

Parkinson's Disease

Parkinson's disease is a devastating brain disorder that gradually robs people of the ability to control their own movements. While the causes and cure of this affliction remain elusive, progressive scientists are continuing to unravel this disease.

During Parkinson's, cells in the parts of the brain that control movement and regulate mood are gradually destroyed. The primary defect in Parkinson's is a loss of dopaminergic neurons (such as dopamine-producing neurons) in a part of the brain called the substantia nigra. Dopamine is a neurotransmitter that modulates movement (Purves D et al 2001). In Parkinson's disease, the dopamine-producing nerve cells are destroyed by high levels of oxidative damage (Atasoy HT et al 2004; Ross GW et al 2004). There is evidence that this oxidative damage is, in turn, caused by defects in the cells' mitochondria, or power-generating centers.

The ideal treatment for Parkinson's disease would be a neuroprotective agent—a treatment that protects the brain. While no neuroprotective prescription agent has been found, studies suggest that high-dose coenzyme Q10 (CoQ10), a natural agent, may have neuroprotective properties. CoQ10 is known to support mitochondria by enhancing energy levels in the brain, as well as by acting as a powerful antioxidant. In one phase 2 clinical trial, CoQ10 significantly slowed the progression of Parkinson's disease (Beal MF 2003).

Conventional therapy for Parkinson's disease focuses on increasing the production and utilization of dopamine. Levodopa, which is the precursor to dopamine, has been the mainstay of Parkinson's disease therapy since its discovery in the early 1960s. Today, levodopa remains the foundation of Parkinson's therapy. However, after 5 years, levodopa begins to lose its effectiveness in patients with Parkinson's disease. If used as the sole treatment, levodopa must then be prescribed in higher and higher doses, leading to more adverse effects and more intense symptoms. Other drugs that target other parts of dopamine production and the utilization cascade are now increasingly prescribed. When used early enough, these drugs can help postpone levodopa therapy.

By supporting the mitochondria with CoQ10, reducing oxidant stress, and enhancing production of dopamine with supplements and alternative prescription agents, the Life Extension Foundation program for Parkinson's described here may help slow the progression of the disease. Later on in this chapter, the Life Extension Foundation presents a unique program that will enhance the effectiveness of levodopa therapy.

PROBLEMS WITH DIAGNOSING PARKINSON'S DISEASE

Parkinson's disease is not uncommon. It is estimated that Parkinson's disease affects about 1 out of 250 people older than 40 years of age and 1 out of 100 people older than 65. Approximately 50,000 new cases are diagnosed annually. Men are affected slightly more often than women. However, after menopause or after having a hysterectomy, the risk increases in women. Parkinson's disease is rarely diagnosed before age 40 (Fishman PS et al 2002).

Unfortunately, it is difficult to diagnose Parkinson's disease in its early stages. A diagnosis of Parkinson's disease is based on the presence of symptoms, some of which occur in elderly people who do not have Parkinson's. There is no lab test or imaging study that can accurately diagnose Parkinson's.

In general, you have to exhibit two of the three following symptoms to be diagnosed with Parkinson's disease:

- Tremor at rest (including nodding or shaking of the head)—the classic symptom of Parkinson's, present in about 85 percent of cases (Kasper DL et al 2004)
- Rigidity
- Abnormally slow movements and reflexes (bradykinesia)

Although a number of tests may be conducted (such as magnetic resonance imaging [MRI] and positron emission tomography [PET]) to rule out other diseases, most diagnoses of Parkinson's disease aren't made until the disease has fairly well progressed. This is a problem, because many studies have shown that early intervention is especially valuable to postpone levodopa therapy. The recommended supplements have minimal adverse effects and are beneficial for even a healthy person. (However, the suggested prescription drugs discussed in these pages should not be taken unless you are under the supervision of a physician.)

RISK FACTORS FOR PARKINSON'S DISEASE

A number of risk factors have been identified that increase the odds of contracting Parkinson's. While the disease's underlying

causes have not been discovered, most researchers believe Parkinson's is caused by overlapping environmental and genetic factors (Kasper DL et al 2004). Interestingly, both smoking and drinking coffee have been associated with a decreased risk of Parkinson's disease (Deleu D 2001; Benedetti MD et al 2000; Smargiassi A et al 1998; Zuber M et al 1991).

Risk factors for Parkinson's disease include:

Exposure to toxic metals. Parkinson's disease is somewhat more common in rural areas and among people who work in agriculture and landscaping, suggesting that exposure to pollutants and toxic metals may be involved in the disease. A few heavy metals are known to be neurotoxic, including mercury, aluminum, copper, and iron (American Parkinson Disease Association 2006; Bardin JA 2000; Brown DJ 1998; Adams CR et al 1983). Metals (iron in particular) may cause some destructive effect through the production of reactive oxygen species (Zecca L et al 2004; Linert W et al 2000). Of course, iron is a necessary nutrient. Also, an iron deficiency can lead to increased absorption of more toxic metals including lead, cadmium, and aluminum (Goyer RA 1997).

Bacterial toxins. Another risk factor for Parkinson's disease may be chronic exposure to toxins produced by intestinal bacteria (Clayman CB 1989). People with "leaky gut" syndrome may absorb excessive amounts of these toxins as the result of damage to the intestinal lining caused by other toxins and oxidants. Liver damage from alcohol and other toxins may further increase exposure to bacterial toxins (Philpott DJ et al 2001; Sullivan A et al 2001; Tancredi C 1992; Gentry LO 1991).

Poor diet. Poor nutrition in general, especially a low dietary intake of B vitamins and a high intake of simple sugars, has been associated with an increased risk of Parkinson's disease and with more rapid progression of the disease in patients who already have it (Yapa SC 1992; Golbe LI et al 1988). High dietary intake of meat increases absorption of iron and animal fats, both of which are associated with an increased risk of Parkinson's (Powers KM et al 2003; Logroscino G et al 1996).

Genetics. Although the cause of Parkinson's disease is unknown in about 90 percent of cases, increasing numbers of genes have been identified that may increase the risk of Parkinson's. According to the American Parkinson Disease Association, people who have a first-degree relative (such as a parent, sibling, or child) with Parkinson's disease are about 50 percent more likely to develop the disease.

THE VALUE OF EARLY INTERVENTION

The leading cause of dopamine-producing nigral cell death in the brain appears to be mitochondrial energy depletion, which contributes to the oxidative stress that hastens the disease (Beal MF 2003). Other causes of nerve cell death include inflammation and excitotoxicity (Koller WC et al 2004).

ENERGY ENHANCERS: COQ10 AND ACETYL-L-CARNITINE

Mitochondria are known as the energy powerhouses of cells. They use glucose and fats, combined with oxygen, to produce energy. This process generates a steady stream of oxidative molecules that are normally neutralized by internal antioxidants. In Parkinson's disease, however, the electron chain in the mitochondria is deficient, causing them to produce much higher levels of oxidative molecules. This steady oxidant stress damages mitochondria and eventually kills the host cells (Abraham S et al 2005; Mazzio E et al 2001; Linert W et al 2000). The holy grail of Parkinson's disease research is a neuroprotective agent (one that reduces damage to mitochondria and cells). According to encouraging study results, CoQ10 may be this promising neuroprotective agent.

CoQ10. CoQ10 levels are about 35 percent lower in the mitochondria of Parkinson's disease patients than in the mitochondria of control subjects of similar age and sex (Shults CW et al 1997), both in blood platelets and in the substantia nigra (Gotz ME et al 2000). CoQ10 supplementation seems to protect substantia nigra neurons against impaired mitochondrial energy production (Shults CW et al 1997) and against glutamate-related excitotoxicity (Mazzio E et al 2001).

In one small placebo-controlled, double-blind study of patients with Parkinson's disease, 360 milligrams (mg) daily of CoQ10 for 4 weeks provided a significant (if somewhat mild) reduction in symptoms and a significant improvement in measures of disease progression (Muller T et al 2003). In a larger trial, CoQ10 was associated with a 44 percent reduction in the decline of motor function and activities of daily living, in comparison with a placebo (Shults CW et al 2002). Doses as high as 3000 mg/day have been well tolerated. Investigators have concluded that 2400 mg/day is the highest appropriate dosage (Shults CW et al 2004).

When Parkinson's disease has been chemically induced in animals, CoQ10 seems to be protective in the disease's early stages; however, CoQ10 may be less effective once dopamine depletion is severe. This suggests that supplements should be started as early as possible (Schulz JB et al 1995).

Based on these studies, patients with Parkinson's disease might consider supplementation with 1200 mg (or possibly more) of CoQ10 daily. Laboratory monitoring of CoQ10 blood levels (Jimenez-Jimenez FJ et al 2000) may help determine optimal dose and response to treatment (Steele PE et al 2004).

Acetyl-L-Carnitine. Acetyl-L-carnitine (ALC) increases energy production by channeling fatty acids into mitochondria. It may also limit brain cell injury, thereby improving memory, motor skills, and possibly other brain functions. ALC also stimulates nerve cells to release dopamine, and it protects dopamine-containing neurons from destruction in animal models with Parkinson's disease (Pettegrew JW et al 2000; Castorina M et al 1994).

Even at high dosages, toxicity with ALC has not been reported. Nausea and headache are infrequent and usually resolve with continued use or with dose reduction. Because ALC is a natural stimulant that typically increases energy levels and decreases fatigue, it is best taken in the morning. If taken before bedtime, it may interfere with sleep by suppressing serotonin and melatonin activity.

When ALC was regularly injected into the brains of infant rats, receptors for nerve growth factor increased in the striatum, where some dopamine-producing neurons reside (De Simone R et al 1991). ALC also increased nerve growth factor levels and utilization in the brains of older rats (Foreman PJ et al 1995; Tagliatela G et al 1994).

ANTIOXIDANT THERAPY TO PROTECT NEURONS

While the underlying defect involves a defective mitochondrial electron transport chain, experts agree that most of the actual damage that occurs during Parkinson's disease is caused by extremely high levels of oxidative stress. Not surprisingly, high levels of antioxidants, such as vitamin E and vitamin C, have been shown to relieve symptoms by protecting brain cells.

Experimental evidence showed that enrichment with vitamin E protected against oxidative stress in the substantia nigra (Roghani M et al 2001). Some scientists suggest that "chronic, high dose vitamin E dietary supplementation . . . may serve as a successful therapeutic strategy for the prevention or treatment of Parkinson's disease" (Fariss MW et al 2003). Treatment with levodopa may be delayed for 2 years (or more) in newly diagnosed patients who receive large amounts of vitamins C and E (Fahn S 1992; Fahn S 1991).

Vitamin C may relieve the symptoms of Parkinson's disease by neutralizing dopamine free radicals (Sakagami H et al 1998) and toxic quinones released from dopamine metabolism (Pardo B et al 1995), thereby protecting brain cells from levodopa-induced damage (Mytilineou C et al 1993). In the laboratory, bathing nerve cells in vitamin C enhanced dopamine synthesis (Seitz G et al 1998).

Bioflavonoids, which provide the red, pink, and purple colors in fruits and vegetables, are even stronger antioxidants than vitamin C. Most are water soluble and easily penetrate the brain. Suggested antioxidant supplements include grape seed extract. The herbal compound Ginkgo biloba contains numerous antioxidants, including proanthocyanins and flavonoids, which help maintain healthy brain function, circulation, and metabolism.

Polyphenols are antioxidants found in green tea, which are being investigated for their potential to protect against Parkinson's disease (Weinreb O et al 2004). Polyphenols are also found in extracts of grape seeds and other plants. Like the bioflavonoids, they are powerful antioxidants. They may also inhibit the nerve cell damage in diseases such as Parkinson's and Alzheimer's.

It's also important to support healthy levels of glutathione, the main mitochondrial antioxidant. Parkinson's disease is characterized by a substantial depletion of mitochondrial glutathione, which further increases oxidative stress, decreases the electron chain transport activity and adenosine triphosphate production, and contributes to cell death (Khaldy H et al 2003). Supplements that can increase levels of glutathione include cysteine, N-acetyl-cysteine, selenium, lipoic acid, and garlic (Abdel-Wahab MH 2005; Abraham S et al 2005; Hsu M et al 2005; Soto-Otero R et al 2000). When taking L-cysteine, N-acetyl-cysteine, or glutathione, three times as much vitamin C should be taken at the same time to prevent these amino acid supplements from being oxidized in the body.

Although melatonin, a hormone produced in the pineal gland, reduces dopamine activity and release in the striatum, its potent antioxidant and mitochondrial-stimulating effects may protect against loss of dopamine-containing neurons (Zisapel N 2001). In rodents with chemically induced symptoms of Parkinson's disease, melatonin prevented cell death and preserved enzyme activity in the substantia nigra (Antolin I et al 2002). Melatonin given orally easily reaches the brain and is well tolerated. Melatonin has been proposed as a potential therapy to prevent development or progression of Parkinson's disease (Chen ST et al 2002) and to regulate disturbed sleep-wake cycles (Sandyk R 1992).

Melatonin has also been shown to work synergistically with deprenyl, a prescription drug that is frequently prescribed in the early stages of Parkinson's disease (see below). In one animal study, a combination of melatonin and deprenyl was shown to protect mitochondria and simultaneously reduce the turnover in dopamine (Khaldy H et al 2003).

AMINO ACIDS TO SUPPORT DOPAMINE PRODUCTION

The dietary amino acid tyrosine is converted in the brain to levodopa and then to dopamine. Phenylalanine, another dietary amino acid, can also be converted to tyrosine. Tyrosine and phenylalanine supplements therefore provide the brain with raw material to synthesize dopamine, and have been shown to increase dopamine formation in the brains of Parkinson's disease patients (Growdon JH et al 1982). These supplements should not be taken in conjunction with deprenyl because of the risk of a hypertensive crisis.

B VITAMINS

Dopamine synthesis requires vitamin B6 (pyridoxine) and its cofactor zinc, which should be provided in high amounts to overcome long-term deficiency symptoms and to stimulate dopamine production. Vitamin B6 (10 to 100 mg/day) decreased cramps, rigidity, and tremors, and also improved walking skills and bladder control (Sandyk R et al 1990).

Niacinamide (nicotinamide) enhances mitochondrial energy production and may help protect mitochondria from damage by toxins. A substance derived from nicotinamide, called nicotinamide adenine dinucleotide (NADH), is essential for cell development and energy production (Bender DA et al 1979). Animal studies suggest that protective effects from oral nicotinamide supplements are greatest when given early in the course of Parkinson's disease, before dopamine is severely depleted. The benefits of NADH in Parkinson's disease may result from its ability to reduce inflammation within the brain and from its effect on the immune system (Nadlinger K et al 2001).

Deficiency of the B vitamin folate may increase the risk of Parkinson's disease by elevating levels of homocysteine, which makes dopamine-containing neurons more vulnerable to environmental toxins (Duan W et al 2002).

Abnormalities in riboflavin (vitamin B2) in Parkinson's disease may be associated with glutathione depletion, mitochondrial DNA mutations, disturbed mitochondrial protein complexes, and abnormal iron metabolism. In one small study of patients with Parkinson's disease, all of whom had abnormally low riboflavin levels, daily supplements of 90 mg of riboflavin and elimination of red meat from the diet led to improvement in motor function with minimal adverse effects (Coimbra CG et al 2003).

EARLY INTERVENTION WITH PRESCRIPTION DRUGS

The ideal goal of early therapy is to slow disease progression and postpone levodopa therapy. A number of promising drugs have been identified that can be used alone (monotherapy) or in conjunction with the supplements mentioned here to control symptoms and enhance dopamine production.

In 2006, the US Food and Drug Administration (FDA) approved a new drug called rasagiline for early intervention of Alzheimer's disease. In clinical trials, rasagiline was shown to block the breakdown of dopamine. Rasagiline belongs to a class of drugs called monoamine oxidase (MAO) inhibitors. MAO acts in the brain to degrade dopamine. MAO inhibitors are especially helpful in younger patients, who are better able to tolerate their adverse effects (including high blood pressure, insomnia, and hallucinations). MAO inhibitors work by inhibiting dopamine breakdown in the brain. Another promising MAO inhibitor is selegiline. Some evidence derived from testing in animals suggests that selegiline and rasagiline have neuroprotective benefits, although this has not been demonstrated in clinical trials (Koller WC et al 2004).

Finally, some physicians recommend the use of dopamine agonists, which directly stimulate dopamine receptors. These drugs can be used as monotherapy early in the disease. Some of the more common dopamine agonists include ropinirole, pramipexole, and bromocriptine. Clinical trials have shown that these drugs can delay motor complications when used early in the disease, although they aren't effective at long-term control (American Parkinson Disease Association 2006).

An interesting study reported in the New England Journal of Medicine involved 268 patients with Parkinson's disease. Of these, 179 were randomly assigned to receive ropinirole; 89 received levodopa. Eighty-five patients in the ropinirole group and 45 patients in the levodopa group completed the 5-year study. After 5 years of treatment, patients taking ropinirole were significantly less likely to develop involuntary movements (dyskinesia). Only 20 percent in the ropinirole group developed dyskinesia, compared to 45 percent in the levodopa group. In addition, only 8 percent of patients taking ropinirole had severe dyskinesia, compared to 23 percent of those taking levodopa. Besides preventing dyskinesia, ropinirole helped control the symptoms of Parkinson's disease about as well as levodopa. On a scale that measured how well participants were able to perform daily living tasks, there were no significant differences between the two groups. The adverse effects in both groups were also similar. Researchers concluded that "early Parkinson's disease can be managed successfully for up to five years with a reduced risk of dyskinesia by initiating treatment with ropinirole alone and supplementing it with levodopa if necessary" (Rascol O et al 2000).

Amantadine is also sometimes prescribed for patients with Parkinson's disease, both early in the disease and in combination with levodopa. Amantadine does not slow disease progression, but has been shown to reduce dyskinesia by blocking N-methyl-D-aspartate (NMDA) receptors, which are responsible for the excitotoxicity associated with Parkinson's.

Studies have also been conducted on drugs that reduce the activity of adenosine, a neurotransmitter that is known to inhibit the release of dopamine. One nonselective adenosine receptor antagonist is theophylline, which was studied in a small trial of 15

patients who had Parkinson's disease. These patients were already taking levodopa, but couldn't tolerate higher doses because of adverse effects. Shortly after beginning theophylline therapy, 11 patients reported moderate or marked improvement in their conditions, which lasted for 3 months (Mally J et al 1994).

NONDRUG TREATMENT

Because drug treatment cannot cure Parkinson's disease and can only partially ameliorate symptoms, nondrug approaches are of great interest. A number of problems common to Parkinson's may respond to nondrug treatments, including constipation, speech, poor nutrition, poor sleep, depression, and motor problems. Patients with Parkinson's disease may benefit from physical therapy, occupational therapy, exercise, and speech therapy.

One modality that is attracting attention is known as deep brain stimulation. During this treatment, a part of the brain known as the subthalamic nucleus is stimulated; this results in long-term benefits for patients with Parkinson's disease. In one recent study, 71 patients were given deep brain stimulation. The patients were observed for up to 2 years. Researchers found that the patients' quality of life was improved after the therapy, and that these improvements were maintained over the long-term (Lyons KE et al 2005).

ENHANCING LEVODOPA THERAPY

Eventually, all patients who have Parkinson's will need to take levodopa, which is converted into dopamine in the brain. As mentioned previously, while levodopa therapy is effective, after about 5 years, the drug begins to lose effectiveness. Eventually, higher doses are needed. The most commonly used levodopa drug is a drug that combines levodopa with carbidopa.

Dosage of the levodopa/carbidopa drug must be individualized based on previous drug treatments, making adjustments by adding or omitting ½ tablet to 1 tablet daily (Silverman HM 2000). Levodopa/carbidopa is also available in a controlled-release, slow-acting form, which is designed to give a smoother release of the drug. Often, somewhat more of the controlled-release form of the drug is required to obtain the same degree of relief obtained from the standard form. The controlled-release form of levodopa/carbidopa is started at a dosage equal to 10 percent more levodopa daily than the standard form of levodopa/carbidopa. The standard form should be taken with food, but the controlled-release form should be taken on an empty stomach (Silverman HM 2000). Food interactions, particularly protein, may impair the effectiveness of the controlled-release form because less of the drug may be absorbed and absorption may be more erratic (PDR 2002).

Another levodopa drug prescribed is a combination of levodopa and the decarboxylase inhibitor benserazide. Further improvement in availability of levodopa to the brain can be made by adding the generic drug entacapone. Entacapone is prescribed when the levodopa/carbidopa combo begins to wear off too soon. Entacapone extends the effect of each dose of levodopa/carbidopa, freeing the patient from stiffness and tremors for a longer period (PDR 2002).

Levodopa is sometimes prescribed in conjunction with a class of drugs called catechol-O-methyltransferase (COMT) inhibitors. These drugs prevent conversion of levodopa to 3-O-methyldopa, thereby increasing the available pool of dopamine. Two COMT inhibitors approved in the United States are entacapone and tolcapone. Both drugs are rarely used as monotherapy but instead enhance the effectiveness of levodopa by increasing the length of time between doses of levodopa (off-periods). A combination of levodopa, carbidopa, and entacapone is also available. Rasagiline can also be used in conjunction with levodopa.

After 5 years of continual use of levodopa, motor fluctuations and abnormal involuntary movements commonly begin to develop. If these involuntary movements are severe and difficult to control by other means, oral levodopa/carbidopa solutions may be beneficial (Kurth MC et al 1993). One study found an 80 percent improvement in severe dyskinesia in patients taking a solution of levodopa/carbidopa tablets combined with ascorbic acid. Ten tablets and 2 g of vitamin C were dissolved in 1 liter (L) of water. Each standard 5 milliliter (mL) teaspoon contained 5 mg of levodopa. An amount proportional to the usual daily intake was taken every hour and adjusted for optimal response. If one were to use this approach, it would be best to have the formulation prepared by a compounding pharmacist to avoid accidental levodopa overdose.

Long-term treatment with levodopa may also result in neurotic or psychotic symptoms (Chacon JR et al 2002; Garcia-Escrig M et al 1999). These symptoms are likely due to accumulation of the oxidation products of levodopa and dopamine in the brain. Similarly, the conditions of schizophrenics deteriorate when given levodopa. In schizophrenia, high doses of niacin/niacinamide and ascorbic acid can minimize or prevent hallucinogenic symptoms.

Levodopa competes with and ultimately reduces brain uptake of tyrosine and tryptophan, which may explain some of its adverse effects (Riederer P 1980), including depression, psychosis, and paranoid hallucinations. L-tryptophan supplementation (150 to 450 mg/day) may reduce visual hallucinations induced by levodopa (Rabey JM et al 1977; Gehlen WMJ 1974).

After about 10 years, another vicious cycle begins in which the drug becomes less effective, causing either spastic, uncontrolled movements or long periods of rigidity. Administering levodopa in different ways has the potential to avoid or reverse this negative spiral.

The consistent use of sufficient levodopa to prevent off-periods appears to overload the brain with potentially toxic or obstructive breakdown products. Because both the eventual loss of effectiveness and increased adverse effects seem to mainly result from the oxidation of dopamine and storage of the resulting toxic products in the brain cells, it is important to take regular "rest periods" from levodopa. Rest periods may be accomplished by withholding levodopa each day at bedtime and then reintroducing it the following morning when the body requires it. If you have low to moderate requirements for levodopa, this method works well (and many patients follow it).

- If you take high levels of levodopa and use frequent on-periods/off-periods, you have more difficulty than patients who have low to moderate requirements. You may find it helpful to take the final levodopa dose of the day so that withdrawal symptoms (or an off-period) are expected to start at about bedtime. To ease your symptoms, take the following relaxation supplements shortly before dinner and about 2 hours before withdrawal time. If the starting doses are not fully effective, try different timing, dosages, and combinations:
 - Magnesium citrate—320 milligrams (mg)

- L-tryptophan—1000 mg
- Melatonin—300 micrograms (mcg) to 10 mg
- Vitamin C—1 to 3 grams (g)
- Natural vitamin E—400 International Units (IU)
- Gamma tocopherol—200 mg
- Grape seed extract—200 mg
- Any other desired antioxidant
- Phosphatidylserine—100 mg
- A good multivitamin mix

If you have advanced Parkinson's disease, you may initially experience a period of uncontrolled movements followed by a period of rigidity. After an hour or two, you should be able to relax, making sleep possible. During the night and in the morning, full mobility without any disabling adverse effects may be possible. However, your energy level will be lower than when you are taking levodopa. Your energy level will progressively become lower during the morning. At this time, your body is operating on dopamine that is stored in the brain from excess levels of levodopa.

As an alternative method, try taking sufficient levodopa before bedtime so that withdrawal occurs while you are asleep. If you can fall asleep using this technique and not wake up during the night with withdrawal symptoms, this might be the preferred method.

Upon rising, the following supplements may help to stimulate natural dopamine production, allowing you to delay the start of daily levodopa therapy. As soon as possible after rising, drink strong coffee and take the following nutrients:

- L-tyrosine—1 g (take well before the protein drink described below)
- ALC—2 g
- NADH—5 to 10 mg
- A good antioxidant multi-nutrient mix

After taking these supplements, prepare a protein drink with a spoonful each of wheat or barley grass powder, spirulina, chlorella, and several spoonfuls of bee pollen. Stir or blend in a liquid (such as grape juice, black currant juice, or fresh vegetable juice) and drink before or with breakfast, 20 to 30 minutes after drinking coffee. Optionally, drink additional coffee. Take additional stimulating supplements, starting with small amounts and increasing them gradually. Try different combinations of the following:

- An antioxidant multi-nutrient mix
- Niacinamide—500 mg
- Vitamin C— 2 to 3 grams
- Vitamin E—400 IU
- CoQ10—1200 to 2400 mg/day
- Different stimulating herbs such as Ginkgo biloba, ginseng, or licorice root (avoid licorice root if you have elevated blood pressure)

The goal is to delay taking your first levodopa dose for as long as possible. Once daily levodopa therapy has started, however, take levodopa at sufficiently close intervals to prevent any unexpected off-periods before beginning the scheduled nightly withdrawal. If you start taking levodopa much later in the day, repeat most of the supplements listed above every 2 hours until about 2 hours before your first dose of levodopa.

With continued therapy, withdrawal symptoms will hopefully ease. Ideally, you will fall asleep without noticing distressing symptoms. Tremors that occur during the day and psychiatric or behavioral problems should also gradually ease or disappear. Taking sufficient amounts of magnesium and tryptophan helps overcome rigidity, tremors, constipation, and insomnia, while taking sufficient amounts of antioxidants (combined with nightly withdrawal of levodopa) helps overcome hallucinations and other psychiatric symptoms.

To keep the nightly withdrawal period as short as possible, let your levodopa level drop steeply after the last tablet. It appears there is a range of brain levodopa levels within which uncontrolled movements are most likely (not only when overdosing, but also when withdrawing). To move quickly through this range, do not take the last tablet after a longer time interval than previous tablets or at a lower dose or after a long-acting tablet in the late afternoon.

However, because experiences are different for everyone, experiment with the various techniques suggested. Increase the amount and variety of supplements gradually. After you notice improvement, stay with a comfortable maintenance dose, which may result in a reduction of some supplements. Also, remember that any emotional, nutritional, or chemical stress can increase your symptoms.

TAKING DRUG HOLIDAYS

The best way to improve the symptoms of advanced Parkinson's disease, especially if levodopa therapy is no longer effective, is to take a "drug holiday" (in which you stop taking levodopa for a short time). A drug holiday should improve the response to levodopa and reduce adverse effects. Drug holidays, if they are attempted, should be done only under the direct supervision of a physician in a hospital setting. Withdrawal may lead to severe depression, immobility, and aspiration pneumonia.

Before taking a supervised drug holiday, it is best to wait until you have augmented levodopa therapy with the supplements recommended in this chapter and until you have been on an effective dietary program for several weeks or months. While under your physician's guidance, try stopping all levodopa therapy for up to 1 week, while still continuing to take the recommended amounts of supplements.

Hope on the Horizon

Researchers are pursuing a number of experimental therapies that offer hope for a lasting cure for Parkinson's. Perhaps the most high profile of these is cell transplant therapy, which involves transplantation of fetal substantia nigra cells into the brains of people who have Parkinson's disease. In laboratory studies, these fetal cells have regenerated the portions of the brain affected by Parkinson's. However, there are significant ethical concerns about using fetal cells that have to be resolved before research can continue.

THE IMPORTANCE OF DIET

Levodopa intake must be adjusted based on diet. With a high-protein diet, levodopa absorption is delayed and less levodopa reaches the brain, which may worsen symptoms. High intake of amino acids significantly reduces the motor response to levodopa (Mizuta E et al 1993), and levodopa competes with and reduces brain uptake of tyrosine and tryptophan, which may contribute to some of its adverse effects (Riederer P 1980). With a high-carbohydrate diet, more levodopa reaches the brain, and dyskinesia may develop. It is best to eat only one protein meal daily, preferably in the evening after taking the final levodopa dose for the day.

Patients with Parkinson's disease may not tolerate sharp cheeses, red wine, dark chocolate, nutmeg, smoked fish, or other foods containing tyramine, because they are more likely than the general population to have a genetic abnormality in the biochemical detoxification process by which sulfur reacts with cysteine to form sulfate (McFadden SA 1996). Patients with Parkinson's should avoid these foods because tyramine can stimulate MAO-A, an enzyme that breaks down the neurotransmitters epinephrine and norepinephrine. Both epinephrine and norepinephrine are produced from dopamine, so stimulation of MAO-A by tyramine may further deplete dopamine levels.

It is best to choose organic chicken or low-mercury fish (both of which are good sources of protein) for your one protein meal a day. Red meat is rich in iron and should be avoided (Powers KM et al 2003). High intakes of sugar and animal fat, especially from junk food, increase body fat, reduce lean muscle mass, decrease delivery of brain fuel, and make brain cells more susceptible to toxins. Inactivity and inadequate exposure to sunlight may further exacerbate abnormalities in body composition (Petroni ML et al 2003). A high-fat diet may also predispose a person to coronary artery disease, reducing blood flow and oxygen delivery to the brain.

The benefits of coffee and tea may include the brain-stimulating effect of caffeine, the niacin found in coffee, and the polyphenols or other nutrients in both beverages (Checkoway H et al 2002).

For a person in the early stages of Parkinson's disease, regular exercise, assistive devices in the home, and participation in support groups and organizations may improve morale and mobility. Physical therapy or muscle strengthening may improve function in daily activities. Depending on individual limitations, therapy may focus on mobility, range of motion, muscle tone, gait, or balance (Hirsch MA et al 2003; Van Vaerenbergh J et al 2003). Speech therapy may reduce difficulties in both speaking and swallowing.

Even without formal therapy, regular weight-bearing exercise (such as walking, jogging, or dancing), swimming, or gardening may be helpful. Stretching before and after exercise improves blood flow to the muscles, reduces stiffness, and improves flexibility and balance. Energy level should determine exercise intensity and duration (Sutoo D et al 2003).

In the early stages of Parkinson's disease, the affected person tends to walk with a stooped, shuffling gait. If you have Parkinson's, try to stand as upright as possible, with your head straight up and aligned over your hips. Your feet should be spaced 8 to 10 inches apart. A good exercise is to take long strides, lifting the legs and swinging the arms. Supportive walking shoes may improve stability. In the event of becoming stuck in place ("freezing"), rocking gently from side to side or pretending to step over an object on the floor may overcome immobility.

Practicing tai chi or performing other exercises that improve balance may help prevent falls. Remove area rugs, secure loose carpeting, install handrails and grab bars, stow electrical and telephone cords, and place the telephone within easy reach (or carry a

cordless phone). For easier dressing, allow plenty of time, lay out your clothes nearby, and choose garments that slip on or fasten easily.

OTHER SUPPLEMENTS

Many additional supplements may enhance energy production, reduce oxidative stress, and/or improve cognitive function in patients with Parkinson's disease. These supplements showed benefit in animal models, are generally well tolerated by patients, and show promise for further testing in Parkinson's disease (Beal MF 2003).

Phosphatidylserine. Phosphatidylserine (PS), a naturally occurring component found in every cell membrane of the body, appears to reduce oxidative stress (Chong ZZ et al 2004). Brain levels of PS typically decline with age, suggesting that supplementation might improve neural function, help maintain cell membrane integrity, and protect brain cells. Lecithin, which contains all the phosphatides found naturally in cell membranes, helps to increase the cell membrane ratio of phosphatidylcholine/phosphatidylethanolamine to cholesterol. This maintains cell membrane structure while increasing cell membrane fluidity.

Essential fatty acids. Essential fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to increase dopamine production in cultured brain cells of mice (Heller A et al 2005). This is an intriguing finding because fatty acids are known to reduce inflammation in many tissues, and inflammation has been implicated in the causation of Parkinson's disease. DHA, in particular, is essential to brain health because it constitutes between 30 percent and 50 percent of the total fatty acid content of the human brain (Young G et al 2005). DHA has also been shown to increase PS (Akbar M et al 2005).

Scientists have recently developed a compound that takes DHA and binds it to a lecithin extract that has itself been shown to reduce the risk of cognitive dysfunction in the elderly. Laboratory studies have documented that this patented compound delivers higher DHA concentrations to brain cells.

Combining DHA with PS. Scientists have discovered that DHA attaches itself to PS molecules and acts as an important ally in the promotion of brain cell energy production. A number of brain researchers, including Dr. Norman Salem, head of the Laboratory of Membrane Biochemistry and Biophysics at the National Institutes of Health, are convinced that PS with attached DHA is among the most critically important molecules for healthy brain function. Scientists believe that PS supplementation works optimally if DHA levels are kept commensurately high (Kidd PM 2005).

In response to an increasing body of research showing the intricate relationship between DHA and PS, scientists have developed a PS-DHA compound that can be incorporated directly into the membranes of brain cells.

To evaluate the effects of PS-DHA on memory loss, a study was done on middle-aged rats that had laboratory-induced accelerated brain aging. Administering traditional sources of DHA did not have an effect on this experimental model, but the group receiving the PS-DHA compound was able to attain a great deal of protection against this neurological challenge. When the brains of these animals were analyzed, there was more DHA incorporated in the cells of the group receiving the PS-DHA than in those receiving other omega-3 agents.

Dehydroepiandrosterone (DHEA) improves neurological function and protects against age-related diseases (Cyr M et al 2000; Goncharova ND et al 2000; Azuma T et al 1999). The positive effects of DHEA on oxidative stress and on NMDA receptors suggest theoretical benefit in patients with Parkinson's disease (Genedani S et al 2004).

PARKINSONISM VS. PARKINSON'S DISEASE

A multitude of disorders and conditions, from drug use to stroke to head injuries, may result in symptoms that are similar to Parkinson's disease. People with these conditions have parkinsonism, or Parkinson's disease-like symptoms. It is estimated that idiopathic Parkinson's disease accounts for about 75 percent of cases of parkinsonism. The rest are associated with a multitude of risk factors, including head injury, exposure to pesticides, consumption of well water, and living in rural areas (Kasper DL et al 2004). Although these cases of parkinsonism have not been studied to the same extent as Parkinson's disease, the condition is marked by the same underlying movement disorders and symptoms. Thus, it makes sense for people who have mild parkinsonism to follow the same approach as people in the early stages of Parkinson's disease. The antioxidants (especially CoQ10) and other nutrients improve symptoms.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Parkinson's disease (and parkinsonism) presents a challenge for both the conventional physician and the alternative medicine physician. You should not try to manage Parkinson's disease on your own; always consult a physician if you have symptoms of Parkinson's disease. The Life Extension Foundation recommends the following supplements, which may help postpone the initiation of levodopa therapy, for patients who are in the disease's early stages:

- **CoQ10**—1200 to 2400 milligrams (mg)/day
- **ALC**—1000 to 2000 mg/day
- **Vitamin E**—400 to 800 international units (IU)/day of alpha-tocopherol with at least 200 mg/day of gamma-tocopherol
- **Vitamin C**—1000 to 5000 mg/day
- **Grape seed extract**—100 to 300 mg/day
- **Ginkgo biloba**—120 mg/day
- **Green tea extract**—at least 725 mg/day (93 percent or higher in polyphenols)
- **Glutathione**—250 to 500 mg/day
- **Cysteine**—500 to 1200 mg/day
- **Selenium**—200 micrograms (mcg)/day
- **Lipoic acid**—150 to 600 mg/day
- **Aged garlic extract**—600 to 1200 mg/day
- **Melatonin**—3 mcg/day to 10 mg/day (taken at night)
- **Tyrosine**—500 to 1000 mg/day
- **Phenylalanine**—500 to 1000 mg/day
- **NADH**—5 to 10 mg/day
- **B complex**—at least 50 mg/day of riboflavin, 75 mg/day of vitamin B6, and 8700 mcg/day of folic acid
- **DHEA**—25 to 50 mg/day (increase dose according to blood test results)
- **PS**—100 to 300 mg/day
- **Fish oil**—at least 700 to 1400 mg/day of EPA and 500 to 1000 mg/day of DHA

In addition, strong coffee upon waking has been shown to reduce symptoms. A number of prescription drugs, including MAO inhibitors and dopamine agonists, may also be used as monotherapy early in the disease to postpone levodopa therapy. Because of the risk of adverse effects, patients who have Parkinson's disease, or people who suspect that they may have Parkinson's disease, should work closely with a physician to determine their optimal dosages of these supplements. Finally, it's important to maintain a "clean" diet and get regular, moderate exercise.

Once levodopa therapy has begun, the goal is to preserve the drug's effectiveness for as long as possible. For specific strategies, please refer to the section "Enhancing Levodopa Therapy" in this chapter.

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.

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.

PARKINSON'S DISEASE 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.

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.

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.

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.

Garlic

- Garlic has blood-thinning, anticlotting properties.
- Discontinue using garlic before any surgical procedure.
- Garlic can cause headache, muscle pain, fatigue, vertigo, watery eyes, asthma, and gastrointestinal symptoms such as nausea and diarrhea.
- Ingesting large amounts of garlic can cause bad breath and body odor.

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.

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.

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

Licorice

- Do not take licorice extract if you have diabetes, high blood pressure, heart irregularities, abnormal muscle tension, poor kidney function, low blood potassium levels, or chronic hepatitis, cirrhosis of the liver, or any disease that impedes the flow of bile from the liver.
- Do not take licorice for more than 6 weeks in a row. High doses of licorice (more than 20 grams of licorice extract daily or 50 grams of licorice root daily) taken for extended periods may lead to excessive loss of sodium from the blood, water retention, high blood pressure, heart irregularities, fatigue, headaches, and muscle cramps.

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.

Magnesium

- Do not take magnesium if you have kidney failure or myasthenia gravis.

Melatonin

- Do not take melatonin if you are depressed.
- Do not take high doses of melatonin if you are trying to conceive. High doses of melatonin have been shown to inhibit ovulation.
- Melatonin can cause morning grogginess, a feeling of having a hangover or a "heavy head," or gastrointestinal symptoms such as nausea and diarrhea.

NADH (Nicotinamide Adenine Dinucleotide)

- NADH can cause gastrointestinal symptoms such as nausea and loss of appetite.

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.

Phosphatidylserine

- Phosphatidylserine can cause gastrointestinal symptoms such as nausea and indigestion
- Consult your doctor before taking phosphatidylserine if you have antiphospholipid-antibody syndrome. See your doctor frequently if you take phosphatidylserine and have antiphospholipid-antibody syndrome.

Selenium

- High doses of selenium (1000 micrograms or more daily) for prolonged periods may cause adverse reactions.
- High doses of selenium taken for prolonged periods may cause chronic selenium poisoning. Symptoms include loss of hair and nails or brittle hair and nails.
- Selenium can cause rash, breath that smells like garlic, fatigue, irritability, and nausea and vomiting.

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

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

LifeExtension[®]

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.