BRAIN HEALTH

A GUIDE TO TREATING COGNITIVE IMPAIRMENT

June 2024

Updates: additional section on Alzheimer's Disease, addition of supplements Uridine Monophosphate, Vinpocetine, Urolithin A, Nattokinase, Serrapeptase, Curcumin, Taurine, TUDCA (Tauroursodeoxycholic acid), Gotu Kola, Phosphatidyl Choline, Phosphatidyl Serine

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About this document

The information in this document is our recommended approach to treating COVID-related cognitive impairment in adults. The guide was prepared by Dr. Suzanne Gazda, founder of the Neurology Institute of San Antonio in collaboration with FLCCC Director of Scientific Research, Dr. Pei Harris.

Patients should always consult with a trusted healthcare provider before starting any medical treatment, as these suggestions may need to be personalized based on the patient's age, demographics, and co-morbidities.

Overview

Definitions

- **Brain-derived neurotrophic factor (BDNF):** BDNF is crucial for neuronal survival and growth. It acts as a neurotransmitter modulator and participates in neural plasticity, which is essential for learning and memory. Decreased BDNF levels are associated with neurodegenerative diseases like Alzheimer's.
- **Insulin-like Growth Factor 1 (IGF-1):** A hormone activated by physical activity and reduced calorie intake. It helps cells survive, inhibits apoptosis, and induces neurogenesis in the hippocampus.
- **Acetylcholinesterase (AchE):** An enzyme that breaks down acetylcholine, a neurotransmitter regulating memory, learning, attention, arousal, and involuntary muscle action. Amyloid-beta (Aβ) increases AchE activity and decreases BDNF levels in the brain.
- **Fas Cell Surface Death Receptor (Fas):** A cell surface protein that regulates apoptosis. Elevated in Alzheimer's disease, it promotes brain cell death by apoptosis and autophagy.
- **TGF Beta:** An inflammatory cytokine with higher levels reported in Alzheimer's disease. Linked to higher levels of β-amyloid in rat models, potentially exacerbating amyloid production.

COVID and Cognitive Impairment

Research has shown that lingering viral fragments after a COVID infection and lingering spike protein after a COVID injection can provoke many downstream effects that damage the brain. In some patients, this results in ongoing brain injury.

As demonstrated in Figure 1, multiple cognitive domains can be affected including memory, concentration, processing speed, mood, and behavior.

Prevalence and Severity

Rising amounts of data indicate disturbing trends showing COVID-19 can lead to lasting cognitive impairment and even a risk of Alzheimer's and other neurodegenerative diseases. Cognitive impairment is regarded as one of the most burdensome long-term consequences of COVID-19 and very well may become a burgeoning problem over time, even in younger people.

The prevalence of cognitive sequelae, also known as cognitive COVID, ranges from 12% to 80% across studies. These are daunting statistics.

Fatigue, headache, and brain fog are the most common neurologic symptoms of long COVID. According to a study from the University of California, San Diego, 68.8% of patients experienced memory impairment six months after being enrolled in the study. (15) Meanwhile, 61.5% experienced decreased ability to concentrate.

Data from React19, a nonprofit working with vaccine-injured patients, shows brain fog and cognitive impairment in over 70% of patients. Half of these patients struggled with the same symptoms at a one-year follow up. (17)

What Causes Alzheimer's Disease (AD)

The exact cause of Alzheimer's disease (AD) remains unknown. Current understanding suggests that the pathophysiological process may begin decades before clinical symptoms become apparent. (17, 18) Research has identified various environmental risk factors linked to the development of Alzheimer's disease, including exposure to electromagnetic fields, solvents, pesticides, toxic metals, and air pollution. (19, 20)

Despite significant advancements in understanding the disease, pinpointing a definitive cause has proven elusive, highlighting the complexity and multifactorial nature of Alzheimer's disease. Continued research is crucial to unravel the intricate mechanisms and potential triggers contributing to this debilitating condition.

Contributing Factors to Alzheimer's Disease (AD)

The development of Alzheimer's disease (AD) is influenced by a multitude of factors. These include exposure to heavy metals, pesticides, persistent organic pollutants, antibiotics, and food additives. Physical factors such as head trauma, post-traumatic stress, and nanomaterials, as well as alterations in the gut microbiome, poor nutrition, and poor metabolic health, also play a role. Additionally, vascular disease, alcohol consumption, smoking, lack of exercise, inadequate sleep, family history, age, gender, and various other factors contribute to the risk of developing AD. (17, 20, 22, 23)

COVID-19 and Neurodegenerative Disease Risk

Recovering from COVID-19 is associated with an increased risk of neurodegenerative diseases. (24-29) Multiple studies have found that COVID-19 increases the incidence of new-onset dementia in adults over 60. (24-29) Furthermore, brain fog and cognitive problems were reported in 80% of individuals who experienced adverse effects from the COVID-19 vaccine. The lingering presence of the spike protein and

its numerous downstream effects are believed to create significant impacts on both the body and brain. (24-29).

Neuropathology in Alzheimer's Disease: Plaques and Tangles

Amyloid originates from amyloid precursor protein (APP), a common and typical protein in the central nervous system. It can be processed in two ways: one producing a healthy soluble protein and the other generating toxic amyloid-beta (Aβ). Both processes occur naturally, and in healthy brains, amyloid-beta (Aβ) is efficiently removed before it causes harm. However, in Alzheimer's disease, there is an overproduction of amyloid-beta and/or a decreased ability to clear it from the brain.

Amyloid-beta is hazardous because it clumps together, forming small clusters called oligomers, which eventually aggregate into larger amyloid plaques. These aggregates trigger various chemical processes that damage and destroy neurons. One mechanism involves activating the immune system to cause inflammation, while another leads to the synthesis of aberrant tau proteins. (18, 30-32)

Tau

Tau proteins are essential for maintaining the proper shape of neurons and are typically located inside their axons. This is crucial because if the axon is disrupted, the messages it transports can leak out, preventing them from reaching the next cell in the chain. Neurofibrillary tangles are abnormal accumulations of tau protein that collect within neurons, disrupting their function. (18, 31, 32)

Recent research indicates that tau and amyloid-beta interact in complex and interdependent ways. Initially, amyloid-beta clusters form, and once these levels surpass a certain threshold, there is an increase in aberrant tau. This interaction triggers a positive feedback loop, further driving the production of both amyloid-beta and abnormal tau, exacerbating the progression of Alzheimer's disease. (31)

Loss of Neuronal Connections and Cell Dysfunction

In Alzheimer's disease, neurons are progressively destroyed and lose their ability to function correctly throughout the brain. This leads to the breakdown of connections between neural networks and the shrinkage of various brain regions. By the end stages of Alzheimer's, this process, known as brain atrophy, becomes widespread, resulting in significant cell death and a substantial decrease in brain volume. (18, 31)

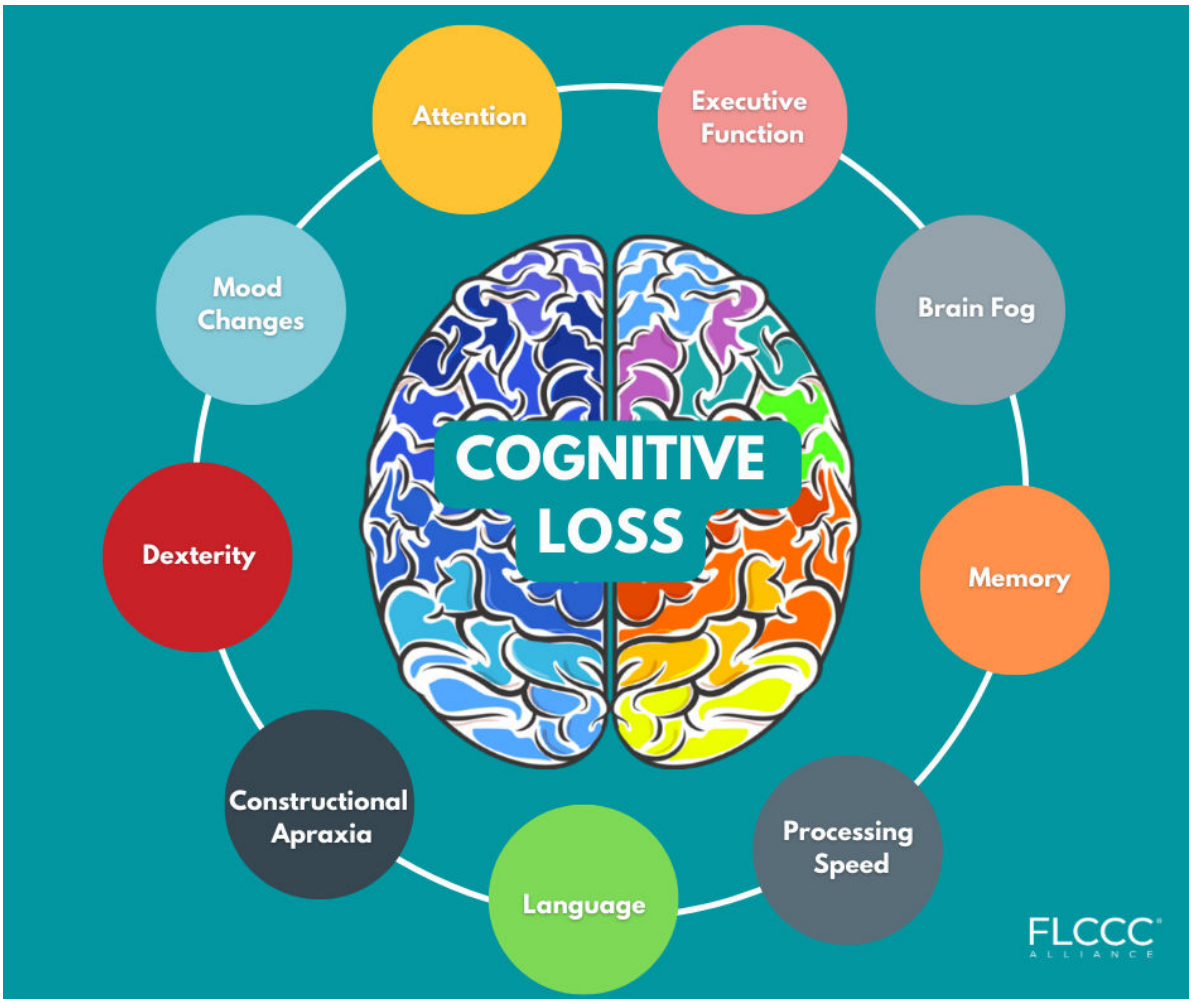

Figure 1: Multiple domains of cognitive loss (Source: FLCCC)

Impacts of Cognitive Impairment

These symptoms can significantly impact a person's quality of life, their ability to perform daily activities, and sometimes even their ability to work. Issues with visuo-spatial function and/or constructional apraxia (the inability to build, assemble, or draw three-dimensional objects) can have relatively subtle presentations with serious day-to-day consequences, including driving safely.

In a study published in The Lancet in January 2024, significant psychomotor slowing was found in individuals diagnosed with post-COVID conditions. These patients had slower reaction times and were 'less vigilant.' (18)

It is important to recognize that these symptoms can be attributed to many health conditions, and we ask that patients please discuss any concerns with their functional medicine or healthcare provider.

All patients with cognitive impairment need a thorough evaluation as part of general health screening. A recent study by Golderisi et al showed an astounding 45% of patients 11 months post COVID had cognitive impairment on testing. (19)

Lifestyle Modifications to Help with Brain Health

If neurological symptoms are secondary to long COVID and/or long vax (post-vaccine syndrome) it is important for patients and providers to also follow the FLCCC I-RECOVER treatment guide. (20)

The following are some lifestyle modifications that are beneficial for brain health. These should be used in conjunction with the nutritional supplements described below.

Dietary Changes

A large study published in 2022 showed that higher consumption of ultra-processed foods was related to a higher risk of dementia. (21) These common foods — including soft drinks, potato chips and other salty snacks, deep-fried or packaged meats, bottled condiments, prepackaged sweets and breads, and flavored breakfast cereals — are high in added sugar, fat, and salt, and low in protein and fiber.

Participants were divided into four groups based on how much ultra-processed food they ate, and they were tracked for a decade. While none had dementia at the start of the study, the risk for Alzheimer's rose 14% for every 10% increase in ultra-processed foods consumed; for dementia overall, the risk increased by 25%. (22)

Patients should start with adjusting their food intake and opt for a low-inflammatory/non-GMO diet. Some patients may also consider eliminating gluten from their diet, as gluten has been linked to neurological problems for decades. (23) In a 2023 study, (23, 24) mice fed a diet with gluten had profoundly more brain inflammation in the hypothalamus, which is a key brain region for metabolic control. (24)

The FLCCC Eat Well Guide to Fasting and Healthy Eating is a good place to start. Also see the section at the end of this document on nutrition.

Intermittent Fasting

Intermittent fasting (25) has many brain benefits, including upregulating and increasing brain-derived neurotrophic factor (BDNF, see section of BDNF below), lowering inflammation, reducing cortisol, and lowering insulin resistance. Fasting can trigger a cell-recycling process called autophagy, which helps our body remove damaged cells, including senescent cells. (25)

Please note that fasting is contraindicated in patients younger than 18 (because it impairs growth) and during pregnancy and breastfeeding. Patients with diabetes, as well as those with endocrine disorders, hormonal imbalances, or any serious underlying medical conditions, should consult their primary care provider before starting a fasting regime, as changes in medications and close monitoring may be required.

What is brain-derived neurotrophic factor (BDNF) and why it is important?

Brain-derived neurotrophic factor, or BDNF, is a growth factor and peptide (long-chain protein). The term is derived from the Greek words *neuro* "nerve" and *trophis* "pertaining to food, nourishment, or growth."

In a nutshell, BDNF supports the survival of neurons and brain cells, enhances synaptic connections between neurons, and is required for learning and long-term memory preservation. (1-3) For adults, BDNF is also important in neurogenesis (the development of new neurons from stem cells). (4)

BDNF can be found in the kidneys, blood plasma, and saliva, but its primary activities are in the brain and central nervous system. (5, 6)

Additional facts regarding BDNF:

- Aging causes decreasing levels of BDNF, which appears to cause gray matter shrinkage and fewer synapses, making learning and memory formation more difficult. (7)

- Antidepressants might function by boosting BDNF levels. (8) Depression and anxiety are associated with reduced BDNF levels; nevertheless, medications may enhance BDNF expression and reverse hippocampal atrophy. (8)

- Cannabinoids like THC raise BDNF levels in those who don't consume cannabis often, but not in chronic smokers, which could explain why smoking cannabinoids regularly can damage your memory. (9)

- People with low BDNF levels may be more prone to anxiety and binge drinking, according to a 2020 study. (10)

- Alzheimer's and dementia patients have extremely low BDNF levels. (11, 12) Some scientists believe that increasing BDNF levels can help people maintain their brain function. (13) Other research suggests that the higher your BDNF levels, the lower your risk of Alzheimer's and dementia. (14)

To summarize, BDNF has an active involvement in the hippocampus, prefrontal cortex, and other brain regions. (16) Because these areas are involved with memory and cognition, BDNF appears to be important for both higher brain functioning and brain cell health.

Optimize Gut Healing

The gut-brain axis is a fascinating and increasingly studied area in both neuroscience and gastroenterology. It refers to the bidirectional communication network that links the central nervous system (which includes the brain and spinal cord) with the enteric nervous system (the nervous system of the gastrointestinal tract). This relationship involves complex interactions through neural, endocrine (hormonal), immune, and metabolic pathways.

Optimal gut health is important because it helps balance the relationship between these systems:

- **Neural Communication:** The gut and brain are connected through the vagus nerve, one of the largest nerves connecting the gut and brain. It sends signals in both directions. For example, stress can lead to gastrointestinal issues, and conversely, gut issues can lead to anxiety or depression.
- **Hormonal and Neurotransmitter Pathways:** The gut produces a wide range of hormones and neurotransmitters that are critical for brain function. For instance, the majority of the body's serotonin (a key neurotransmitter that affects mood and social behavior) is produced in the gut.
- **Immune System Regulation:** The gut is a key part of the immune system. An imbalanced gut microbiome can lead to chronic inflammation, which is implicated in many brain disorders including depression and Alzheimer's disease.
- **Metabolic Contributions:** The gut microbiome influences the body's metabolism, including the production of short-chain fatty acids (SCFAs) like butyrate, propionate, and acetate. These SCFAs have various beneficial effects on brain health, including neuroprotection and reducing inflammation.

These dietary components can lead to a range of gut health issues, including:

- **Dysbiosis:** An imbalance in the gut microbiota, which can lead to gastrointestinal disorders, inflammation, and increased susceptibility to infections.
- **Increased Gut Permeability:** the intestinal barrier becomes compromised, allowing bacteria and toxins to pass into the bloodstream.
- **Inflammation:** Chronic low-grade inflammation in the gut can contribute to various health issues, including inflammatory bowel diseases, obesity, and metabolic disorders.
- **Reduced Diversity of Gut Microbiota:** A less diverse gut microbiome is associated with poorer health and increased risk of chronic diseases.

Emerging research also suggests a strong gut-brain link in mental health and that an imbalanced gut microbiome has been associated with cognitive decline. Conditions like anxiety, depression, and even autism spectrum disorder have been linked to imbalanced gut health.

The pursuit of optimal gut health is much more than a dietary trend; it's a fundamental aspect of holistic health and wellbeing. By nurturing our gut health through a balanced diet rich in fiber, probiotics, and prebiotics, along with mindful lifestyle practices, we can support our mental and physical health in profound ways.

Exercise

Regular exercise has positive effects on the brain, including increasing BDNF, restoring neurotransmission and remyelination, refining the integrity of the blood-brain-barrier, and improving immune responses. Exercise can also mitigate the effects of chronic inflammation and auto-immunity.

Exercise does not have to be extreme. In fact, it can be as simple as increasing the amount of movement you get throughout the day and avoiding sitting for extended periods. Incorporate a daily walk, preferably outdoors, and work up to walking for a minimum of 30 minutes. A study published in JAMA Neurology found that as little as 3,800 steps a day reduced the risk of dementia by 25%. (26) Increasing that amount and increasing the intensity reduces the risk even further. Walk with a purpose, as if you were late to an appointment. Vary your speed and add periods of running as you're able.

Resistance or strength training brings about an increase in muscle mass. (27) This helps improve insulin sensitivity, which is important to reduce the risk of Alzheimer's disease. It also prevents the sarcopenia (muscle loss) often associated with aging.

Aerobic exercise training can increase the size of the anterior hippocampus, a section of the brain involved in cognitive functions such as memory, navigation, and perception. In a 2011 randomized controlled trial with 120 older adults, exercise training led to improvements in spatial memory. Participants started by walking for 10 minutes and increased the walking duration weekly by 5-minute increments until they were walking 40 minutes at a targeted heart rate (50–60% of the maximum heart rate reserve for weeks 1 to 7 and 60–75% for the remainder of the program.) Results showed an increased hippocampal volume of 2%, effectively reversing age-related loss in volume by 1 to 2 years. The researchers also demonstrated that increased hippocampal volume is associated with greater serum levels of BDNF, a mediator of neurogenesis in the dentate gyrus. (28)

Also, consider adding a mind-body practice such as yoga, tai chi, or even ballroom dancing. Some experts believe that the act of going upside down in a 'downward dog' or headstand can help clear the fog in our minds. When you attend a yoga class, you may also get a chance to work on your mindful breath work, which is sometimes referred to as *pranayama*.

Outdoor Activities

A large body of research points at nature as a positive promoter of mental health. (29) Nature-based activities can mean things like skiing, hiking, snowmobiling, horseback riding, or fishing, but can also include viewing, photographing, and studying nature. Even visiting a garden or taking part in gardening activities can have positive effects on well-being.

Sleep

Growing evidence shows that getting quality sleep is correlated with improved brain health. The glymphatic system — a waste clearance system active in the central nervous system during the first half of the night, in slow wave sleep — is a major 'power wash,' for the brain, clearing it of all the toxins from a day of activity.

Past research has demonstrated the role of the immune system in clearing up toxins that can contribute to Parkinson's disease and Alzheimer's disease. (30) New research from neurologists presenting at the Annual Meeting of the American Neurological Association (ANA) looks at how getting good sleep can decrease the risk of neurological disorders like Alzheimer's disease and Parkinson's disease. (31)

According to the results of a February 2024 survey published in Frontiers in Public Health*,* 76% of people who reported mild COVID-19 infections in the six months prior to the survey said they now experience insomnia, with 22.8% of those respondents saying their insomnia is severe. (32)

Poor sleep affects our ability to make decisions, solve problems, and control our emotions. Sleep deprivation can increase the risk of chronic health problems such as high blood pressure, obesity, and heart disease.

Prioritize sleep by making these simple lifestyle changes:

- Try to go to bed and get up around the same time every day, even on weekends.
- Minimize the number of non-sleep-related things in your bedroom (e.g., a TV or desktop computer) and avoiding intellectual activity or social media in your bedroom.
- Maintain a cool bedroom temperature (65-68°) to improve sleep. Adjust your thermostat for your personal comfort level.
- Find a relaxing pre-bedtime routine that does not include screens (perhaps reading or a warm bath, gentle stretching, or applying lavender essential oil).
- Wind down at least one hour before bed by shutting off your electronics, which are associated with a higher incidence of insomnia and shorter sleep duration, per 2018 research. (33)
- Avoid caffeine and nicotine patches in the afternoon, are they are stimulants that can interfere with sleep.
- Keep your room dark (use blackout shades, if necessary) and consider running a sleep sound machine to mask street or household noises.

Address Hearing Loss

Improved hearing seems tied to better brain outcomes, and hearing loss appears to cause structural changes in the brain. (34) As Medical News Today reported, "A landmark 2020 study found that people with hearing loss are more likely to develop dementia. Though an association between the two conditions is clear, their exact relationship is less so."

Early Morning Light

A study in the Journal of Sleep Research demonstrates that exposure to bright light in the morning can notably increase alertness. (35) The research on college students found that just 1.5 hours of bright light early in the day not only improved sleep quality but also significantly reduced morning sleepiness, emphasizing the role of morning light in enhancing daily alertness. Incorporating morning light into daily routines is like using a natural medicine.

Stress Reduction

Stress can also impact how the brain functions: when you're in 'fight-or-flight' mode, more energy, nutrients, and resources are funneled to parts of the brain associated with survival and threat mitigation. Meanwhile, other areas, including those responsible for creating memories and high-level cognitive processing, get the bare minimum.

A study published in the journal *Neurology* helps shed new light on just how damaging chronic stress can be to the brain. (36) Researchers examined cortisol levels, brain size, and structure — plus memory and cognitive functioning — in more than 2,000 people in their 40s and 50s. Those with higher levels of cortisol in their systems had smaller brains and scored worse on memory and cognitive tests — even though none of the participants exhibited noticeable symptoms of cognitive decline or memory problems. More specifically, changes and damage were seen in parts of the brain that move information between the right and left hemispheres, plus areas associated with thought, speech, emotions, and muscle function. (36)

Social Connections

Loneliness leaves us anxious and depressed. It also changes our biochemistry, contributing to inflammation and reduced immunity. (37) Social isolation is also linked to a higher risk of stroke, obesity, and neurodegenerative diseases such as Alzheimer's. (38)

Look for ways to foster real, in-person social connections. Ideas include spending more time with family and friends — think about how you can share activities you already do as a matter of course (exercising or eating, for example) with someone else. Look to join a group, club, or class based on an interest or hobby you may have, volunteer with a local organization that has a mission you care about or get involved in your community. As much as possible, look for ways to interact face to face. Television, phone calls, and online platforms are weak substitutes.

Key Supplements to Help With Brain Health

Multivitamins

Far too often, whether because of a lack of access or a lack of time, we turn to convenience foods that are highly processed and contain excess salt, fat, refined sugar, and numerous additives. This Standard American Diet (SAD) nutritional approach tends to provide very few vitamins.

Even if you try to follow a healthy dietary regimen (i.e., non-GMO, organic, grass-fed and free-range products), there is mounting evidence that many whole foods simply do not contain the same levels of vitamins and nutrients as they did decades ago. Over time, this can potentially impact our health.

Therefore, a daily multivitamin is recommended. Micronutrients provide critical building blocks of neurotransmitters, which enable the brain to produce and transmit signals. Consuming adequate micronutrients may prevent and potentially help treat neurological diseases like Alzheimer's and Parkinson's Disease, according to research published in Nutrients. (39)

In the third COcoa Supplement and Multivitamin Outcomes Study (COSMOS), researchers looked at the effects on cognitive health in 573 participants who took a daily multivitamin containing 20+ micronutrients; study methods included close examination of all participants through direct visits. In conjunction with the research, a meta-analysis of more than 5,000 individuals was also conducted across three cognition studies within the trial. (40)

The findings showed adults taking the multivitamin supplement exhibited a statistically significant reduction in memory loss and cognitive aging compared to those on a placebo.

The mineral manganese is essential for proper utilization of the neurotransmitter acetylcholine, which transmits signals from the brain to cells throughout the body. Acetylcholine is a neurotransmitter that plays a role in memory, learning, attention, and arousal.

The minerals selenium, copper, and zinc help reduce elevated homocysteine levels associated with cognitive impairment. (41-43) High levels of this homocysteine have been linked to vascular damage, reduced blood flow to the brain, and heightened susceptibility to neurodegenerative disorders. Vitamins A, B, C, D, and E can also help prevent high homocysteine levels, according to the study.

Micronutrient deficiency is associated with increased Parkinson's disease risk, according to the research. For example, low vitamin B6 (Riboflavin) levels have been linked to a high risk for the disease. Additionally, Parkinson's patients with impaired sense of smell had low dietary vitamin B1 (thiamine) and folate intake for about two years before symptom onset.

For more information on vitamins and nutraceuticals, please refer to the Tools and Guides section of the FLCCC website and, specifically, the FLCCC From A to Zinc Nutrient Guide.

B Vitamins

The eight types of B vitamins include Vitamin B1 (thiamin), Vitamin B2 (riboflavin), Vitamin B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folate), and B12 (cobalamin). (44) While the B vitamins all have a similar molecular structure, they each have very different roles within the body.

B-complex vitamins will supply at least 100% of the daily value for each B vitamins needed (*niacin, folate and riboflavin)* to fuel the mitochondria.

Riboflavin ameliorates oxidative stress, mitochondrial dysfunction, neuroinflammation and glutamate excitotoxicity, all of which take part in the pathogenesis of Parkinson's disease, migraine headaches, and other neurological disorders. (45-47)

Follow dosage recommendations for the particular product you are using.

Note: Vitamins such as B vitamins need to be converted in the body into their active or methylated form to be used. Depending on one's genetics (e.g., presence or absence of MTHFR mutation) there can be great benefit from a methylated option of B vitamins.

Resveratrol

Resveratrol (500-1000 mg daily) increases cerebral blood flow, boosts BDNF, protects mitochondria, and prevents the release of toxic glutamate during a stroke. Resveratrol is associated with the removal of β-amyloid peptides from the Alzheimer's brain and neurons. It increases nitric oxide bioavailability and thereby facilitates the endothelium-dependent vasodilatation necessary for adequate cerebral perfusion. (48-51)

Omega-3 Fatty Acids

Omega-3 fatty acids promote cognition, neuronal preservation, protection against neurodegeneration, and synaptic plasticity. It is needed to help make cell membranes and upregulates autophagy. Omega-3s also enhance the glymphatic system. (52-55)

A combination of EPA/DHA with an initial dose of 1 g/day (combined EPA and DHA) and increasing up to 4 g/day (of the active omega-3 fatty acids) is recommended. (52-55)

Methylene Blue

Methylene Blue helps lower neuroinflammation, supports mitochondria, upregulates autophagy, restores important neurotransmitters like acetylcholine and serotonin, and has been shown to help reduce prions. It is also able to help spike-infected cells remove spike protein by degrading and recycling cellular and mitochondrial materials. (56-59)

Refer to the FLCCC I-RECOVER: Post-Vaccine Syndrome guide for detailed information on sourcing, dosing, and mixing methylene blue, as well as important safety precautions and contraindications. Note that the optimal dose is highly individualized to each patient.

Melatonin

This multifunctional molecule has been shown to have antioxidant, anti-inflammatory, and immunomodulatory properties. It also has antithrombotic effects and can upregulate autophagy. (60-62) In a study published in NeuroReport, melatonin promoted long-term memory by modulating protein phosphorylation. (60)

As we age, our melatonin levels decrease. Low melatonin levels are associated with an acceleration of biological aging. (63) Normal brain aging is linked to cellular senescence, in which aging cells linger in the body, causing accelerated free-radical, or oxidative, damage.

The neuroprotective effects of melatonin can be attributed to many factors. It easily crosses the blood-brain barrier. It appears to cushion the brain from the effects of "stress" hormones such as epinephrine, cortisol, and norepinephrine, which can impair memory. It also increases levels of a protein known as a brain-derived neurotrophic factor (BDNF), which increases the formation of neurons. (64)

Suggested dosing is 1-5 mg, ideally of a slow-release formulation, before bedtime. Increase as tolerated. Patients who are slow metabolizers may have very unpleasant and vivid dreams with higher doses.

Berberine

Berberine raises neurotransmitters in the brain like acetylcholine, norepinephrine, and serotonin. Berberine downregulates four enzymes (monoamine oxidase A, monoamine oxidase B, acetylcholinesterase, and butyrylcholinesterase) that play key roles in the development of Alzheimer's disease. (65-74)

Suggested dosing is 500-1500 mg daily.

Green Tea/EGCG

EGCG, a type of polyphenol antioxidant found in a variety of tea leaves including green tea, can prevent or delay the amyloidogenic process. There is evidence for EGCG's ability to inhibit the aggregation of α-synuclein, amyloid-β, and huntingtin proteins, respectively associated with Parkinson's, Alzheimer's, and Huntington's diseases. EGCG also has anti-platelet effects, which can prevent micro-clotting. (75, 76)

Suggested dosing is 500-1000 mg daily.

Luteolin

Luteolin is a flavonoid that is more potent than quercetin and can enter the brain. It has neuroprotective properties and, according to a 2012 research publication, has antioxidant, anti-inflammatory, anti-allergy, and neuroprotective properties. (77)

N-acetyl cysteine (NAC)

NAC comes from the amino acid L-cysteine and is a powerful antioxidant. NAC can also increase levels of glutathione, which is vital in cellular antioxidant pathways. Glutathione levels in the brain decline as we age and decline further in patients with neurodegenerative disease. (78) NAC easily crosses the blood-brain barrier, can help modulate glutamate, can boost neurogenesis, and is neuroprotective. NAC's ability to replenish glutathione and regulate brain glutamate levels can boost brain health. The neurotransmitter glutamate is involved in a broad range of learning, behavior, and memory functions, while the antioxidant glutathione helps reduce brain cell oxidative damage associated with aging.

Suggested dosing is 600-1200 mg daily.

More on GABA, Glutamate, and Brain Health

GABA is synthesized from glutamate via the enzyme glutamic acid decarboxylase. GABA and glutamate operate as "on" and "off" switches. They operate in opposing ways. GABA is the brain's primary inhibitory neurotransmitter, preventing chemical messages from traveling from nerve cell to nerve cell. Glutamate, on the other hand, is the primary excitatory neurotransmitter in the brain, allowing chemical messages to be transmitted from nerve cell to neuron cell. (79, 80)

To have a fully functioning brain, a delicate equilibrium must be maintained between GABA's inhibitory and glutamate's excitatory actions. (79, 80) A disturbance in the excitatory/inhibitory balance, can cause faulty signaling, which can result in reduced cognitive and motor performance or neurological disorders/diseases, in some cases, significant neuronal injury. (80) GABA also interacts with another neurotransmitter, serotonin. In fact, numerous neurotransmitters interact with and against one another, and a specific relationship must be maintained for the body and brain to function effectively. (79, 80)

Uridine Monophosphate (UMP or 5’-uridylic acid) and Phosphatidylcholine (PC)/ CDP-choline

There is growing evidence indicating that individuals with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) often exhibit a significant deficit in three critical brain nutrients: uridine, choline, and docosahexaenoic acid (DHA). (96-98)

Uridine Monophosphate (UMP or 5’-uridylic acid), a pyrimidine nucleoside found in all living organisms including humans and microbes, plays a vital role in the development of neurons and synapses. UMP efficiently crosses the blood-brain barrier and promotes the formation of neurites—projections from neurons that facilitate connections with other neurons. (96, 99) Notably, a deficiency in uridine cannot be remedied through regular dietary intake, underscoring its importance as a conditionally essential supplement for those affected. (96)

Choline is an essential micronutrient crucial for proper brain development and cognitive function throughout life. (96, 100) Cytidine Diphosphate Choline (CDP-Choline), also known as Citicoline, is a unique source of choline naturally present in every cell of the body. Upon digestion, it splits into cytidine and choline, which, once in the brain, recombine to form CDP-Choline. This process is vital for memory, learning, cognition, and recall, as these functions rely on precise electrical transmission between neurons. Cholinergic insufficiency is a notable characteristic of Alzheimer's disease. (101, 102)

Choline offers protection against Alzheimer's disease by lowering homocysteine levels, an amino acid associated with neurodegeneration and amyloid plaque formation, and by suppressing microglia activation, thereby reducing brain inflammation. As a precursor to acetylcholine, a neurotransmitter essential for brain and nervous system function, choline plays a significant role in fetal brain development, memory, muscle control, mood, and gene expression. (103)

Phosphatidylcholine (PC) is a choline-containing phospholipid and a significant component of lecithin, a yellow-brown fatty substance found in egg yolk, organ meats, nuts, and spinach. While lecithin and phosphatidylcholine are often used interchangeably in medical literature, lecithin contains other substances besides PC. Phosphatidylcholine is crucial for brain cell reproduction and can enhance attention and concentration. It rapidly crosses the blood-brain barrier and may help mitigate inflammation and metabolic stress response circuits within the NEM stress response. (103)

In summary, PC supports long-term memory, neuron repair, and serves as a precursor for acetylcholine (ACH) synthesis. It helps prevent brain cell death during pneumonia, protects neuronal membranes from free radical damage, and assists in liver repair. (103)

CDP-Choline is essential for synthesizing phosphatidylcholine (PC), a precursor of the neurotransmitter acetylcholine (ACh) produced by neurons. (101, 102) Increased levels of PC and acetylcholine are associated with enhanced cognitive function. (96, 100, 102, 104, 105) Additionally, CDP-Choline boosts adenosine triphosphate (ATP) in brain cells. (100, 104, 105)

Clinical evidence from randomized controlled trials indicates that a multi-nutrient product enriched with uridine, choline, and DHA can help manage mild cognitive impairment (MCI) caused by Alzheimer's disease. (96, 98)

Uridine and choline synergistically interact with DHA to promote phosphatidylcholine synthesis.
For optimal benefit, take uridine with DHA (Omega-3) and CDP-Choline.

Suggested dosing is 150-250 mg twice daily.

Note: Higher doses were used in clinical trials, ranging from 1g/day in depressive teens to 2g/day in healthy adults. This amount can be divided into two or three doses throughout the day. Since poor methylators might not tolerate uridine well, it is advisable to start with a low dose and gradually increase it. (96)

Recommended dose of CDP-Choline is 250-500 mg per day, taken once in the morning and once in the early afternoon. Do not exceed twice daily. (100)

Recommended dose of Phosphatidylcholine (PC) is 1200-5000 mg per day, divided into three or four doses with fats/meals. Choose between PC or CDP-Choline. (103)

Phosphatidylserine (PS)

Phosphatidylserine (PS) is significantly more abundant in the brain than in any other organ, and it has the greatest clinical value as a brain nutrient. Nerve cell homeostasis, maintenance, and specific functions are all membrane-based processes that use membrane phosphatidylserine. Cognitive performance may benefit when individual nerve cell health improves. (81) PS improves the brain's fuel

efficiency by increasing neuronal metabolism and accelerating acetylcholine synthesis. As we age, our bodies' production of phosphatidylserine decreases, affecting our ability to operate fully. PS supplementation has been shown in studies to reduce and even reverse diminishing memory and concentration, sometimes known as age-related cognitive decline, in middle-aged and elderly people. (81-85) The 16 clinical trials with PS for cognition (11 double-blind, 5 less stringently controlled) consistently showed that PS provides metabolic support for memory, learning, concentration and behavior. (81, 82, 86-90)

Difference Between PC and PS
PC is required for making PS; the human body can convert PC to PS but not vice versa. PS is made from PC by substituting the ethanolamine head of phosphatidylethanolamine (PE) with L-serine, a non-essential amino acid. (86, 87)

PS May Lower Cortisol Levels and Regulate Circadian Rhythms
Available research indicates that PS may suppress cortisol levels, and both PC and PS are implicated in circadian rhythm regulation. (81, 88-95) PS and omega-3 fatty acids may be useful in treating late-life depression by regulating basal levels and the circadian rhythm of salivary cortisol. (93) Supplementation with PS may also aid to preserve hypothalamic function and benefit the aging hypothalamus-pituitary-adrenal axis. (81)

Hellhammer et al. studied the effects of a three-week soy lecithin phosphatidic acid and phosphatidylserine complex (PAS) consumption on mental and emotional stressors in a randomized, placebo-controlled study of chronically stressed males. When compared to placebo, 400 mg of PAS resulted in a significant reduction in serum ACTH and cortisol levels, as well as favorable effects on emotional reactions; however, higher doses (600 mg and 800 mg) did not provide the same results. (95)

PS' membrane-based action mechanisms make it compatible with other nutrients that are safe but have distinct methods of action, such as Ginkgo biloba extract and acetyl-L-carnitine. PS is also completely compatible with vitamins, minerals, antioxidants, and other nutrients, all of which are expected to enhance its effectiveness. PS is not drug contraindicated, is unlikely to interfere with the effects of the limited pharmaceuticals available for cognitive decline, and can be safely used in conjunction with them. (81)

Recommended dose: 100-300 mg per day; take with fats or meals. (82)

Intakes in the trials ranged between 200 to 500 mg per day; an acceptable supplementation strategy would be to take 200-300 mg per day (in two or three separate doses with meals) for the first month, then reduce to 100-200 mg per day. (81)

Fisetin

Fisetin has been shown in preclinical models to be effective at preventing the development and/or progression of multiple neurological disorders including Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis, stroke (both ischemic and hemorrhagic) and traumatic brain injury, as well as to reduce age-associated changes in the brain. (96) Other research has found that fisetin supports the aging brain by inducing autophagy. (97)

The recommended dosage of fisetin varies depending on the individual's health status and the specific health goal. For general health maintenance, a daily dosage of 100-500 mg is often suggested. However, for those seeking to leverage fisetin's potential anti-ageing benefits, a higher dosage of up to 1000 mg per day may be recommended.

Nicotinamide Adenine Dinucleotide (NAD)

Nicotinamide adenine dinucleotide (NAD) is an essential cofactor in all living cells, and it is involved in fundamental biological processes. NAD levels decline with age, which has been linked to age-related conditions. NAD depletion has been associated with hallmarks of aging and may underlie a wide range of age-related diseases, such as metabolic disorders, cancer, and neurodegenerative diseases. (98, 99)

NAD-boosting precursors replenish this essential molecule, enabling the transfer of energy from the foods we eat to vital cell functions, especially in the brain. (100, 101)

Follow dosage instructions on package.

Vitamin D

Low vitamin D affects astrocytes and the blood-brain barrier. Vitamin D deficiency is linked to brain volume loss. (102) Recommended Vitamin D blood levels are between 60 and 100 ng/ml.

Vitamin D can inhibit TLR-4, which drives microglial activation. TLR4 is activated by spike protein. (103) A recent study found that vitamin D supplementation is linked to lower incidence of dementia (104) and may help clear amyloid. (105)

Taurine

Taurine is abundant in dairy products like cow's milk and ice cream and is found in large quantities in shellfish such as mussels, scallops, and clams. It is also present in the dark meat of chicken and turkey. Remarkably, cooking does not diminish taurine levels. In most mammals, taurine is primarily produced in the liver and transported across the blood-brain barrier into the brain parenchyma (116). Taurine levels decrease with age, but supplementation has been shown to improve mitochondrial function and lifespan in animals, suggesting its potential for promoting longer, healthier lives (117, 123). At the molecular level, taurine reduces inflammation, oxidative damage, endoplasmic reticulum (ER) stress, and calcium dysregulation while enhancing neuronal activity (116). ER stress significantly contributes to prion diseases and other neurodegenerative disorders such as Parkinson’s and Alzheimer’s diseases. Taurine has neuroprotective effects against ER stress pathways, which are activated when the ER's protein-folding capacity is exceeded (116, 125).

Additionally, taurine has been shown to improve brain function and protect against dementia-related changes and brain injuries (122). It defends against neurotoxins and may slow age-related neurological decline. Higher taurine intake is linked to improved cognitive performance in the elderly. In a 14-week study with elderly women, a daily intake of 1,500 mg of taurine, combined with bi-weekly exercise, reduced inflammation, protected the blood-brain barrier, and enhanced cognitive test scores (128).

Patients with Long-COVID have lower taurine levels compared to controls, and supplementation can aid in managing Long-COVID due to taurine's antiviral properties and its ability to regulate endothelial inflammation (129). Taurine also helps manage mast cell activation and mitigates allergic inflammatory reactions, reducing symptoms of allergic rhinitis and decreasing eosinophilic and mast cell infiltration in the nasal cavity (116, 130). Moreover, taurine offers numerous cardiovascular benefits, including improved endothelial health, better blood pressure management, enhanced cardiac fitness, and overall vascular health (124).

Therapeutic areas of taurine include treatment of the following diseases or disorders:

- Depression (116)
- Neurodegenerative Disease: Recent studies have demonstrated taurine's pharmacological potential against neurodevelopmental disorders. Taurine protects against toxicity in models of neurodegenerative diseases such as Parkinson's, Alzheimer's, and Huntington's. (116-121)
- Stroke (116)
- Traumatic Brain Injury (TBI): Taurine significantly enhances functional recovery and reduces glial fibrillary acidic protein accumulation and water content in the penumbral region following induced traumatic brain injury. (116, 122)
- Spinal Cord Injury (116)
- Epilepsy (116)
- Diabetic Neuropathy (116)

Recommended dose of Taurine is 500 mg twice daily.

Magnesium L-Threonate

Magnesium protects against high levels of glutamate excitotoxicity and helps to raise GABA, the calming neurotransmitter. Most people are deficient in magnesium; therefore, supplementation is recommended in some form.

Its functions include helping with muscle and nerve function, regulating blood pressure, and supporting the immune system. Magnesium improves mitochondrial ATP synthesis, and thus provides greater ATP availability (energy source). It has been shown to be the activator of ATP synthesis.

Magnesium is not only a required cofactor but also an ATP chelate for all SAMe methylations, which occur in the mitochondria. Numerous clinical studies have found that magnesium has beneficial effects in patients suffering from neuropathic pain.

Acetyl-L-Carnitine (ALCAR)

Acetyl-L-Carnitine (ALCAR) is a derivative of L-Carnitine, an amino acid naturally produced in the body. (106) ALCAR promotes memory and cognitive function and mitochondrial support and can stimulate acetylcholine receptors in the brain. (107, 108)

Low Dose Naltrexone (LDN)

Naltrexone is an opiate receptor antagonist at doses of 50 mg, but at lower doses of 1-4.5 mg it appears to have unique immunomodulation activity. At these doses, it is known as LDN. LDN reduces the production of inflammatory cytokines.

LDN dosage varies from .5-4.5 mg daily. Begin with 1 mg daily and increase to 4.5 mg daily, as required. It may take 2 to 3 months to see the full effect.

Ashwagandha

Ashwagandha likely enhances GABA receptors (the receptors that calm your anxiety response) and boosts serotonin in the brain, inhibiting an overactive fight-or-flight reaction. (109, 110) It works as an antioxidant, an anti-inflammatory, blocks Aβ production, inhibits neural cell death, promotes dendrite extension, neurite outgrowth and restores synaptic function, neural regeneration, reverses mitochondrial dysfunction, improves auditory–verbal working memory, executive function, processing speed, and cognition in patients. A recent study published in the journal Cytokine found that an isolated extract from ashwagandha improved cognitive skill, and reduced inflammation. Ashwagandha can also be helpful for adrenal fatigue. (109, 110)

Recommended dose is 500-1000 mg daily with food. (109)

Lion's Mane

Lion’s Mane is an ancient Chinese medicinal mushroom. It has proven neuroprotective qualities, an ability to stimulate the production of nerve growth factor (NGF), and potential for cognitive enhancement and relief of depression and anxiety. NGF is a specific type of brain protein that plays an essential role in brain plasticity, learning, and memory and it may help reduce amyloid. (111, 112))

Other benefits of lion’s mane may include: (113)

- Antioxidant and anti-inflammatory properties
- Supporting immune function
- Relieving anxiety and depression
- Lowering cholesterol
- Cancer prevention or treatment
- Controlling blood sugar
- Cognitive benefits

Recommended dose is 500 to 3000 mg daily.

Lithium Orotate

The accumulating evidence from epidemiological and cellular investigations suggests that lithium is an essential trace element for optimal brain function. (114) Lithium appears to be neuroprotective, but insufficient lithium consumption (particularly in sensitive individuals) may predispose to and/or exacerbate a variety of mental and neurological diseases. (115) Lithium regulates the function of

glutamate, dopamine, serotonin, gamma-aminobutyric acid, acetylcholine, and glycine. (116) Lithium inhibits the activity of glycogen synthase kinases (GSK3), associated with cell proliferation, metabolism, inflammation, and apoptosis. Furthermore, lithium increases the expression of protective substances such as the brain-derived neurotrophic factor (BDNF) and its receptor. Lithium can resynchronize circadian cycles by altering clock gene expression. Lithium therapy has been proven to improve gray matter density as well as the size of the amygdala and hippocampus. Lithium has also been shown to boost the development of brain stem cells and protect against the effects of oxidative stress. (116, 117)

Lithium carbonate has been used for decades to treat bipolar depression. Lithium carbonate has a very narrow therapeutic index and a large spectrum of adverse effects, therefore its application is limited. (118) Lithium orotate (LO) has a broad therapeutic index and is linked with little toxicity even at high doses. Due to variations in pharmacokinetics, LO is more effective with fewer side effects than lithium carbonate. (119, 120) Orotic acid is a mineral transporter that easily transports inorganic ions like lithium, magnesium, and calcium across biological membranes. (119, 120)

It has been shown that microdose lithium (300 ug LO) can stabilize cognitive deterioration in Alzheimer's patients. (121) Long-term low-dose lithium exposure appears to exert antiaging properties and unambiguously reduces mortality in evolutionary diverse animals. (122) There are no established guidelines for the daily dose of LO. However, the standard dose prescribed by alternative health practitioners is a dose equivalent to 5 mg of elemental lithium. (115) The dosage of LO (elemental lithium) can be increased to 10-15 mg per day. Given the extended half-life of LO, it is recommended to administer it once daily. (119, 120)

Vinpocetine

Vinpocetine is derived from a compound found in common periwinkle plants. It is used as a prescription medicine in Japan, Europe, Mexico, and Russia to treat cognitive and cerebrovascular conditions, and is available as an over-the-counter nutritional supplement in the United States and Canada. Vinpocetine has been shown to increase cerebral circulation, reduce inflammation and oxidative stress, and improve alertness, cognition, concentration, memory, and mood. (148-150)

Vinpocetine exerts its effects through several mechanisms. Firstly, it inhibits phosphodiesterase type 1 (PDE1) and reduces calcium levels in brain cells, which increases blood flow to and within the brain by relaxing smooth muscle in blood vessels. This enhanced blood flow delivers more oxygen and glucose, essential for ATP production, thus powering brain cells. Participants report better focus, memory, and overall well-being (148, 149). Secondly, vinpocetine has anti-inflammatory effects as it inhibits the upregulation of NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) by TNFα (tumor necrosis factor alpha), a protein complex involved in DNA transcription, cytokine synthesis, and cell survival, thereby reducing inflammation in neurons (148, 149). Additionally, vinpocetine possesses neuroprotective properties by preventing the buildup of sodium in neurons, decreasing oxidative stress, scavenging free radicals, and protecting against glutamate and NMDA toxicity (148, 149). Furthermore, vinpocetine improves neuroplasticity by increasing cAMP and cGMP levels, which activate kinases that phosphorylate transcription factors (CREB and SRF), leading to the activation of plasticity-related genes. This results in improved cognition and memory (148, 149, 151).

A placebo-controlled, randomized, double-blind trial conducted by the University of Surrey with 203 dementia patients showed that vinpocetine significantly improved cognitive performance and quality of life measures, including depression. Both 10 mg and 20 mg doses of vinpocetine three times daily were effective. (152) Research by Golovacheva et al. indicates that vinpocetine can help manage cognitive impairment in COVID-19 patients by regulating neurotransmitters and providing anti-inflammatory and antioxidant benefits. This is particularly beneficial for those suffering from the neuroinflammatory and oxidative stress consequences of lingering spike protein. (153, 149)

The recommended dosage is 10 mg three times per day. The daily dosage range is 15-60 mg, with a standard low dose of 5 mg at each of three meals and a higher dose of 20 mg at each meal. (150) Note: Vinpocetine should not be used by individuals with low blood pressure or those on blood thinners. It should be discontinued two weeks before any surgical procedure and can be resumed 48-72 hours post-procedure. (148)

Urolithin A (UA)

Urolithin A (UA) does not naturally occur in our diet but is produced by specific gut bacteria converting ellagitannins, found in fruits and nuts like raspberries, strawberries, pomegranates, walnuts, and almonds, into urolithin A. Mitophagy, the process of eliminating damaged mitochondria, is essential for maintaining normal physiological function and neuron health. In Alzheimer's disease, autophagy is disrupted, leading to the buildup of amyloid-beta (Aβ) in neurons and the formation of senile plaques. Research indicates that decreased lysosomal function is a contributing factor to Alzheimer's disease.

Studies have shown that UA enhances cellular health by activating autophagy and mitophagy while reducing harmful inflammation. Long-term UA treatment has significantly improved learning, memory, and olfactory function in several AD transgenic mice models. Additionally, UA reduces Aβ and tau pathologies and enhances long-term potentiation. An increase in glial fibrillary acidic protein (GFAP), an astrocyte marker linked to Alzheimer's pathology, was significantly elevated in AD brains but reverted with UA therapy.

Researchers found that long-term UA treatment improved learning, memory, and olfactory function in AD model mice. It affected the production of cathepsin Z, a protein that appears overactive in Alzheimer's brains and contributes to inflammation. UA therapy reduced cathepsin Z levels to those comparable to non-Alzheimer's brains, restoring certain cellular functions involved in biological waste breakdown. UA therapy also influenced immunological responses and other physiological mechanisms associated with Alzheimer's disease, reducing Aβ and tau pathologies and increasing long-term potentiation.

Mitochondrial dysfunction, commonly known as defective mitophagy, is prevalent in neurodegenerative disorders, indicating that the brain has difficulty removing weak mitochondria, impairing brain function. UA helps eliminate damaged mitochondria. Previous research identified elevated levels of dual-specific tyrosine phosphorylation-regulated kinase 1A (DYRK1A) in AD patients' brains. A newer study found that UA drastically lowered DYRK1A activity, resulting in tau dephosphorylation and additional stabilization of microtubule polymerization, significantly improving memory impairment in an Alzheimer's-like mice model.

Long-term UA supplementation has also shown to improve muscle endurance and plasma biomarkers, suggesting it may prevent age-related muscle deterioration. However, more research is needed to corroborate this finding.

Recommended dose is 500 mg twice a day.

Curcumin

Curcumin is one of the most extraordinary phytochemicals, exhibiting numerous biological and pharmacological activities, including anti-inflammatory, antioxidant, neuroprotective, chemoprotective, anti-arthritis, anti-atherosclerosis, anti-bacterial, anti-diabetic, anti-fungal, anti-hypertensive, anti-hyperlipidemic, anti-tumor, antiphlogistic, anti-psoriasis, antithrombotic, and anti-hepatotoxic properties. It has a unique molecular structure that modulates multiple signaling molecules affecting inflammatory and antioxidant processes, as well as directly impacting amyloid formation.

Curcumin enhances BDNF, lowers oxidative stress, and possesses anticoagulant, antiplatelet, and fibrinolytic activities. It inhibits senescence and can decrease spinal neuroinflammation by altering astroglia-mediated cascades, ensuring the treatment of devastating neurological disorders. Curcumin has been found to provide neuroprotection and prevent α-synuclein aggregation in Parkinson's disease models induced by lipopolysaccharides.

A study published online in 2019 in the American Journal of Geriatric Psychiatry investigated the effects of an easily absorbed curcumin supplement on memory performance in people without dementia, as well as curcumin's potential impact on microscopic plaques and tangles in Alzheimer's patients' brains. The results indicated that daily oral administration of a bioavailable and safe form of curcumin enhances memory function in middle-aged and older non-demented persons over an 18-month period. Furthermore, daily oral curcumin administration may reduce neuropathological accumulation in the amygdala and hypothalamus.

A study published in June 2021 in the journal Antioxidants builds on prior studies proving curcumin's significant antioxidant, anti-inflammatory, and anti-amyloid effects. Turmeric, the most concentrated form of curcumin, has been shown to disaggregate beta amyloid and prevent the formation of fibrils and oligomers. Curcumin has also been shown to be protective in animal models of seizures, migraine, ALS, Parkinson's disease, multiple sclerosis, and neuroinflammation.

The recommended dose is 500-2000 mg per day.

Tauroursodeoxycholic Acid (TUDCA)

Tauroursodeoxycholic acid (TUDCA) is a bile acid produced naturally in the liver. It has been used to treat liver disease and has a generally favorable safety profile. TUDCA serves as a mitochondrial stabilizer and anti-apoptotic agent in a variety of neurodegenerative disease types. In animal models, TUDCA exhibits cytoprotective, neuroprotective, and anti-apoptotic activity. It works by regulating and inhibiting the apoptotic cascade, reducing oxidative stress, protecting mitochondria, producing an anti-neuroinflammatory effect, and acting as a chemical chaperone to maintain protein stability and correct folding.

Ischemic-injured tissue induces ROS and oxidative stress, further increasing endoplasmic reticulum (ER) stress and transplanted-cell death. In vivo investigations have demonstrated that TUDCA diminishes ER stress-mediated cell death by modulating Akt-dependent cellular prion protein. TUDCA reduces amyloid-β deposition in the brain and levels of amyloid-β 1-40 and 1-42 in transgenic APP/PS1 AD mice, indicating reduced amyloidogenicity. Immune cell profiling revealed that patients using TUDCA supplements had significantly lower levels of numerous types of inflammatory T-cells than those who received a placebo.

A randomized, double-blind, placebo-controlled, single-center phase 1/2a experiment conducted at Johns Hopkins University from June 2018 to April 2022 assessed the safety and efficacy of TUDCA supplementation in 47 people with progressive MS. The TUDCA arm showed higher serum levels of several bile acids with no significant changes found in clinical or fluid biomarker outcomes. TUDCA treatment reduced central memory CD4+ and Th1/17 cells while increasing CD4+ naïve cells relative to placebo, with changes in the composition and function of gut microbiota also observed.

JNK, or c-Jun N-terminal kinase, is involved in the death of dopaminergic neurons in the substantia nigra pars compacta. A 2012 study on Parkinson's disease found that TUDCA is neuroprotective in an in vivo model of PD, functioning primarily by modulating JNK activity and cellular redox thresholds, as well as activating the Akt pro-survival pathway.

TUDCA was well-tolerated in two phase 2 trials, suggesting that adding it to standard therapy might delay ALS progression. The TUDCA-ALS research is the largest clinical trial ever done to assess the efficacy of TUDCA as an add-on treatment in persons with ALS.

TUDCA is not known to cause any major adverse effects when used in normal doses, with the most common being soft stools, diarrhea, nausea, and stomach bloating. Some patients who took more than 1,500 mg per day of TUDCA supplements reported diarrhea but no other negative effects.

Recommended dose is 1 gram twice a day.

Nattokinase (NK)/Serrapeptase (SP)/Lumbrokinase (LK)

Nattokinase (NK), a bacterial serine protease derived from Bacillus subtilis, has been reported to have potent fibrinolytic activity. (123, 124) It is one of the most active functional ingredients present in natto, a popular Japanese food made from fermented soybeans. (123, 125) This enzyme is known to directly degrade fibrin, particularly in its cross-linked form. (123, 126) It has four times the thrombus-dissolving activity of plasmin and has been demonstrated to enhance endogenous fibrinolysis by cleavage and inactivate plasminogen activator inhibitor 1 (PAI-1), resulting in efficient lysis of the body's detrimental blood coagulation. (123, 126, 127) Not only does NK dissolve blood clots, but it also breaks down amyloid fibrils. (123, 128, 129)

Serrapeptase (SP) is a type of serine protease. It's developed from the non-pathogenic enterobacteria Serratia E15.It is generated in silkworm intestines to dissolve cocoon walls. It has anti-inflammatory effects. (123, 130) This enzyme is thought to promote the breakdown of insoluble protein products such as fibrin, biofilm, and inflammatory mediators. As a result, SP has been utilized to treat a variety of inflammatory disorders. (123, 131, 132)

Brain-derived neurotrophic factor (BDNF) contributes to neuronal survival and growth, acts as a neurotransmitter modulator, and participates in neural plasticity, which is necessary for learning and memory. (123)

Lumbrokinase (LK): Earthworms, also known as earth dragons (Dilong), have been utilized as traditional medicine in China, Japan, and other Far Eastern countries for thousands of years. (133-135) Dry earthworm powder used orally is thought to be a powerful and useful remedy for promoting good blood circulation in those practice. (133, 134) Lumbrokinases are a collection of enzymes identified and purified from various species of earthworms. (133, 136-138) These enzymes are recognized as fibrinolytic agents, which can be utilized to treat various thrombotic disorders. (133, 139-141)

LK is a highly potent antithrombotic agent that decreases blood viscosity and platelet aggregation while also degrading fibrin, a major contributor in clot formation. (142-145) Most research has shown that lumbrokinase is primarily a fibrinolytic enzyme with both direct and indirect fibrinolytic effects.(144, 146) In a 2007 paper, Zhao et al. revealed that lumbrokinase stimulates both fibrinolysis and prothrombin activation (hence fibrinogenesis). (144, 147) It is approximately 300 times stronger than serrapeptase and nearly 30 times stronger than nattokinase as a fibrinolytic enzyme. (142, 144, 145, 148, 149) It is also good for breaking down biofilms, which are colonies or groups of microorganisms that form a structure that gives protection and resistance. This is highly useful in treating chronic Lyme disease. (144, 145, 149)

LK Has Been Shown to be Neuroprotective in Stroke

LK's antiplatelet action prevents cerebral ischemia. (142, 144) Liu et al. found that administering earthworms extract orally for two weeks to rats with middle cerebral artery occlusion (MCAo) reduced cerebral infarction regions in the cortex and striatum, as well as neurological impairment scores. (150) Long-term oral fibrinogen-depleting therapy with LK may improve secondary ischemic stroke prevention. (151) Lumbrokinase is effective in the treatment of cerebral ischemia. (134, 135) Lumbrokinase has been demonstrated to offer potential as an adjuvant treatment for ischemic stroke. (135, 148, 152-154)

Earthworms with healthy neural systems may regenerate amputated body parts. (134, 135) A few studies have shown LK to be helpful in peripheral nerve recovery. (134, 135, 155-159)

Neuroinflammation, in addition to the basic pathology characteristics of Alzheimer's disease, is involved in its etiology. (160) Brain-derived neurotrophic factor (BDNF) promotes neuronal survival and growth, acts as a neurotransmitter modulator, and participates in neural plasticity, which is required for learning and memory.GF-1 is a hormone that is stimulated by physical activity and a reduced calorie intake. This hormone increases cell survival, inhibits apoptosis, and induces neurogenesis in the hippocampus. (123)

Animal studies have revealed that SP and NK can pass the blood-brain barrier. In a rat model, oral administration of proteolytic enzymes, SP and/or NK, effectively modulated certain factors characterizing AD, such as increasing BDNF and IGF-1 levels, degrading insoluble proteins like amyloid while decreasing toxicity, reducing AchE activity, and blocking the inflammatory cascade by preventing the production of proinflammatory cytokines such as TGF-β, Fas, and IL-6 in the brain. (123)

Extracts from the earthworm have been shown to alleviate inflammation in neurons. (135, 161) LK has been shown to have antioxidant properties. High levels of oxidative stress are one of the mechanisms underlying peripheral nerve damage and neurodegenerative diseases like Alzheimer's

Disease and Parkinson’s. (135, 162, 163) NK and SP contain proteolytic enzyme activity that has been shown to alleviate oxidative stress in the brain by scavenging free radicals. (160)

Degrading Amyloid

Preclinical research found that LK and SP have the capacity to degrade Aβ 1-42 amyloid and minimize toxicity, making them a promising therapeutic candidate for Alzheimer's. (160, 164) Both SP and NTK can pass the blood-brain barrier and may have a role in modifying certain AD-causing factors. They can destroy insoluble proteins such as amyloid. Degrading amyloid inhibits the inflammatory cascade and prevents the synthesis of proinflammatory cytokines like TGF-β and IL-6 in the brain. (160) A study compared the activity of lumbrokinase (LK) to Nattokinase (NK), a common amyloid degrading enzyme. LK was discovered to be a potential alternative to NK, as it can partially dissolve insulin amyloids, which are insoluble aggregates that develop due to prolonged subcutaneous insulin infusion in diabetic patients. (165)

Recommended dosage: It is critical to consider how to best deliver Lumbrokinase fibrinolytic/proteolytic enzymes into the bloodstream. If you consume it with a meal, a large portion of it can be used to break down food. Taking it on an empty stomach may improve absorption into the bloodstream, allowing it to function on the ''interior'' of the body. 300,000 IU, or around 20mg of Lumbrokinase, is a decent starting dose, and most people may benefit from 600,000 IU (40mg). (149)

SP or NK can boost the expression of ADAM9 and ADAM10 genes in brain tissue, shifting the amyloidogenic pathway to a non-amyloidogenic one. (123) SP or NK has other additional activities, including promoting α-secretase-like activity in the brain and reducing oxidative stress by free radical scavenging. (123)

Gotu Kola

Gotu Kola has been used for millennia to improve memory and cognitive functioning while also combating the effects of aging in the brain. It is recognized for its calming effects and its ability to decrease oxidative stress, amyloid-beta (Aβ) levels, and apoptosis. Additionally, Gotu Kola increases dendritic growth and mitochondrial health, enhances mood and memory, speeds up the repair of injured neurons, enhances acetylcholine availability, improves cerebral blood flow, and removes free radicals.

The recommended dose is up to 600 mg per day. However, it should be avoided in individuals with liver disease. (173)

Other Interventions to Improve Brain Health

Address Vascular Issues

These may include cerebral blood flow and micro-clotting in long COVID and long vax (post-vaccine injury). See the FLCCC I-RECOVER guide for more information.

Retrain or Stimulate Vagal Nerve

Stimulating the vagal nerve can inhibit inflammation, promote neuroprotection, help maintain the integrity of the blood-brain barrier, and have multisystemic modulatory effects. It can even transmit signals from the gut flora to the brain. Vagal nerve stimulation helps the body switch back and forth between flight-or-fight response and a more relaxed, parasympathetic mode. (166) Stress or age can cause the vagal nerve to lose its ability to switch back to parasympathetic mode. (166) This dysfunction can lead to many different chronic health issues. (166)

Vagal function can also be restored through grounding and mindfulness, as well self-biofeedback such as breathwork, meditation, yoga, singing, humming, or listening to music. Research also shows that cold-water immersion may help with stress by slowing the heart rate and directing blood flow to the brain. Try placing an ice pack on your face or neck or taking a cold shower. (167, 168)

Neuroplasticity Training

Neuroplastic healing is truly one of the life-changing breakthroughs of modern science. It involves the reshaping of our brain's neural connections as we learn and grow. By allowing us to rewire our brains — structurally and functionally — neuroplasticity allows us to return to a healthy state with subsequent effects on our bodies. (169) Neuroplasticity allows us to replace old negative neural pathways with new positive ones. (170)

There are many benefits of brain neuroplasticity. Allowing your brain to adapt and change helps promote the ability to learn new things. (171) Some ways to encourage neuroplasticity:

- Exercise
- Hiking
- Hyperbaric oxygen therapy
- Handwriting (The intricate movements involved in handwriting activate more regions of the brain associated with learning than typing does.) (172).
- Reading, listening to music, dance, or learning a new language.
- Travel (173)
- Having a pet (174)
- Continuous learning (175)
- Gratitude (176, 177) (Try keeping a daily gratitude journal, listening to positive affirmations, and offering gratitude to others. (i.e., "I am grateful for your help.")

Mindfulness and Meditation

Mindfulness and meditation can help reduce stress (and thus brain fog) by focusing attention on the present moment. It teaches how to observe the fluctuations of the mind without emotionally engaging in them, which can help to step back from powerful emotions like anxiety and stress. It teaches how to observe the world “as it is”, resulting in a calmer, less reactive headspace overall — and a less foggy one. (178)

Meditation has been shown to lower serum levels of Aβ40, which implies increased autophagy in brain nerve cells and a reduced risk of dementia. It has been discovered that the gray matter volume of the meditators did not shrink with age, but even increase, suggesting that meditation reverses the aging of, and damage to, the brain. (179)

In one 2016 study, 64 healthy women were followed, half of whom were given a vacation, while the other half meditated. (180) After one week, researchers found that the meditators had significantly lower serum levels of Aβ40 (a 40-amino-acid proteolytic product from the amyloid precursor protein), which implies the potential effects of meditation in reducing amyloid-like substances. (180) A 2017 review published in the journal Frontiers in Immunology found that meditation and other mind-body interventions can actually “reverse” the molecular reactions in our DNA that cause illness. (181, 182)

Dr. Dharma Singh Khalsa and Dr. Andrew Newberg found that a specific kind of meditation, known as Kirtan Kiyra, is a crucial component in the development of enhanced cognition and well-being. (183) Kirtan Kirya impacts the frontal lobes that regulate emotional responses and the thalamus, which helps regulate information flow in the nervous system. This may help prevent and reverse cognitive decline. (183) Another study published in the Journal of Alzheimer’s Disease found that Kirtan Kirya meditation not only improved memory, cognitive function, quality of life, sleep, stress, and mood, but also affected the blood biomarker of Beta-amyloid 40 that is linked as a potential predictor of Alzheimer’s disease. (184, 185)

Breath Work

One study found that diaphragmatic breathing (another term for deep, belly breathing) lowered cortisol levels and improved attention and mood, while a control group saw no effects.

Breathing exercises or breathwork is another practice backed by research for its benefits on cognitive function. “We know the sympathetic [fight-or-flight] and parasympathetic systems [rest-and-digest] influence the production and clearance of Alzheimer’s related peptides and proteins,” said USC Leonard Davis School of Gerontology Professor Mara Mather in an article by the University of Southern California on breathing exercises and Alzheimer’s risk. (186)

Deep and slow breathing improved all measurements of retention and attention, working memory, and spatial perception in participants aged 65 and older according to a study published just last year. (187) Another study found that daily breathing exercises may help release peptides in the bloodstream, which could lower the risk of Alzheimer’s disease according to this study. (188, 189)

To practice deep belly breathing, inhale through your nose and exhale through either your mouth or nose (whichever is more comfortable for you). Place a hand on your belly and inhale so that it expands

like a balloon. On your exhale, let your belly contract fully. Over time, try to lengthen your exhalation; the slower the exhalation, the more you will stimulate the vagus nerve. (190)

Photobiomodulation

Photobiomodulation (PBM) is defined as the use of light energy to trigger photochemical changes within cellular structures (mitochondria) that are receptive to red and near infrared (NIR) light. The mitochondria produce cellular energy by producing a molecule called adenosine triphosphate (ATP). The energy from ATP enables us to carry out all physiological activities and provides energy to the brain cells. In addition, application of light energy leads to greater blood flow to the brain – allowing delivery of nutrients and removal of waste products. This is a new way of 'charging' the brain and now research is starting to show significant benefit of this therapy for brain health. (191)

Recent research has investigated the potential of PBM to enhance cognitive function, and one promising approach involves using gamma light flicker. An investigation, featured in the journal Neuron, has shown that boosting gamma oscillations can improve the connection between nerve cells, reduce inflammation, and preserve against cell death in mouse models of Alzheimer's. (192, 193) Researchers believe this therapy potentially activates cells in the brain to eliminate beta-amyloid plaques that are common in Alzheimer's disease.

Nutrition

The Western diet, characterized by its high intake of processed and unhealthy foods, can have a significant adverse impact on gut health and therefore on brain health. Here's a list of common components of the Western diet that are detrimental to the gut microbiome:

- **Processed and Packaged Foods:** Often high in additives, preservatives, and artificial ingredients that can disrupt the balance of gut bacteria.
- **High Sugar Intake:** Excessive sugar, especially high-fructose corn syrup, can lead to an overgrowth of harmful bacteria and yeast in the gut, disrupting the microbiome balance.
- **Refined Carbohydrates:** Foods like white bread, pastries, and other processed grains are quickly digested, leading to rapid spikes in blood sugar and feeding undesirable bacteria in the gut.
- **Trans Fats and Hydrogenated Oils:** Found in many processed and fried foods, trans fats can promote inflammation and negatively impact gut health.
- **Processed Meats:** High consumption of red meat, especially processed meats like sausages, bacon, and deli meats, is associated with an increased risk of colon cancer and may negatively impact gut flora.
- **Artificial Sweeteners:** Some studies suggest that artificial sweeteners like aspartame, sucralose, and saccharin may disrupt the gut microbiome and potentially lead to glucose intolerance.
- **Excessive Alcohol Consumption:** While moderate alcohol consumption might have some health benefits, excessive drinking can damage the gut lining, alter the gut microbiome, and impair liver function, which is closely linked to gut health.
- **Fast Food:** Typically high in calories, fat, and sodium but low in fiber and nutrients, fast food can contribute to poor gut health.
- **Low Fiber Intake:** The Western diet is often low in fiber, which is essential for a healthy gut. Fiber feeds beneficial gut bacteria and is crucial for regular bowel movements.
- **Saturated Fats:** High levels of saturated fats, found in many fast foods and processed products, can contribute to inflammation and an imbalance in gut bacteria.

Diet for a Healthy Microbiome

- Whole, Fiber-Rich Foods:
    - High-fiber foods like fruits, vegetables, legumes, and whole grains are crucial for a healthy gut.
    - Fiber serves as a prebiotic, providing nourishment for beneficial gut bacteria and promoting their growth.
    - A diet rich in fiber can also help prevent constipation and maintain regular bowel movements.

- Anti-Inflammatory Diet:
    - Focus on foods that reduce inflammation in the body, such as leafy greens, berries, nuts, and seeds.
    - Incorporate omega-3 fatty acids found in fish like salmon, mackerel, and sardines.
    - Include spices known for their anti-inflammatory properties like turmeric and ginger.

- Variety of Vegetables and Fruits:
    - Aim for a colorful array of vegetables and fruits, as different colors often indicate various beneficial nutrients and antioxidants.
    - The variety ensures a diverse range of fibers and nutrients, supporting different types of beneficial gut bacteria.

- Lean Proteins:
    - Choose lean protein sources like poultry, fish, tofu, and legumes.
    - Reducing red meat and processed meats can also be beneficial for gut health.

- Healthy Fats:
    - Include healthy fats such as avocados, olive oil, nuts, and seeds. These fats are not only good for overall health but also help in the absorption of fat-soluble vitamins.

- Fermented Foods:
    - Fermented foods like yogurt, kefir, sauerkraut, kimchi, and kombucha are rich in probiotics, which can enhance the gut microbiome.

- Prebiotic Foods:
    - Foods like garlic, onions, leeks, asparagus, and bananas are excellent prebiotics.
    - Prebiotics provide the necessary fuel for beneficial bacteria to thrive in the gut.

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