

Amyotrophic Lateral Sclerosis (ALS) Lou Gehrig's Disease

Amyotrophic lateral sclerosis (ALS) was made famous by Lou Gehrig, the New York Yankees great whose baseball career was cut short in 1939. Two years after calling himself the “luckiest man on the face of the earth” at his tearful early retirement ceremony in Yankee stadium, Gehrig died of the disease. Today, ALS is widely known as Lou Gehrig's disease.

ALS is a degenerative neuromuscular disease that quickly progresses and destroys nerve cells in the brain and spinal cord. This rapid destruction soon begins to affect motor skills and basic movement while preserving the mind and the ability to see, hear, touch, feel, and taste. In Gehrig's case, it became obvious at the start of the 1939 season that the ballplayer was off his game, having trouble fielding throws and running bases. Gehrig was benched in the beginning of the season, never to play baseball again.

The loss of control Gehrig experienced is the hallmark of the disease. ALS is characterized by symptoms such as tripping, clumsiness, difficulty talking and slurred speech, muscle cramps, and twitching. In its advanced stages, muscle wasting and atrophy set in. The most common cause of death among ALS patients is respiratory failure or pulmonary infection when the nerve damage eventually affects the muscles that control breathing. The average survival time after diagnosis with ALS is three to five years.

Scientists have struggled to identify the cause of ALS. To date, two main forms of the disease have been identified: familial and sporadic. Of these, sporadic ALS is by far the most common, accounting for about 90 percent of cases. Its cause is unknown, although researchers are pursuing a number of theories, including oxidative stress, glutamate toxicity, and mitochondrial dysfunction (Rowland L 1994; Cleveland DW 1999).

A number of other theories have been proposed, including autoimmune disorders, heavy metal poisoning, and even viral infection, but much more study is needed before these can be linked conclusively to ALS (Mitchell J 2000). However, there is evidence that ALS may be caused by poorly understood environmental factors. For example, the disease tends to cluster in geographical pockets, yet so far researchers have been stymied in their search for a common influence (Mitchell J 2000).

The second form of ALS, familial, is much more rare, occurring in only 5 percent to 10 percent of cases. Approximately 20 percent of familial ALS is caused by a genetic defect in an antioxidant enzyme called superoxide dismutase-1, or SOD (Sung JJ et al 2002; Rosen DR et al 1993). SOD's role in the body is to scavenge for unstable free radical molecules. When this enzyme is deficient, as in ALS, a buildup of free radicals may occur. The free radicals cause oxidative damage to nerve cells, eventually destroying them.

Because of familial ALS's close association with free radical damage, oxidative stress has emerged as a leading theory to explain sporadic ALS. Free radicals are molecules that have an unpaired electron. They can react with other molecules in the body that contain oxygen, thereby creating reactive oxygen species such as nitric oxide and the hydroxyl radical. Free radicals have been implicated in a large number of diseases. They can be neutralized to some degree with antioxidants such as vitamins C, E, or A; selenium; and coenzyme Q10.

It is important to understand, however, that free radical damage is likely only one factor among many involved in ALS. In reality, ALS is probably caused and aggravated by a number of conditions that work together. By designing a careful regimen of nutrients and supplements, individuals with ALS may be able to blunt the effects of individual factors, thereby slowing the progression of the disease and lessening its symptoms. Conventional medicine, which has fared poorly in treating ALS, also attempts to lessen symptoms by slowing progression. Currently only one drug is approved for ALS patients, and it has been shown to extend life span by only two months (Lacomblez L et al 1996).

ALS remains relatively rare. It occurs in one to three people per 100,000 and tends to affect people between 30 and 60 years of age, although it can occur in younger people. In the United States and Europe, it affects men slightly more than women. In some parts of the western Pacific (e.g., Guam), ALS is more common.

What You Have Learned So Far...

- ALS is a progressive, degenerative, neuromuscular disease that attacks the motor neurons in the brain and spinal cord. Once diagnosed, the disease progresses rapidly, and most patients die within three to five years after symptoms appear.
- ALS affects a person's ability to move, but brain function and the senses remain intact. Symptoms include clumsiness, tripping, slurred speech, and disabilities related to muscular function. The most common cause of death among ALS patients

is respiratory complications and infection after the muscles that control breathing are affected.

- The cause of ALS is unknown, but scientists are pursuing a number of theories, including free radical damage, glutamate toxicity, mitochondrial dysfunction, and even viral causes. It is thought that these factors may work together to cause and advance the disease.
- There is no cure for ALS, but a comprehensive nutritional approach can be designed to address the underlying defects of the disease, possibly slowing its progression and lessening its symptoms.

POSSIBLE CAUSES OF ALS

To identify the underlying cause of sporadic ALS, a number of scientific studies have examined various theories. A growing body of evidence suggests that multiple, complicated factors may work together to cause and advance ALS. Studies have also shown that many of these factors are linked to underlying nutritional deficiencies that can be addressed through diet and nutrient supplementation.

Oxidative damage. Free-radical nerve damage, which can be caused by a defect in the SOD gene, has been implicated in familial ALS. As free radicals build up as a result of a deficiency in the antioxidant SOD, they assault and eventually destroy nerve cells. Researchers have discovered that sporadic ALS patients have many of the same underlying problems experienced by patients with familial ALS, including abnormal protein aggregation, increased levels of calcium between cells, and mitochondrial injury (Cameron A et al 2002). These conditions contribute to neuronal death and muscle wasting common in ALS.

Glutamate excitotoxicity. Glutamate is important to proper brain function because of its role in communication between neurons. Under normal conditions, its concentrations are tightly regulated during its release into the extracellular space and its reuptake into cells. In the case of stroke or seizure, however, excess amounts of glutamate are released into the space between cells. This excess glutamate can excite the nerve cells beyond their capacity and result in nerve cell death.

In ALS, there is evidence that the glutamate reuptake system may not work correctly (Rothstein JD 1995), resulting in an accumulation of glutamate in the space between cells (Cameron A et al 2002). The excess glutamate allows more calcium to enter the cell. The interiors of motor-neuron cells are highly sensitive to excess calcium, which increases cell activity beyond normal levels (excitotoxicity) and contributes to cellular injury through the production of free radicals.

A common approach in treating ALS is to decrease the level of glutamate available in the body or to prevent cells from absorbing excess glutamate. In fact, this is the therapeutic target of the only drug approved by the Food and Drug Administration (FDA) for the treatment of ALS. Dietary restrictions or supplements can be beneficial in reducing glutamate excitotoxicity (Doble A 1999; Rothstein JD 1995; Martin D et al 1993). Effective nutrients include pycnogenol, grape seed extract, creatine, and alpha-lipoic acid. Each of these is discussed in detail later in this chapter.

Mitochondrial abnormalities. The mitochondria are the powerhouses, or energy factories, of cells. They are responsible for many aspects of proper cellular function, including the production of ATP, the scavenging of radical oxygen species, and the maintenance of intracellular calcium concentrations. In ALS patients, changes in mitochondria have been identified (Menzies FM et al 2002). Mitochondrial abnormalities can directly lead to free radical production or increased calcium levels between cells. Additionally, because proper mitochondrial function is so essential, other processes, as yet unidentified, could be altered when mitochondrial health is impaired (Fosslie E 2001).

Supplements that support healthy mitochondrial function may help stabilize mitochondrial health. Supplements that have been proven to support the mitochondria include coenzyme Q10 (CoQ10), creatine, and Ginkgo biloba.

Heavy metals and environmental agents. The role of heavy metals in ALS is highly controversial. Because ALS tends to cluster in certain geographical areas, such as a small town in Wisconsin, researchers have searched for an underlying common theme, including heavy-metal poisoning. So far, the results of these studies have been conflicting and confusing. However, some studies have connected ALS to environmental factors such as mercury (Mano Y et al 1990). Still other studies have been unable to prove a link between ALS and any of the common heavy metals (Gresham LS et al 1986). The same findings apply for environmental agents such as neurotoxic fertilizers and pesticides. While there is good reason to think that neurotoxic agents like these may be somehow linked to degenerative brain and nerve conditions like ALS, researchers have so far been unable to meet the demanding scientific standard needed to establish a causal relationship (Caban-Holt A et al 2005).

Spreading Symptoms: The Onset and Conventional Treatment of ALS

Like many neuromuscular diseases, it can be difficult to make an early diagnosis of ALS. Its symptoms vary from person to person, depending on which group of muscles is affected first. A person can notice tingling in the fingers or toes or cramping in the arms or legs while stretching in bed, for example. There could be trouble with tongue and facial movements, including chewing and

swallowing.

As the disease progresses, it will move up the affected leg or arm until eventually all muscle groups become involved. This spread into all muscle groups is the defining characteristic of ALS. In fact, the term amyotrophy refers to the atrophy (wasting) of muscle tissue, while lateral sclerosis refers to the hardening of the spinal column from the buildup of scar tissue (Rowland LP et al 2001).

Currently, only one drug, riluzole, has been approved by the FDA for the treatment of ALS. Riluzole blunts the effects of glutamate by decreasing glutamate release and blocking the ability of glutamate to bind to its receptors, which decreases the excitotoxicity that leads to cell death. It has been shown to prolong survival times in ALS patients by approximately two months (Lacomblez L et al 1996). Albeit small, this increase in survival time indicates that controlling glutamate levels in the brain could be an essential component in fighting ALS, and it provides valuable information toward ultimately finding a treatment for the disease.

The rest of conventional medical treatment for ALS focuses on improving quality of life for ALS patients. Physicians frequently recommend prescription medications to relieve painful muscle cramps, excessive salivation, and other symptoms. ALS patients are often advised to engage in moderate exercise to maintain muscle strength and function, and to seek physical therapy. As the disease progresses, splints, braces, and wheelchairs are used to help with mobility. Occupational and speech therapy also helps patients as their motor control gradually deteriorates.

ARE STEM CELLS THE GREAT HOPE FOR CURING ALS?

One of the most exciting areas of research into ALS is stem cell therapy. Stem cells, which are immature cells that can differentiate into specialized adult cells, could represent the next great advance for ALS therapy.

Because of federal restrictions on stem cell therapy and the difficulty of designing studies, very few studies have been conducted so far on the treatment of ALS with stem cells. The ones that have been conducted, however, are encouraging, and early animal results show great promise. Researchers have found the following:

- Stem cells delayed motor neuron degeneration in mouse models of ALS (Salini V et al 2004).
- Bone-marrow-derived stem cells injected into human ALS patients were safe (Silani V et al 2004).

Even as researchers push forward with a promising study of stem cells in ALS, there is an understanding that antioxidant therapy will remain an important part of ALS therapy (Silani V et al 2004).

ATTACKING ALS WITH NUTRITION

There is no question that adequate nutrition is crucial to survival for ALS patients. As the disease progresses, patients gradually lose the ability to chew or swallow easily. At the same time, the abdominal and pelvic muscles weaken, and depression frequently sets in. Patients often lose the ability and desire to eat, and malnutrition is a common problem (Cameron A et al 2002).

Unfortunately, the lack of adequate nutrition is especially dangerous for ALS patients. An ALS patient's increased efforts to breathe can result in a greater metabolic rate and the need for a higher caloric intake. Inadequate nutrition can further accelerate the breakdown of muscle tissue and weaken the immune system. This can lead to infection, which is a common cause of death in ALS patients (Aldrich TK 1993).

Studies have consistently indicated that the use of nutrient supplements and antioxidants help ALS patients reduce symptoms and maintain quality of life (Cameron A et al 2002). The following sections, based on Life Extension's survey of the literature, highlight evidence supporting various promising supplements.

Vitamins and Minerals: The First Line of Defense

Vitamin B12 (methylcobalamin). Ultrahigh doses of vitamin B12 (25 mg) have been shown to improve or slow muscle wasting, which is common among ALS patients in the later stages of the disease (Kaji R et al 1998).

Vitamin E. Vitamin E has attracted significant attention from ALS researchers as a result of its antioxidant properties. Vitamin E protects cell membranes against a process known as lipid peroxidation (Cameron A et al 2002). Lipid peroxidation is the breakdown of the cell membrane, which could play a role in degenerative diseases such as ALS. A recent study in humans indicated that vitamin E can help prevent ALS because of its antioxidant properties (Ascherio A et al 2005)).

Zinc. Zinc is an important mineral involved in many physiological processes. During periods of oxidative stress, changes in zinc metabolism that lead to neurodegeneration can occur (Cuajungco MP et al 1997). Furthermore, mutations in the SOD enzyme that decrease its ability to bind to zinc have been demonstrated and may lead to ALS (Banci L et al 2002). However, a study conducted

at the Linus Pauling Institute found that large doses of zinc inhibit copper absorption. In the study, researchers added a small dose of copper to animal ALS models receiving zinc (.3 mg/kg/day of copper with 18 mg/kg/day of zinc) and found the copper prevented early death associated with high doses of zinc (Ermilova IP et al 2005)

Herbal Supplements

Ginseng. In an animal model of ALS, ginseng was shown to significantly delay the onset of ALS symptoms (Jiang F et al 2000). This was likely due to its antioxidant properties. For more information about the safety profile of ginseng, see “Safety Caveats” at the end of this chapter.

Ginkgo biloba. Ginkgo biloba also has antioxidant properties (Ernst E 2002). Additionally, Ginkgo biloba has been shown to promote healthy mitochondrial function (Fosslien E 2001), and during an in vitro study, it was found to protect against glutamate-induced excitotoxicity (Kobayashi MS et al 2000). In animal studies, Ginkgo biloba also limited weight loss among female models for ALS (Ferrante RJ et al 2001).

Rounding Out Your Program

Coenzyme Q10. CoQ10 is essential for proper mitochondrial function and acts as an antioxidant (Murray R et al 1999). Human studies have found that ALS patients have a higher percentage of oxidized CoQ10, a condition the researchers blamed on oxidative stress caused by the disease (Sohmiya M et al 2005). Several animal studies, including the following, have indicated the promise of CoQ10 in treating ALS:

- Among mice models of familial ALS, administration of coenzyme Q10 significantly extended life span, and oral administration significantly increased CoQ10 concentrations in the brains and mitochondria of the test animals (Matthews RT et al 1998).
- Another study found that CoQ10 significantly reduced weight loss, delayed motor deficits, and extended survival in ALS (Beal MF 2002).

Acetyl-L-carnitine. Acetyl-L-carnitine has been shown to improve mitochondrial function (Carta A et al 1993), which is impaired in ALS. It could have neurotrophic activity and increase glutathione concentrations (Thal LJ et al 2000). In one animal study, the effects of acetyl-L-carnitine were increased when it was administered in conjunction with alpha-lipoic acid (Hagen TM et al 2002).

Alpha-lipoic acid. Alpha-lipoic acid has been shown to have antioxidant properties, increase intracellular levels of glutathione (Zhang WJ et al 2001), and chelate metals such as iron and copper (Pioro EP 2000). Furthermore, alpha-lipoic acid has been shown to protect cells against glutamate-induced excitotoxicity (Muller U et al 1995). In one study, significant increases in survival and delays in symptom onset were measured among animal models of ALS (Andreassen OA et al 2001b).

Amino acids. Studies have shown that ALS patients are significantly deficient in up to nine amino acids. A Portuguese study suggested that dietary supplementation with amino acids may have some beneficial effects on the course of the disease (Palma A et al 2005).

Creatine. Creatine is synthesized in the kidneys, liver, and pancreas. In cells, creatine aids in the formation of ATP, which is the primary source of cellular energy. In multiple animal studies, creatine has been shown to provide protective mechanisms against neurodegenerative diseases. For example, it has been suggested that creatine helps to stabilize cellular membranes and mitochondrial energy-transfer complexes (Persky AM et al 2001). Creatine may also reduce oxidative stress (Tarnopolsky 2001) and increase glutamate uptake (Andreassen OA et al 2001a). Furthermore, creatine supplementation has been shown to increase survival times and improve motor performance (Tarnopolsky MA 2001; Andreassen OA et al 2001a). In human ALS patients, there is evidence to suggest that creatine may reduce motor neuron death by improving mitochondrial function (Vielhaber S et al 2001). In addition, a small preliminary study found that creatine supplementation helps reduce the loss of muscle strength in ALS patients (Mazzini L et al 2001).

Curcumin. Curcumin is a pigment found in turmeric, one of the main ingredients in curry. There is evidence that curcumin has antioxidant properties (Li J et al 2001; Naidu KA et al 2002; Lim GP et al 2001). More recent data has suggested that curcumin may help improve calcium status in muscle tissue and reduce inflammatory processes in the mouse brain (Logan-Smith MJ et al 2001; Sumbilla C et al 2002). While human studies are needed to confirm these results, preclinical evidence suggests that curcumin could be useful in ALS.

Dehydroepiandrosterone (DHEA). DHEA is a naturally occurring steroid hormone with anti-aging properties. In several in vitro studies, DHEA has been shown to protect against glutamate-induced toxicity (Lapchak PA et al 2001; Kimonides VG et al 1998; Mao X et al 1998), although few studies have examined DHEA in ALS patients.

Glutathione. Glutathione is a peptide with antioxidant properties that is naturally synthesized by the body. Increasing glutathione levels could help prevent free radical damage to cells (Exner R et al 2000). The glutathione precursor N-acetylcysteine (NAC) has been shown to boost blood levels of glutathione.

Green tea. Green tea contains a high concentration of catechins, which are flavonoids with strong antioxidant properties (Hu M et al 2002). Green tea extracts have been demonstrated to have metal-chelating properties (Levites Y et al 2002) and anti-inflammatory activity (Hong JT et al 2000).

N-acetylcysteine. Along with being a glutathione precursor, NAC has antioxidant activity of its own. In mouse models of ALS, NAC administration has also been shown to decrease motor neuron loss, improve muscle mass, and increase survival time and motor performance (Andreassen OA et al 2000; Henderson JT et al 1996).

Pycnogenol. Pycnogenol is an extract of marine pine bark that includes procyanidins and phenolic acids (Packer L et al 1999). It has been shown to have antioxidant properties (Packer L et al 1999), as well as protective effects against glutamate excitotoxicity (Kobayashi MS et al 2000). Procyanidins, which can also be found in grape seeds, cranberries, blueberries, almonds, and peanuts,

demonstrate potent antioxidant properties (Packer L et al 1999). Pycnogenol is a common complementary therapy option among ALS patients (Cameron A et al 2002).

Resveratrol. A powerful antioxidant found in red grape skins, resveratrol has been found to suppress the influx of calcium into cells, which is associated with glutamate-induced cell toxicity (Wu SN 2003). Resveratrol may also affect the movement of calcium into the cells that line the inside of arteries (Li HF et al 2000).

Selenium. Used in conjunction with a traditional calcium channel blocker, such as nimodipine, and antioxidants, selenium was shown to increase the amount of vitamin E in the blood and increase the activity of glutathione, a powerful internal oxidant, among ALS patients. Antioxidant activity is often impaired in ALS patients, and treatment with this regimen was demonstrated to slow the course of the disease (Apostolski S et al 1998).

Vinpocetine. Vinpocetine inhibits the influx of calcium into the cell, which has been associated with glutamate-induced cell toxicity (Wu SN et al 2001). This is similar to the mechanism of action of riluzole, the only FDA-approved drug used to treat ALS.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

The goal of dietary and supplement therapy with ALS patients is twofold. First, patients need to slow neuronal damage, potentially slowing progression of the disease. Second, therapy must promote the optimization of function of the neuromuscular junction, thus maintaining a high quality of life. Life Extension's recommendations address both these areas by offering a comprehensive portfolio of supplements. No one should begin a regimen of dietary supplementation unless under the supervision of a qualified physician. Also, blood tests are highly recommended prior to DHEA supplementation to establish a baseline hormone level. Blood testing is available by calling 1-800-544-4440. Life Extension's recommendations include the following nutrients:

Vitamins and Minerals

- **Vitamin B12:** up to 25 mg daily, sublingual or administered intramuscularly (IM).
- **Vitamin E (Gamma E Tocopherol/Tocotrienols):** one to two softgels per day with food.
- **Zinc:** 15 mg daily. ALS patients can also consider taking 1 mg of copper in conjunction with zinc.

Herbal Supplements

- **Ginseng:** 400 mg daily.
- **Ginkgo biloba:** Ginkgo Biloba Standardized Extract, one capsule per day.

Other Dietary Supplements

- **CoQ10:** 1200 mg daily.
- **Creatine:** Micronized Creatine, two to four capsules per day with or without food.
- **DHEA:** A typical starting dose of DHEA is 15 mg to 75 mg. Blood testing is recommended after three to six weeks to make sure levels of this hormone are optimal.
- **Glutathione:** L-Glutathione, L-Cysteine and C, one capsule one to three times per day before food.
- **N-Acetyl Cysteine:** one capsule one to three times per day.
- **R-lipoic acid:** one to two capsules per day.
- **Acetyl-L-Carnitine:** one to four capsules per day on an empty stomach with water or juice.
- **Mega Green Tea Extract:** one capsule per day with or without food. Decaffeinated green tea is available for people sensitive to caffeine.
- **Resveratrol:** 20 mg daily.
- **Selenium:** 200 mcg daily. This may be administered in conjunction with a calcium channel blocker, such as nimodipine. Calcium channel blockers are available only by prescription.
- **Super Curcumin:** 900 mg
- **Mitochondrial Energy Optimizer.** This is a special antioxidant blend available only through the Life Extension Foundation. Please note that this product contains the proper doses of R-dihydro-lipoic acid and acetyl-L-carnitine arginate. Therefore, individuals may eliminate them from the list above if they take this product.
- **Vinpocetine:** 5 mg daily.

ALS 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.

Creatine

- Do not take creatine if you have diabetes, kidney failure, a kidney disorder such as nephrotic syndrome, or are otherwise at risk of having a kidney disorder.
- If you take creatine, have your serum creatinine level monitored frequently.
- Creatine can cause muscle cramping, muscle strains, and gastrointestinal symptoms such as nausea and diarrhea.

Curcumin

- Do not take curcumin if you have a bile duct obstruction or a history of gallstones. Taking curcumin can stimulate bile production.
- Consult your doctor before taking curcumin if you have gastroesophageal reflux disease (GERD) or a history of peptic ulcer disease.
- Consult your doctor before taking curcumin if you take warfarin or antiplatelet drugs. Curcumin can have antithrombotic activity.
- Always take curcumin with food. Curcumin may cause gastric irritation, ulceration, gastritis, and peptic ulcer disease if taken on an empty stomach.
- Curcumin can cause gastrointestinal symptoms such as nausea and diarrhea.

DHEA

- Do not take DHEA if you could be pregnant, are breastfeeding, or could have prostate, breast, uterine, or ovarian cancer.
- Ginkgo biloba
- Do not take ginkgo biloba if you have a known risk factor for intracranial hemorrhage such as systematic arterial hypertension, diabetes, or amyloid senile plaque.
- Ginkgo biloba can cause allergic skin reactions, elevated blood pressure, and gastrointestinal symptoms such as nausea and diarrhea.

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.

Ginseng

- Consult your doctor before taking ginseng if you have high blood pressure. Overuse of ginseng can increase blood pressure.
- Consult your doctor before taking ginseng if you take nonsteroidal anti-inflammatory drugs (NSAIDs) and/or warfarin (Coumadin). Taking NSAIDs or warfarin with ginseng can increase the risk of bleeding.
- Consult your doctor before taking ginseng if you have diabetes. Taking ginseng can cause an extreme drop in your blood glucose level.

- Ginseng can cause breast pain, vaginal bleeding after menopause, insomnia, headaches, and nosebleeds.

Green Tea

- Consult your doctor before taking green tea extract if you take aspirin or warfarin (Coumadin). Taking green tea extract and aspirin or warfarin can increase the risk of bleeding.
- Discontinue using green tea extract 2 weeks before any surgical procedure. Green tea extract may decrease platelet aggregation.
- Green tea extract contains caffeine, which may produce a variety of symptoms including restlessness, nausea, headache, muscle tension, sleep disturbances, and rapid heartbeat.

Lipoic Acid

- Consult your doctor before taking lipoic acid if you have diabetes and glucose intolerance. Monitor your blood glucose level frequently. Lipoic acid may lower blood glucose levels.

NAC

- NAC clearance is reduced in people who have chronic liver disease.
- Do not take NAC if you have a history of kidney stones (particularly cystine stones).
- NAC can produce a false-positive result in the nitroprusside test for ketone bodies used to detect diabetes.
- Consult your doctor before taking NAC if you have a history of peptic ulcer disease. Mucolytic agents may disrupt the gastric mucosal barrier.
- NAC can cause headache (especially when used along with nitrates) and gastrointestinal symptoms such as nausea and diarrhea.

Rhodiola rosea

- Do not take Rhodiola rosea if you have anxiety or bipolar disorder.

SODzymes

- Do not take SODzymes if you are allergic to soy, corn, or wheat.

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.

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.

Zinc

- High doses of zinc (above 30 milligrams daily) can cause adverse reactions.
- Zinc can cause a metallic taste, headache, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea.
- High doses of zinc can lead to copper deficiency and hypochromic microcytic anemia secondary to zinc-induced copper deficiency.
- High doses of zinc may suppress the immune system.

For more information see the Safety Appendix

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