

# Parkinson's disease

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## DIAGNOSTIC SUMMARY

- Resting tremor (trembling or shaking). The tremor usually gets worse when the person is at rest and better when the person moves. This tremor often begins on one side of the body.
- “Pill rolling” motion of the thumb and forefinger
- Slow movement (bradykinesia) or an inability to move (akinesia)
- Difficulty initiating movement
- Rigid limbs
- Shuffling gait
- Stooped posture.
- Reduced or fixed facial expressions (“masked face”) and low volume and/or monotone voice.
- Small handwriting (micrographia)- which decreases in size towards the end of a writing sample.
- Dysphagia may indicate later disease stage
- Occasionally, the disease also causes depression, personality changes, dementia, sleep disturbances, speech impairments, or sexual difficulties.

- Parkinson's Disease still remains a clinical diagnosis based on signs and symptoms that are present on neurological exam
- Lewy bodies, microscopic protein aggregates, which can be seen only during an autopsy, are regarded as a hallmark of classical Parkinson's Disease.

## GENERAL CONSIDERATIONS

First described by James Parkinson in 1817, Parkinson's disease occurs in approximately 0.3 % of the general population and about 1% of the population over the age of 55 to 60 in industrialized countries.<sup>49,1</sup> This progressive neurological disorder results from a deterioration of neurons in the region of the brain that controls muscle movements. This degeneration creates a shortage of the neurotransmitter dopamine, causing the movement impairments that characterize the disease. People with Parkinson's often experience trembling, muscle rigidity, difficulty walking, and problems with balance and coordination. In the United States, at least 500,000 people are believed to suffer from Parkinson's disease and about 50,000 new cases are reported annually. These figures are expected to increase as the average age of the population increases. The disorder appears to be slightly more common in men than women. The prevalence and incidence of Parkinson's rises with age, with the average age of onset being around 60.. The disease rates are very low in people under 40 and rise among people in their 70's and 80's. Parkinson's disease is found in many geographic regions of the world. The rates vary from country to country, but it is not clear whether this reflects true ethnic and/or geographic differences or just discrepancies in data collection.

## Etiology

Although there are many theories about the cause of Parkinson's disease, the etiology remains largely unexplained. Various research groups have suggested mitochondrial abnormalities, environmental neurotoxic exposures, selective generation of potential toxins or reduced detoxification capacity, infectious agents and/or genetic factors as possible reasons for this disease. Some researchers believe neurons from the involved brain regions are selectively vulnerable to this disease due to their heightened propensity to take up both endogenous and extrinsic toxic compounds through selective carrier mechanisms, such as the dopamine transporter.<sup>2</sup> Most likely a combination of all the aforementioned, over the course of time, lead to clinical disease.

## Genetics

Although the rates of heritability for Alzheimer's Disease are between 40% and 60%,<sup>3</sup> research is beginning to show evidence that late-onset Parkinson's is probably not a question of genetic susceptibility. Most likely the onset of Parkinson's may require the interaction of genetic and environmental factors.<sup>3,5</sup> Most people with Parkinson's disease do not have a family history and only about 15% of patients have a first-degree relative with the disease, typically without a clear mode of inheritance.<sup>1</sup> Surprisingly, the risk of Alzheimer's disease is not increased among relatives of patients with Parkinson's disease compared with relatives of controls.<sup>4</sup> Although many neurodegenerative schools of thought believe there may be a major shared genetic etiology between these two diseases, the data does not support this possibility.

Population-based studies have shown some increased risk for relatives of Parkinson's patients. Some data suggest a recessive or an oligogenic inheritance where the interaction of two or more genes is

needed.<sup>5</sup> Mutations have been identified in five genes: *α-synuclein*, *parkin*, *ubiquitin carboxy-terminal hydrolase L1*, *DJ-1*, and *NR4A2* and six loci have been linked to Parkinson's Disease.<sup>6</sup> Most of these genes are associated with early-onset Parkinson's, which accounts for only a small percentage of total Parkinson's cases. Genetic variations do not appear to explain most intermittent cases of Parkinson's, which are typically of the late-onset type. Further dissuading information tells us that genetic mutations found in late onset individuals usually show no clinical correlation with disease states, in comparison to those with Parkinson's who do not have genetic mutations.<sup>7</sup>

One fascinating study of all Swedish twins born in 1950 or earlier that were alive in 1998 was conducted to evaluate the role of genetics in Parkinson's. To accomplish this, the authors screened 33,780 twins for Parkinson's Disease by telephone interviews. Out of these, 247 with self-reported Parkinson's or possible Parkinson's Disease and 517 twins who reported parkinsonian symptoms or use of antiparkinsonian medication ("suspected parkinsonism or movement disorder") were identified. The somewhat surprising results suggest to us that environmental factors are most important in the etiology of Parkinson's Disease. The authors went on to explain that compared with other complex diseases, the importance of genetic effects in Parkinson's is "notably low."<sup>6</sup> This study is quite valuable for it substantiates the importance of working to prevent and treat environmental factors, lifestyle and nutritional factors, many of which are under our control, as risk factors for this neurogenerative condition. Nevertheless, future genetic studies may still help us understand some of the mechanistic events of Parkinson's Disease.

Apoptosis

Apoptosis accounts for much of the pathology seen in Parkinson's, as well as diseases like Alzheimer's, Huntington's and amyotrophic lateral sclerosis (Lou Gehrig's disease), which are marked by the loss of brain neurons. Elevated apoptosis in these neurological diseases seems to be related to lack of production of nerve growth factor and to free radical damage. It seems likely that a combination of such factors could cause many cells to destroy themselves. Manipulation of this process of apoptosis may help in treating these neurological diseases. In fact, studies in animal models imply that long-term delivery of nerve growth factors could protect against programmed cell death in these conditions.<sup>8,9,10</sup> Until the mechanisms of apoptosis are elucidated, some natural therapeutics that may decrease programmed cell death, such as melatonin therapy, may be of benefit in Parkinson's (see melatonin below).

Toxic exposures - pesticides, solvents, metals, and manganese

Long and short term exposures to pesticides, solvents, certain metals, and manganese have been implicated in the etiology of Parkinson's disease. It has been demonstrated that even short-term toxicity exposures may also hasten disease onset.<sup>11</sup>

Pesticide exposure, living in rural areas of industrialized countries, and drinking well water have all been linked to Parkinson's disease.<sup>11,12</sup> One report demonstrated that rats exposed to the organic pesticide, rotenone, had developed parkinson-like symptoms as well as changes in the brain resembling those seen in Parkinson's disease in humans. It was observed that chronic, systemic inhibition of complex I by the lipophilic pesticide, rotenone can cause highly selective nigrostriatal dopaminergic degeneration that is associated behaviorally with hypokinesia and rigidity. Additionally, nigral neurons in rotenone-treated rats accumulate fibrillar cytoplasmic inclusions that contain ubiquitin and alpha-synuclein.<sup>13</sup> These inclusions are the major constituent of intracellular protein inclusions forming the

Lewy bodies and Lewy neuritis in dopaminergic neurons of the substantia nigra. Other studies have also shown that chronic administration of rotenone over a long period is capable of increasing nitric oxide and lipid peroxidation products in the brain cortex and striatum and clearly mimic Parkinson's-like behavioral symptoms such as akinesia and rigidity in rats.<sup>14</sup>

One report of a series of patients who developed parkinsonism after exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxic product of pesticide production, and a contaminant found in synthetic heroin.<sup>15</sup> It was found that MPTP may freely cross the blood-brain barrier, will selectively taken up by dopaminergic cells and will inhibit mitochondrial complex 1 function in the respiratory chain.<sup>16</sup> MPTP is the only environmental agent that has been directly linked to development of levodopa-responsive parkinsonism, a form that is clinically indistinguishable from Parkinson's disease.<sup>1</sup> However, since similar chemicals like this are ubiquitous in our environment, it is probable that chronic exposures to other pesticides can contribute to this disorder.

Some case-control studies and case reports have shown an association between solvent exposure and parkinsonisms.<sup>17</sup> Records from a major United Kingdom engineering company were culled in order to explore the relationship of metal and solvent exposure and Parkinson's disease. The results of this survey demonstrated a significant exposure-response relationship for solvents and almost a 400% increase in risk for employees exposed for 30 years or more. This study suggests that sustained cumulative exposure is probably a key for there was no evidence of overall increase in risk for those who were exposed for shorter durations. The authors of this study do note that it is possible that the heavier exposures workers experienced before the introduction of stricter industrial environmental controls later in the 20th century, or exposure to older solvents, such as trichloroethylene, 1,1,1-trichloroethane, carbon tetrachloride, kerosene, white spirit, and acetone, which were more widely used three or more decades ago may play a greater etiological role.<sup>18</sup>

Although the study cited immediately above showed no increased risk of Parkinson's disease in relation to metal exposure, occupational exposure to specific metals, especially manganese, copper, lead, iron, mercury, zinc, aluminum, appears to be a risk factor for Parkinson's disease based on epidemiological studies.<sup>19</sup> Elevated levels of several of these metals have also been reported in the substantia nigra of Parkinson's disease subjects. Like pesticides, several di- and trivalent metal ions are also found to contribute to accelerations in the rate of alpha-synuclein fibril formation. In one study, aluminum contributed to fibril formation, along with copper(II), iron(III), cobalt(III), and manganese(II).<sup>19</sup> Chronic mercury inhalation has also been linked to cortical and cerebellar atrophy, dementia, Parkinson's syndrome and ataxia of the lower limbs.<sup>20</sup> Manganese-induced damage is found in the substantia nigra, globus pallidus, and caudate nucleus, with depletion of dopamine and serotonin levels and has been linked to psychiatric changes followed by impaired motor activity with muscle rigidity and tremors.<sup>15</sup>

Although poorly understood as to the cause, iron accumulation has been related to some neurologic disorders such as Alzheimer disease, Parkinson disease, type I neurodegeneration with brain iron accumulation, and other disorders. Increased levels of iron, as well as an accompanying lipid peroxidation combined with a decreased level of glutathione and superoxide dismutase activity are present in the substantia nigra of patients with Parkinson's disease.<sup>36,24</sup> Although it is not well elucidated whether the accumulation of iron in the brain is primary or secondary to development of neurodegenerative disorders,<sup>21</sup> one animal study has shown that unilateral injection of FeCl<sub>3</sub> into the substantia nigra of adult rats results in a 95% decrease of striatal dopamine which impaired dopamine-related behavioral responses. This supports the assumption that iron may trigger the dopaminergic neurodegeneration of Parkinson's disease.<sup>22</sup>

## Oxidative Stress and Glutathione Deficiency

Biochemical changes including increased levels of neurotoxic metals, the inhibition of complex I activity, and depleted glutathione levels occurring in substantia nigra<sup>23</sup> all suggest that oxidative stress is present and pathologically involved in Parkinson's disease patients.<sup>24</sup> Using healthy patients as a control, studies in areas of patients dying from Parkinson's have observed 40% reduced glutathione levels in these patients while oxidized glutathione was non-significantly marginally elevated.<sup>25</sup> Depletion of glutathione levels may be an early component of the process, since these suboptimal levels have also been found to occur in presymptomatic Parkinson's disease, also known as incidental Lewy body disease,<sup>26</sup> although some animal studies demonstrate that depletion is not the primary factor.<sup>27</sup> Some researchers are finding that this glutathione deficiency may be a common denominator in all Parkinsonian conditions associated with nigral damage.<sup>23</sup> Although not completely elucidated, it is known that glutathione exhibits several functions in the brain by acting as an antioxidant and a redox regulator. Glutathione depletion has been shown to affect mitochondrial function probably via selective inhibition of mitochondrial complex I activity. Oxidative damage due to glutathione depletion may also encourage aggregation of defective proteins leading to cell death of nigral-striatal dopaminergic neurons.<sup>24</sup>

Glutathione depletion may enhance the susceptibility of substantia nigra to destruction by endogenous or exogenous toxins. Replenishment of normal glutathione levels within the brain may hold an important key to therapeutics for Parkinson's Disease.<sup>23</sup>

## Detoxification

Research has begun to validate the hypothesis that the dysfunction of the body's detoxification ability may underlie various chronic neurologic diseases such as Parkinson's and Alzheimer's.<sup>28</sup> Research into the etiology of Parkinson's disease has discovered defects in patients' abilities to adequately metabolize sulfur-containing xenobiotics.<sup>29</sup> Altered detoxification, then, may render susceptible individuals at higher risk to neurotoxicity when exposed to sulfur-containing compounds.<sup>30</sup> Connections with Alzheimer's and other motor neuron diseases have also been made.<sup>31</sup> Certainly genetic determination is but one factor and must be looked at in light of the strong support that has been found for the role of nutritional and environmental factors discussed elsewhere in this chapter.<sup>32</sup>

## DIAGNOSTIC CONSIDERATIONS

There is no diagnostic test that can clearly identify Parkinson's disease. Parkinson's is usually diagnosed by a neurologist who can evaluate symptoms and their severity. However, diagnosis is usually left to clinical judgment. Some individuals with suspected Parkinson's disease can receive therapeutic trials of dopamine, where a positive response would be strongly suggestive of disease. Other tests, such as brain scans, can help doctors differentiate as to whether a patient may have true Parkinson's disease or some other similar disorder such as vascular parkinsonism. Interestingly, approximately 25-40% of patients with Parkinson's Disease develop dementia thereby making it difficult to distinguish Parkinson's Disease with Lewy bodies from Alzheimer's with parkinsonian characteristics. Furthermore, individuals with Parkinson's may not exhibit the classic resting tremor, but may exhibit more of an essential tremor. The essential tremor is characterized by a unilateral postural tremor most evident in the upper extremities. In this case, the most reliable way to determine Parkinson's is by characterizing the presence of an accompanying bradykinesia and rigidity. Parkinson's is divided into 5 stages, which are listed in Table 1.

Pathologically, Lewy bodies are considered the hallmark of classical Parkinson's. Found in the substantia nigra, Lewy bodies are acidophilic inclusions of the cytoplasm characterized by a dense core and peripheral halo. Diffuse neuronal loss is observed in the substantia nigra with an associated deficit of dopamine production in the nigrostriatal pathway.<sup>33</sup> The presence of Lewy bodies cannot be used as a diagnostic criteria, for these can only be seen during an autopsy. Autopsies have uncovered Lewy bodies in a surprising number of older persons without diagnosed Parkinson's: 8% of people over 50, almost 13% of people over 70, and almost 16% of those over 80.

Since its introduction in 1987, the Unified Parkinson's Disease Rating Scale (UPDRS)<sup>34</sup> has been used extensively by researchers and clinicians around the world to help grade the patient on a number of criteria: behavior, activities, motor function, therapeutic complications, staging by symptoms, and a scale of daily living. There also are several neuro-imaging tests that aid in the diagnosis of Parkinson's (PET scan using 18-fluorodopa, Beta-CIT SPECT). However, the UPDRS and neurological exam are sensitive enough to make the diagnosis.

The differential diagnosis of this disorder includes normal ageing, essential tremor, drug-induced parkinsonism, the Parkinson-plus syndromes, vascular parkinsonism, and normal pressure hydrocephalus. Less common entities with parkinsonism include dopa-responsive dystonia, juvenile-onset Huntington's disease, and pallidopontonigral degeneration.<sup>1</sup>

Some related diagnoses include the following:

- **Parkinsonism Plus Syndrome:** is defined when parkinsonism is accompanied by other abnormal neurological symptoms. The most notable is Progressive supranuclear palsy. In this condition, the patient develops early symptoms of Parkinson's, but then later develop characteristic abnormal eye movements. These patients also demonstrate neck dystonia, dysphagia and a decreased response to levodopa.

- Shy-Drager Syndrome (multi system atrophy): this condition is characterized by parkinsonism with concomitant autonomic nervous system abnormalities. These patients may have cranial nerve abnormalities, peripheral polyneuropathy, spasticity, and/or anterior horn cell dysfunction.
- Drug-induced Parkinsonism: due to phenothiazines, butyrophenones, reserpine and related hypertensives, manganese poisoning and exposure to carbon monoxide.

## THERAPEUTIC CONSIDERATIONS

### Conventional medicine

Unfortunately, there is no therapy which can modify the progressive pathology of Parkinson's neurologic degeneration.<sup>35</sup> However, unlike other serious neurologic diseases, Parkinson's disease is somewhat treatable. For decades, the drug levodopa, commonly known as L-dopa, has been the mainstay of Parkinson's disease treatment. It is synthesized by the enzyme tyrosine hydroxylase from the diet-derived aromatic amino acid tyrosine. Modern treatment combines levodopa with a peripheral decarboxylase enzyme inhibitors to minimize conversion of levodopa to dopamine outside the nervous system.<sup>36</sup>

Although initially very effective in the early stages of the disease, l-dopa provides only symptomatic relief without altering disease progression, and it loses efficacy with time.<sup>49</sup> L-dopa side effects include motor complications, particularly fluctuations and dyskinesias, as well as nausea, vomiting, orthostatic hypotension, sedation, hallucinations, delusions, and accelerated growth of malignant melanoma.<sup>37</sup> L-dopa contributes to decreased slow wave peristaltic activity,<sup>38</sup> which may contribute to inadequate digestive function. It may also contribute to subtle detrimental effects on cognitive function<sup>39</sup> as well as a wide array of other psychiatric complications manifestations such as propensity to gamble.<sup>40</sup> Responses to the drug may become more erratic over time. For that reason,

newer drugs are now also used either alone or in combination with levodopa. Table 2 lists the medications commonly used to treat Parkinson's Disease.

After being virtually abandoned for 20 years, another allopathic treatment which is gaining more prominence is deep brain stimulation (DBS). DBS involves implanting a brain stimulator, a device similar to a heart pacemaker, in certain areas of the brain. The desired effect is to decrease the overactivity of the excitatory glutamatergic subthalamo-internal pallidum pathway caused by the loss of dopaminergic neurons within the substantia nigra. How deep brain stimulation works is not well known but it has been hypothesized that the stimulatory effect may modulate the neuronal activity and thus avoid disease-related abnormal neuronal discharges. Potential candidates for deep brain stimulation are selected according to strict criteria. For some people, DBS may control symptoms so well that medications can be greatly reduced.<sup>41</sup> Large randomized studies are needed to compare stimulation at different brain targets and to contrast neurosurgical techniques.

Fetal nigral transplantation has also been attempted to restore neuronal tissue lost to neurodegeneration. Due to mixed results, and high percentage of post-surgical dyskinesias, transplantation is not currently a treatment option for Parkinson's disease. In the future, stem cells may offer various means to restore dopaminergic circuitry. In theory these cells could become dopamine-producing cells or possibly programmed to release neurotrophic factors necessary for proper function.<sup>1</sup>

## Diet

Healthy dietary habits might be very useful to treat and prevent Parkinson's Disease. In terms of detoxification from heavy metals, high sulfur-containing foods like garlic, onions, and eggs, as well as

water-soluble fibers such as guar gum, oat bran, pectin, and psyllium seed are recommended. From an antioxidant point of view, vegetables and fruits would be very important.

One large case-control study<sup>42,43</sup> revealed that Parkinson's disease patients tended to consume fewer raw vegetables, less alcohol and coffee, and more meat than control subjects. Patients with Parkinson's disease also reported higher carbohydrate consumption, and equivalent intakes of protein and fat. Other researchers have shown an increased consumption of animal source fat in patients with Parkinson's disease.<sup>44,45</sup> Although more needs to be learned about how food choices relate to Parkinson's Disease, a higher intake of vegetables, with low intake of fat seems to be a reasonable choice to help prevent and possibly treat neurodegeneration.

Interestingly, there are certain foods which are a good source of natural levodopa. Anecdotal reports exist that demonstrate that patients with Parkinson's disease will show improved symptom control when consuming meals of broad beans. In some cases, the response to *Vicia faba* (fava beans) may be even greater than to conventional levodopa medication. Fava beans are a good source of levodopa: a 100-g serving of *V. faba* pods contains about 250 mg of levodopa, equivalent to the levodopa content of one of the standard pharmaceutical formulations.<sup>36</sup> Until more is known about how to use fava as an L-dopa source, unsupervised replacement or co-administration of L-dopa with fava beans is not recommended.

Ketogenic diets have been used for more than 70 years in order to help stabilize patients with epileptic seizures. D-beta-hydroxybutyrate (DbetaHB) is a ketone body produced by hepatocytes and, to a lesser extent, by astrocytes when diets extremely low in carbohydrates and glucose are administered. One study infused DbetaHB into MPTP induced-Parkinson mice models and demonstrated that the infusion conferred partial protection against dopaminergic neurodegeneration and motor deficits. The authors of this study support the use of this diet citing the safety record of ketone bodies in the treatment of epilepsy.<sup>46</sup> In one clinical study, DbetaHB had been administered orally for several months to two 6-

month-old infants with hyperinsulinemic hypoglycemia. Although some of these infants were given dosages of up to 32 g/day, tolerance for the treatment was high.<sup>47</sup> However, the long-term effects of the chronic use of DBHB on the cell metabolism and mitochondrial function are not known well known.

For those patients taking levodopa, low protein intake may be useful. One double-blind study compared a low protein intake of 50 grams per day for men and 40 grams per day for women, to high protein intake of 80 grams per day for men and 70 grams per day for women. By the end of the trial, total performance scores were significantly improved in the treatment group given lower protein intakes. Additionally, tremor, hand agility, and mobility in the low protein groups also improved.<sup>48</sup>

It is known that levodopa absorption is delayed or diminished by amino acids in protein meals.<sup>37</sup> It has been shown that modifying meal patterns so that the majority protein intake was in the evening also improved symptoms.<sup>48</sup> As a result, it is recommended that patients on levodopa take their medication with a high carbohydrate meal and delay protein intake until the final meal of the day in an effort to optimize the therapeutic efficacy of the medication.<sup>36</sup>

## Smoking

A number of epidemiological studies demonstrate that smoking is associated with a lower incidence<sup>49</sup> and delayed onset<sup>50</sup> of Parkinson's disease. Although unclear which exact mechanisms account for this effect, it is postulated that nicotine may enhance striatal stimulation of dopaminergic neurons that are selectively damaged in Parkinson's. The inverse association between smoking and Parkinson's has been demonstrated in over 40 studies authored by different investigators conducted over the past 50 years.<sup>49</sup> Other non-nicotine chemicals in cigarettes may also play a role in neuroprotection by decreasing monoamine oxidase B activity, which effectively lowers the levels of hydrogen peroxide, a by-product of

dopamine metabolism.<sup>51</sup> Other possible explanations include a neuroprotective effect of a substance in cigarette smoke, possibly carbon monoxide, which is a free radical scavenger, or may reduce dietary intake as stated above, thus conferring an advantage.<sup>1</sup> Since the risk to benefit ratio is quite high with smoking, it is not advised to suggest smoking as a reasonable prevention for Parkinson's. Smoking should be further studied for there may be components of cigarettes, that once elucidated, may prove useful for future therapies.

## Estrogen

Increasing evidence suggests that estrogens may modulate the activity of dopamine,<sup>52,53</sup> may act as an antiapoptotic agent,<sup>54</sup> and could affect the neuronal pathways affected in Parkinson's disease.<sup>55</sup> Animal studies have demonstrated that estrogens influence the synthesis, release, and metabolism of dopamine and may actually modulate dopamine receptor expression and function. Some clinical studies have also suggested that Parkinson symptoms may get worse after menopause and that hormone replacement therapy can be protective<sup>56,57</sup> while others hypothesize that estrogen decreases may improve Parkinson's disease.<sup>52</sup> The conflicting findings suggest that several variables, including age, estrogen dose and formulation, and timing and length of dosing period, may determine whether benefits are seen and the nature of these benefits.<sup>55</sup> At this time, it may be best for clinicians to pay close attention to menstrual pattern correlations to symptomatic disease in order to make the best patient specific choices with regards to hormone replacement.

## Detoxification

There are nutritional factors which combat heavy metal poisoning.<sup>58,59,60,61,62</sup> These include: a high potency multiple vitamin and mineral supplement, minerals such as calcium, magnesium, and chromium, vitamin C and B-complex vitamins, sulfur-containing amino acids (methionine, cysteine, and taurine). For natural ways to support the detoxification and elimination, please see the Detoxification chapter in this textbook. Heavy metal toxicity and detoxification are discussed in detail in Chapters 18 and 37.

## Nutritional considerations

### 5-HTP

The use of 5-HTP in Parkinson's disease provides some benefit, but only if used in combination with the drug Sinemet (the combination of L-dopa with the decarboxylase inhibitor, carbidopa). Although brain levels of serotonin are decreased in Parkinson's disease, the reduction in dopamine receptors is more severe.<sup>63</sup> One of the key benefits of taking 5-HTP in Parkinson's disease is that it can help to counteract the negative effects that the L-dopa in the Sinemet has on sleep and mood.<sup>64,65,66</sup> In addition, 5-HTP has also been shown to improve the physical symptoms of Parkinson's disease.

About 9 out of 10 people with Parkinson's disease suffer from depression. The degree of depression in Parkinson's disease is a reflection of their serotonin levels. The lower the level of serotonin, the more severe is their depression. One study examined the effect of 5-HTP in seven Parkinson's disease patients, all of whom were on Sinemet.<sup>64</sup> The initial dosage of 5-HTP was 75mg, which was increased by 25mg every 3 days until the patients reported a relief of their depression, or up to a maximum of 500mg/day for 4 months. The impressive results obtained in these patients are shown in Table 3. Six out of seven patients responded to 5-HTP. Note that the dosages of 5-HTP in these five out of the six patients who responded ranged from only 75 to 125mg. The only patient who did not respond took 500mg of 5-HTP.

As a cautionary note, increasing serotonin levels with 5-HTP in patients not taking Sinemet are associated with worsening of symptoms, especially rigidity.<sup>63</sup>

### *Antioxidants*

Because vitamins C and E and carotenoids prevent damage from oxidation, they may reduce the risk of developing Parkinson's Disease. In some studies, antioxidant nutrients like vitamin C and E have been shown to be quite effective in slowing the progression of Parkinson's disease in those patients not yet on medications. However, high dosages are required because it is more difficult to increase antioxidant levels in brain tissue compared with other body compartments.

In one vitamin C and E pilot study, 21 patients with early Parkinson's disease were given 3,000mg/day of vitamin C and 3,200IU/day of vitamin E. The patients were followed closely for a period of 7 years. Although all patients eventually required drug treatment (Sinemet or Deprenyl), the progression of the disease as determined by the need for medication was considerably delayed in those receiving the nutritional antioxidants. Dividing the patients in both groups into younger-onset and older-onset patients, those not receiving antioxidants required medication at 40 and 24 months, respectively, after the onset of the disease. In contrast, the two age groups in the pilot study were able to delay the need for drug therapy for 65.3 and 59.2 months, respectively. Thus, the patients receiving the vitamins were effectively able to delay the need for medication for up to 2–3 years longer.<sup>67</sup>

Another study evaluated 76,890 women for 14 years and 47,331 men for 12 years. All the participants were health care professionals, mostly doctors and nurses. Every 2 to 4 years they filled out detailed surveys about their diets, including their vitamin intake from both foods and pills. A total of 371 people developed Parkinson's Disease during the study. The investigators found that neither vitamin C nor carotenoid intake lowered the Parkinson's risk. The results were the same for the use of vitamin E

pills. This case seems to support the idea that vitamin E supplementation does not help protect against Parkinson's. However, those participants who ate vitamin E-rich foods as part of their diets curiously developed the fewest cases of Parkinson's.<sup>68</sup> The authors dismissed this fact by stating that "other constituents of foods rich in vitamin E may be protective." Well more likely, it may be that the dosages or quality of supplementation in many of the participants may have been low, whereas the quality of antioxidants in the actual foods in people who tend to eat them may have been higher. Furthermore, even though alpha-tocopherol is the main form of vitamin E in food and the sole form of vitamin E in supplements, it is known that beta-, gamma-, and delta-tocopherol are also present in food. These other forms of vitamin E also play important antioxidant roles. For instance, gamma-tocopherol is more effective than alpha-tocopherol at inhibiting peroxynitrite-induced oxidation.<sup>69</sup> Furthermore, supplementation of only alpha-tocopherol is known to substantially decrease the levels of the other forms of vitamin E.<sup>70</sup> While food may be the best source of all vitamin E forms, vitamin E supplements which contain the mixed tocopherols would be a better choice than less expensive supplements that only contain alpha-tocopherol.

### *Glutathione*

Given the importance of glutathione as a powerful brain tissue antioxidant, effective repletion should be a therapeutic priority. Combined intravenous and oral glutathione replacement is safe and well tolerated, and is known to provide ongoing benefit.<sup>48</sup> N-acetylcysteine and alpha-lipoic acid are glutathione precursors that may also be of use. As a systemic antioxidant, glutathione's ongoing repletion may help ameliorate Parkinson's-related damage in the heart, liver, muscles, and other organs as well. It is also

recommended to synergistically support with other antioxidants. Especially noteworthy is high-dose vitamin C, which provides antioxidant reducing equivalents known to conserve glutathione.<sup>48</sup>

### *B vitamins, folic acid*

Epidemiologic evidence has linked elevation of serum homocysteine to an increased risk of coronary artery disease, stroke, and dementia. An increase in homocysteine levels in Parkinson disease recently has been discovered. Although B vitamin status and genetic factors are important modifying influences determining the degree of this elevation, the main cause appears to be therapy with levodopa. It has been suggested that breakdown of this medication by catechol-*O*-methyltransferase results in increased homocysteine formation.<sup>71</sup> Therefore, there are reasons to suggest that management of Parkinson's Disease may render patients at an increased risk of stroke, heart disease, dementia, and possibly accelerated nigral degeneration.

Pyridoxine (vitamin B6) is one of the B vitamins very useful to lower homocysteine levels (see Homocysteine chapter). Confoundingly, it has been shown that the effects of levodopa may be enhanced through low intake of pyridoxine where daily doses of 5 mg or more of pyridoxine can cause reversal of the drug effect. Because vitamin B<sub>6</sub> is present in many foods in varying amounts, some literature warns patients who take levodopa that they should avoid foods containing high amounts of the vitamin.<sup>36</sup> Instead of globally restricting foods which containing B6, possibly lowered B6 should be encouraged in those unresponsive to levodopa treatment. Conversely, those Parkinson's patients with high homocysteine with a high risk for cardiac disease who are responding well to the medication may consider increasing levels of the B vitamins, with careful monitoring for exacerbated Parkinsonian symptoms.

## Coenzyme Q<sub>10</sub>(CoQ<sub>10</sub>)

Also known as ubiquinone, the primary biochemical action of CoQ<sub>10</sub> is as a cofactor in the electron-transport chain, the series of redox reactions that are involved in the synthesis of ATP. Known for its use in cardiovascular diseases, AIDS and cancer, animal models of Parkinson's have shown effectiveness related to neurodegenerative conditions.<sup>72</sup>

Although more study is needed there are enough studies to support the use and safety of CoQ<sub>10</sub>, even at higher dosages. One randomized, placebo-controlled, double-blind clinical pilot study has suggested that high-dose coenzyme Q<sub>10</sub> may also help slow symptom progression in early Parkinson's disease. In this study, 80 unmedicated patients with early stage disease were randomly given CoQ<sub>10</sub> at dosages of 300, 600, 1200mg/day or a placebo. Using the UPDRS, they were followed up for 16 months or until disability requiring treatment with levodopa had developed. It was found that patients on CoQ<sub>10</sub> fared significantly better than their placebo counterparts, with those taking 1200mg showing the greatest results (UPDRS rating was +11.99 for placebo and +6.69 for the 1200mg/day group).<sup>73</sup> A second placebo controlled, double-blind experiment used 360 mg CoQ<sub>10</sub> for 4 weeks in 28 treated and stable PD patients. CoQ<sub>10</sub> supplementation provided a significant mild symptomatic benefit on PD symptoms and a significantly better improvement visual defects compared with placebo.<sup>74</sup>

High doses of CoQ<sub>10</sub> have proven to be safe in the short term. A 2 week, open label trial where 17 patients with Parkinson's disease received an increasing dosage of coenzyme Q<sub>10</sub> (1200, 1800, 2400, and 3000 mg/day) with an unvarying dosage of 1200 IU/day of the alpha-tocopherol form of vitamin E. The plasma level of coenzyme Q<sub>10</sub> was measured at each dosage. Thirteen of the subjects were increased to the 3000mg dose, with no CoQ<sub>10</sub>-related side effects. One patient became orthostatic and one was dyspeptic, but these conditions were unrelated to the CoQ<sub>10</sub>. Looking at the blood, plasma levels of

ubiquinone reached a plateau at the 2400 mg/day dosage. This study was not long enough to assess any clinical effect on the disease itself.<sup>75</sup> Although serum levels of CoQ10 are not necessarily lower in Parkinson's patients versus healthy controls,<sup>76</sup> there may be an added benefit of doses up to 2400mg for symptomatic patients. Due to expense of CoQ10 it may be most practical to start at the 1200mg dose, and ramp up if benefits are not seen in the first few months.

### *Melatonin*

Melatonin is a hormone manufactured from serotonin, and is secreted by the pineal gland. Known as a powerful antioxidant, melatonin is an established treatment option for jet-lag, various types of sleep problems, and cancer. Although studies show melatonin does not induce any increase in cerebral vascular blood flow,<sup>77</sup> there is evidence to support the role of melatonin as a protector of neuronal cells, most likely by supporting mitochondrial function, and preventing apoptosis.

As an antioxidant, melatonin can directly scavenge oxidants produced during the normal metabolism and it indirectly promotes the activity of the antioxidant enzymes such as superoxide dismutase and catalase. Secondly, melatonin increases the activities and the expression electron transport chain complexes during physiologic and pathologic situations. As a result melatonin is able to increase ATP production and promote glutathione homeostasis. It has also been postulated that melatonin may interact with the mitochondrial genome in order to enhance production of proteins.<sup>78</sup> Tissue culture models of Parkinson's Disease using low doses of 6-hydroxydopamine to induce apoptosis of undifferentiated and neuronal rat adrenal pheochromocytoma cells have also shown melatonin to prevent apoptosis in these models.<sup>79</sup>

It is theoretically possible that melatonin may actually exacerbate symptoms Parkinson's because of its putative interference with dopamine release.<sup>80</sup> But the larger body of literature agrees that since Parkinson's Disease is probably due to multiple issues of compromised mitochondrial activity in the substantia nigra,<sup>81</sup> and loss of glutathione,<sup>82</sup> oxidative damage, and increased apoptotic events. Reasonably, melatonin supplementation may yield a direct benefit. Clinical studies are needed to evaluate the effectiveness of melatonin in Parkinson's disease. At this point, if the clinician chooses to use melatonin, it may be best to start with a low dose (1 - 5mg), and gradually increase dose while carefully monitoring symptoms would be the most prudent.

#### Reduced Nicotinamide Adenine Dinucleotide (NADH)

Found useful in treating animal models of Parkinson's Disease,<sup>72</sup> the coenzyme NADH is known to enhance endogenous dopamine production by supplying reducing equivalents to the rate-limiting, tyrosine hydroxylase-catalyzed step of dopamine synthesis in both tissue culture and human evaluations.<sup>83</sup> A positive effect has been found using NADH both intravenous and intramuscularly in 34 Parkinson patients in an open label trial. In this trial, every patient experienced a beneficial clinical effect where 21 showed a "very good" (better than 30 percent) improvement of disability and 13 patients a "moderate" (up to 30 percent) improvement. The effect of NADH was dependent on both the dosage given and the severity of the case. Optimal therapeutic range for NADH was 25 to 50 mg per day. Intravenous administration seemed to work better than intramuscular injection. Presence of homovanillic acid in the urine was significantly increased in all patients. The presence of this metabolite indicates a stimulation of the endogenous L-dopamine biosynthesis.<sup>84</sup> A second study of 15 patients prospectively investigated the administration of one 10 mg treatment over a 30 minute everyday

for 7 days. These patients were also taking levodopa medications. These patients UPDRS scores improved and significant increases in plasma levodopa was observed.<sup>85</sup>

Nevertheless, due to lack of sufficient studies, and theoretical considerations for underlying NADH disposal, many in the medical community do not currently recommend its widespread use for Parkinson's Disease.<sup>83</sup> As with many newer therapies, more rigorous studies are needed to confirm their benefit, and elucidate any side effect risk.

### Phosphatidylserine

Phosphatidylserine is the major phospholipid in the brain, where it plays a major role in determining the integrity and fluidity of cell membranes. Low levels of phosphatidylserine in the brain are associated with impaired mental function and depression in the elderly.

Known to be clinically effective in patients with senile dementia,<sup>86</sup> phosphatidylserine is considered a promising treatment for the early stages of Alzheimer's Disease, with greater treatment effects in patients with less severe cognitive deficits.<sup>87</sup> Using EEG brain studies, one double blind study did find the acceleration of a slowed EEG in Parkinsonian patients with senile dementia of the Alzheimer's type. Positive effects on anxiety, motivation and affect were observed clinically as well.<sup>88</sup>

Deficient phospholipid metabolism found in the Parkinson's brain may be due to toxic insult or oxidative stress.<sup>89</sup> Normally the brain can manufacture sufficient levels of phosphatidylserine, but if there is a deficiency of methyl donors like S-adenosylmethionine (SAM), folic acid, and vitamin B<sub>12</sub>, or essential fatty acids, the brain may not be able to make sufficient phosphatidylserine. This may make adequate intake of these nutrients important as well. In addition co-supplementation with DHA should be

encouraged when using phosphatidylserine from soy sources (See Phosphatidylserine chapter for more information). Absorption studies in animals indicate that phosphatidylserine is well absorbed orally.

## Creatine

Creatine is an important player in brain homeostasis, and acts as a temporal and spatial buffer for cytosolic and mitochondrial pools of the cellular energy currency, adenosine triphosphate and its regulator, adenosine diphosphate.<sup>90</sup> Well known mostly as a body-building supplement, oral creatine monohydrate supplementation has also been shown to enhance memory, and is being studied for the treatment of neurological, neuromuscular and atherosclerotic disease.<sup>72</sup>

In a placebo controlled study, thirty-six patients with various types of muscular dystrophies found mild but significant improvement in muscle strength and daily-life activities.<sup>91</sup> In another study, one patient with extrapyramidal movement disorder and extremely low creatinine concentrations in serum and urine, oral intake of creatine significantly increased brain creatine levels. Phosphorus magnetic resonance spectroscopy of the brain revealed no detectable creatine phosphate before oral substitution of creatine and a significant increase afterward. Partial restoration of cerebral creatine concentrations was accompanied by improvement of the patient's neurologic symptoms as well.<sup>92</sup>

Other studies using creatine for neuromuscular diseases have not proven much benefit from creatine. A double-blind, cross-over trial study of 34 patients with myotonic dystrophy found no significant improvement using manual and quantitative muscle strength, daily-life activities, and patients' own global assessment comparing. As in the other studies, creatine supplementation was well tolerated without clinically relevant side effects, however the supplement did not result in significant improvement of muscle strength or daily-life activities.<sup>93</sup> A third study used 5 g/day in a double-blind trial of 41

patients with Huntington's disease. After one year of creatine intake at a level known to improve muscle functional capacity in healthy subjects, patients with Huntington's Disease did not experience improvements in functional, neuromuscular, or cognitive status.<sup>94</sup> Finally, one placebo-controlled trial using creatine did not find evidence of a beneficial effect of creatine monohydrate on survival or disease progression in patients with Amyotrophic Lateral Sclerosis.<sup>95</sup> It is doubtful whether creatine intake will prove beneficial to Parkinson's patients in the future.

## Botanical Medicines

### *Camellia Senensis (Green Tea)*

As a good source of polyphenols, green tea may play a role in preventing and treating the oxidative stress. The biological properties of green tea polyphenols reported in the literature include significant blood brain barrier penetration of these polyphenols, antioxidant actions, free radical scavenging, iron-chelating properties, (3)H-dopamine and (3)H-methyl-4-phenylpyridine uptake inhibition, catechol-O-methyltransferase activity reduction, protein kinase C or extracellular signal-regulated kinases signal pathway activation, and cell survival/cell cycle gene modulation.<sup>96,97</sup> Green tea polyphenols have demonstrated neuroprotectant activity in cell cultures and animal models, such as the prevention of neurotoxin-induced cell injury.<sup>96,98</sup>

Green tea polyphenols, such as the major green tea polyphenol (-)-epigallocatechin-3-gallate, are now being considered as therapeutic agents in well-controlled epidemiological studies, aimed to alter brain aging processes and to serve as possible neuroprotective agents.<sup>99</sup> Although human clinical data is still limited, the circumstantial data from several recent studies suggest that green tea polyphenols may

promote health and reduce disease occurrence, and possibly protect against Parkinson's disease and other neurodegenerative diseases.<sup>96</sup>

In animal models of Parkinson's disease, both green tea and the oral administration of (-)-epigallocatechin-3-gallate prevented the loss of tyrosine hydroxylase positive cells in the substantia nigra and of tyrosine hydroxylase activity in the striatum and prevented neurotoxin-induced elevations in antioxidant enzymes superoxide dismutase and catalase. These treatments also retained striatal levels of dopamine and its metabolite homovanillic acid and inhibited of nitric oxide synthetase in the substantia nigra.<sup>98,97</sup>

### *Ginkgo Biloba (Ginkgo)*

Ginkgo biloba extract (GBE) exerts profound, widespread tissue effects, including membrane-stabilizing, antioxidant, and free radical-scavenging effects. GBE also enhances the utilization of oxygen and glucose. GBE is an extremely effective inhibitor of lipid peroxidation of cellular membranes. Although there are no clinical studies in Parkinson's patients, Ginkgo biloba is well researched for its beneficial effects in Alzheimer's disease.<sup>100,101</sup> and has been shown useful in animal models of Parkinson's disease.<sup>72,102</sup> GBE possesses protective effect on the Parkinson's Disease models both in vivo and in vitro. The anti-oxidation and anti-apoptosis may be one of the mechanisms underlying the neuroprotective effect of GBE.<sup>102</sup>

Ginkgo may also help decrease toxicity of levodopa. In order to observe toxic neuronal effect of levodopa and investigate if using Levodopa together with GBE would be a feasible method to treat Parkinson's disease, rat models of Parkinson disease were administered either levodopa (50 mg/kg every day for 3 days, 5 days, 7 days,) or levodopa combined with EGb (100 mg/kg every day). The results

showed that in the L-dopa group, the numbers of apoptosis of substantial nigra, rings of rotational behavior were more than those in the levodopa group. These results suggest that levodopa had neurotoxic effect and that Ginkgo extract may decrease the toxicity of levodopa. The authors concluded that a combined use of GBE with levodopa may be a practical method to treat Parkinson's patients and may be better than using Levodopa alone.<sup>103</sup>

Although a dose-response relationship is not yet established for humans, 240 mg per day of Ginkgo Biloba extract seems to show a higher rate of treatment response than does 120 mg per day. Regarding safety, in all trials reviewed the adverse event profile of GBE was not different from that of the placebo.<sup>104</sup> It must be pointed out that GBE should be taken consistently for at least 12 weeks in order to determine effectiveness. Although some people with AD report benefits within a 2–3 week period, most will need to take GBE for a longer period of time.

#### *Piper Methysticum (Kava-Kava)*

Although no side-effects have been reported using standardized kava extracts at recommended levels in the clinical studies, there have been isolated reports of kava causing onset of Parkinson-like symptoms.<sup>105</sup> Additionally, several case reports have been presented indicating that kava may interfere with dopamine and worsen Parkinson's disease.<sup>106,107</sup> Until this issue is resolved, kava extract should not be used in Parkinson's patients or those considered genetically susceptible.

#### *Homeopathy*

No clinical studies are available to support the use of homeopathy for Parkinson's Disease, although anecdotal success stories are known. Some of the Parkinson remedies and their symptom picture may include:

- Agaricus muscarius: crawling sensations, vertigo with impulse to fall backwards, symptoms worse in cold weather
- Antimonium crudum: Parkinsonism movements associated with gastric symptoms, desires sour foods which do not sit well in the digestive tract, a thickly white coated tongue, stubbornness, anxiousness, a general disgust of life, with worse symptomology with heat, wine, or moonlight.
- Argentum nitricum: tremulousness

### Weak Electromagnetic Fields

Extracranial treatment with low frequency picoTesla magnetic fields may prove to be an effective, safe, and a revolutionary modality in the symptomatic management Parkinsons disease. It is theorized that intermittent pulsed applications of picotesla EMFs may induce in Parkinson's a reactivation of reticular- limbic-pineal systems<sup>108</sup> and nondopaminergic systems might be positively affected by weak EMFs. Some success has been recorded in individual case studies where there has been a decrease in the need for Parkinson medications,<sup>109</sup> decreased micrographic symptoms,<sup>110</sup> and the return of absent dream recall, a symptom which is associated with right hemispheric dysfunction.<sup>108</sup> Unfortunately, only one researcher is mainly responsible for this work, and no follow up has been attempted in a decade since the original work.

### Hypnosis

Although mechanistically not well understood, the clinical association between mindset and severity of most movement disorders, including Parkinson's disease has been observed where symptoms improve with relaxation and are exacerbated by anxiety.<sup>36</sup> In one case study, hypnotic sessions were employed while the patient was monitored with polygraphic electroencephalogram-electromyogram. These recordings showed a direct correlation between the degree of trance and tremor cessation. Although this effect only lasted for a few hours after each session, significant clinical gains were achieved over a period of 6 months with repeated practice consisting mostly of guided imagery. Among the different techniques used during the trance, a technique called role-play time distortion was the most effective in halting tremors.<sup>111</sup>

#### Ayurvedic medicine

In Ayurvedic medicine, Parkinson's disease, or "kampavata," is described as an imbalance of the vata dosha.<sup>36</sup> *Mucuna puriens* is a legume and is a rich source of the antioxidant vitamin E. Although not well understood, rat studies have demonstrated a clear antiparkinson effect, which may be due to components other than levodopa or that it has an levodopa enhancing effect.<sup>112</sup> One 12 week open clinical trial of 60 patients with Parkinson's disease were treated with a powdered preparation of this legume. Of these patients, 26 patients were taking synthetic levodopa/carbidopa formulations before treatment, and the remaining 34 had not used the medications. The preparation is called HP-200 and is a powder supplied as a 7.5 g sachet that is mixed with water and given orally three to six times a day. Statistically significant reductions in Hoehn and Yahr stage and UPDRS scores were seen from baseline to the end of the 12-week treatment. Adverse effects were mild and were mainly gastrointestinal in nature.<sup>113</sup> More research is needed to learn more about this legume.

## Acupuncture and Tui Na

In Traditional Chinese Medicine, pathogenic wind is the main agent responsible for the symptoms of Parkinson's Disease. The treatment strategy is thus to calm this wind and tranquilize the mind. In more conventional terms, it is hypothesized that acupuncture may increase levels of dopamine in the brain and augment the excitability of the dopamine neurons.<sup>114</sup> Animal studies have shown neuroprotective effects of acupuncture on the nigrostriatal system.<sup>115,116</sup> Acupuncture and tui na, which is a Chinese therapeutic massage, have both been shown to improve clinical disease symptoms and signs, and possibly delay disease progression.<sup>117, 118</sup> In one study, 20 patients with Parkinson's Disease were treated twice a week with acupuncture. Standard scales including the UPDRS and Hoehn and Yahr staging were used. In addition quantitative motor tests, including timed evaluations of arm pronation supination movements, finger dexterity, finger movements between two fixed measured points, the stand-walk-sit test, and a patient questionnaire designed for the study were employed. Objective improvements were noted in the sleep and rest categories, with no other obvious improvements. However on the patient questionnaire, 85% of patients reported subjective improvement of individual symptoms including tremor, walking, handwriting, slowness, pain, sleep, depression, and anxiety.<sup>119</sup> Another study of 26 patients found improvements in auditory evoked brain stem potential examinations.<sup>114</sup> Acupuncture treatments are considered safe and well tolerated<sup>119</sup> and should be considered as a safe means to improve sleep and improve patient perception of Parkinsonian symptoms. More studies are needed to confirm objective improvements in clinical presentations.

## THERAPEUTIC APPROACH

## Diagnosis

Besides standard neurologic rating scales and imaging, serum iron, ferritin and total iron binding may be useful tests to look for iron overload as a contributor to Parkinsonian symptoms. Also, a careful history and laboratory testing that evaluates for heavy metal and pesticide toxicities is an important consideration.

## Dietary recommendations:

- eat a low fat, low animal, and high fiber vegetable diet.
- eat vitamin E rich foods: sunflower seeds, almonds, chard, mustard greens, broccoli, olives, kale, turnip greens and papaya.
- avoid foods high in pesticides and attempt to eat organic foods exclusively.
- to detox heavy metals, eat high sulfur-containing foods like garlic, onions, and eggs, as well as water-soluble fibers such as guar gum, oat bran, pectin, and psyllium seed.
- for patients taking levodopa: lower protein intake is recommended (50 grams per day for men and 40 grams per day for women) and it is recommended that patients on levodopa take their medication with a high carbohydrate meal and delay protein intake until the final meal of the day in an effort to optimize the therapeutic efficacy of the medication.
- due to constant movement, weightloss may be an issue with some patients, therefore caloric intake may need to be adjusted to specific patient needs.

## Lifestyle Recommendations

- avoid cooking in aluminum pots
- banisters along walls and chairs with higher arms may ease the ability walk through the halls and sit, respectively
- thick carpeting may be helpful to avoid falls

### Nutritional Supplementation

- Iron and manganese supplements should be avoided
- 5-HTP in doses of 75 to 125mg/day in those patients taking Sinemet (Levodopa plus Carbidopa).

Those not on this drug should avoid 5-HTP.

- 3,000mg/day of vitamin C
- 1000IU/day of vitamin E as mixed tocopherols. Avoid vitamin E supplements that are solely alpha-tocopherol.
- glutathione: orally and/or intravenously
- It may be best to restrict B vitamins in those patients who are levodopa unresponsive to see if drug treatment efficacy improves. B vitamins and folic acid may be increased in patients with high homocysteine levels and those who are at a greater cardiac risk providing there is careful monitoring of Parkinson symptoms (see B vitamin section in Therapeutic Considerations section above).
- CoQ10: 1200 - 2400mg/day
- Phosphatidylserine: 100mg three times daily

### Botanical medicine

- Green tea: three cups daily or about 3g of soluble components providing roughly 240–320mg of polyphenols. For a green tea extract standardized for 80% total polyphenol and 55% epigallocatechin gallate content, this would mean a daily dose of 300–400mg.
- Ginkgo biloba extract: 240 mg per day for at least 12 weeks

### Homeopathy

- Agaricus muscarius, Antimonium crudum, Argentum nitricum

### Ayurvedic Medicine

- *Mucuna puriens*: 7.5 g mixed with water and given orally three to six times a day

### Acupuncture

- Treatments involving needling and tui na massage according to TCM diagnosis is recommended.

Table 1. Hoehn and Yahr Grading for Motor Dysfunction<sup>34</sup>

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STAGE 0 = No signs of disease.

STAGE 1 = Unilateral disease.

STAGE 1.5 = Unilateral plus axial involvement.

STAGE 2 = Bilateral disease, without impairment of balance.

STAGE 2.5 = Mild bilateral disease, with recovery on pull test.

STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.

STAGE 4 = Severe disability; still able to walk or stand unassisted.

STAGE 5 = Wheelchair bound or bedridden unless aided.

Table 2: Conventional Medications:

- *Sinemet*- is a combination of L-Dopa and Carbidopa
- *Amantadine (Symmetrel)*- modulates motor fluctuations; a dopamine receptor agonist
  - Other dopamine receptor agonists: Bromocriptine, Pergolide, Pramipexole, Ropinirole
- *Tolcapone (Tasmar)* or *Entacapone (Comtan)*- inhibit dopamine breakdown
- *Anticholinergic drugs*- for resting tremor
- *Clozapine* – for levodopa induced dyskinesias

(Note: All of these medications can produce hallucinations and daytime somnolence)

Table 3 The effect of HTP on depression in Parkinson's disease

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Patient no.	HDS				
	L-dopa	Carbidopa	5-HTP		
	(mg/day)	(mg/day)	(mg/day)	Before	After
1	1,000	175	125	22	11
2	300	75	75	14	3
3	400	150	100	21	13

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4	1,000	100	100	12	6
5	500	125	500	18	22
6	1,125	112.5	300	18	7
7	500	50	100	17	13

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