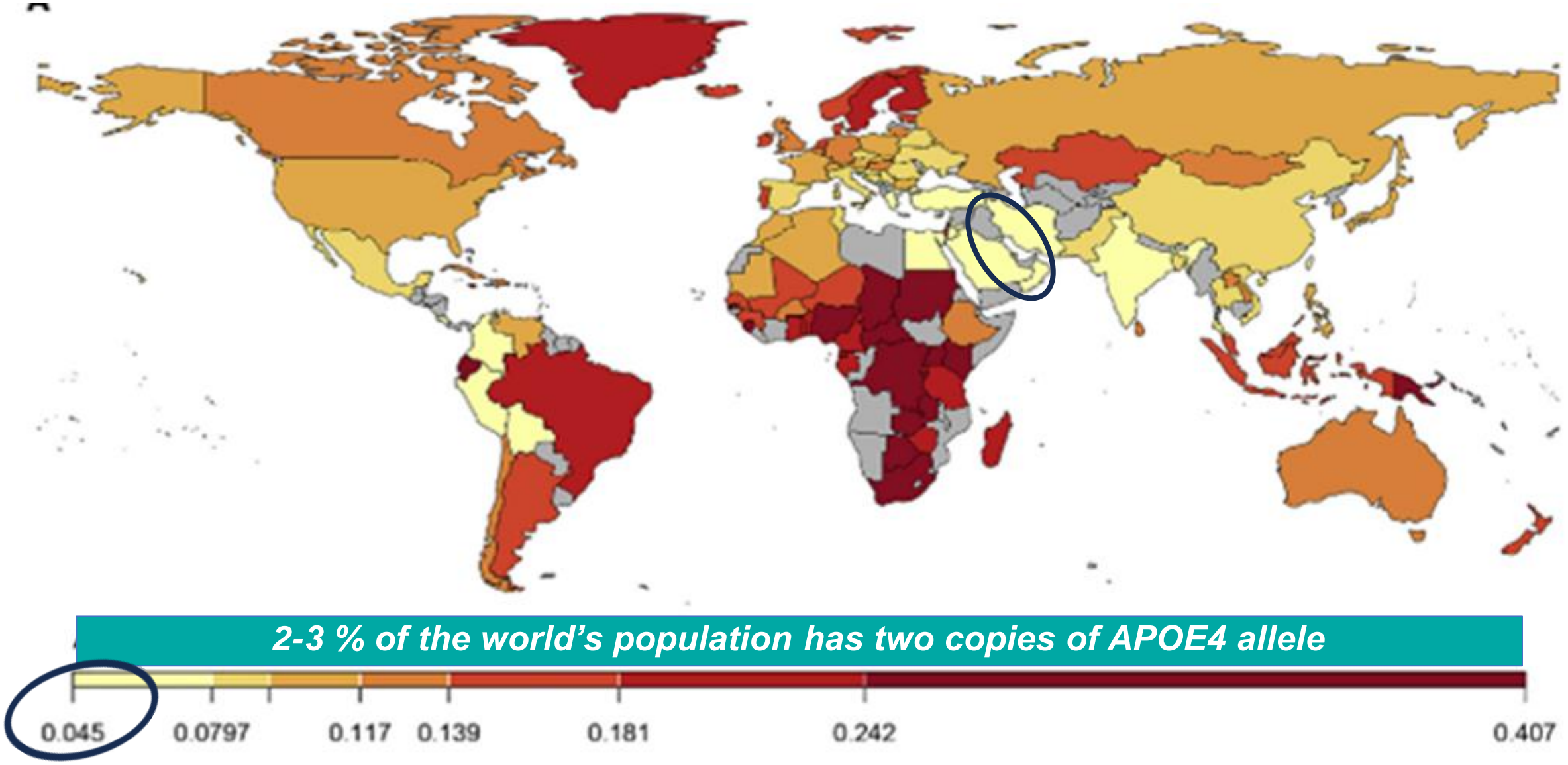
Several Genes Implicated…

The Apolipoprotein E (*APOE)* gene

Three alleles: e2, e3, e4

The APOE gene on chromosome 19 provides instructions for making apolipoprotein E, a protein that binds lipids involved with cholesterol metabolism.

- APOE3 is found in more than half of the population.
- **APOE4** alleles associated with amyloid plaques in brain.


2-3 % of the world's population has two copies of APOE4 allele
0.045
0.0797
0.117
0.139
0.181
0.242
0.407

APOE4 and AD risks…

Having 1 APOE4 allele ↑ person's risk for AD…

- Those who inherit 2 copies are at greatest risk.
  - ~ 60% develop AD by age 85
- Many people with an APOE4 allele never get AD
- Others develop AD do not have any APOE4 alleles

Other genes implicated…

ATP-binding Cassette Genes (ABCA7) transfer amyloid precursors

- African-Americans w/ABCA7 gene are 1.8 times more likely to develop *late-onset AD* than those w/o the gene.

Sortilin-related receptor 1 gene (SORL1) removes amyloid precursor protein (APP) from neuronal cellular endosomes.

- Loss of the SORL1 gene results in endosomal swelling
  - ***AD's hallmark cytopathologic finding..***

Cell Mol Life Sci. 2022 Feb 28;79(3):162. doi: 10.1007/s00018-022-04182-9; *JAMA*. 2013;309(14):1483-1492. doi:10.1001/jama.2013.2973

When to obtain Genetic testing?

- Early Onset Dementia
- Rapid decline
- + Family History → Genetic Counseling

What about Brain Scans?

CT/MRI to R/O other causes (NPH, SDH, tumors)

- General cerebral atrophy seen in AD

Positron emission tomography (PET) imaging

- Detects amyloid plaques/neurofibrillary tau tangles
  - ➢ *Still primarily a research tool…*

Cerebral Spinal Fluid?

- Beta-amyloid and tau protein CSF levels are elevated in AD….
- Considered if young/accelerated course of dementia..

What about a Blood Test?

- Research has validated ***beta-amyloid*** and ***tau*** blood tests by comparing to imaging and cognitive testing.
- ***Alpha synuclein*** - a pre-synaptic protein implicated in Parkinson's and Lewy Body dementia
- ***Neurofilament light*** a neuro protein detected in the blood in neurodegenerative diseases.

Beta-amyloid Test - PrecivityAD

Commercially available test quantifies the concentration ratio of 2 beta-amyloid peptides and the APOE genotype.

- Algorithm provides an ***Amyloid Probability Score***:
  - Low (≤ 35)
  - Intermediate (36-57) - requires further evaluation
  - High (58-100) – likely that amyloid plaques will be seen on amyloid positron emission tomography (PET)

Tau (p-tau217)

- Study of 786 (mean age, 66.3) with MRI and PET scans, CSF markers (β-Amyloid and Tau) compared to plasma p-tau.
- Found that a commercially available plasma tau immunoassay was comparable with CSF results

Accurately identified biological AD, including at the preclinical stage with longitudinal changes..

JAMA Neurol. doi:10.1001/jamaneurol.2023.5319

Medications to address cognitive function…

1. Cholinesterase Inhibitors

Donepezil

Galantamine

Rivastigmine

2. Glutamate Receptor Antagonist

Memantine

3. ß-amyloid Monoclonal antibodies

Aducanumab

Lecanemab

Donanemab

1. Cholinesterase Inhibitors

(donepezil, galantamine, rivastigmine)

AD associated with depletion of acetylcholine - involved in cognition, learning memory….

- Colinesterase inhibitors ↑ brain acetylcholine concentrations and can produce modest improvements in cognition, psychological symptoms, and activities of daily living.
- Few trials in patients > 85 years old and data on their use for more than one year are limited.

Cholinesterase Inhibitors…

Donepezil: A 3-year RCT of 565 patients with mild to moderate AD, oral donepezil ***demonstrated no significant benefit on institutionalization or disability progression***…

Galantamine: In two, 3-year long RCTs (2048 patients with MCI), there was ***no significant difference in the rate of progression to AD*** between galantamine and placebo.

Rivastigmine: A SR of 4775 patients with mild to moderate AD found that rivastigmine slowed the rate of cognitive decline and improved activities of daily living, but the ***effects were modest and the clinical significance was unclear***.

Neurology 2008; 70:2024 ;Lancet 2004; 363:2105; Cochrane Database Syst Rev 2015; 9:CD001191

Cholinesterase inhibitors: *Bottom-Line…*

(donepezil, galantamine, rivastigmine)

These medications appear similar in efficacy and safety in patients with AD, but RCTs comparing these drugs are lacking.

Modest improvements in cognitive and functional measures, but improvements in behavior and prevention of disability and institutionalization are disappointing…

Medications to address cognitive function…

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2. Glutamate Receptor Antagonists
(*Memantine)*

An N-methyl-D-aspartate (NMDA) receptor antagonist – memnatine reduces glutamatergic stimulation.

- A meta-analysis of 15 trials of patients (n=3700) with moderate to severe AD found a small benefit for memantine vs placebo in cognitive function, activities of daily living, behavior, and mood.

But no consistent evidence for any significant clinical usefulness in mild AD, Parkinson's or Lewy body dementia.

Cochrane Database Syst Rev 2019; 3:CD003154; Curr Alzheimer Res 2008; 5:83.

Medications to address cognitive function…

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3. ß-amyloid Monoclonal Antibodies

(*Aducanumab, Lecanemab, Donanemab)*

Antibodies bind to beta amyloid, reducing amyloid plaques

FDA approval based on the surrogate endpoint of reduction in amyloid beta plaques in the brain….

But …. the role of amyloid plaques in the pathogenesis of cognitive decline is unclear→ trials with other agents *have failed to demonstrate that reducing amyloid plaques in patients with AD results in a meaningful clinical benefit*.

Aducanumab (Adyhelm) Data..

2 RCTs (3285 patients) with early AD given aducanumab or placebo IV every 4 weeks for 18 months.

- Both trials were terminated early after an ***initial*** analysis concluded that the drug was not more effective than placebo in *slowing* cognitive decline.
- A post-hoc analysis found high doses were associated with *improvements* in of cognitive and functional tests in one trial
- PET imaging revealed ↓cerebral amyloid beta plaques.

Aducanumab Adverse Effects

- MRIs showed 19% w/ microhemorrhages and 35 % w/ cerebral edema w/high-dose aducanumab.
- Amyloid-related imaging abnormalities (ARIA) accompanied by headache, dizziness, unsteadiness, confusion, visual changes and seizures (rarely).
- Carriers of the ApoE4 gene had a higher incidence of ARIA.
- One fatality related to ARIA reported.

Biogen relinquished ownership of Adyhelm in January 2024, because of slow sales….

Lecanemab (Leqembi)

Targets amyloid plaques/oligomers.

- Over 18-months, patients declined cognitively at a slower rate vs those on placebo - ***but no perceived improvement***
- Brain swelling in 15 %; some w/intracerebral hemorrhage.
  - 3 died w/ major bleeding (2 were on a blood thinner**)**
- Those w/*APOE4* less responsive and ↑ chance of side effects.

Donanemab

Targets N3pG - a modified form of beta-amyloid

TRAILBLAZER-ALZ Phase 2 Trial showed slowing of decline in cognition in early symptomatic AD

- FDA declined to grant accelerated approval and asked for Phase 3 trial data for a traditional FDA approval over concerns for side effects/ serious risks.

Clinical Trials for AD Drugs And Devices

Supplements???

Vitamin E

A RCT (613 patients) with mild to moderate AD compared 2000 IU/day of vitamin E, with 20 mg of memantine, a combination of both or placebo.

- Compared to placebo, functional decline was slower with vitamin E, but not with memantine or the combination of vitamin E and memantine.
- A long-term prevention study of antioxidant supplements found that vitamin E did not prevent dementia…

JAMA Neurol 2017;74:567.

Ginkgo biloba

In several randomized, double-blind trials, Ginkgo biloba was not effective in preventing or treating dementia or for preventing cognitive decline in older adults…

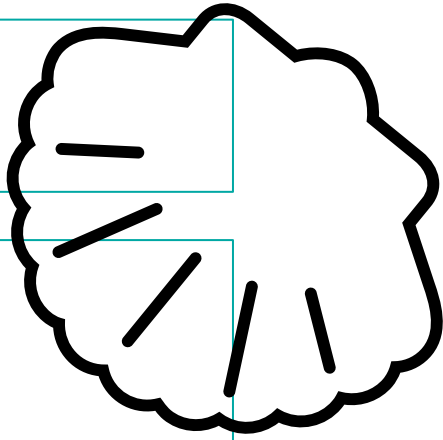
Prevagen

Jellyfish calcium-binding protein apo-a equorin

- ? an imbalance of calcium in neurons might play a role in aging the cells…
- The apo-a equorin in Prevagen likely gets digested before being absorbed.
- No acceptable evidence that the drug is effective for memory improvement….

Med Lett Drugs Ther 2021; 63:175

Scallop-derived plasmalogen (sPlas)



A study showed scallop-derived plasmalogen

- improved cerebral blood flow
- improved motor and cognitive deficits
- reduced β-amyloid pathology and inhibited neuronal loss.

In chronic cerebrally hypo-perfused mice

J Alzheimers Dis. 2022;86(4):1973-1982. doi: 10.3233/JAD-215246

Multivitamins or Cocoa??

COSMOS-Mind *(COcoa Supplement and Multivitamin Outcomes Study of the Mind)*

- *A large (n=21,442) clinical trial of daily cocoa (500 mg) and a multivitamin/mineral supplement (MVM) on global cognition outcomes.*

Cognitive questionnaires completed at baseline and annually for 3 years.

- *The primary outcome measured was a global cognition composite score and secondary outcomes looked a memory and executive function.*

They <u>did not find a benefit</u> from the cocoa.
MVM supplementation led to <u>relative improvements</u> in global cognition and in both memory and executive function testing….

Alzheimer's Dement.2022;1-12. https://doi.org/10.1002/alz.12767

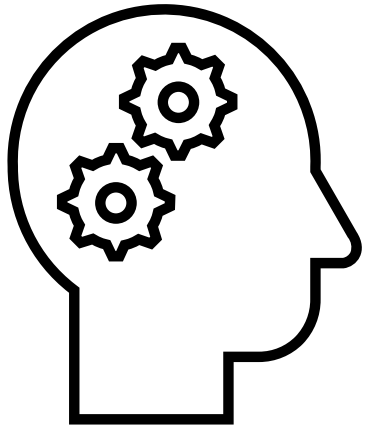
Supplements – Bottomline…

There is no consistent evidence of benefit for any supplements such as Ginkgo biloba or others containing vitamin B_6, vitamin E, folic acid, omega-3 fatty acids, cocoa extracts…..

However, a daily multi-vitamin/mineral supplement may provide a benefit!

Med Lett Drugs Ther 2021; 63:175 *CMAJ.* 2013;185(10):881-885.

Mental exercises ??



Some RCTs examined the effectiveness of of training to prevent cognitive decline among healthy older adults by measuring performance on cognitive tests.

- Evidence suggests that cognitive training & mentally stimulating activities can delay cognitive decline.
- However, no evidence that such interventions prevent Alzheimer disease or related dementias….

Preventing Cognitive Decline and Dementia: A Way Forward. The National Academies Press; 2019

What about physical exercise???

A RCT of 585 elderly underwent 18 months of:

- Mindful stress reduction (MBSR) meditation (*60 minutes/day*) ***or***
- Aerobic exercise with strength training (*300 minutes/week*) ***or***
- Combined MBSR and exercise ***or***
- Health education group classes w/home practice (control group).

Among older adults with subjective cognitive concerns, mindfulness training, exercise, or both did not result in significant differences in improvement in memory or executive function….

JAMA. 2022;328(22):2218-2229. doi:10.1001/jama.2022.21680

Prevention - the best strategy ?

UK Biobank study

302,239 individuals (50-73 years) without dementia completed baseline examinations from 2006 -10. Followed for years.

- ~1800 (0.6%) developed dementia. Those with a 'favorable lifestyle' had the slowest rates of memory decline ($P < .001$).

Favorable lifestyles measures associated with less memory decline:

- Healthy diet
- Active cognitive
- Regular physical exercise
- Active social contact
- Never/former smoking
- Never drinking

www.healio.com/news/cardiology/20210526/adopting-healthy-lifestyle-behaviors-may-reduce-dementia-risk-in-those-with-family-history

So, What do I tell my patients?

(AD – Not Normal Aging)

- Memory Problems: forgetting recent events, names, faces
- Asking questions repeatedly
- Easily confused in unfamiliar places
- Difficulty with numbers/handling money/time
- Become more fearful/withdrawn/anxious/easily upset
- Difficulty with tasks/activities that require organization/planning

So, What do I tell my patients??
(Best evidence for preventive interventions)

1. Eat a healthy diet (Mediterranean-DASH Diet)
2. Take a multi-vitamin daily
3. Maintain a healthy weight
   - Get adequate physical activity (at least 150 minutes/week)
4. Prevent/Control diabetes mellitus
5. Control blood pressure/lipids
6. Avoid smoking
7. Limit alcohol use to less than 1 drink per day
8. Engage your mind both socially and cognitively

Stroke. 2021;52(6):e295-e308; Nat Acad Press:2017.doi:10.17226/24782; doi:10.1001/jamaneurol.2023.5491; BMJ 2023;380:e072691

And Get Vaccinated!

- Cohort study of ~ 30,000 patients (≥ 65) who were free of dementia during a 2-year look-back were followed for 8-years.
- Prior vaccination associated with a ↓ risk for developing AD!
  - *30% RRR for Tdap/Td; 20% RRR for Zoster, pneumococcal vaccines..*
- Vaccines reduce the risk for infection, limit severity, and reduce the neuroinflammatory immune mechanisms that likely contribute to the development of AD.

J of Alzheimer's Disease. 9.12.2023; Vol(95)(2).

So, What do I tell my patients about Medications?

All provide only a small, short-term benefit and are associated with clinically meaningful harms….

Ann Fam Med 2024;22:50-58. https://doi.org/10.1370/afm.3050

Questions???

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Latozinemab

monoclonal antibody targeting sortilin

FDA granted ‘breakthrough’ therapy designation

- Phase 3 trials to treat frontal-temporal lobe dementia
- Blocks sortilin and increases progranulin