A Functional Approach to Dementia

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Disclosures

Born Integrative Medicine Specialists, PLLC
- Co-owner and medical director
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Allergy Research Group LLC
- Head of new product development, Scientific Advisor, Editor-in-chief of Focus Newsletter

International Society for Naturopathic Medicine
- President, Advisor and Lead Educator
  http://isnm-us.org

International Medical Wellness Association
- Medical Wellness Advisor
  https://www.medicalwellnessassociation.com/

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Webinar Outline

1) Terminology
2) Stats
3) Risk Factors and Genetics
4) Prevention
5) Evidence-Based Interventions

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Cognitive Impairment Terminology

- Mild Cognitive Impairment (MCI)
  - → a syndrome between the cognitive changes of aging and dementia
- Age-related cognitive changes
  - Harada C, et al. Normal Cognitive Aging. Clin Geriatr Med. 2013 November; 29(4): 737–752.
- Dementia
  - a disorder that is characterized by a decline in cognition involving one or more domains (learning and memory, language, executive function, complex attention, perceptual-motor, social cognition)
  - Signs/Symptoms:
    - Progressive memory loss
    - Impaired cognition, language and behavior
      - American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington 2013.

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Dementia Types

Alzheimer's Disease*
Vascular*
Parkinson's*
Creutzfeldt-Jacob Disease
Lewy Body Dementia
Frontotemporal
Huntington's
Mixed
Korsakoff Syndrome
AIDS Dementia

*Most common

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MCI Prevalence

- Age 60-64 years: 6.7%
- Age 65-69 years: 8.4%
- Age 70-74 years: 10.1%
- Age 75-79 years: 14.8%
- Age 80-84 years: 25.2%

Petersen RC, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018;90(3):126. Epub 2017 Dec 27.

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Percentage of Adults with Subjective Cognitive Decline, who discussed their symptoms of memory loss and confusion with a health care professional

Figure 3: Adults 45 years of age and older with Subjective Cognitive Decline who report discussing memory their memory loss and/or confusing with a healthcare provider

CDC. Subjective Cognitive Decline — A Public Health Issue. Division of Population Health, National Center for Chronic Disease Prevention and Health Promotion. Alzheimer's Disease and Healthy Aging. Feb 2019. https://www.cdc.gov/aging/publications/publications-science-agenda.htm

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MCI Risk Factors

- Age
- Lower educational level
- Vascular risk factors, including hypertension, midlife diabetes, obesity
- History of stroke or heart disease
- Apolipoprotein E (*APOE*) epsilon 4 genotype
- Neuropsychiatric symptoms (agitation, apathy, depression, anxiety)

McDade E, et al. Mild cognitive impairment: Epidemiology, pathology, and clinical assessment. UpToDate. May 2019

Strachan MW Price JF. Diabetes. Cognitive decline and T2DM--a disconnect in the evidence? Nat Rev Endocrinol. 2014 May;10(5):258-60.

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Dementia Epidemiology

- 44 million people worldwide
- Only 1 in 4 have been diagnosed
- Top cause for disabilities later in life
- In 2016, 15.9 million family caregivers provided an estimated 18.2 billion hours and $230 billion.
- In 2017, Alzheimer's cost the United States $259 billion

https://www.alzheimers.net/resources/alzheimers-statistics/

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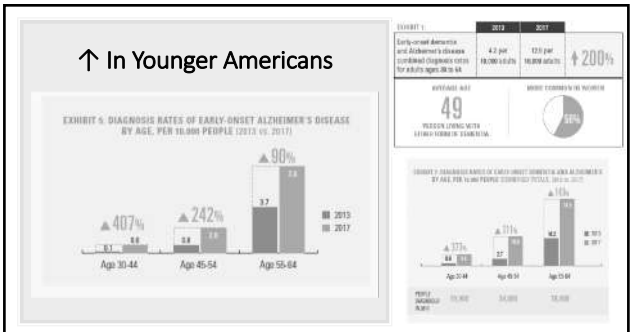
↑ In Younger Americans



Early-Onset Dementia and Alzheimer's Rates Grow for Younger Americans. Blue Cross Blue Shield Association (BCBSA). Feb 27, 2020. https://www.bcbs.com/the-health-of-america/reports/early-onset-dementia-alzheimers-disease-affecting-younger-american-adults?utm_source=prnw&utm_medium=&utm_content=&utm_campaign=&utm_term=

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Pathology

- Neuritic plaques from injury → amyloid beta formation + dystrophic neurites with phospho-tau immunoreactivity
- Extracellular deposits of amyloid beta peptides
- Neurofibrillary tangles
- Others

Masliah E, et al. Re-evaluation of the structural organization of neuritic plaques in Alzheimer's disease. J Neuropathol Exp Neurol. 1993 Nov;52(6):619-32.

Terry RD, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol. 1991 Oct;30(4):572-80.

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Pathogenesis

- Unclear, but all forms of AD share overproduction and/or decreased clearance of amyloid beta peptides.
- Tau proteins become overactive and hasten formation of neurofibrillary tangles.
  - **Accumulation of altered protein is toxic to neurons.**

Image from https://www.statnews.com/2019/04/30/amyloid-failures-new-tack?treating-alzheimers/

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Risk Factors & Potential Etiologies

2017 Lancet Commission reports 35% are attributable to nine potentially modifiable risk factors.

1. Low education attainment
2. Midlife hypertension
3. Midlife obesity
4. Hearing loss
5. Late-life depression
6. Diabetes
7. Physical inactivity
8. Smoking
9. Social Isolation

Livingston G, et al. Dementia prevention, intervention, and care. Lancet. 2017;390(10113):2673. Epub 2017 Jul 20.

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Risk Factors & Potential Etiologies

Heavy metals (e.g., Cu, Se, Zn, Pb, and Hg)

- Giacoppo S, et al. Heavy metals and neurodegenerative diseases: an observational study. Biol Trace Elem Res. 2014 Nov;161(2):151-60.
- McLachlan DRC, et al. Intramuscular desferrioxamine in patients with Alzheimer's disease. Lancet. 1991;337:1304-1308.

Toxicants

- Genius S & Kelln K. Toxicant Exposure and Bioaccumulation: A Common and Potentially Reversible Cause of Cognitive Dysfunction and Dementia. Behav Neurol. 2015; 2015: 620143. Published online 2015 Feb 4.
- "Organophosphates, which inhibit acetylcholinesterase…have also been shown to lead to microtubule derangements and tau hyperphosphorylation, a hallmark of AD."
- Zaganas L, et al. Linking pesticide exposure and dementia: what is the evidence? Toxicology. 2013 May 10;307:3-11.
- Steventon GB, et al. Xenobiotic metabolism in Alzheimer's disease. Neurology. 1990;40:1095-1098.

- **BBB Hyperpermeability**
  - Nation DA, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. Nat Med. 2019 Feb; 25(2): 270–276.

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Environmental Research

Hallmarks of Alzheimer disease are evolving relentlessly in Metropolitan Mexico City infants, children and young adults. APOE4 carriers have higher suicide risk and higher odds of reaching NFT stage V at ≤ 40 years of age

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Other Risk Factors

Infections

HSV, HHV (6 & 7), CMV, Toxoplasma, HIV, Cryptococcus, Borrelia, Tuberculosis, et al.

- Readhead B, et al. Multiscale Analysis of Independent Alzheimer's Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus. Neuron. 2018 Jul 11;99(1):64-82.e7.
- Almeida OP & Lautenschlager NT. Dementia associated with infectious diseases. Int Psychogeriatr. 2005;17 Suppl 1:S65-77.
- Lollis SS, et al. Cause-specific mortality among neurosurgeons. J Neurosurg. 2010;113:474-478.
- Chan PK, Ng HK, Hui M, Cheng AF. Prevalence and distribution of human herpesvirus 6 variants A and B in adult human brain. J Med Virol. 2001;64:42-46

Gut Microbiome

- Nho K, et al. Altered Bile Acid Profile in Mild Cognitive Impairment and Alzheimer's Disease: Relationship to Neuroimaging and CSF Biomarkers. BioRxiv. 18 March 2018.
- Vogt NM, et al. Gut microbiome alterations in Alzheimer's disease. Sci Rep. 2017 Oct 19;7(1):13537.

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The Gut Microbiome Alterations and Inflammation-Driven Pathogenesis of Alzheimer's Disease—a Critical Review

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Other Risk Factors

Brain Injuries

- Nordström A & Nordström P. Traumatic brain injury and the risk of dementia diagnosis: A nationwide cohort study. PLoS Med. 2018 Jan 30;15(1):e1002496.

Stress!

"Higher serum cortisol was associated with lower brain volumes and impaired memory in asymptomatic younger to middle-aged adults, with the association being evident, particularly in women."

- Echouffo-Tcheugui JB, et al. Circulating cortisol and cognitive and structural brain measures: The Framingham Heart Study. Neurology. 2018 Oct 24. pii: 10.1212/WNL.0000000000006549.

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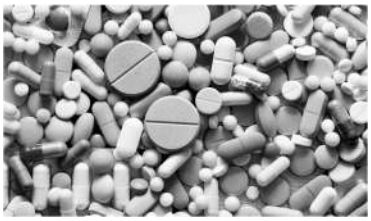

Medications as a Risk Factor

Anticholinergics (↑ 11-80%!)

- Antidepressants
- 1st generation antihistamines
- Bladder antimuscarinics
- Anti-Parkinson medications

Richardson K, et al. Anticholinergic drugs and risk of dementia: case-control study. BMJ. 2018 Apr 25;361:k1315.

Gray SL, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. JAMA Intern Med. 2015 Mar;175(3):401-7.

Benzodiazepines (↑ 5.7%)

Tapiainen V, et al. The risk of Alzheimer's disease associated with benzodiazepines and related drugs: a nested case-control study. Acta Psychiatr Scand. 2018 Aug;138(2):91-100.

Statins (goes both ways)

- Impairs cognition in some, decreases dementia risk in others

Schultz BG, et al. The role of statins in both cognitive impairment and protection against dementia: a tale of two mechanisms. Transl Neurodegener. 2018; 7: 5.

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Genetics

Amyloid precursor protein (*APP*), presenilin-1 (*PSEN1*) and presenilin-2 (*PSEN2*)→< 1% of cases, but 60-70% of early onset.

APOE4: susceptibility gene, not a determinative one.

- 40% of AD patients are negative
- Heterozygous: 2-3x more likely
- Homozygous: 8-12x more likely

Farrer LA, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 1997;278(16):1349.

Myers RH, et al. Apolipoprotein E epsilon4 association with dementia in a population-based study: The Framingham study. Neurology. 1996;46(3):673.

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Diagnosis

- Criteria from National Institute on Aging and the Alzheimer's Association (NIA-AA)
  - Should be suspected in any older adult with insidious onset, progressive decline in memory and at least one other cognitive domain leading to impaired functioning.
    - McKhann GM, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May;7(3):263-9. Epub 2011 Apr 21.
- Definitive is histopathologic exam.

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Diagnosis

- Assessment tools
  - Montreal Cognitive Assessment (MoCA)
    - www.mocatest.org
  - Mini-Mental State Examination (MMSE)
- Neuropsychologic testing
- Neuroimaging
- Biomarkers (not routine)
  - Aβ protein deposition
  - Tau and phospho-tau

McKhann GM, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May;7(3):263-9. Epub 2011 Apr 21.

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Laboratory Evaluation

Standard

- CBC, CMP, Insulin, HbA1c, TSH, FT4, FT3, B12, MMA, Pregnenolone, DHEA-S, Testosterone [total, free and % bio), estrogen, progesterone, 25(OH)D3, Iron panel + Ferritin, Testosterone, Homocysteine

Advanced

- Infectious disease(s), molds, mycotoxins, heavy metals, GI microbiome

Knopman DS, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001;56(9):1143.

McKhann GM, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May;7(3):263-9. Epub 2011 Apr 21.

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The Integrative Team

- GP/PCP
- Neurology
- Integrative/Functional/Naturopathic Physician
- Social worker
- Support
  - Friends, family, pets, loved ones, etc.
  - https://www.care.com/
  - https://www.aplaceformom.com/
  - http://www.dana.org/

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Strategies & Interventions

- Behavior modification
- Diet
- Sauna
- Nutrients
  - Antioxidants
  - Amino Acids
  - Neuroprotection
- Homeopathy
- EFA
- Botanicals
  - Acetylcholinesterase inhibitors
  - Acetylcholine precursors
  - Nootropics
  - Antimicrobial/viral/fungal
- Hormones
- Dale Bredesen, MD
  - "The End of Alzheimer's"
  - ReCODE Report (https://www.drbredesen.com/protocoloverview)

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Strategies & Interventions

Infectious

Toxicants

GI Microbiome

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Prevention is Key

Diet

- **Mediterranean**
  - High in vegetables, fruits, nuts, legumes and fish. Low-moderate alcohol, low meat and low dairy. High in polyphenolics and polyunsaturated fats.
    - Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol 2006;59:912-921.
    - Scarmeas N, Stern Y, Mayeux R, Luchsinger JA. Mediterranean diet, Alzheimer disease, and vascular mediation. Arch Neurol 2006 12;63(12):1709-1717.
    - Dai Q, et al. Fruit and vegetable juices and Alzheimer's disease: the Kame Project. Am J Med 2006;119:751-759.
    - McEvoy CT, et al. Dietary patterns during adulthood and cognitive performance in midlife: The CARDIA study. Neurology. 2019 Mar 6. pii: 10.1212/WNL.0000000000007243.
- Better diet quality relates to larger brain tissue volumes: The Rotterdam Study.
  - Croll PH, et al. Neurology. 2018 Jun 12;90(24):e2166-e2173

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Fruit and Vegetable Juices and Alzheimer's Disease: The *Kame* Project

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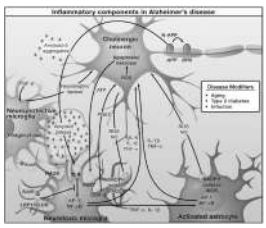
Importance of an Anti-Inflammatory Diet



"Amyloid-β peptide, produced by cleavage of amyloid precursor protein (APP), forms aggregates that activate microglia, in part by signaling through Toll-like receptors (TLRs) and RAGE. These receptors activate the transcription factors NF-κB and AP-1, which in turn induce the production of reactive oxygen species (ROS) and drive the expression of inflammatory mediators such as cytokines. These inflammatory factors act directly on cholinergic neurons and also stimulate astrocytes, which amplify proinflammatory signals to induce neurotoxic effects. Apoptosis and necrosis of neurons result in release of ATP, which further activates microglia through the purinergic P2X7 receptor. Microglia can also play protective roles by mediating clearance of Aβ through ApoE-dependent and ApoE-independent mechanisms. Cholinergic neurons in the basal forebrain, the neurons that are primarily affected in AD, are presumed to be important targets of inflammation-induced toxicity, but other types of neurons, such as glutaminergic and GABAergic neurons, may also be affected.

Taken from: Glass CK, et al. Mechanisms Underlying Inflammation in Neurodegeneration. Cell. 2010 Mar 19; 140(6): 918–934

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Exercise & Meditation

Exercise

- ↑ hippocampal volume, improved spatial memory, improves neuronal connectivity, brain derived neurotrophic factors (BDNF), neuroprotection, neuroplasticity.
  - Ahlskog E, et al. Physical Exercise as a Preventive or Disease-Modifying Treatment of Dementia and Brain Aging. Mayo Clin Proc. 2011 Sep; 86(9): 876–884.

Meditation

- Telomere length (TL), telomerase activity (TA), and plasma amyloid-β (Aβ) levels have emerged as possible predictors of cognitive decline and dementia.
- 12 minutes/day of Kirtan meditation increased TL, TA and Aβ, which improved cognition, mood, stress, sleep and QOL.
  - Innes KE, et al. Effects of Meditation and Music-Listening on Blood Biomarkers of Cellular Aging and Alzheimer's Disease in Adults with Subjective Cognitive Decline: An Exploratory Randomized Clinical Trial. J Alzheimers Dis. 2018 Oct 11.

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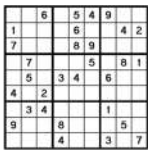

Prevention is Key

Brain games/exercises

- Less cognitive decline
- Slows memory loss
- Shorter part of life in a state of decline
- Reduces neuronal damage, grows new cells and connections

https://www.webmd.com/alzheimers/guide/preventing-dementia-brain-exercises#1

Sleep

- Insomnia increases risk. Dementias induce more sleep dysfunction. Insomnia impairs memory.
  - Hung CM, et al. Risk of dementia in patients with primary insomnia: a nationwide population-based case-control study. BMC Psychiatry. 2018; 18: 38.
  - Deschenes C& McCurry S. Current Treatments for Sleep Disturbances in Individuals With Dementia. Curr Psychiatry Rep. 2009 Feb; 11(1): 20–26.
  - Haimov I. Association between memory impairment and insomnia among older adults. Eur J Ageing. 2006 Jun; 3(2): 107.

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Sauna bathing is inversely associated with dementia and Alzheimer's disease in middle-aged Finnish men

Tanjaneva Laukkanen[1], Setor Kunutsor[2], Jussi Kauhanen[3], Jari Antero Laukkanen[1]

Abstract

Background: there are no previous studies linking repeated lone exposure of sauna and the risk of common diseases. We aimed to investigate whether frequency of sauna bathing is associated with risk of dementia and Alzheimer's disease.

Setting: prospective population-based study.

Methods: the frequency of sauna bathing was assessed at baseline in the Kuopio Ischaemic Heart Disease population-based prospective cohort study of 2,315 apparently healthy men aged 42–49 years at baseline, with baseline examinations conducted between 1984 and 1989. Hazard ratios (HRs) with 95% confidence intervals (CIs) for dementia and Alzheimer's disease were ascertained using Cox regression modelling with adjustment for potential confounders.

Results: during a median follow-up of 20.7 (interquartile range 19.1–22.6) years, a total of 204 and 123 diagnosed cases of dementia and Alzheimer's disease were respectively recorded. In analysis adjusted for age, alcohol consumption, body mass index, systolic blood pressure, smoking status, Type 2 diabetes, previous myocardial infarction, resting heart rate and serum low-density lipoprotein cholesterol, compared with men with only 1 sauna bathing session per week, the HR for dementia was 0.78 (95% CI: 0.57–1.06) for 2–3 sauna bathing sessions per week and 0.34 (95% CI: 0.18–0.73) for 4–7 sauna bathing sessions per week. The corresponding HRs for Alzheimer's disease were 0.80 (95% CI: 0.55–1.20) and 0.38 (95% CI: 0.14–0.94).

Conclusions: in this male population, moderate to high frequency of sauna bathing was associated with lowered risks of dementia and Alzheimer's disease. Further studies are warranted to establish the potential mechanisms linking sauna bathing and memory disease.

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MAYO CLINIC

REVIEW

Cardiovascular and Other Health Benefits of Sauna Bathing: A Review of the Evidence

Jari A. Laukkanen, MD, PhD; Tanjaniina Laukkanen, MSc; and Setor K. Kunutsor, MD, PhD

Abstract

Sauna bathing, an activity that has been a tradition in Finland for thousands of years and mainly used for the purposes of pleasure and relaxation, is becoming increasingly popular in many other populations. Emerging evidence suggests that beyond its use for pleasure, sauna bathing may be linked to several health benefits, which include reduction in the risk of vascular diseases such as high blood pressure, cardiovascular disease, and neurocognitive diseases; nonvascular conditions such as pulmonary diseases; mortality; as well as amelioration of conditions such as arthritis, headache, and flu. The beneficial effects of sauna bathing on these outcomes have been linked to its effect on circulatory, cardiovascular, and immune functions. It has been postulated that regular sauna bathing may improve cardiovascular function via improved endothelium-dependent dilatation, reduced arterial stiffness, modulation of the autonomic nervous system, beneficial changes in circulating lipid profiles, and lowering of systemic blood pressure. This review summarizes the available epidemiological, experimental, and interventional evidence linking Finnish sauna bathing and its effects on cardiovascular outcomes and other disease conditions on the basis of a comprehensive search for observational studies, randomized controlled trials, and non–randomized controlled trials from MEDLINE and EMBASE from their inception until February 24, 2018. An overview of the postulated biological mechanisms underlying the associations between sauna bathing and its health benefits, areas of outstanding uncertainty, and implications for clinical practice is also provided.

 Mayo Clin Proc. 2018;93(8):1111-1121

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Sauna as a Valuable Clinical Tool for Cardiovascular, Autoimmune, Toxicant-induced and other Chronic Health Problems

Walter J. Crinnion, ND

Abstract

Sauna therapy has been used for hundreds of years in the Scandinavian region as a standard health activity. Studies document the effectiveness of sauna therapy for persons with hypertension, congestive heart failure, and for post-myocardial infarction care. Some individuals with chronic obstructive pulmonary disease (COPD), chronic fatigue, chronic pain, or addictions also find benefit. Existing evidence supports the use of saunas as a component of depuration (purification or cleansing) protocols for environmentally-induced illness. While far-infrared saunas have been used in many cardiovascular studies, all studies applying sauna for depuration have utilized saunas with radiant heating units. Overall, regular sauna therapy (either radiant heat or far-infrared units) appears to be safe and offers multiple health benefits to regular users. One potential area of concern is sauna use in early pregnancy because of evidence suggesting that hyperthermia might be teratogenic.

(Altern Med Rev 2011;16(1):235-225)

Radiant-heat Saunas (Finnish Steam Saunas and Dry-heat Saunas)

When the term "sauna" is used in the medica literature without any modifiers (e.g., infrared) generally refers to the Finnish steam sauna. Th sauna uses a wood-paneled room with wooden benches and a radiant heater that keeps the temperature between 70 and 100°C (158-212°F with a face level temperature of 80-90°C (176-194°F). Steam is produced by pouring water on heated rocks. Generally enough steam is produ to create a humidity of 50-60 g H_2O vapor/M^3. Standard length of a Finnish sauna is 5-20 min in the sauna, followed by cold immersion (swim shower) and a period of room temperature rest ery before repeating. In a single sauna session, pattern is repeated 2-3 times.

Dry-heat saunas are essentially the same as Finnish steam saunas; however, the room used

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Vitamin Prevention and Treatment

Vitamin B12 (as methyl and/or hydroxocobalamin) 1000 mcg IM 2-3/week x 4 weeks and as needed.

- Cole MG & Prchal JF. Low serum vitamin B12 in Alzheimer-type dementia. Age Ageing.1984 Mar;13(2):101-5.
- Ikeda T, et al. Treatment of Alzheimer-type dementia with intravenous mecobalamin. Clin Ther.1992;14:434-437.

Nicotinamide adenine dinucleotide (NADH) (10 mg before breakfast)

- NADH is a coenzyme that plays a key role in cellular energy production and stimulates dopamine production
- Demarin V, et al. Treatment of Alzheimer's disease with stabilized oral nicotinamide adenine dinucleotide: a randomized, double-blind study. Drugs Exp Clin Res.

Pyridoxine (B6) and Folate (20 mg & 800 mcg + 500 mcg B12)

- Slows gray matter atrophy, but only in those with elevated homocysteine.
- Douaud G, et al. Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. Proc Natl Acad Sci U S A. 2013 Jun 4;110(23):9523-8.

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Vitamin Prevention and Treatment

Thiamine B1 (3 grams daily)

- Biochemical abnormalities in B1-dependant enzymes (esp, transketolase)
- Some studies show benefit, others show none.
  - Meador K, et al. Preliminary findings of high dose thiamine in dementia of Alzheimer's [illegible]

Vitamin E family (100-200 IU→prevention, 1,000IU twice a day→treatment)

- Beta-tocopherol lowered risk most significantly. Alpha-tocotrienol most neuroprotective
  - Mangialasche F, et al. High plasma levels of vitamin E forms and reduced Alzheimer's disease risk in advanced age. J Alzheimers Dis. 2010;20(4):1029-37.
  - Sano M, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med. 1997 Apr 24;336(17):1216-22.
  - Chin KY & Tay SS. A Review on the Relationship between Tocotrienol and Alzheimer Disease. Nutrients. 2018 Jul 9;10(7). pii: E881.

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Vitamin D and Risk

Deficiency (< 10 ng/ml or 25 nmol/L) increases all cause dementia risk by **2.25-fold**; insufficiency (10-20 ng/ml or 25-50 nmol/L) by **1.53-fold**.

- Littlejohns TJ, et al. Vitamin D and the risk of dementia and Alzheimer disease. Neurology. 2014 Sep 2; 83(10): 920–928.

"Optimal" levels of 40-50 ng/ml. Toxicity at 88 ng/ml.

- Krishnan AV & Feldman D. Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin D. Annu Rev Pharmacol Toxicol. 2011;51:311-36.
- Moyad MA. Vitamin D: a rapid review. Urol Nurs. 2008 Oct;28(5):343-9, 384; quiz 350.
- Carrol A. Why Take Vitamin D Supplements if They Don't Improve Health? JAMA Forum. March 2016.
- Szabo L. The Man Who Sold America On Vitamin D --And Profited in the Process. Medscape Aug 24, 2018.

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Mineral Prevention and Treatment

Magnesium (200-800 mg)

- Lemke MR. Plasma magnesium decrease and altered calcium/magnesium ratio in severe dementia of the Alzheimer type. Biol Psychiatry 1995;37:341-343.
- Kieboom BCT, et al. Serum magnesium is associated with the risk of dementia. Neurology. 2017;89(16):1716-1722.

Lithium (300 mcg as gluconate or carbonate)

- Neuroprotective; inhibits amyloid formation & tau hyperphosphorylation.
  - Nunes MA, et al. Microdose lithium treatment stabilized cognitive impairment in patients with Alzheimer's disease. Curr Alzheimer Res. 2013 Jan;10(1):104-7.

Iron (10-30 mg elemental)

- Yavuz BB, et al. Iron deficiency can cause cognitive impairment in geriatric patients. J Nutr Health Aging. 2012 Mar;16(3):220-4.

Selenium (50-200 mcg)

- Plays an important antioxidant role through selenoproteins
  - Cardoso R, et al. Effects of Brazil nut consumption on selenium status and cognitive performance in older adults with mild cognitive impairment: a randomized controlled pilot trial. Eur J Nutr. 2016 Feb;55(1):107-16.

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Amino Acid Prevention and Treatment

Acetyl-L-carnitine (2-3 grams)

- Structurally similar to acetylcholine and functions as a cholinergic neurotransmitter.
  - Salvioli G & Neri M. L-acetylcarnitine treatment of mental decline in the elderly. Drugs Exp Clin Res. 1994;20:169-176.
  - Pettegrew JW, et al. Clinical and neurochemical effects of acetyl-L-carnitine in Alzheimer's disease. Neurobiol Aging. 1995;16:1-4.
  - Spagnoli A, et al. Long-term acetyl-L-carnitine treatment in Alzheimer's disease.

L-Arginine (1.6 grams)

- ↑ NO, needed for learning and memory
  - Ohtsuka Y & Nakaya J. Effect of oral administration of L-arginine on senile dementia. Am J Med. 2000 Apr 1;108(5):439.

L-theanine (200-600 mg)

- ↑ BDNF & NGF
  - Takeda A, et al. Facilitated neurogenesis in the developing hippocampus after intake of theanine, an amino acid in tea leaves, and object recognition memory. Cell Mol Neurobiol. 2011 Oct;31(7):1079-88.
  - Tamano H, et al. Advantageous effect of theanine intake on cognition. Nutr Neurosci. 2014 Nov;17(6):279-83.

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EFA Prevention and Treatment

- **Omega-3 fatty acids (1-4 grams)**
  - EPA & DHA well known for lower risk of mild cognitive impairment but has failed to show decreased dementia risk.
  - Seems more beneficial in those without APOE4 and those with vascular dementias.
    - Fotuhi M, et al. Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer disease: a complex association. Nat Clin Pract Neurol. 2009;5(3):140-152.
    - Whalley LJ, et al. n-3 Fatty acid erythrocyte membrane content, APOE varepsilon4, and cognitive variation: an observational follow-up study in late adulthood. Am J Clin Nutr. 2008;87(2):449-454.
- ***Caveat***: maybe just not enough omegas? What about ω's-6 and 9?

41

Glutathione (GSH), NAC & Citicoline

GSH (1000-3000 mg) & N-Acetyl Cysteine (500-2000 mg)

A causative factor in AD/Dementia is oxidative stress

- Saharan S & Mandal PK. The emerging role of glutathione in Alzheimer's disease. J Alzheimers Dis. 2014;40(3):519-29.
- Pocernich CB & Butterfield DA. Elevation of glutathione as a therapeutic strategy in Alzheimer disease. Biochim Biophys Acta. 2012 May;1822(5):625-30.

Citicoline (1-2 grams)

Upregulates cytidine triphosphate:phosphocholine cytidylyltransferase (CCT), an enzyme critical for cellular phosphatidylcholine synthesis.

- Spiers PA, et al. Citicoline improves verbal memory in aging. Arch Neurol 1996;53:441-8.
- Alvarez, XA, et al. Double-blind placebo-controlled study with citicoline in APOE genotyped Alzheimer's disease patients. Effects on cognitive performance, brain bioelectrical activity and cerebral perfusion. Methods Find Exp Clin Pharmacol. 1999 Nov;21(9):633-44.

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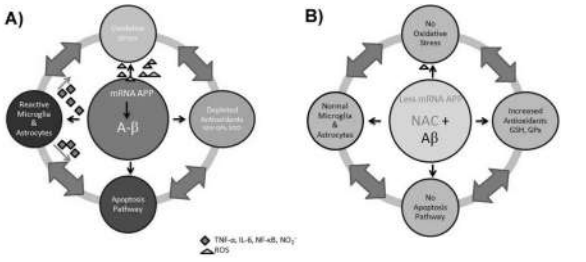
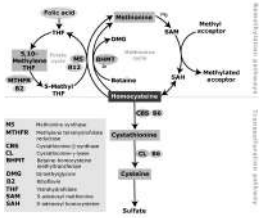


Taken from: Elevation of Glutathione as a Therapeutic Strategy in Alzheimer Disease Biochim Biophys Acta.1822(5):625-630.

43

S-adenosyl methionine (SAMe)

- Essential for methylation (DNA protection) and transsulfuration (GSH generation)
- AD has ↓SAMe & ↑SAH
- Currently no decent studies with dosing



Shea TB & Chan A. S-adenosyl methionine: a natural therapeutic agent effective against multiple hallmarks and risk factors associated with Alzheimer's disease. J Alzheimers Dis. 2008 Feb;13(1):67-70.

44

Carotenoids

Beta-carotene (25 mg or ~1-2 carrots)

- Grodstein F, et al. A randomized trial of beta carotene supplementation and cognitive function in men: the Physicians' Health Study II. Arch Intern Med. 2007 Nov 12;167(20):2184-90.

Astaxanthin (12-18 mg)

- Antioxidant, anti-inflammatory
  - Katagiri M, et al. Effects of astaxanthin-rich Haematococcus pluvialis extract on cognitive function: a randomised, double-blind, placebo-controlled study. J Clin Biochem Nutr. 2012 Sep;51(2):102-7.
  - Grimmig B, et al. Neuroprotective mechanisms of astaxanthin: a potential therapeutic role in preserving cognitive function in age and neurodegeneration. GeroScience. 2017 Feb; 39(1): 19–32.

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Botanical Prevention and Treatment

***Ginkgo biloba* leaf (Ginkgo, 120-240 mg). Standardized to flavone glycoside and terpene lactone content.**

- Inhibit toxicity and cell death induced by beta-amyloid peptide. Influences cholinergic system. (-) COMT. ↑brain alpha-adrenoreceptors
- Has not shown to prevent dementia but has been shown to increase brain functional activity.
- COMT is important in the prefrontal cortex, which is involved with personality, planning, inhibition of behaviors, abstract thinking, emotion, and working (short-term) memory.
  - Ernst E & Pittler MH. Ginkgo biloba for dementia: a systematic review of double-blind, placebo-controlled trials. Clin Drug Investig. 1999;17:301-308.
  - https://ghr.nlm.nih.gov/gene/COMT

***Bacopa monnieri* leaf (Brahmi, 300-600 mg). Standardized to bacoside and bacopasaponin constituents.**

- Modulation of acetylcholine release, choline acetylase activity, and muscarinic cholinergic receptor binding and neuroprotective.
  - Chaudhari KS, et al. Neurocognitive Effect of Nootropic Drug *Brahmi* (*Bacopa monnieri*) in Alzheimer's Disease. Ann Neurosci. 2017 May; 24(2): 111–122.
  - Morgan A & Stevens J. Does Bacopa monnieri improve memory performance in older persons? Results of a randomized, placebo-controlled, double-blind trial. J Altern Complement Med 2010;16:753-9.

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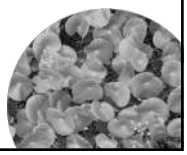
Botanical Prevention and Treatment

Centella asiatica aerial parts (Gotu kola, 60-180 mg). Standardized to triterpenoids.

- Neuroprotective, anxiolytic
  - Mook-Jung I, et al. Protective effects of asiaticoside derivatives against beta-amyloid neurotoxicity. J Neurosci Res. 1999 Nov 1;58(3):417-25.
  - Gohil KJ, et al. Pharmacological Review on *Centella asiatica*: A Potential Herbal Cure-all. Indian J Pharm Sci. 2010 Sep-Oct; 72(5): 546–556.

Curcuma longa root (Turmeric, 1-4 grams). Standardized to curcuminoids.

- (-) amyloid and/or tau accumulation in the amygdala and hypothalamus. Delays degradation of neurons, metal-chelation, anti-inflammatory, antioxidant and decreases microglia formation.
  - Small GW, et al. Memory and brain amyloid and tau effects of a bioavailable form of curcumin in non-demented adults: A double-blind, placebo-controlled 18-month trial. Am J Geriatr Psychiatry. 2018;26(3):266-277.
  - Mishra S & Palanivelu K. The effect of curcumin (turmeric) on Alzheimer's disease: An overview. Ann Indian Acad Neurol. 2008 Jan-Mar; 11(1): 13–19.



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Botanical Prevention and Treatment

***Panax ginseng* root (Asian 4.5-9 grams; S.E. 200-1000 mg). Standardized to ginsenosides.**

- Ginsenosides (-) beta-amyloid peptides. Anti-inflammatory. ↑hippocampal neuroplasticity.
  - Heo JH, et al. An open-label trial of Korean red ginseng as an adjuvant treatment for cognitive impairment in patients with Alzheimer's disease. Eur.J Neurol. 2008;15(8):865-868.

***Panax quinquefolius* root (American 100-400 mg). Standardized to ginsenosides.**

- Scholey A, et al. Effects of American ginseng (Panax quinquefolius) on neurocognitive function: an acute, randomised, double-blind, placebo-controlled, crossover study. Psychopharmacology (Berl) 2010;212(3):345-56.

Vinpocetine (*Vinca minor* periwinkle 10-40 mg)

- Neuroprotective & increases cerebral blood flow and metabolism
  - McDaniel MA, et al. "Brain-specific" nutrients: a memory cure? Nutrition. 2003;19(11-12):957-975.
  - Wolters EC, et al. A double-blind placebo and piracetam controlled multicenter trial of vinpocetine in dementia of Alzheimer's type and vascular dementia. Neurobiology of Aging 1992;13(Suppl 1):S127.

48

Botanical Prevention and Treatment

***Coffea arabica* whole fruit (200 mg)**

- ↑ BDNF → protein promotes the survival of neurons by playing a role in the growth, maturation (differentiation), and maintenance of these cells.
  - Reyes-Izquierdo T, et al. Modulatory effect of coffee fruit extract on plasma levels of brain-derived neurotrophic factor in healthy subjects. Br J Nutr. 2013 Aug 28;110(3):420-5.

Huperzine A (*Huperzia serrata* 400 mcg)

- Repairs NMDA receptors, antioxidant and neuroprotective
  - Xu SS, et al. Efficacy of tablet huperzine-A on memory, cognition, and behavior in Alzheimer's disease. Zhongguo Yao Li Xue Bao 1995;16:391-5.

***Menta spicata* leaf (Spearmint, 900 mg). Standardized to rosmarinic acids.**

- Rich in phenolic compounds, strong antioxidant to hippocampal region. ↑ ACh, neuronal growth and protects neurons.
  - Herrlinger KA, et al. Spearmint Extract Improves Working Memory in Men and Women with Age-Associated Memory Impairment. J Altern Complement Med. 2018 Jan;24(1):37-47.
  - Kantar Gok D, et al. Protective role of rosmarinic acid on amyloid beta 42-induced echoic memory decline: Implication of oxidative stress and cholinergic impairment. Neurochem Int. 2018 Sep;118:1-13.

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Botanical Prevention and Treatment

***Rosmarinus officinalis* leaf (Rosemary, dose?)**

- Diterpene phenolics inhibit neuronal death & amyloid formation.
  - Habtemariam S. The Therapeutic Potential of Rosemary (*Rosmarinus officinalis*) Diterpenes for Alzheimer's Disease. Evid Based Complement Alternat Med. 2016; 2016: 2680409.

***Pinus pinaster* bark (French Maritime Pine, 150 mg)**

- Antioxidant d/t phenolics, proanthocyanidins & procyanidins
  - Ryan J et al. An examination of the effects of the antioxidant Pycnogenol on cognitive performance, serum lipid profile, endocrinological and oxidative stress biomarkers in an elderly population. J Psychopharmacol. 2008 Jul;22(5):553-62.

***Camellia sinesis* leaf (tea, at least 1 cup)**

- Catechins, theaflavins, thearubigins and L-theanine
- ↓50% experience cognitive degeneration
- APEO4 carriers, 85% less likely!
  - Feng L, et al. Tea Consumption Reduces the Incidence of Neurocognitive Disorders: Findings from the Singapore Longitudinal Aging Study. J Nutr Health Aging. 2016;20(10):1002-1009.

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Crocus sativus (saffron)

- Antispasmodic, thymoleptic, carminative, cognition enhancer, aphrodisiac, and emmenagogue
- Safranal & Crocin (active constituents in saffron) interact with the GABAergic system, modulates levels of serotonin (possibly by inhibiting reuptake), alters levels of dopamine and norepinephrine and may inhibit the aggregation and deposition of amyloid β
- Effective in ADHD, AD, anxiety and depression
- No known interactions
- Typical dosage: 30 mg

Akhondzadeh S, et al. Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo-controlled trial. J Clin Pharm Ther. 2010 Oct;35(5):581-8.

Akhondzadeh S, et al. A 22-week, multicenter, randomized, double-blind controlled trial of Crocus sativus in the treatment of mild-to-moderate Alzheimer's disease. Psychopharmacology. 2010;207:637-43.

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Hericium erinaceus **(Lion's mane mushroom, 1-3 grams)**

Mechanism of Action of *H. erinaceus* in Alzheimer's Disease

Taken from: Spelman K, et al. Neurological Activity of Lion's Mane (Hericium erinaceus). Journal of Restorative Medicine 2017; 6: page 19-26.

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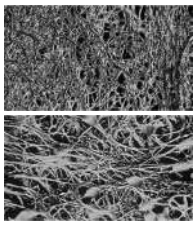
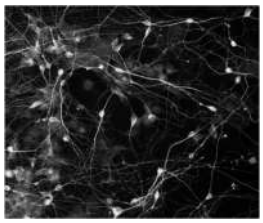
"Doctrine of Signatures"

Lion's Mane



Human Nerves



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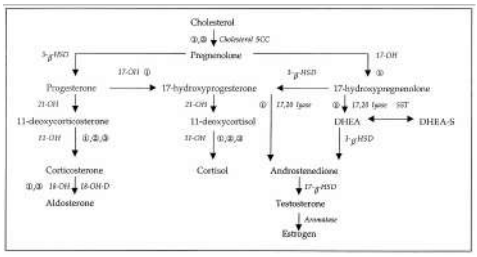
Hormones



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Hormone Treatment

Pregnenolone (100 mg)	Lapchak PA, Araujo DM. Preclinical development of neurosteroids as neuroprotective agents for the treatment of neurodegenerative diseases. Int Rev Neurobiol. 2001;46:379-97. Baulieu EE. Neurosteroids: of the nervous system, by the nervous system, for the nervous system. Recent Prog Horm Res. 1997;52:1-32.
Dehydroepiandrosterone (DHEA) (5-50 mg, depending on DHEA-S level)	Hillen T, et al. DHEA-S plasma levels and incidence of Alzheimer's Disease. Biol Psychiatry. 1997;41:805-808. Wolkowitz OM, et al. DHEA treatment of Alzheimer's disease: a randomized, double-blind, placebo-controlled study. Neurology. 2003;60:1071-1074.
Melatonin (0.5-2 mg)	Wade AG, et al. Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer's Disease: a 6-month, randomised, placebo-controlled, multicenter trial. Clin Interv Aging. 2014;9:947-961.
Testosterone, Estrogen/Progesterone	Balance accordingly

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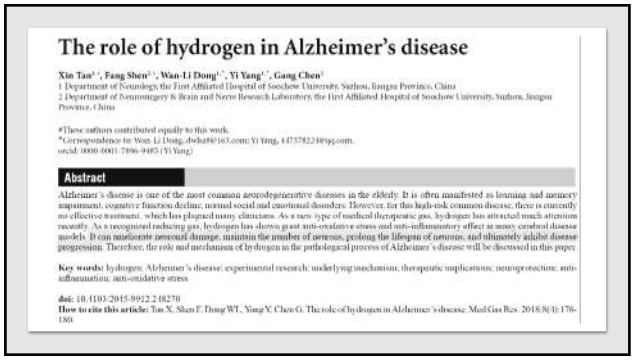

The role of hydrogen in Alzheimer's disease

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Abstract

Alzheimer's disease is one of the most common neurodegenerative diseases in the elderly. It is often manifested as learning and memory impairment, cognitive function decline, normal social and emotional disorders. However, for this high-risk common disease, there is currently no effective treatment, which has plagued many clinicians. As a new type of medical therapeutic gas, hydrogen has attracted much attention recently. As a recognized reducing gas, hydrogen has shown great anti-oxidative stress and anti-inflammatory effect in many cerebral disease models. It can ameliorate neuronal damage, maintain the number of neurons, prolong the lifespan of neurons, and ultimately inhibit disease progression. Therefore, the role and mechanism of hydrogen in the pathological process of Alzheimer's disease will be discussed in this paper.

Key words: hydrogen; Alzheimer's disease; experimental research; underlying mechanism; therapeutic implications; neuroprotection; anti-inflammation; anti-oxidative stress

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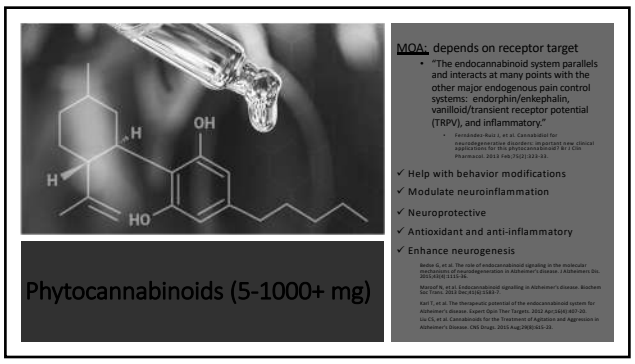

Phytocannabinoids (5-1000+ mg)

MOA: depends on receptor target

- "The endocannabinoid system parallels and interacts at many points with the other major endogenous pain control systems: endorphin/enkephalin, vanilloid/transient receptor potential (TRPV), and inflammatory."
  - Fernández-Ruiz J, et al. Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? Br J Clin Pharmacol. 2013 Feb;75(2):323-33.

- ✓ Help with behavior modifications
- ✓ Modulate neuroinflammation
- ✓ Neuroprotective
- ✓ Antioxidant and anti-inflammatory
- ✓ Enhance neurogenesis

Bedse G, et al. The role of endocannabinoid signaling in the molecular mechanisms of neurodegeneration in Alzheimer's disease. J Alzheimers Dis. 2015;43(4):1115-26.

Marsicano G, et al. Endocannabinoid signaling in Alzheimer's disease. Biochem Soc Trans. 2012 Dec;40(6):1544-7.

Karl T, et al. The therapeutic potential of the endocannabinoid system for Alzheimer's disease. Expert Opin Ther Targets. 2012 Apr;16(4):407-20.

Liu CS, et al. Cannabinoids for the Treatment of Agitation and Aggression in Alzheimer's Disease. CNS Drugs. 2015 Aug;29(8):621-32.

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Closing Remarks

- Dementias are a set of complex systems that are best addressed via preventative measures, given the complicated and multiple variables of interaction in an individual's genetic and epigenetic circumstances.
- No known specific etiology or etiologies exist, but there many known anteceding events, risk factors and triggers.
- Dementia treatment seems to best addressed with a multi-modal, multi-system, multi-team approach, via, at the very least, anti-infection, anti-inflammatory, antioxidant (from polyphenolics), gastrointestinal and CNS interventions.

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