

## Mild Cognitive Impairment Nutrition to Stay Sharp

It is estimated that up to one third of adults will experience a gradual decline in cognitive function known as mild cognitive impairment as they age (Low LF et al 2004; Busse A et al 2003). Less severe than dementia, mild cognitive impairment is defined as cognitive defects that do not interfere with daily living. It may include slower thinking, a reduced ability to learn, and impaired memory. While many conventional physicians view these defects as an inevitable consequence of aging, newer research has uncovered possible reasons for mild cognitive impairment and has also identified potential therapies that may enable people to battle age-related mental decline more effectively than ever before. Minimizing cognitive defects will become even more important as the average life span continues to lengthen and hundreds of thousands of people head into their 80s and 90s, when the risk for cognitive decline is greatest.

Researchers have discovered multiple factors that influence our ability to think and remember as we age. These include well-known culprits such as alcohol abuse, and also newly discovered causes of mental decline, including chronic inflammation, vascular diseases, and even stress.

Physical changes that occur in the aging brain are also implicated in mild cognitive impairment. For example, the number of nerve impulses and nerve cells decreases with age (Beers MH et al 1999). Also, levels of neurotransmitters such as serotonin and acetylcholine, a primary transmitter for learning and memory, decrease. This loss of acetylcholine was noticed three decades ago, giving rise to a theory that coupled the loss of acetylcholine with cognitive decline. Once acetylcholine had been identified as a possible target for improving brain function, researchers began looking for ways to boost acetylcholine levels. At least three supplements have been discovered that do just that.

Blood flow to the brain is also an important factor in brain health. Blood delivers the oxygen and nutrients necessary for normal functioning. Unfortunately, even during normal aging, blood flow to the brain may decrease by an average of 20 percent. The decreased blood flow that results from aging and associated diseases can cause nerve cells in the brain to be lost prematurely. This loss may contribute to the decline of cognitive function (Beers MH et al 1999).

### POSSIBLE CAUSES OF MENTAL DECLINE

Of course, the best strategy for treating mild cognitive impairment is to avoid it in the first place. This means getting plenty of exercise and good sleep, eating a healthy diet, keeping body weight down, avoiding diabetes, and taking the right nutritional supplements before you experience any signs of cognitive decline.

Researchers have identified a number of factors that may contribute to cognitive decline:

**Diet.** In one prospective study, more than 500 participants age 55 or older without clinical symptoms of dementia were evaluated. Their diets were assessed at the onset of the study, and participants were screened for symptoms of dementia an average of two years later. After adjusting for other factors, participants with the highest total fat intake were found to have a significantly elevated relative risk of dementia. An increased risk of dementia was also associated with a high dietary intake of saturated fat and cholesterol. On the other hand, a high intake of fish was associated with a significantly lower risk of dementia (Kalmijn V et al 1997). These findings have been supported in several other studies (Solfrizzi V et al 2005; Solfrizzi V et al 2003; Solfrizzi V et al 1999; Panza F et al 2004; Capurso A et al 2000).

**Inflammation.** The theory linking inflammation to cognitive decline is relatively new, but it appears to be consistent with our increasing understanding of the damage of chronic inflammation (as measured by C-reactive protein or interleukin-6 levels). Various studies have examined the association between inflammation and mild cognitive impairment and found compelling evidence. For example, one study of 2632 participants (mean age: 74 years) found that people who had both metabolic syndrome and high inflammation levels were more likely to experience cognitive impairment than were patients who suffered from neither. Metabolic syndrome is a cluster of abnormalities including high blood pressure, high insulin levels, obesity, and abnormal blood lipid levels. It is closely associated with increased risk of heart attack and stroke. In contrast, those with metabolic syndrome and low inflammation were not at increased risk of mild cognitive impairment (Yaffe K et al 1998).

**Free radical damage.** Free radicals are highly unstable molecules that react with other molecules in a damaging process known as oxidation. Areas of the body with high energy output, such as the brain, are particularly vulnerable to damage from free radicals. The body normally defends itself against the harmful effects of free radicals with antioxidants, including superoxide dismutase and glutathione peroxidase, as well as vitamins C and E. Animal studies have suggested that diets high in antioxidants can delay age-

related memory loss (Joseph JA et al 1998; Perrig WJ et al 1997).

**Vascular disease.** Atherosclerosis that occurs in the arteries serving the brain (cerebrovascular disease) can reduce blood flow to the aging brain and increase the risk of stroke. The decreased blood flow can cause nerve cells in the brain to be lost prematurely. Consequently, mental function may decline. One study of 400 men (40 to 80 years old) found that vascular risk factors, such as excessive alcohol intake and elevated homocysteine levels, were associated with reduced processing capacity and speed of information processing (Aleman A et al 2005).

**Stress.** One interesting new theory about cognitive impairment associates it with stress. Studies have shown that older men with elevated levels of epinephrine (a stress hormone) are more likely to suffer from mild cognitive impairment than are their peers with normal levels (Karlamangla AS et al 2005). It has also been shown that everyday stresses combined with major stressful events may exert a cumulative effect over a lifetime that exacerbates cognitive decline (VonDras DD et al 2005).

**Dehydroepiandrosterone deficiency.** Dehydroepiandrosterone (DHEA) levels naturally decline as people age. Numerous studies have connected lowered DHEA levels to memory loss and decreased cognitive function (Racchi M et al 2001; Tan RS et al 2001).

**Thyroid hormone.** Hypothyroidism (low levels of thyroid hormone) is associated with poor concentration, memory disturbances, and depression. Low levels of thyroid hormone have also been linked to impaired cognitive function (Schindler AE 2003; Luboshitzky R et al 1996).

## TRACKING MENTAL FUNCTION

Screening for cognitive changes should be done even before overt changes in cognitive ability are apparent so that diet and lifestyle changes, as well as supplementation, can be started early.

The test most often used to evaluate memory and cognitive function is the Mini-Mental Status Examination, which tests multiple aspects of cognitive function, including orientation to time, place, and person; memory; verbal and mathematical abilities; judgment; and reasoning. In elderly patients, the clinician should differentiate early-stage dementia from normal age-associated memory impairment. People with memory impairment have a relative deficiency in recall compared with others their age. They also tend to learn new information more slowly, but if they are given extra time for such tasks, their intellectual performance is usually adequate.

## MEDICAL TREATMENT OF COGNITIVE DECLINE

Age-related cognitive decline presents a clinical challenge, and there are no drugs approved by the FDA specifically for mild cognitive impairment. However, several drugs are regularly used in Europe for cognitive enhancement but are not approved for this use in the United States. The following drugs are commonly used to combat cognitive decline:

**Piracetam.** Piracetam has been shown to improve many cognitive activities, especially higher cortical functions. The evidence for piracetam's effectiveness comes from animal studies and from human studies in Alzheimer's disease and other organic brain disorders. It may enhance memory, particularly when used in combination with choline; increase attention and cognition; improve spatial learning; improve the brain's ability to utilize glucose; and improve circulation of blood in the brain (Bartus RT et al 1981; Pragina LL et al 1990; Senin U et al 1991; Gallai V et al 1991; Canonico PL et al 1991; Heiss WD et al 1988, 1991; Qian ZN et al 1992).

One study showed that after two months of oral treatment with piracetam in older human volunteers, single photon emission computed tomography imaging of the brain indicated a regional improvement in cerebral blood flow, particularly in the cerebellum (Dormehl IC et al 1999). It has also been shown to improve mild cognitive impairment and dementias among older study participants (Tariska P et al 2000).

Despite its extensive clinical use in Europe, piracetam has not been approved by the Food and Drug Administration (FDA) in the United States. For more information, visit [www.piracetam.com](http://www.piracetam.com).

**Hydergine.** Hydergine was discovered in the 1940s and later approved by the FDA to treat individuals over age 60 with signs or symptoms of mental incapacity. Unfortunately, when one study showed that hydergine was not effective in treating Alzheimer's disease, U.S. physicians virtually stopped prescribing it, even though the drug was never approved for the treatment of Alzheimer's disease. However, hydergine remains a popular prescription medication among health-conscious people seeking to slow age-related mental decline. Studies have revealed several mechanisms by which hydergine may protect against brain aging:

- Increasing blood supply and oxygen to the brain (Emmenegger H et al 1968)
- Enhancing metabolism in brain cells (Emmenegger H et al 1968)
- Protecting the brain from damage during periods of decreased or insufficient oxygen supply (Boismare F et al 1978)

- Slowing the deposit of age pigment (lipofuscin) in the brain (Amenta D et al 1988)
- Preventing free radical damage to brain cells (Cahn J et al 1983)
- Increasing intelligence, memory, learning, and recall (Ditch M et al 1971)
- Enhancing the use of glucose by brain cells (Nagasawa H et al 1990)
- Normalizing the brain levels of serotonin (Markstein R 1985)
- Increasing superoxide dismutase and catalase in the brain while decreasing toxic levels of monoamine oxidase (MAO) (Sozmen EY et al 1998)

A review of existing studies found that hydergine might help prevent dementia (Olin J et al 2001). Although generally well tolerated, hydergine may induce mild nausea in approximately 5 percent of people.

**L-deprenyl hydrochloride.** MAO A and B are the primary enzymes that degrade neurotransmitters in the central nervous system and peripheral tissues. Elevated MAO levels may be associated with age-related neuronal deterioration. Elevated MAO levels are also associated with Parkinson's disease. L-deprenyl hydrochloride (deprenyl), an MAO inhibitor, may be prescribed for Parkinson's disease (Orru S et al 1999; Abell CW et al 2001).

Deprenyl has also been shown to induce rapid increases in nitric oxide production in blood vessels in the brain, which causes them to expand and increases blood flow to the brain. It was also shown to protect the endothelium from the toxic effects of amyloid beta-peptide, which is the main component of the plaques associated with Alzheimer's disease (Thomas T 2000). Another study showed that deprenyl protected cells from cell death caused by a neurotoxin, N-methyl(R)-salsolinol, and reactive oxygen species nitric oxide and peroxynitrite (Naoi M et al 2000).

**Centrophenoxine.** Centrophenoxine (meclofenoxate), a nootropic drug that enhances blood flow to the brain and acts as a free radical scavenger, is widely used in Europe in combination with piracetam to improve memory. Although centrophenoxine is readily available in Europe, it is not sold in the United States.

Researchers have proposed several mechanisms of action for centrophenoxine, including the following:

- Increasing activity of free radical scavengers, especially in rat brain and heart tissues (al-Zuhair H et al 1998).
- Providing antioxidant action (Zs-Nagy I 1989)
- Increasing acetylcholinesterase activity in the brain of rats (Sharma D et al 1995)
- Decreasing the deposition of the age-pigment lipofuscin, which has been shown to cause neuronal damage (Patro N et al 1992)
- In animals, inhibiting total MAO, MAO-A, and MAO-B, which have been shown to damage brain cells (Stancheva SL et al 1988)
- In animals, increasing the level of serotonin, a key neurotransmitter that can be depleted by elevated MAO levels (Stancheva SL et al 1988)
- In animals, significantly increasing the fluidity of brain membranes, which can reverse the dehydration of nerve cells (Lustyik G et al 1985; Wood WG et al 1986)

### ***Memory Drugs on the Horizon***

One of the most promising memory-enhancing drugs is a group of compounds called ampakines, first developed by researchers at the University of California, Irvine. Ampakines work by enhancing communication among brain cells, which scientists believe gradually weaken or fail. A recent study in primates showed that ampakine (Ampakine CX717) improved cognitive performance and reversed the deleterious effects of sleep deprivation (Porrino LJ et al 2005).

At the University of Vermont, scientists are studying the connection between loss of nicotinic receptors on the one hand and cognitive impairment and Alzheimer's disease on the other. These receptors, located on the surface of neuron cells in the brain, modulate neuronal transmission. They bind acetylcholine and nicotine. Scientists have shown that nicotinic receptors appear to be important in regulating learning and memory, anxiety, and motor performance. Stimulation of these receptors with nicotine or novel nicotinic agonists improves certain aspects of attention and memory functioning in normal individuals as well as in patients with Alzheimer's disease, attention deficit/hyperactivity disorder, and schizophrenia. The group is now recruiting patients with amnesiac mild cognitive impairment for a six-month trial of transdermal nicotine to demonstrate cognitive symptom relief.

## **NATURAL HORMONE REPLACEMENT**

Fortunately, there are a number of strategies people can use to slow age-related memory loss and cognitive decline. Chief among them is bioidentical hormone replacement. As we age, levels of virtually all hormones decline. Ideally, hormone replacement with bioidentical hormones seeks to restore hormone levels to those of a healthy person in his or her mid-20s.

**Testosterone.** Testosterone may provide a protective mechanism against age-related mental decline as well as Alzheimer's disease. Researchers in England found that lower levels of testosterone were present in men with Alzheimer's disease than in controls (Hogervorst E et al 2001). It appears that normal testosterone levels protect brain cells from a toxic peptide called beta-amyloid, which tends to accumulate in certain regions of an aging brain. Beta-amyloid has been implicated in the development of Alzheimer's disease. One study observed the effects on cultured neurons exposed to beta-amyloid in the presence of testosterone. The resulting toxicity from beta-amyloid was significantly reduced by testosterone (Pike CJ 2001). Other researchers have found that testosterone supplementation in elderly men may be beneficial in preventing beta-amyloid buildup in the brain and possibly in treating Alzheimer's disease (Goodenough S et al 2000; Gouras GK et al 2000).

Several effects of low testosterone have been reported. These effects include a decreased ability to concentrate, moodiness and emotionality, reduced intellectual agility, feelings of weakness, passive attitudes, and reduced interest in surroundings (Wright AS et al 1999). A consistent finding in the scientific literature is that testosterone replacement therapy produces an increased feeling of well-being, just as low testosterone levels correlate with symptoms of depression and other psychological disorders (Moger WH 1980; Barrett-Connor E et al 1999; Rabkin JG et al 1999; Schweiger U et al 1999; Seidman SN et al 1999).

Testosterone supplementation should be carried out only under the supervision of a qualified physician and after comprehensive blood testing. Some cancers are hormone dependent, and the growth of certain hormone-dependent cancers may be increased by testosterone therapy.

**Melatonin.** Melatonin, a pineal hormone that regulates the body's circadian rhythm, should also be considered. Decreased levels of melatonin may result in poor sleep quality, decreased immune system function, and reduced scavenging of free radicals (Karasek M 2004).

**Pregnenolone.** Pregnenolone is a neurosteroid hormone that is produced from cholesterol and that has been shown to have a direct influence on brain function. In animal studies, pregnenolone was found to boost levels of the vital neurotransmitter acetylcholine, which is deficient in animal models of Alzheimer's disease and cognitive decline. In the same study, it also boosted the animals' ability to sleep, which is connected to memory (Mayo W et al 2001). Other animal studies have demonstrated that pregnenolone levels decline in Alzheimer's patients and that this hormone has a neuroprotective effect (Weill-Engerer S et al 2002).

**DHEA.** DHEA levels have been shown to decline significantly with advanced age (Ferrari E et al 2001; Ferrari E et al 2004). One of the effects of DHEA replacement therapy is an enhanced sense of general well-being. This effect was found at doses of 50 mg and 100 mg daily (Yen S et al 1995). Very few adverse side effects have been reported with DHEA, although in women, androgenic side effects such as facial hair growth and acne can occur with doses as low as 50 mg (Casson P et al 1995). Life Extension suggests periodic, systematic blood testing to assess an individual's response to DHEA dosing.

**Thyroid hormone.** Hypothyroidism is a well-known and relatively common cause of reversible dementia and the most treatable cause of cognitive decline in the older population. A recent study indicates that even subclinical hypothyroidism may be a predisposing factor for depression, cognitive impairment, and dementia (Davis JD et al 2003).

Thyroid hormone blood tests can help detect suboptimal hormone levels and confirm the diagnosis of hypothyroidism. Thyroid peroxidase antibodies should be measured in all patients with subclinical hypothyroidism because these patients are at greatest risk of progressing to overt hypothyroidism (Beers MH et al 1999). Several thyroid hormone preparations are available, including synthetic preparations of L-thyroxine (T4), triiodothyronine (T3), combinations of the two synthetic hormones, and desiccated animal thyroid.

Most physicians specializing in antiaging recommend a combination of T4 and T3 rather than T4 alone in treating hypothyroidism or subclinical hypothyroidism. Furthermore, thyroid function should be evaluated by measuring thyroid-stimulating hormone, T4, and free T3 levels. Since T3 is the most metabolically active form of thyroid hormone and mediates effects at the cellular level, physicians should consider restoring thyroid hormone in patients with clinical symptoms consistent with low thyroid hormone and restoring normal thyroid-stimulating hormone levels if T4 and T3 levels are low. Physicians specializing in antiaging should also consider prescribing T3 if thyroid-stimulating hormone and T4 levels are normal but T3 levels are low and the patient manifests signs and symptoms consistent with hypothyroidism.

## 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 (Tagliatela 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-Laceuva 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 have problems with efficient absorption of nutrients from food. Even healthy older people often exhibit deficiencies in vitamin B6, vitamin B12, and folate.

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 capsules. 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](http://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 allergic 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

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