

## Depression

Depression is considered the most common cause of disability in the United States (Norman TR 2006). According to the National Institutes of Health, clinical depression will affect up to 25 percent of women in their lifetimes and up to 12 percent of men. People with depression suffer in many areas of their lives, including sleep, eating, relationships, school, work, and self-image.

Depression is more than the normal feelings of sadness that people experience from time to time. It is a clearly defined disorder that affects both mind and body. People suffering from clinical depression cannot just will their blues away, and in most cases the depression will not subside without active intervention. Unfortunately, however, many people do not seek professional treatment for their depression, so the disorder is likely to be underdiagnosed. Among those who do seek professional help, many people do not find relief for their condition among conventional therapies.

Treatment for depression is usually multifaceted, and there is no doubt that nutrition plays an important role. Research has shown that the body chemistry of depressed people is altered in various ways and that deficiencies in neurotransmitters, hormonal imbalances, and other nutritional deficits can contribute to clinical depression. Also, many people with depression do not eat enough, overeat, or eat nonnutritious foods. New research has also connected depression to inflammation and oxidative stress, which are both appropriately managed with nutritional supplements.

Finally, the role of hormones in depression is underappreciated in the medical community. Many people who suffer from depression that cannot be treated effectively with conventional antidepressants may actually be suffering from hormonal imbalances that are causing their disease. Unfortunately, few physicians routinely test their depressed patients for hormonal imbalances.

Ultimately, the treatment of depression usually touches on many facets of a person's life. Exercise is important, and treatments such as massage and acupuncture have a long history of effectiveness when used as part of a treatment program. Counseling and psychiatric therapy can also help people deal with the feelings of anxiety and hopelessness that accompany depression.

The good news is that depression can be treated successfully. Many people who seek treatment for their depression realize they may have been suffering its symptoms for a long time and respond favorably to treatment.

### DIAGNOSING DEPRESSION

In recent years, researchers have identified various kinds of depression, including major depressive disorder, dysthymic disorder, bipolar disorder, seasonal affective disorder, postpartum depression, and premenstrual dysphoric disorder (PMDD). For more information on seasonal affective disorder and PMDD, please see the chapters in this book pertaining to those topics. This chapter will focus on major depressive disorder, and the term depression will be used to refer to major depressive disorder.

Major depressive disorder is sometimes called major depression, clinical depression, or unipolar depression. Unipolar depression is so named because the disorder is characterized only by depression, as opposed to bipolar disorder, which is characterized by both depression and episodes of mania. People with major depressive disorder may have recurrent episodes of depression, and there is evidence that many people experience their first episodes of depression at a young age (Kessler RC et al 1998; Larsson B et al 1998). Episodes of depression may be separated by years or months and may become more common as a person ages. After an episode is over, most people will recover completely. People who recover only partially are more likely to experience another episode. Among adolescents, clinical depression is associated with substance abuse and suicide (Kessler RC et al 1998), and even among adults, as many as 15 percent of people diagnosed with depression die by suicide. Clinical depression is also associated with vascular and cerebrovascular disease (Thomas AJ et al 2003, 2004; Tiemeier H 2003).

Guidelines for the diagnosis of depression can be found in the fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders. To be diagnosed with clinical depression, the patient must experience at least five of the nine symptoms below for two weeks or more, most of the time, almost every day. The symptoms must include either a depressed mood or loss of interest.

- Depressed mood
- Reduced level of interest or pleasure in activities
- A considerable loss or gain of weight or appetite
- Insomnia or excessive sleeping
- Behavior that is agitated or slowed down

- Fatigue or diminished energy
- Thoughts of worthlessness or guilt
- Reduced ability to think or concentrate
- Frequent thoughts of suicide or death, or suicide attempts

In addition, the following conditions must be present:

- The symptoms are not part of a mixed episode of psychiatric disorders.
- The symptoms are a cause of distress at home, work, school, or other social settings.
- The symptoms are not caused by a substance, including alcohol or illicit drugs.
- The symptoms are not caused by normal bereavement, they continue for more than two months, or they cause difficulty in functioning.

The causes of clinical depression are not fully known. It is likely that several factors, including a genetic predisposition and hormone imbalances, work together in any particular individual to bring on a depressive episode. One of the leading factors associated with depression is reduced levels of norepinephrine, serotonin, and dopamine (the so-called amine theory) (Hou C et al 2006; Prange AJ et al 1974). There is also evidence that the structure of the brain itself may be altered in depression, especially the hippocampus (Campbell S et al 2004), although few studies have been conducted on effective treatment for these changes. Other factors that may contribute to depression include oxidative stress, which can cause cell membrane and DNA destruction in the brain (Khantzode SD et al 2003), inflammation (Elenkov IJ et al 2005), and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis (Antonijevic IA 2006).

### **THE PROBLEM WITH CONVENTIONAL TREATMENT OF DEPRESSION**

Conventional medicine's track record in treating depression has improved in recent decades, but many patients are still unable to find relief from their condition with conventional antidepressants, or they face the prospect of unpleasant and even dangerous side effects from their therapy. In 2004, for example, a federal advisory panel announced its safety recommendations for the newest and most common class of antidepressants, selective serotonin reuptake inhibitors (SSRIs).

The panel found that SSRIs not only increase the risk of suicide for some younger patients but are often ineffective. The panel urged the Food and Drug Administration (FDA) to impose its strongest caution—known as a black box warning—regarding the use of this class of antidepressants in children and adolescents (Food and Drug Administration 2004). In October 2004, the FDA adopted the recommendation and mandated warnings for all SSRI drugs.

The panel's investigation came on the heels of several highly publicized incidents in which children and adolescents on the drugs committed suicide, and it highlighted the downside of antidepressant drugs. Although only Prozac® is approved by the FDA for the treatment of depression in children and adolescents, they are often given prescriptions for other medications, such as Zoloft®, Paxil®, and Celexa®. All of these drugs belong to the SSRI class of antidepressants and are believed to work similarly.

The debate in the United States was prompted in 2005, when British officials banned all SSRIs except Prozac® for use in children. Despite that action, most experts agree it is unlikely that Prozac® is inherently safer than other SSRIs for use in children and adolescents. Although the various SSRIs differ chemically, their mechanism of action in the body is essentially the same. All inhibit activity at structures known as uptake pumps, located on nerve endings. Most affect the reuptake of serotonin from the synapses, or spaces, between nerve endings. Some affect another messenger chemical, norepinephrine, in a similar manner. These drugs are known as serotonin norepinephrine reuptake inhibitors.

Serotonin and norepinephrine are neurotransmitters that regulate mood, sleep, appetite, and emotion and are involved in a variety of physiological and behavioral functions. If the immediate reuptake of serotonin (or norepinephrine) is prevented, more of these precious brain chemicals remain available to do their intended work (Vaswani M et al 2003; Bourin M et al 2002).

### **ANTIDEPRESSANT THERAPY'S HIGH COST**

Unfortunately, even in adults, the depression relief afforded by SSRIs often comes at a steep price, and not just in monetary terms, though most SSRIs are far from inexpensive. The list of potential side effects includes headache, nausea, diarrhea, anxiety, sleep disturbances, weight gain, fatigue, and most common of all, sexual dysfunction (Degner D et al 2004; Wilson K et al 2004; Gregorian RS et al 2002). The latter strikes up to 60 percent of patients taking SSRIs and usually manifests as loss of libido, insufficient lubrication or arousal, or an inability to achieve orgasm (Clayton AH et al 2002; Gregorian RS et al 2002). Among men who experience sexual side effects, erectile dysfunction occurs in up to 90 percent of cases (Rosen RC et al 2003). Understandably, many patients find this side effect particularly distressing.

Drug interactions with antidepressants are also a concern. Alcohol, the most common drug of all, may be especially risky. It

causes potentially perilous sedation when mixed with antidepressants, many patients discontinue their medication and risk sinking back into depression. Not all patients respond to SSRIs, even when they follow the dosage recommendations of the prescribing physician. Treatment failures range from 40 to 60 percent, and relapse rates are similarly discouraging. According to a recent report from Duke University Medical Center, an analysis of more than a decade of research on the subject shows that recurrence and relapse rates for drug-treated depression range as high as 80 percent (Masand PS 2003). The same report noted that up to 44 percent of patients starting drug therapy discontinue the drug within three months. Many patients (28 percent) discontinue drug therapy due to intolerable side effects, often within the first month, before the drug takes effect (Masand PS 2003).

Although they are not perfect, SSRIs are a vast improvement over previously available drugs and therapies for depression. In the first half of the 20th century, physicians could offer little more than talk therapy or electroconvulsive therapy (ECT) as treatment for their patients with major depression. Although the former was often ineffectual, the latter works very well. However, ECT is time consuming, requires multiple treatments, and often produces some memory loss, as the brain is literally zapped with electrical current. Understandably, a certain amount of stigma is associated with the use of ECT. According to a survey of thousands of Consumer Reports subscribers who had recently undergone treatment for depression, talk therapy, while often useful, may require at least 13 sessions to achieve relief comparable to that available through drug therapy (Drugs vs. Talk Therapy 2004).

Thus, when the first true antidepressant drug, a monoamine oxidase inhibitor, was introduced in the 1950s, doctors hailed the dawn of a hopeful new era in the treatment of depression. However, monoamine oxidase inhibitors are particularly risky drugs; their side effects are numerous and often severe, and drug interactions are potentially fatal. The advent of tricyclic antidepressants in the 1960s marked a further advance in treatment. But even tricyclics, such as imipramine and amitriptyline, come with unpleasant side effects. Dosages must be carefully monitored because therapeutic ranges are narrow and overdoses are potentially fatal. Side effects tend to manifest quickly, but onset of action can take so long (from four to six weeks) that many patients discontinue the drug long before experiencing mood elevation (Masand PS 2003; Nemeroff CB 2003).

## BALANCING HORMONES

A survey of the scientific literature suggests that one reason antidepressants have such a high failure rate is that the role hormones play in the disease is underappreciated. In fact, hormones are well-known regulators of mood, and many, such as dehydroepiandrosterone (DHEA), are present in large quantities in the brain. For example, estrogen, alone or in combination with antidepressant drugs, has been shown to improve mood, whereas progesterone affects mood and memory adversely (Birzniece V et al 2006). Among men, declining hormone levels caused by aging are associated with depressed mood (Amore M 2005).

These findings are important because they offer an alternative avenue of therapy for people who may not receive adequate relief from conventional medicines. Both men and women are affected by declining hormone levels as they age (menopause in women and andropause in men). Hormone replacement therapy seeks to reestablish the hormone levels of a healthy young adult. It is important to understand that no single hormone exists in a vacuum. The major sex hormones are all synthesized from cholesterol, and they exist in a cascade in which a change in one hormone affects levels of other hormones. Thus, if you and your physician are considering hormone replacement therapy, it is important to test for all the hormones, including pregnenolone, DHEA, estrogen, progesterone, and testosterone, and design a comprehensive program of bioidentical hormone replacement.

**DHEA.** DHEA is an important steroid hormone whose levels decrease with age. People with depression have low levels of DHEA, and DHEA has been shown to modulate serotonin levels in the brains of laboratory rats (Karishma KK et al 2002; Abadie JM et al 1993). A number of studies have examined the role of DHEA in depression, with very encouraging results. In one study, patients with HIV/AIDS and depression benefited significantly from DHEA therapy (Rabkin JG et al 2006). In a randomized, placebo-controlled, double-blind study that lasted for six years, researchers tested 90 mg DHEA daily for 3 weeks and 450 mg/d for 3 weeks as a monotherapy for both mild and severe depression. They found that DHEA therapy resulted in a significant improvement in symptoms, compared with placebo (Schmidt PJ et al 2005).

**Testosterone.** Studies indicate that levels of testosterone are reduced in some depressed men (Barrett-Connor E et al 1999; Schweiger U et al 1999). A clinical trial using transdermal testosterone gel showed that patients treated with testosterone experienced significant improvements in depressive symptoms (Pope HG Jr et al 2003).

**Estrogen.** Estrogen is also linked to depression. It is of particular importance in perimenopausal or postmenopausal women (Grigoriadis S et al 2002). Women using estrogen replacement therapy to alleviate menopause symptoms appear to experience reduced depression (Miller KJ et al 2002). In some older women being treated for depression, estrogen replacement therapy may actually improve the effects of conventional antidepressants (Schneider LS et al 2001).

Estrogen is thought to produce its antidepressant effects by regulating serotonin in the central nervous system (Joffe H et al 1998; Rubinow DR et al 1998). Estrogen is also thought to reduce monoamine oxidase activity, increasing levels of neurotransmitters. Animal studies show that removing estrogen eliminates downregulation of serotonin receptors produced by antidepressants, an effect that is reversed with reintroduction of estrogen. This suggests that estrogen affects antidepressant activity and modulates

serotonergic transmission within the central nervous system (Bethea CL et al 1998; Kendall DA et al 1982).

## HOMOCYSTEINE AND DEPRESSION

Many nutrients and supplements can influence the body's management of vital neurotransmitters. Much like the prescription drugs used to treat depression, these natural therapies act by increasing production of neurotransmitters or reducing their rates of degradation. Unlike prescription drugs, however, natural therapies can also minimize the effects of oxidative stress and inflammation that contribute to depression.

One intriguing target for therapy is homocysteine, which is an intermediary amino acid that has been associated with various disease states. Studies have shown that elevated homocysteine is also associated with depressive disorders and anger attacks caused by depression (Chen CS et al 2005).

Homocysteine levels can be lowered by the following nutrients, some of which (especially S-adenosyl-L-methionine, or SAME) have been found to improve depression independently.

**Folic acid.** Clinical trials have demonstrated that folic acid relieves depression on its own and enhances the antidepressant effect of conventional antidepressants. In one study, patients given 500 mcg folic acid daily in conjunction with fluoxetine experienced a significant improvement in depressive symptoms compared with patients receiving the antidepressant alone, and women benefited particularly (Coppin A et al 2000). Because relapse is associated with low serum folate, it is important to maintain folate supplementation for a year following a depressive episode (Morris MS et al 2003).

**Vitamin B12 (cobalamin).** Deficiency in vitamin B12 has been cited as a risk factor for developing depression (Gottfries CG 2001) and is associated with increased homocysteine (Parnetti L et al 1997; Stabler SP et al 1990). People with high vitamin B12 levels have better treatment outcomes for major depression (Hintikka J et al 2003). Vitamin B12 supplementation is important for depressed individuals, particularly older patients, in whom low vitamin B12 levels are common (Lindeman RD et al 2000; Penninx BW et al 2000).

**Vitamin B6 (pyridoxine).** In 2005, a team of researchers from Yale University examined all the published studies on vitamin B6 and depression. Although the researchers did not find evidence of benefits from vitamin B6 treatment in the results of all the studies, they did find that premenopausal women suffering from depression benefited from vitamin B6 (Williams AL et al 2005).

**Trimethylglycine and zinc.** Trimethylglycine (TMG) operates along a different pathway from that of the B vitamins. In fact, some individuals who have a severely elevated homocysteine level respond only to TMG because its activity is limited to the liver and kidneys. To decrease a severely elevated homocysteine level, repeated high doses of TMG must be taken throughout the day. One small study found that TMG supplementation taken concurrently with vitamin B6 and folic acid significantly reduced homocysteine (Dudman NP et al 1996).

Zinc acts in concert with vitamin B6 to promote remethylation of homocysteine to methionine. Zinc is also needed for the conversion of homocysteine to cysteine and glutathione.

**SAME.** SAME is derived directly from methionine. Its job is to provide methyl groups for reactions throughout the body, including the methylation of nucleic acids (RNA and DNA), proteins, and structures throughout the brain. SAME is the precursor to such nutrients as creatine, glutathione, taurine, L-carnitine, and melatonin and can be found in almost every tissue in the body. Clinical trials comparing both oral and intramuscular forms of SAME to tricyclic antidepressants show SAME to be as effective as tricyclic antidepressants in reducing depressive symptoms (Mischoulon D et al 2002; Pancheri P et al 2002). SAME is associated with fewer adverse events (Pancheri P et al 2002) and is better tolerated than conventional antidepressants (Delle CR et al 2002). Studies show a significant correlation between plasma levels of SAME and improvement of depressive symptoms (Bell KM et al 1994). Some researchers propose that SAME produces its antidepressant effects faster than conventional antidepressants and may potentiate the effects of tricyclic antidepressants (Mischoulon D et al 2002). It has been studied in the treatment of depression, schizophrenia, demyelination diseases, liver disease, dementia, arthritis, and other conditions. It is also necessary for normal circadian rhythms. High doses of SAME, 1600 mg daily, increased phosphocreatine levels in the human brain (Silveri MM et al 2003), indicating that SAME is important in forming creatine. Although SAME is part of the methionine cycle, taking supplemental SAME does not increase the production of homocysteine. It does, however, encourage the conversion of homocysteine to cysteine and glutathione (Devlin TM 2001), thus lowering homocysteine levels.

**Selenium.** The trace mineral selenium is necessary for the antioxidant activity of glutathione, which is converted from homocysteine. Selenium deficiency has been shown to increase oxidative damage in animals. By boosting selenium levels, you can raise your level of glutathione and help lower your homocysteine level (Devlin TM 2001).

**N-acetylcysteine.** Consuming N-acetylcysteine may reduce homocysteine levels by encouraging the production of cysteine, which is critical to the conversion of homocysteine to glutathione. By increasing the production of cysteine, people with depression may

be able to boost the amount of homocysteine converted into glutathione.

**Cysteine.** Like N-acetylcysteine, cysteine may prevent the release of stored homocysteine into the bloodstream. Life Extension Foundation favors maintaining an adequate level of cysteine to preserve normal glutathione levels.

Not all the homocysteine created is released directly into the bloodstream as free homocysteine. In fact, less than 1 percent of the homocysteine in the blood is free. The majority, about 98 to 99 percent, is bound to proteins in the blood and considered stored. This store of homocysteine may be released in response to decreased methylation or oxidative damage or in response to other influences. The following nutrients have been shown to inhibit the release of homocysteine:

**Creatine.** Somewhere between 50 and 90 percent of the SAMe required by the body goes into the production of creatine (Silveri MM et al 2003; Devlin TM 2001; Stead LM et al 2001; Lee H et al 1998; Finkelstein JD et al 1984). Supplementation with creatine diminishes the need for SAMe and reduces the formation of homocysteine and the need for homocysteine remethylation. In animal studies, supplementation with creatine for two weeks reduced homocysteine levels by 25 percent (Stead LM et al 2001).

**Choline-producing nutrients.** SAMe is involved in the production of choline. If you take choline-producing nutrients, your body produces less SAMe, which reduces the amount of homocysteine needed, thus helping to maintain normal levels. Choline-producing nutrients include cytidine diphosphate choline, lecithin, alpha-glycerolphosphorylcholine, and choline chloride.

**A prescription alternative to folic acid.** For people who do not achieve results with supplements, a new drug called Metafolin® was recently introduced. The drug is a natural folate (folic acid is a synthetic folate) and is readily available to the body. According to its manufacturer, Metafolin® may be superior to folic acid supplementation because it does not bear the risk of unmodified folic acid accumulation and is less likely to mask signs of a vitamin B12 deficiency.

## OTHER NUTRIENTS

**Omega-3 fatty acids.** Omega-3 fatty acids are long-chain polyunsaturated fatty acids found in fish and various oils, such as flaxseed or canola oil (Logan AC 2003). The brain has a high concentration of polyunsaturated fatty acids (Yehuda S et al 1999; Bourre JM et al 1991), and depressed people have lower levels of omega-3 fatty acids compared with the pro-inflammatory omega-6 fatty acids (Tiemeier H 2003). Adding the omega-3 fatty acid eicosapentaenoic acid (EPA) to conventional antidepressant treatment relieves depressive symptoms (Puri BK et al 2001). Among children with depression, supplementation with omega-3 fatty acids has shown “highly significant” effects on symptom scores (Nemets H et al 2006). In 2006, researchers analyzed results from six published studies on depression and omega-3 fatty acids. They found that omega-3 fatty acids can reduce symptoms of depression among adults (Williams AL et al 2006).

Omega-3 fatty acids are also beneficial because they reduce the risk of cardiovascular disease, which is highly associated with depression (Burr ML et al 1989; Singh RB et al 1997).

**Zinc.** Zinc is a trace element known to have a regulatory function in the human nervous system (Nowak G et al 2002). It not only promotes creation of new brain cells but acts as an antioxidant, decreasing oxidative stress. Decreased blood levels of zinc are associated with depression (Maes M et al 1994, 1997; McLoughlin IJ et al 1990), and maintaining a healthy zinc level in the brain is essential to normal brain function (Takeda A 2000).

Animal studies show that antidepressants and electroconvulsive shock treatments change zinc concentrations in areas of the brain associated with depression (Nowak G et al 1999). In an animal study, zinc was also shown to enhance antidepressant effects of imipramine (Krocicka B et al 2001).

**Vitamin C and vitamin E.** Vitamin C is a well-known antioxidant. Studies indicate that levels of vitamin C are lower in people with depression than in those without depression (McKee T et al 1999a; Khanzode SD et al 2003). Ascorbic acid indirectly inhibits oxidative stress by enhancing the activity of other antioxidants, such as vitamin E (McKee T et al 1999b). Low serum levels of vitamin E are linked to major depression (Maes M et al 2000).

**St. John’s wort.** St. John’s wort (*Hypericum perforatum*) is a medicinal herb used for the treatment of neurological and psychiatric disorders, including depression (Nangia M et al 2000). Compared to placebo, *H. perforatum* extract can effectively treat mild to moderate depression, reducing symptoms and recurrence rate (Lecrubier Y et al 2002).

The mechanism of action of St. John’s wort in depression is not entirely clear. One idea is that St. John’s wort affects presynaptic serotonin uptake and inhibits norepinephrine reuptake (Nangia M et al 2000). By affecting or inhibiting reuptake mechanisms of presynaptic neurons, St. John’s wort may increase availability of serotonin and norepinephrine. Clinical trials show positive response rates to treatment with St. John’s wort (Kim HL et al 1999; Linde K et al 1996). Please see the important safety information on St. John’s wort at the end of this chapter.

**Ginkgo biloba.** The herb *Ginkgo biloba* has been shown to produce an antioxidant. Ginkgo has been studied in animal models of depression with good results. In one study, rats were subjected to chronic stress—the same kind of stress that may lead to depression in humans. When the rodents were treated with the antidepressant venlafaxine, *Ginkgo biloba* was able to protect the brain while mitigating the side effects of the synthetic antidepressant (Qin XS et al 2005). Another study examined the ability of ginkgo to reduce the sexual dysfunction that sometimes accompanies conventional antidepressant drugs. Ginkgo was administered at 240 mg daily for 12 weeks. Interestingly, although the researchers didn’t find any statistically significant change across the whole group, they noted “spectacular individual responses” (Wheatley D 2004).

**L-phenylalanine and tyrosine.** Just as tryptophan and 5-hydroxytryptophan are precursors to serotonin, L-phenylalanine and tyrosine are precursors to dopamine and norepinephrine. Although not many clinical studies have examined the effects of these two amino acids, one review study found that people experiencing mild to moderate depression may find it helpful to “preload” with precursors of valuable neurotransmitters (Meyers S 2000).

**Tryptophan and 5-hydroxytryptophan.** Available as dietary supplements, these two substances are immediate precursors to serotonin. In some countries, tryptophan is licensed as an antidepressant (Murphy SE et al 2006). In one study, healthy women given tryptophan for 14 days experienced increased recognition of happy faces and words and decreased recognition of negative words. The research team concluded that tryptophan had improved the study participants’ supply of serotonin, much like a conventional SSRI (Murphy SE et al 2006). More study is needed on the use of these supplements in depression.

## LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Treatment of depression often takes place on several fronts. Depressed patients may benefit from exercise and other strategies,

such as acupuncture, yoga, or meditation. In addition, psychiatric counseling can help people deal with the feelings of sadness and hopelessness that accompany depression.

If there are any underlying conditions, these should also be treated. Heart and vascular disease are associated with depression, and hypothyroidism can also cause depression. For more ideas on how to treat these conditions, please see the chapters on thyroid disorders and heart disease.

The following dietary supplements have been shown to help restore neurotransmitter levels and alleviate depression:

- **B vitamins**—A full complement of B vitamins (including at least 1000 micrograms (mcg) vitamin B12, 250 milligrams (mg) vitamin B6, and 800 mcg of folic acid daily)
- **Zinc**—15 to 30 mg daily
- **TMG**—2 to 4 grams (g) daily
- **Cytidine diphosphate choline**—250 to 500 mg daily (alternatively, 1 to 3 teaspoons liquid choline chloride mixed with 2 ounces juice daily, 1 tablespoon pure lecithin granules daily, or 250 mg glyceryl phosphoryl choline daily)
- **Micronized creatine**—500 mg (in capsule form) four to eight times daily
- **N-acetylcysteine**—600 mg (in capsule form) one to two times daily on an empty stomach
- **Vitamin C**—1 to 3 g daily
- **Vitamin E**—400 International Units (IU) daily, with 200 mg gamma tocopherol
- **EPA/DHA**—1400 mg EPA and 1000 mg DHA daily
- **SAME**—400 to 1200 mg daily without food
- **St. John's wort**—300 to 900 mg daily
- **Ginkgo biloba**—120 mg daily
- **L-phenylalanine**—500 to 1000 mg early in the day
- **Tyrosine**—500 to 1000 mg daily
- **Tryptophan**—500 to 1000 mg once or twice daily on an empty stomach
- **DHEA**—15 to 75 mg daily, followed by blood testing in three to six weeks to make sure optimal levels are maintained

In addition, hormone therapy may be necessary to balance levels of important hormones, including pregnenolone, estrogen, progesterone, and testosterone. Hormone testing is recommended, followed by hormone supplements if necessary. Progesterone creams are available for application directly to the skin, while testosterone is available in a number of delivery systems. Special compounding pharmacies can help produce estrogen supplements that reflect the natural balance of estrogens rather than the strong animal estrogens used in conventional hormone replacement therapy. For more information, see the chapters Female Hormone Modulation and Male Hormone Modulation.

## PRODUCT AVAILABILITY

All the nutrients and supplements discussed in this section are available through the Life Extension Foundation Buyers Club, Inc. For ordering information, call anytime toll-free 1-800-544-4440, or visit us online at [www.LifeExtension.com](http://www.LifeExtension.com).

The blood tests discussed in this section are available through Life Extension National Diagnostics, Inc. For ordering information, call anytime toll-free 1-800-208-3444, or visit us online at [www.LifeExtension.com](http://www.LifeExtension.com).

### ***Depression 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:

#### **Choline**

- Do not take choline if you have primary genetic trimethylaminuria.
- Choline can cause fishy body odor, excessive perspiration, hypotension (low blood pressure), depression, and gastrointestinal symptoms such as nausea and diarrhea.

#### **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.

## **DHEA**

- Do not take DHEA if you could be pregnant, are breastfeeding, or could have prostate, breast, uterine, or ovarian cancer.
- DHEA can cause androgenic effects in woman such as acne, deepening of the voice, facial hair growth and hair loss.

## **D,L-Phenylalanine**

- Do not take D,L-phenylalanine if you have phenylketonuria.
- Do not take D,L-phenylalanine if you are taking nonselective monoamine oxidase inhibitors (MAOIs).
- Do not take D,L-phenylalanine if you have schizophrenia. D,L-phenylalanine can exacerbate tardive dyskinesia (involuntary facial movements) in people who have schizophrenia.
- Consult your doctor before taking D,L-phenylalanine if you have high blood pressure. D,L-phenylalanine can exacerbate high blood pressure. D,L-phenylalanine can also cause high blood pressure.

## **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.

## **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.

## **L-Tryptophan**

- Do not take L-tryptophan if you have carcinoid tumors.
- Do not take L-tryptophan while taking monoamine oxidase inhibitors (MAOIs) (type A) or within 2 weeks of discontinuing MAOIs.
- Do not take L-tryptophan with any antidepressant medications, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants or MAOIs.
- Do not take L-tryptophan with serotonin 5-HT receptor agonists, including naratriptan, sumatriptan and zolmitriptan.
- Do not take L-tryptophan if you have ischemic heart disease (e.g., a history of myocardial infarction, angina pectoris or documented silent ischemia), coronary artery spasm (e.g., Prinzmetal angina), uncontrolled hypertension or any other significant cardiovascular disease.
- L-tryptophan can trigger excess serotonin formation in tissues other than the target organ and cause significant adverse reactions.
- L-tryptophan can cause nausea, diarrhea, loss of appetite, vomiting, difficulty breathing, pupil dilation, abnormally sensitive reflexes, loss of muscle coordination, blurry vision and cardiac dysrhythmia.

## **L-Tyrosine**

- Do not take L-tyrosine if you have inborn errors of metabolism alkaptonuria and tyrosinemia type I and type II.
- Do not take L-tyrosine if you are taking non-selective monoamine oxidase (MAO) inhibitors.

- Do not take L-tyrosine if you have hypertension.
- Do not take L-tyrosine if you have melanoma

## **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.

## **Niacin (nicotinic acid)**

- Do not take high doses of nicotinic acid (1.5 to 5 grams daily or more) if you have liver dysfunction, an unexplained elevation in your serum aminotransferase (transaminase) level, active peptic ulcer disease, arterial bleeding, or if you consume large amounts of alcohol.
- Consult your doctor before taking high doses of nicotinic acid if you have a history of jaundice, peptic ulcer disease, gastritis, disease of the liver or bile ducts, gout, kidney dysfunction, or cardiovascular disease (especially acute myocardial infarction or unstable angina).
- Consult your doctor before taking high doses of nicotinic acid if you have diabetes. High doses of nicotinic acid can negatively affect glucose tolerance. Monitor your serum glucose level frequently if you take nicotinic acid and have diabetes.
- Have your doctor monitor your serum aminotransferase level if you take high-doses of nicotinic acid.
- Nicotinic acid may cause flushing, principally of the face, neck, and chest. This flushing is thought to be prostaglandin-prostacyclin mediated. Histamine may also play a role in the flushing.
- Nicotinic acid can cause dizziness, palpitations, rapid heartbeat, shortness of breath, sweating, chills, insomnia, nausea, vomiting, abdominal pain, and muscle pain.
- High doses of nicotinic acid can cause blurred vision, macular edema, toxic amblyopia, and cystic maculopathy.

## **PABA (Para-aminobenzoic Acid)**

- Do not take PABA if you are taking sulfonamides or have a kidney disease.
- PABA can cause anorexia, nausea, vomiting, fever, and rash.

## **Saint John's Wort**

- St. John's wort can increase sensitivity to sunlight. To avoid a sunburn while taking St. John's wort, minimize your exposure to the sun.
- St. John's wort can cause bloating and constipation.

## **SAMe**

- Consult your doctor before taking SAMe if you have bipolar disorder. See your doctor frequently if you take SAMe and you have bipolar disorder.
- Consult your doctor before taking SAMe if you take antidepressants. See your doctor frequently if you take SAMe in place of or in addition to antidepressants.
- Consult your doctor before taking SAMe if you have cancer. Nucleic acid methylation patterns may change in people who have cancer and take SAMe.
- Do not take SAMe if you are undergoing gene therapy.
- SAMe can cause anxiety, hyperactive muscle movement, insomnia, hypomania, and gastrointestinal symptoms such as nausea and diarrhea.

## **Vitamin B1 (Thiamin)**

- Consult your doctor before taking vitamin B1 for a thiamin deficiency, lactic acidosis secondary to thiamin deficiency, Wernicke-Korsakoff syndrome, Wernicke's encephalopathy, or Korsakoff's psychosis.

## **Vitamin B2 (riboflavin)**

- High doses of vitamin B2 (riboflavin) may interfere with the Abbott TDx drugs-of-abuse assay.
- Riboflavin absorption is increased in hypothyroidism and decreased in hyperthyroidism.
- If you are taking nucleoside reverse-transcriptase inhibitors, even a mild riboflavin deficiency can increase your risk of lactic acidosis.

## 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.

For more information see the Safety Appendix

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