## *Health Concerns*







# *Mild Cognitive Impairment*

## Complementary Nutrients and Supplements

In addition to hormone therapy, a number of nutrients and supplements have been studied for their ability to enhance cognitive function. These agents act through a variety of mechanisms, including boosting antioxidant capabilities, improving blood flow to the brain, and reducing the rate of neuronal destruction.

**Ginkgo (Ginkgo biloba).** Ginkgo extracts act as free-radical scavengers, preventing induced lipid peroxidation in neural tissue (Koc R et al 1995; Dorman D et al 1992; Huang P et al 2004a; Huang P et al 2004b). Ginkgo has also been shown to relax blood vessel walls, inhibit platelet-activating factor, enhance microcirculation, and stimulate neurotransmitters (Yoshikawa T et al 1999).

Several trials show cognitive benefits with the use of ginkgo (Gebner B et al 1985; Vorberg G 1985). For example, a year-long study of more than 300 participants with dementia who received 120 mg of an extract of ginkgo showed stabilized or even improved cognitive performance during the study (Le Bars PL et al 2000).

**Ginseng (Panax ginseng).** Ginseng may also be helpful for cognitive support, especially when taken with ginkgo. In both animal and clinical research, a combination of ginseng and ginkgo seems promising. In rats, for example, a ginkgo/ginseng combination was shown to enhance the learning ability of both older and younger rats (Petkov VV et al 1993). A recent trial tested more than 250 middle-aged human participants over a 14-week period. The participants' cognition and memory were assessed every four weeks. Overall, there was significant improvement in participants who received the botanical combination (120 mg daily of ginkgo and 200 mg daily of ginseng), including gains in working and long-term memory (Wesnes KA et al 2000).

**Huperzine A.** Huperzine A, one of the constituents found in a species of club moss (Huperzia serrata), has been studied in China for its effects on memory, cognition, and behavior in patients with Alzheimer's disease and a variety of other conditions involving impaired memory and cognition. Preliminary and double-blind research on huperzine A suggests that it may benefit patients suffering from dementia (Xu SS et al 1995; Zhang RW et al 1991). This possibility needs further research and validation, and huperzine is currently in clinical trials in the United States as a potential treatment for Alzheimer's.

**Bacopa.** *Bacopa monniera* is an Ayurvedic medicinal herb that has been used clinically for enhancing memory and ameliorating epilepsy and insomnia and as a mild sedative. The antioxidant role of Bacopa may help explain its reported antistress, immunomodulatory, cognition-facilitating, anti-inflammatory, and antiaging effects (Russo A et al 2003; Kidd PM 1999).

A study measured bacopa's ability to enhance memory and reduce anxiety in 76 adults between 40 and 65 years of age. A significant effect of Bacopa was shown in the retention of new information (Roodenrys S et al 2002). Another trial examined the chronic effects of Bacopa on cognitive function in healthy human participants. The participants were randomly assigned to receive either 300 mg bacopa or placebo. The results showed significant improvement in speed of visual information processing, learning rate, memory consolidation, and anxiety compared with the placebo group. Maximal effects were evident after 12 weeks (Stough C et al 2001).

Bacopa may also have the potential to increase T4 levels. The importance of Bacopa (200 mg/kg) in the regulation of thyroid hormone concentrations in male mice was investigated. Bacopa had a thyroid-stimulating effect and increased T4 concentrations by 41 percent (Kar A et al 2002). It did not affect levels of T3. Patients under the care of a physician for hypothyroidism should not take bacopa without the consent of their doctor.

**Vinpocetine.** Vinpocetine, derived from the periwinkle plant, has been shown to enhance circulation and oxygen utilization in the brain, increase the brain's tolerance for diminished blood flow, and inhibit abnormal platelet aggregation that can interfere with circulation or cause a stroke (Nosalova V et al 1993).

The effects of vinpocetine on memory function were studied in 50 patients with disturbances of cerebral circulation. Improvement of cerebral circulation was observed after vinpocetine was administered, and after one month of vinpocetine treatment, psychological tests showed an improvement in memory (Hadjiev D et al 1976). In a clinical trial, vinpocetine produced a significant cognitive improvement in older patients with chronic cerebral dysfunction (Balestreri R et al 1987).

In a study to determine how vinpocetine boosts cognition, scientists measured the electrical firing rate in the neurons of anesthetized rats. The administration of vinpocetine produced a significant increase in the firing rate of neurons, and the dose of vinpocetine used to increase electrical firing corresponded to the dose range that produced memory-enhancing effects (Gaal L et al 1990).

Additionally, vinpocetine has been shown to protect against oxidative damage (Pereira C et al 2000). One study suggests that the antioxidant effect of vinpocetine might contribute to reducing neuronal damage (Santos MS et al 2000).

## Nutraceuticals

**Acetyl-L-carnitine.** Acetyl-L-carnitine has been studied extensively relative to the treatment of dementia. It is believed to be a precursor in the synthesis of acetylcholine and participates in cellular energy production as well as in the removal of toxic accumulation of fatty acids. In one study, 30 participants with mild dementia were treated with 2 g daily of acetyl-L-carnitine, and 30 were treated with placebo. The results after three months showed a significant improvement in the group receiving the acetyl-L-carnitine (Passeri M et al 1990). Several other studies also indicate that acetyl-L-carnitine may be helpful in improving cognitive function in patients and possibly slowing the progression of Alzheimer's disease (Rai G et al 1990; Bonavita E 1986). Animal studies have shown that acetyl-L-carnitine reverses the age-related decline in the number of neuron membrane receptors (McDaniel MA et al 2003), and an analysis of 21 clinical trials of acetyl-L-carnitine in the treatment of mild cognitive impairment and mild Alzheimer's disease in rats showed it has demonstrated significant efficacy versus placebo (Ames BN et al 2004).

**Acetyl-L-carnitine arginate.** Acetyl-L-carnitine arginate is a patented form of acetyl-L-carnitine that protects brain cells against the toxic effects of beta-amyloid, the protein implicated in Alzheimer's disease (Scorziello A et al 1997). It works by stimulating the growth of neurites, which are long, branchlike fibers that connect the brain cells and allow them to communicate, by as much as 19.5 percent (Taglialatela G et al 1995).

**Blueberry extract.** Numerous studies have shown that fruit extracts, which are rich in polyphenols, have the ability to reverse and slow age-related brain deterioration. Among these, blueberry extract seems especially effective. One study of rats with beta-amyloid plaques showed that blueberry extract helped improve their performance in a maze, leading the authors to state, "Our data indicate for the first time that it may be possible to overcome genetic predispositions to Alzheimer disease through diet" (Joseph JA et al 2003). An earlier study by the same research team looked at blueberry extract's ability to suppress oxidative stress in the brain, which is linked to numerous age-related cognitive problems. The study found that blueberry extracts in particular were powerful neural antioxidants (Joseph JA et al 2000). These findings have been supported in more recent studies examining blueberries' role as antioxidants (Lau FC et al 2005; Andres-Lacueva C et al 2005).

**Ashwagandha.** Derived from an Indian herb, ashwagandha has been studied for its ability to rebuild damaged neural networks and restore memory in amnesiac mice. Several lab and animal studies have shown that ashwagandha can increase the growth of dendrites in the brain (Tohda C et al 2005; Tohda C et al 2000). In mice, large doses of ashwagandha (50, 100, and 200 mg/kg) were shown to exert a dose-dependent improvement in memory after administration of electroconvulsive shock. After one week of therapy with ashwagandha, the mice exhibited significantly improved memory, leading the authors to suggest that ashwagandha exhibited a brain enhancing-effect on the animals (Dhuley JN 2001).

**Glyceryl phosphoryl choline.** Glyceryl phosphoryl choline (GPC) is a form of choline that is naturally present in all the body's cells. Among aging adults, the rationale for GPC therapy goes back to the hypothesis, developed more than 30 years ago, that declining levels of acetylcholine—and a concurrent decrease in the number of neurons that are its intended target—are responsible for a range of cognitive deficits (Koistinaho M et al 2005). Acetylcholine is an essential neurotransmitter involved in muscle control, sleep, and cognition. Research has shown that GPC is a precursor of acetylcholine that is safe and well tolerated (Amenta F et al 2005). A review of 13 published studies, involving more than 4000 participants, found that patients taking GPC exhibited neurological improvement and relief of clinical symptoms of chronic cerebral deterioration that was clearly superior to placebo and equal or superior to that obtained with prescription drugs (Parnetti L et al 2001). The same authors found that GPC was superior to choline and lecithin and that it deserved wider study as a therapy for stroke patients seeking to regain full cognitive function (Parnetti L et al 2001).

**Phosphatidylserine.** Phosphatidylserine facilitates the efficient transport of glucose into brain cells and boosts the production of acetylcholine. It is sold in Europe and Japan as a prescription drug but is available in the United States as a dietary supplement.

European studies have shown enhancement in cognitive function when phosphatidylserine is administered to patients in various stages of dementia (Corrigan FM et al 1998). Phosphatidylserine has also been shown to attenuate many neuronal effects of aging and to restore normal memory in a variety of tasks in animal models (McDaniel MA et al 2003).

In one study, 15 healthy elderly volunteers were given 100 mg of phosphatidylserine three times daily. They were evaluated at baseline, after 6 weeks of treatment, and at the end of the 12-week trial. All but two outcome measures showed significant improvements in cognitive function (Schreiber S et al 2000).

**Coenzyme Q10.** Coenzyme Q10 (CoQ10) is a powerful antioxidant. CoQ10 is incorporated into the mitochondria of cells throughout the body and facilitates and regulates the oxidation of fats and sugars into energy. Unfortunately, levels of CoQ10 decrease with aging. CoQ10 levels in older individuals are only 50 percent of those present in young adults. A National Academy of Sciences study has documented that CoQ10 enhances metabolic energy levels of brain cells (Matthews RT et al 1998).

**Vitamins.** A typical American diet does not provide enough essential vitamins. Worse yet, older people are at greater risk for vitamin deficiency because they tend to eat less, although their requirements for certain vitamins, such as B6, actually rise with age. Older people may also have problems with efficient absorption of nutrients from food. Even healthy older people often exhibit deficiencies in vitamin B6, vitamin B12, and folate.

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Vitamins are involved in biochemical processes throughout the body and appear to be involved in protecting and enhancing cognitive function. In particular, the B vitamins play an integral role in the functioning of the nervous system and help the brain synthesize chemicals that affect mood. A balanced complex of the B vitamins is essential for energy and for balancing hormone levels. An article in the Journal of Psychopharmacology described a study of 76 older men who were given vitamin B6 or placebo and then tested on memory function. The authors concluded that vitamin B6 improved storage and information retrieval (Deijen JB et al 1992). Another study reviewed vitamin B12 deficiency in relation to memory impairment and neuropathy in older people and concluded that both memory impairment and neuropathy can be successfully managed with vitamin B12 injections or supplementation (Carmel R 1996). One study determined that low levels of folate (a B vitamin) are associated with cognitive deficits and that patients treated with folic acid for 60 days showed a significant improvement in both memory and attention efficiency (Fioravanti MFE 1997).

**Essential fatty acids.** Essential fatty acids are required for many biological functions, including protection from the oxidative effects of free radicals. They are also known to be important for good overall brain health, and a recent study demonstrated in animal models that supplementation with omega-3 fatty acids actually switched on brain cell genes that contribute to enhanced functioning (Fontani G et al 2005; Kitajka K et al 2004). These biochemical details may help us understand why diets rich in fish oils and other sources of omega-3 fatty acids are associated with better memory and improved cognition (Kalmijn S et al 1997).

One of the omega-3 fatty acids in particular, docosahexaenoic acid (DHA), has attracted significant attention for its ability to boost brain function. DHA is found in very high concentrations in cell membranes and is required by developing infant brains. A lack of DHA in a developing brain results in cognitive and learning deficiencies (Turner N et al 2003). Studies have shown that DHA helps protect brain cells by suppressing a neurotoxic substance called amyloid-beta (Likuw WJ et al 2005), and that supplementation with DHA can reverse the cognitive effects of DHA deficiencies in childhood (Moriguchi T et al 2003). DHA is so valuable to healthy brain function that some experts believe infant formula should be supplemented with it (McCann JC et al 2005).

## Lifestyle Changes

Taking steps to improve one's overall health is highly recommended to help prevent or minimize age-associated mental impairment. For example, exercising regularly, not smoking, and monitoring blood cholesterol levels can reduce the risk of stroke and heart disease and keep arteries open, supplying the brain with essential oxygen and nutrients. Abstaining from alcohol can also help preserve mental function.

Since most people tend to eat less as they age, the consumption of low-fat, nutrient-rich food is recommended to help prevent nutrient deficiencies. Eating large quantities of foods rich in antioxidants, such as blueberries, may provide protection from age-related mental decline.

## Life Extension Foundation Recommendations

In recent years, inflammation has been implicated in the gradual loss of mental function that is known as mild cognitive impairment. Although researchers haven't yet examined anti-inflammatories such as ginger and rosemary in the context of mild cognitive impairment, we believe natural nutrients may play a role in cognitive health. It is always better to be safe than sorry and to reduce inflammation as much as possible. There are many positive benefits to reducing inflammation besides perhaps lowering the risk of cognitive decline. For a complete description of Life Extension's anti-inflammatory program, please see the chapter titled Inflammation.

The following supplements have also been shown to boost brain function directly:

- **Cognitex**—This special formulation was created by the Life Extension Foundation to supply a mix of nutrients that support healthy brain function. The recommended amount is three softgels. Each recommended daily supplement of Cognitex contains the following:
  - Glyceryl phosphoryl choline (GPC)—600 milligrams (mg)
  - Phosphatidylserine—100 mg
  - Vinpocetine—20 mg
  - Phosphatidylcholine-Grape Seed Extract—150 mg
  - Sensoril® Ashwagandha (Withania somnifera) Extract—125 mg
  - Perluxan™ Hops (Humulus lupulus) Extract—50 mg
  - Ginger (Zingiber officinale) Extract (root)—25 mg
  - Rosemary (Rosmarinus officinalis) Extract—50 mg
  - Wild blueberry extract—150 mg
  - Uridine-5'-monophosphate--50 mg
- **Ginkgo biloba**—120 mg/day (200 mg/day of Panax ginseng may amplify ginkgo's effect)
- **Acetyl-L-carnitine and acetyl-L-carnitine arginate**--1500 to 3000 mg early in the day
- **Huperzine A**—50 to 100 mcg daily
- **Vitamin B6**—100 to 750 mg daily (Be sure to take a complete B complex each day when taking daily doses of vitamin B6 in excess of 200 mg.)
- **Methylcobalamin (B12)**--1000 to 5000 microgram (mcg) daily sublingually
- **Folic acid**—800 mcg daily orally; should be taken with vitamin B12
- **Vitamin C**—at least 2000 mg daily
- **Mixed vitamin E**—400 International units (IU) daily
- **CoQ10**—30 to 300 mg daily of a highly absorbable form
- **Vinpocetine**—15 to 30 mg daily

- **Bacopa**—As directed, depending on extract strength
- **EPA/DHA**—700 to 2100 mg EPA and 500 to 1500 mg DHA daily with food

In addition, hormone restoration with bioidentical hormones may be indicated, depending on the levels of vital hormones, including pregnenolone, estrogen, and testosterone. For more information on hormone blood testing and hormone restoration, call 1-800-544-4440 or visit www.lef.org. A reasonable beginning dose of DHEA is 15 to 75 mg, followed by blood testing in three to six weeks to make sure you have achieved optimal levels of this hormone.

## Mild Cognitive Impairment Safety Caveats

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

**Acetyl-L-Carnitine**

- Acetyl-L-carnitine can cause gastrointestinal symptoms such as nausea and diarrhea.

**Coenzyme Q10**

- See your doctor and monitor your blood glucose level frequently if you take CoQ10 and have diabetes. Several clinical reports suggest that taking CoQ10 may improve glycemic control and the function of beta cells in people who have type 2 diabetes.
- Statin drugs (such as lovastatin, simvastatin, and pravastatin) are known to decrease CoQ10 levels.

**EPA/DHA**

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

**Folic Acid**

- Consult your doctor before taking folic acid if you have a vitamin B12 deficiency.
- Daily doses of more than 1 milligram of folic acid can precipitate or exacerbate the neurological damage caused by a vitamin B12 deficiency.

**Ginger**

- Do not take ginger if you have a bile duct obstruction or gallstones. Ginger may stimulate bile production.
- High doses of ginger (6 grams or more) can cause damage to the stomach lining and ulcers.
- Ginger can cause anllergic skin reactions.
- Consult your doctor before taking ginger if you take blood thinners such as warfarin (Coumadin). Ginger can increase the risk of bleeding.

**Ginkgo biloba**

- Individuals with a known risk factor for intracranial hemorrhage, systematic arterial hypertension, diabetes, or seizures should avoid ginkgo.
- Do not use prior to or after surgery.
- Avoid concomitant use of ginkgo with NSAIDS, blood thinners, diuretics, or SSRI's.
- Gastrointestinal symptoms (nausea and diarrhea) may occur.
- Allergic skin reactions may occur.
- Elevations in blood pressure may occur.

**Huperzine A**

- Do not take huperzine A if you have a seizure disorder, cardiac arrhythmias, asthma, irritable bowel syndrome, inflammatory bowel disease, or malabsorption syndrome.
- Huperzine A can cause excessive perspiration, blurred vision, fasciculations (involuntary muscle twitching), dizziness, bronchospasm, bradycardia, arrhythmias, seizures, urinary incontinence, increased urination, excessive salivation, and gastrointestinal symptoms such as nausea, abdominal cramps, diarrhea, and vomiting.

**Phosphatidylcholine**

- Phosphatidylcholine can cause increased salivation, a metallic taste, headache, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea.

**Vitamin B6**

- Individuals who are being treated with levodopa without taking carbidopa at the same time should avoid doses of 5 milligrams or greater daily of vitamin B6.

**Vitamin B12 (cyanocobalamin)**

- Do not take cyanocobalamin if you have Leber's optic atrophy.

**Vitamin C**

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute.
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

**Vitamin E**

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

**Vinpocetine**

- Do not take vinpocetine if you have a history of allergic or hypersensitivity reactions to any vinca alkaloids.
- Consult your doctor before taking vinpocetine if you take warfarin (Coumadin). Have your international normalized ratio monitored frequently by your doctor if you take vinpocetine and warfarin.
- Consult your doctor before taking vinpocetine if you have low blood pressure (including transient low blood pressure or orthostatic hypotension). Prolonged use of vinpocetine may lead to slight reductions in systolic and diastolic blood pressures.
- Vinpocetine can cause temporary rapid heartbeat, pressure headache, facial flushing, dizziness, insomnia, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea.

For more information see the Safety Appendix