Parkinson’s Disease

Medications

By David Houghton, MD, MPH,
Howard Hurtig, MD,
and Sharon Metz, RN, MPH,
with guest author Melanie Brandabur, MD
# Table of Contents

Chapter 1  Introduction to Parkinson’s Disease ..............................................5  
Chapter 2  Medications for Motor Symptoms ...............................................8  
Chapter 3  Medications for Non-Motor Symptoms ........................................21  
Chapter 4  Complementary Therapies: Herbs, Nutritional Supplements and Exercise ............................................................................46  
Chapter 5  Research and Future Developments: Symptomatic Treatment, Neuroprotection and Neurorestoration .....................54

Summary of Tables

Table 1  Symptoms in Parkinson’s Disease ................................................6  
Table 2  Medications for Motor Symptoms in PD .....................................9  
Table 3  Medications for Depression and Anxiety in PD .........................25  
Table 4  Medications for Dementia and Hallucinations in PD ..................32  
Table 5  Medications for Gastrointestinal (GI) Symptoms and Drooling in PD..........................................................41

Appendix A  Glossary ......................................................................................59  
Appendix B  Medical Alert Card .....................................................................62  
Appendix C  Formula for Liquid Sinemet® ......................................................63  
Appendix D  Epworth Sleepiness Scale .........................................................64  
Appendix E  Selected Readings .......................................................................65

About the Authors ....................................................................................................67
Introduction

This book concentrates on the medications used in Parkinson’s disease (PD). Ideally, the treatment of PD would be symptomatic (control or reduction of symptoms), neuroprotective (halting or slowing of disease progression) and neuroregenerative (reversal of disease process).

At present, proven therapies only help to relieve symptoms. More than a dozen different medications are now being used routinely to combat the motor symptoms of PD. Many others target the non-motor complications of PD. Considerable research remains dedicated to uncovering neuroprotective or neuroregenerative strategies, but to date, no such definitive therapies have been discovered. Since the publication of the fourth edition of this book, more data have been published on nutritional supplements (nutriceuticals) and their value in PD.

Throughout this manual, medications currently available for symptomatic treatment and future developments in the treatment of PD are discussed. In addition, nutriceuticals are discussed.
Classic Symptoms

The primary symptoms of Parkinson’s disease (PD) were first described by James Parkinson in 1817 in his *Essay on the Shaking Palsy*. These include:

- Tremor (usually most noticeable when the limb is at rest)
- Bradykinesia (slowness of movement)
- Rigidity (stiffness of movement)
- Postural instability (imbalance when standing or walking)

A PD diagnosis is based on evidence of at least two out of three specific signs and symptoms: tremor, slowed mobility (bradykinesia) and/or stiffness (rigidity). The occurrence of symptoms on only one side of the body is typical of the disease in its earliest stage. The diagnosis of Parkinson’s disease remains clinical; that is, there are no conventional or readily available laboratory tests or brain images that can “prove” PD, though dopamine transporter scanning may help with diagnostic puzzles (see discussion in Pathology section).

Other characteristic features of PD include:

- Micrographia (small handwriting)
- Hypophonic dysarthria (soft, less understandable speech)
- Stooped posture
- Shuffling steps
- Diminished facial expression
- Infrequent eye blinking

Early falling or postural instability, commonly seen later in classic PD, may suggest other parkinsonian syndromes such as:

- Progressive supranuclear palsy (PSP)
- Corticobasal degeneration (CBD)
- Multiple system atrophy (MSA)
- Dementia with Lewy bodies (DLB)

As the above symptoms predominantly involve movement, they are called **motor symptoms**. Parkinson’s disease is not only a disorder of motor symptoms. It is now well known that **non-motor symptoms** also can be prominent and even disabling in PD. Non-motor symptoms include changes in mood, memory, blood pressure, bowel and bladder...
function, sleep, fatigue, weight and sensation (Table 1). Some symptoms have features of both (i.e., mixed motor and non-motor symptoms).

**Table 1. Symptoms in Parkinson’s Disease**

<table>
<thead>
<tr>
<th>MOTOR SYMPTOMS</th>
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<tbody>
<tr>
<td>• Bradykinesia (slowness of movement)</td>
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<tr>
<td>• Rigidity (stiffness of movement)</td>
</tr>
<tr>
<td>• Tremor (involuntary shaking of the hands, feet, arms, legs, jaw or tongue; usually more prominent at rest)</td>
</tr>
<tr>
<td>• Postural instability (tendency to fall, usually when pivoting)</td>
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</table>

<table>
<thead>
<tr>
<th>NON-MOTOR SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mood changes (depression, anxiety, irritability)</td>
</tr>
<tr>
<td>• Cognitive changes (memory problems, personality changes, psychosis/hallucinations)</td>
</tr>
<tr>
<td>• Orthostatic hypotension (lightheadedness and low blood pressure when standing)</td>
</tr>
<tr>
<td>• Constipation and early satiety (a feeling of fullness after eating small amounts)</td>
</tr>
<tr>
<td>• Hyperhidrosis (excessive sweating)</td>
</tr>
<tr>
<td>• Seborrhea (oily skin)</td>
</tr>
<tr>
<td>• Urinary urgency and incontinence</td>
</tr>
<tr>
<td>• Sexual dysfunction</td>
</tr>
<tr>
<td>• Loss of sense of smell</td>
</tr>
<tr>
<td>• Sleep disorders</td>
</tr>
<tr>
<td>• Insomnia, excessive daytime sleepiness (EDS), rapid eye movement behavioral disorder (RBD) or active dreaming, dream enactment, involuntary movements and vocalizations during sleep, restless leg syndrome (RLS)/periodic limb movement disorder (PLMD)</td>
</tr>
<tr>
<td>• Fatigue</td>
</tr>
<tr>
<td>• Sensory problems (pain, tightness, tingling, burning)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MIXED MOTOR AND NON-MOTOR SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drooling due to slowed swallowing (sialorrhea)</td>
</tr>
<tr>
<td>• Speech and swallowing problems</td>
</tr>
</tbody>
</table>
Much clinical research is being conducted to try to recognize early features of Parkinson’s disease. Motor symptoms typically begin on one side of the body, often as a rest tremor or a reduced ability to use the hand, arm or leg on the affected side. Prior to the appearance of the motor features of PD, individuals may also recognize that they have experienced constipation, vivid dreams, depression and/or diminished sense of smell for months or even years. These “pre-motor” symptoms may provide the opportunity for earliest recognition of the PD complex, with more clinical trials and earlier treatment strategies on the horizon.

**Pathology**

Parkinson’s disease is a result of the loss of specific types of brain cells (neurons) that produce a chemical called dopamine. The motor symptoms come from the slow and progressive degeneration and death of these neurons in an area of the brain called the substantia nigra, which is in the brain stem. One reason these brain cells begin to die may be due to genetic abnormalities. The earliest symptoms of PD usually don’t appear for several years after the onset of neurodegeneration because there is plenty of dopamine left in reserve to compensate for the declining supply.

In other words, a person will lose at least 50% of the dopamine in his or her brain before noticing that something is wrong with his or her body. We now also know that the non-motor features of PD arise from the loss of neurons in areas of the brain outside of the substantia nigra and involve chemicals other than dopamine, particularly acetylcholine. In 2011, a computerized brain scan utilizing a radio-isotope that labels the molecule transporting dopamine into the cell (DaTscan™) first became available in the United States. A DaTscan™ may be used to assist with the clinical diagnosis of PD and other parkinsonian syndromes when the patient’s presenting symptoms are not straightforward.

**Treatment**

It is important for persons with PD to realize that although the underlying disease progresses slowly, the clinical course over many years varies greatly with each person. Effective management of PD symptoms requires an experienced and compassionate healthcare provider, the person with PD and his or her care partner to determine a treatment plan consisting of appropriate medications, regular exercise, a healthy diet, social engagement and cognitive activities, counseling and other therapies. As the disease progresses and problems accumulate, deep brain stimulation (DBS) surgery may be a reasonable therapeutic option for some individuals, although many people with PD do not qualify for DBS for a variety of reasons. However, the majority of people with PD can lead full and active lives with good symptom control for many years.
Chapter 2
Medications for Motor Symptoms

The following medications used to treat Parkinson’s disease are discussed in this chapter:

- Levodopa
- Dopamine agonists
- MAO-B inhibitors
- COMT-inhibitors
- Amantadine
- Anticholinergics

The central objective of using any of the above medications is to control or manage motor symptoms. Since these symptoms are largely due to the diminishing supply of dopamine in the brain, most symptomatic medications are designed to replenish, mimic or enhance the effect of this chemical.

For quick reference, Table 2 provides a summary of the medications used to treat the primary motor symptoms of PD including typical dosages, side effects and indications. Detailed discussions of the medications follow.

Remember that medication usage is only a part of the whole treatment plan for effectively treating PD. Regular exercise, physical therapy, occupational therapy, speech therapy, holistic practices, nutritional consultation, support groups, education, psychological counseling, intelligent use of assistive devices and caregiver relief are all important aspects of the best treatment plan.

**Pronunciation Key**
(accented syllable in **bold**)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pronunciation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa</td>
<td>Lee-voe-doe-pa</td>
</tr>
<tr>
<td>Carbidopa</td>
<td>Car-bee-doe-pa</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Row-pin-er-ole</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>Pram-i-pex-ole</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>Row-tig-oh-teen</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Ae-poe-more-feen</td>
</tr>
<tr>
<td>Selegiline</td>
<td>Sell-edge-ah-leen</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>Rah-saj-ah-leen</td>
</tr>
</tbody>
</table>
### Parkinson’s Disease: Medications

#### Table 2. Summary of Medications for Motor Symptoms in PD

<table>
<thead>
<tr>
<th>Medication (product name in parentheses)</th>
<th>Dosages in Milligrams (mg); tablets unless otherwise noted</th>
<th>Typical Treatment Regimens*</th>
<th>Potential Side Effects</th>
<th>Indications for Usage (italics = approved by FDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Levodopa</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbidopa/levodopa immediate-release (Sinemet®)</td>
<td>10/100, 25/100, 25/250</td>
<td>150–1000 mg of levodopa total daily dose (divided 3-4 times)</td>
<td>Low blood pressure, nausea, confusion, dyskinesia</td>
<td>Monotherapy or combination therapy for slowness, stiffness and tremor</td>
</tr>
<tr>
<td>Carbidopa/levodopa oral disintegrating (Parcopa®)</td>
<td>10/100, 25/100, 25/250</td>
<td>150–1000 mg of levodopa total daily dose (divided 3-4 times)</td>
<td>Same as above</td>
<td>Same as above, plus need for dissolvable medication in mouth especially if swallowing is impaired</td>
</tr>
<tr>
<td>Carbidopa/levodopa extended-release (Sinemet CR®)</td>
<td>25/100, 50/200</td>
<td>150–1000 mg of levodopa in divided doses, depending on daily need</td>
<td>Same as above</td>
<td>Monotherapy or combination therapy for slowness, stiffness and tremor</td>
</tr>
<tr>
<td>Carbidopa/levodopa/entacapone (Stalevo®) [see COMT-inhibitors below]</td>
<td>12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200</td>
<td>150–1000 mg of levodopa total daily dose, depending on daily need</td>
<td>Same as above, plus diarrhea and discolored urine (due to entacapone)</td>
<td>Replacement for carbidopa/levodopa, for motor fluctuations (benefit of entacapone)</td>
</tr>
<tr>
<td>Carbidopa/levodopa extended-release capsules (RytaryTM)</td>
<td>23.75/95, 36.25/145, 48.75/195, 61.25/245</td>
<td>855-2340 mg of levodopa total daily dose</td>
<td>Same as above</td>
<td>Monotherapy or adjunct therapy for slowness, stiffness and tremor. Note that dosages of Rytary are not interchangeable with other carbidopa/levodopa products.</td>
</tr>
<tr>
<td>Carbidopa/levodopa enteral solution (Duopa™)</td>
<td>Clinician-determined</td>
<td>Up to 2000 mg of levodopa over 16 hours</td>
<td>Same as above</td>
<td>For the treatment of motor fluctuations in patients with advanced Parkinson’s disease</td>
</tr>
<tr>
<td><strong>Dopamine Agonists</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Ropinirole (Requip®)</td>
<td>0.25, 0.5, 1, 2, 3, 4, 5</td>
<td>9–24 mg total daily dose (divided 3–4 times)</td>
<td>Low blood pressure, nausea, leg swelling and discoloration, confusion, sleep attacks, compulsive behaviors</td>
<td>Monotherapy or combination therapy for slowness, stiffness and tremor</td>
</tr>
<tr>
<td>Ropinirole XL (Requip XL®)</td>
<td>2, 4, 6, 8, 12</td>
<td>8–24 mg once/day</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>Pramipexole (Mirapex®)</td>
<td>0.125, 0.25, 0.5, 0.75, 1, 1.5</td>
<td>1.5–4.5 mg total daily dose (divided 3–4 times)</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>Pramipexole ER (Mirapex ER®)</td>
<td>0.375, 0.75, 1.5, 2.25, 3, 3.75, 4.5</td>
<td>1.5–4.5 mg once/day</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>Rotigotine (Neupro®)</td>
<td>1, 2, 3, 4, 6, 8 patch</td>
<td>4–8 mg once/day</td>
<td>Same as above</td>
<td>Same as above; patch delivery an advantage for some</td>
</tr>
</tbody>
</table>
### Parkinson’s Disease: Medications

#### Table 2, continued. Summary of Medications for Motor Symptoms in PD

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosages in Milligrams (mg); tablets unless other-wise noted</th>
<th>Typical Treatment Regimens*</th>
<th>Potential Side Effects</th>
<th>Indications for Usage (italics = approved by FDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine Agonists, cont.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apomorphine (Apokyn®)</td>
<td>30 mg/3 ml vial</td>
<td>2–6 mg</td>
<td>Significant nausea; must take anti-nausea medication with dose, especially when starting therapy</td>
<td>Adjunct therapy for sudden wearing off; the only injectable, fast-acting dopaminergic drug</td>
</tr>
<tr>
<td><strong>MAO-B Inhibitors</strong></td>
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<tr>
<td>Selegiline (l-deprenyl, Eldepryl®)</td>
<td>5</td>
<td>5 mg once or twice a day</td>
<td>Nausea, dry mouth, light-headedness, constipation; may worsen dyskinesia; possible rare interaction with anti-depressants and other drug classes</td>
<td>Monotherapy for slowness, stiffness and tremor; adjunct therapy for motor fluctuations</td>
</tr>
<tr>
<td>Rasagiline (Azilect®)</td>
<td>0.5, 1.0</td>
<td>1 mg once/day</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>Zydis selegiline HCL</td>
<td>1.25, 2.5</td>
<td>1.25–2.5 mg once/day</td>
<td>Same as above</td>
<td>Same as above, plus need for dissolvable medication in mouth (absorbed in mouth)</td>
</tr>
<tr>
<td><strong>COMT-Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entacapone (Comtan®)</td>
<td>200</td>
<td>200 mg 4–8 times daily (with each levodopa dose)</td>
<td>Diarrhea, discolored urine, plus enhancing side effects of levodopa, especially dyskinesia and confusion</td>
<td>Combination therapy with levodopa for motor fluctuations (not pharmacologically active by itself)</td>
</tr>
<tr>
<td>Tolcapone (Tasmar®)</td>
<td>100, 200</td>
<td>100 mg up to 3 times daily</td>
<td>Same as above plus increased risk of liver inflammation</td>
<td>Same as above (second-line due to side effects)</td>
</tr>
<tr>
<td><strong>Other Antiparkinson Medications</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Amantadine (Symmetrel®)</td>
<td>100 mg capsules; 50mg/5ml syrup</td>
<td>100 mg 2–3 times daily</td>
<td>Nausea, confusion, lividity discoloration (livido reticularis), mild anti-cholinergic effects (see below)</td>
<td>Monotherapy for slowness, stiffness, and tremor; combination therapy with levodopa for levodopa-induced motor fluctuations; especially helpful for suppressing dyskinesia</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
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<tr>
<td>Trihexyphenidyl (formerly Artane®)</td>
<td>2, 5 mg tablets; 2 mg/5 ml elixir</td>
<td>1–2 mg 2 or 3 times daily</td>
<td>Confusion, memory issues, hallucinations, dry mouth, blurry vision, urinary retention</td>
<td>Monotherapy or combination therapy, predominantly for tremor in younger people; should be avoided in elderly</td>
</tr>
<tr>
<td>Benztropine (Cogentin®)</td>
<td>0.5, 1, 2</td>
<td>0.5–2 mg 2 or 3 times daily</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

Key: monotherapy = medication used alone  
combination or adjunct therapy = medication added to other medications  
* “Typical treatment regimens” should act only as a guide. The dosage prescribed by your doctor and your effective dose may vary from dosages listed.
Levodopa

Scientific investigators in the 1950s discovered that experimental depletion of dopamine in the brains of mice caused a condition that resembled Parkinson’s disease in humans and that dopamine replacement abolished those symptoms. As they continued to explore ways to translate these observations to the human condition, their efforts led ultimately to the successful development of levodopa in the late 1960s.

Levodopa was the first medication proven effective for treating a chronic degenerative neurologic disease. Levodopa in pill form is absorbed into the blood stream from the small intestine and travels through the blood to the brain, where it is converted into the active neurotransmitter dopamine. Unconverted levodopa has no impact on Parkinson’s symptoms. Dopamine cannot be given to treat PD because its chemical structure will not allow it to cross the “blood-brain barrier,” a physiologic screen that protects the brain by keeping out drugs and other chemicals that might be harmful.

In the early days of levodopa therapy, large doses were required to relieve symptoms. As a result, nausea and vomiting were common. The solution to this inefficient delivery of the drug was the development of carbidopa, a levodopa enhancer. When added to levodopa, carbidopa enables an 80% reduction in the dose of levodopa for the same benefit and a marked reduction in the frequency of side effects.

Carbidopa/levodopa is marketed as Sinemet® in the United States. In fact, the name says it all: “sin” “emet” roughly translates from “without” “vomiting” in Latin. This is a vast improvement upon levodopa alone, though nausea can be one of the more common side effects of carbidopa/levodopa. The generic product is intended to be chemically identical to the name brand and, for most people, is just as effective. The bioavailability of generic medication in the body may vary by 20% (20% more or 20% less available) compared to the original branded drug. If you observe a difference in your response to medication immediately after switching from name brand to generic, or between two different generics, speak with your physician about ways to optimize your medication.

KEY POINT: Forty years after it was first introduced, levodopa is still the most effective medication available for treatment of the motor symptoms of PD.

The Parkinson’s Outcomes Project is the largest clinical study of Parkinson’s in the world. As of May 2015, more than 19,000 evaluations had taken place on almost 8,000 people with Parkinson’s. This chart shows the percentage of people using and not using levodopa at each of those 19,000+ visits. At 2% of the visits, doctors started a patient on levodopa. At 1% of visits, doctors took the patient off levodopa.

In the early days of levodopa therapy, large doses were required to relieve symptoms. As a result, nausea and vomiting were common. The solution to this inefficient delivery of the drug was the development of carbidopa, a levodopa enhancer. When added to levodopa, carbidopa enables an 80% reduction in the dose of levodopa for the same benefit and a marked reduction in the frequency of side effects.
Carbidopa/levodopa greatly reduces PD symptoms in the majority of persons with a clinical diagnosis of PD, although the tremor response may lag behind the response of the other symptoms. Facial expression, posture, speech and handwriting may also improve. Levodopa’s half-life — a measure of how long a drug stays in the bloodstream before being metabolized by the body’s tissues — is relatively short, about 60-90 minutes. This results in fluctuations of blood and brain levels of dopamine and is responsible for the motor fluctuations that people with PD experience after long-term levodopa use.

A controlled release formulation (Sinemet CR®) was originally designed to provide extended benefits of the same dosing of carbidopa/levodopa and possibly decrease the number of pills needed per day. The CR pill is absorbed more slowly than regular carbidopa/levodopa. Advantages may be seen for some patients needing longer responses or overnight dosing. But, for other patients, this may be less desirable as there may be a delay in effect and only about 70% of the effective levodopa is usually absorbed before the pills pass through the intestinal tract.

A new formulation of longer acting carbidopa/levodopa was approved by the FDA in January 2015. Carbidopa/levodopa extended release (ER) capsules (Rytary™) contain beads of carbidopa and levodopa that dissolve and are absorbed at different rates. Therapeutic levodopa levels are reached about an hour after taking it, similar to carbidopa/levodopa immediate release (IR). These plasma levodopa concentrations are maintained for 4-5 hours before declining. Clinical trials indicate that patients with motor fluctuations on other oral carbidopa/levodopa products may be able to switch to carbidopa/levodopa ER and experience a reduction in “off” time while requiring fewer medication administrations. Dosages of carbidopa/levodopa ER are not interchangeable with dosages of other carbidopa/levodopa products. For prescribing and dosing information to share with your doctor, visit parkinson.org/rytary.

Carbidopa/levodopa ER can be taken with or without food. Interestingly, high fat meals delay absorption and reduce the amount absorbed, but can potentially lengthen the duration of benefit. People who have difficulty swallowing intact capsules can carefully open the Rytary capsule and sprinkle the entire contents on a small amount of applesauce (1 to 2 tablespoons), and consume it immediately.

Another formulation, the orally-disintegrating carbidopa/levodopa, Parcopa®, is also useful for people who have difficulty swallowing or who don’t have a liquid handy to wash down a dose of medication.

The most common side effects of carbidopa/levodopa are:

- Nausea
- Vomiting
- Loss of appetite
- Lightheadedness
- Lowered blood pressure
- Confusion
Such side effects can be minimized with a low starting dose when initiating treatment with any antiparkinson drug and increasing the dose slowly to a satisfactory level. This is particularly helpful in elderly people with PD whose tolerance for medications is often less than in younger persons. Taking drugs with meals can also reduce the frequency and intensity of gastrointestinal side effects. For those patients who have persistent problems, adding extra carbidopa (Lodosyn®) to each dose of carbidopa/levodopa can help.

Carbidopa/levodopa is absorbed into the bloodstream through similar channels that transport amino acids, the building blocks of proteins. As a result, some patients experience less benefit if they take their carbidopa/levodopa with a stomach full of protein like meats, cheeses and other dairy products. For improved medication absorption, one can take carbidopa/levodopa one hour before a protein-rich meal or two hours afterwards. After several years of using carbidopa/levodopa and the development of motor fluctuations, many people with PD notice that the onset of benefit from a dose of levodopa is quicker when the drug is taken on an empty stomach. Fortunately, most patients should have no problem with feeling “on” even if they take their medication with a meal.

**KEY POINT:** After several years of a smooth response to levodopa, many people with PD notice the appearance of motor fluctuations (“wearing-off”) and involuntary movements (dyskinesia). These complications can usually be managed by adjusting the amount of drug and the timing of the doses.

The chemical composition of carbidopa/levodopa prevents the drug from dissolving completely in water or other liquid, but a liquid can be prepared for use in certain unusual situations (see Appendix C).

1) If the person with PD feels full after eating small amounts and carbidopa/levodopa pills are slow to pass through the stomach to the small intestine where they are absorbed into the bloodstream, liquid Sinemet® might be absorbed faster.

2) A smaller fraction of a levodopa dose can be given with the liquid formula than with the available tablet formulations, allowing for very careful adjustments in the person with PD who is experiencing dyskinesia and “wearing-off” on standard amounts of medication.

A commercially available product has been developed with this strategy in mind. Duopa™, marketed as Duodopa® outside the United States, combines carbidopa/levodopa in a gel that is slowly and consistently pumped through a tube inserted surgically through the stomach into the intestine. This provides a smooth absorption of the medicine and can cut down on motor fluctuations and dyskinesia.

One of the major drawbacks to the pump approach is the need for a percutaneous gastrojejunostomy (a small feeding tube). These types of tubes can be the starting locations for infections and other complications. Here is information every patient interested in the pump should be familiar with:
• The current version of the pump requires wearing an external device.
• The pump requires changing a dopamine cassette once or twice a day. The cassettes are a little smaller than a cellular phone, and usually last about 14-16 hours.
• Even with the pump, some patients will need additional medications during the bedtime hours.
• The pump requires continuous maintenance and programming by a qualified professional.
• The tube connected to the stomach requires constant monitoring for infection and/or inflammation.
• Many patients and family members in the clinical trials for the dopamine pump commented that the pump required a lot of care and that an active caregiver may be critical for the success of the therapy.
• There is a need to compare pump effectiveness against deep brain stimulation therapy (DBS). Understanding which patients are appropriate for each technique will be important. This is currently not clearly delineated and will require a detailed discussion with the neurologist or expert clinician.
• It remains unknown if patients with dementia are viable candidates for the pump.
• Pumps are powerful symptomatic therapies, but not cures.
• The continuous infusion pump will not address the dopamine-resistant symptoms of walking, talking and thinking.
• Pumps have not been shown to delay disease progression, and they are not a cure.

Recent research underscores the safety of levodopa use for persons with PD. While there has been occasional concern about levodopa accelerating disease progression or producing toxicity, a post-mortem study of human brains, conducted in London in 2011, concluded that chronic use of levodopa did not lead to disease progression in human beings with PD. Multiple studies across many countries, including the ELLDOPA study, confirm that levodopa is extremely beneficial to the human patient, and that levodopa has had a positive effect on disease course. Expert practitioners in NPF’s Parkinson’s Outcomes Project report utilizing levodopa more than any other drug for Parkinson’s therapy, and they used levodopa more (not less) as disease durations increased.

People with PD who use levodopa long-term may experience dyskinesia at some point, usually three to five years after starting the medication. The term dyskinesia describes involuntary, erratic, writhing movements of the face, arms, legs and/or trunk. These usually occur one to two hours after a dose of levodopa has been absorbed into the bloodstream and is having its peak clinical effect. Dyskinesia tends to be more severe as the dose of levodopa increases. They can be severe enough to interfere with a person’s normal functioning and to cause discomfort if they can’t be controlled. In advanced PD, when motor fluctuations are common, it is often difficult to produce the “on”
response without dyskinesia. This makes it difficult to achieve the satisfactory benefit characteristic of the smooth “on” response that is typical of the levodopa response early in the course of the illness.

Patients should be reassured that the likelihood of developing dyskinesia remains low early in the disease, and – if it occurs – is usually quite mild. Most people with PD prefer to tolerate some dyskinesia in order to derive the benefits of levodopa. This is considered a reasonable tradeoff for getting the best “on” time. The ideal strategies for management of dyskinesia and the associated phenomenon of “wearing-off” are detailed below in discussing the adjunctive therapies to levodopa (dopamine agonists, MAO-B inhibitors, COMT-inhibitors, Amantadine and DBS).

In 1988, the FDA recommended that the daily dose of Sinemet® not exceed 800 mg per day, and as of August 2013, this recommendation has not been revised. As movement disorder specialists, general neurologists and primary care doctors have learned, patients often require doses of Sinemet® that exceed 800 mg/day and can easily tolerate the higher doses used to minimize symptoms. Some patients encounter problems with insurance reimbursement of higher daily doses because of the FDA regulation. An insurance decision can be appealed if necessary, and reference made to the following paper, published on-line in BMJ in 2012, which addresses the 800 mg threshold: “Carbidopa/levodopa dose elevation and safety concerns in Parkinson’s patients: a cross-sectional and cohort design” by Brodell DW, Stanford NT, Jacobson CE, Schmidt P, Okun MS.

**Dopamine Agonists**

A dopamine agonist (DA) is a chemical that has been manufactured to act similarly to dopamine – that is, it attaches to the same cells in the brain known as receptors that dopamine activates to produce its clinical effect. Unlike levodopa, dopamine agonists are not converted into dopamine. Different dopamine agonists have been created that bind to different dopamine receptors with varying strengths. Historical and current DAs in the U.S. include:

- **Bromocriptine** (Parlodel®)
- **Pergolide** (Permax®)
- **Pramipexole** (Mirapex®, Mirapex ER®)
- **Ropinirole** (Requip®, Requip XL®)
- **Rotigotine** (Neupro® patch)
- **Apomorphine** (Apokyn® injection)

Generally DAs effectively improve the motor symptoms of PD, but they are less potent than levodopa. A DA can be used early in the course of PD as a single drug (monotherapy) or later in combination with carbidopa/levodopa (combination or adjunct therapy). Dopamine agonists have longer half-lives (longer duration of action) than levodopa and for that reason can be helpful in reducing the intensity of the “wearing-off” reaction or to generally enhance the effect of levodopa.

**KEY POINT:** Dopamine agonists can be used effectively as a single drug in early PD or in combination with carbidopa/levodopa later on.
The adverse effects of DAs are generally similar to those associated with the use of carbidopa/levodopa. However, certain side effects, such as excessive daytime sleepiness, visual hallucinations, confusion and swelling of the legs, occur more commonly with the use of dopamine agonists than with levodopa. Elderly people with PD are probably more likely than younger people to have troublesome adverse effects when using DAs. This may be partly due to a higher likelihood of other illnesses (also known as comorbidities) and the greater risk of undesirable interactions between Parkinson’s drugs and drugs taken for other purposes. Dyskinesia can be seen with the use of DAs but less frequently than with levodopa therapy. In fact, clinical trials have shown that when combined with levodopa, treatment with a DA permits the use of a lower dose of levodopa and consequently a reduced probability that dyskinesia will occur.

One possible adverse effect of dopamine agonists is the occurrence of drug-induced compulsive behaviors, such as uncontrolled eating, shopping, gambling and sexual urges. Patients may also engage in repetitive and relatively purposeless activities like organizing, sorting or collecting items. This is called punding. We collectively refer to these behaviors as impulse control disorders (ICDs). The underlying physiology is likely related to over-stimulation of dopamine receptors in the part of the brain responsible for instant gratification.

Frequency surveys have shown that these abnormal behaviors are more common with dopamine agonists but can also be seen with carbidopa/levodopa. The DOMINION study published in 2010 was designed to look at the association between ICDs and dopamine replacement therapy – both dopamine agonists and levodopa. Over 3,000 patients participated in the study to quantify the four major ICDs listed above. Nearly 14% of PD patients in the study exhibited an ICD, and these were two or three times more common in patients receiving dopamine agonist therapy compared to those who were not taking agonists. Those at greatest risk include patients with a family history of gambling and those who are younger, unmarried, and/or cigarette smokers. A more recent study of baseline ICD in untreated PD patients using a newer questionnaire revealed nearly 20% of patients demonstrate some impulsivity, but this was actually no different than healthy participants without PD. Additional study will likely provide more insight into the true risk associated with the addition of these dopaminergic medications, as the newer questionnaire may be more likely to pick up such behaviors. Until more information is available to clarify this issue, people with PD should be aware of the risks.
before using dopamine agonists, and clinicians prescribing dopamine agonists should monitor for behavioral disorders. Remember also that the people suffering from impulse control issues may not have insight into the behavioral problems, and this lack of insight underscores the importance of involving caregivers in any proactive monitoring plan.

**KEY POINT:** Be aware of possible compulsive behaviors (shopping, gambling, eating, hypersexuality) related to treatment with dopamine agonists, and be sure to contact your healthcare provider if these occur.

**Bromocriptine** (Parlodel®) and **Pergolide** (Permax®) were developed in the 1970s, and both of these dopamine agonists (DAs) were derived from a plant (fungus) called ergot. When it was confirmed that pergolide can cause heart valve abnormalities in a significant minority of users, the FDA determined that the risk of using pergolide outweighed the benefit, and removed it from the U.S. market for use in PD in March 2007. Bromocriptine, the first of the DAs to become commercially successful, is still available for other medical uses; it is not used in PD.

**Pramipexole** (Mirapex®) and **Ropinirole** (Requip®) were approved by the FDA in 1997 and are currently the most commonly used DAs. Neither of these dopamine agonists is ergot-derived, nor have they been associated with abnormalities of the heart valves. They are both effective in the early treatment of the motor symptoms of PD and play an important role in controlling motor fluctuations despite the greater occurrence of side effects compared with levodopa.

**Rotigotine** (Neupro®), the newest dopamine agonist, was approved by the FDA in 2007 and is formulated for use as a once-daily transdermal (skin) patch that is changed every 24 hours. Clinical trials have shown that it is just as effective as the oral DAs pramipexole and ropinirole. The side effects are similar, with the addition of usually mild local skin irritation under the patch in up to 40% of patients. Most people with PD have been able to tolerate the patch by rotating the sites where they adhere the patch on their bodies. Fewer than 5% of those studied in the clinical trials discontinued its use due to skin irritation. The initial formulation of the patch was removed from the market worldwide in 2008 because of technical problems with the delivery system. The original patches had a tendency to show a crystallized substance on their surface after they were stored in pharmacies and in patient medicine cabinets for weeks. Neupro® was redesigned and returned in 2012 with dosing available in 1, 2, 3, 4, 6 and 8 mg daily.

**Apomorphine** (Apokyn®) was first used to treat PD in 1950, but its use was associated with many side effects, especially nausea and vomiting. It was resurrected in the 1990s in a more tolerable formulation and has found a particular niche as a self-injectable “rescue” drug for people with advanced PD and severe “off” episodes. Its short half-life (average 40 minutes) and chemical structure make it difficult, if not impossible, to take by mouth. In the person affected by severe “off” reactions, during which disabling bradykinesia and rigidity interfere with function, a self-injected dose of Apokyn® can reverse the “off” period within minutes and bridge the gap of one to two hours until the next dose of levodopa takes effect. An anti-nausea medication (usually
trimethobenzamide or Tigan®) is required prior to injection in the early phase of treatment but can be discontinued after the first week or two. Apokyn® can be used as many as five times per day as a rescue agent. Each individual’s response to Apokyn® is different.

**MAO-B Inhibitors**

Monoamine Oxidase Type B (MAO-B) is an enzyme in our body that naturally breaks down several chemicals in the brain, including dopamine. By giving a medication that blocks the effect of MAO-B (an MAO-B inhibitor), more dopamine is available to be used by the brain. Thus, all the motor symptoms of PD can be modestly improved.

In addition, it was suggested in animal trials that MAO-B inhibitors might actually slow the progression of PD, offering neuroprotection. This was first tested in humans in the late 1980s in a clinical trial of the MAO-B inhibitor l-deprenyl, now sold under the name selegiline (Eldepryl®). The goal of the study was to determine if selegiline (compared to Vitamin E and a placebo) could delay the need for levodopa as PD symptoms worsened over time. Selegiline was shown to delay the need for levodopa by nine months, suggesting neuroprotection, but this benefit may simply have been from the antiparkinson symptom effect of selegiline. Of note, Vitamin E had no benefit in the clinical trial.

As MAO-B inhibitors do provide modest benefit for the motor features of PD, they are usually used as early monotherapy or as an adjunct (add-on) to other medications, including levodopa. When used in combination with other medications, MAO-B inhibitors may reduce “off” time and extend “on” time.

**KEY POINT:** MAO-B inhibitors are used by themselves for modest symptom control in early PD or in combination with other medications to reduce “off” time and extend “on” time.

Selegiline is available in two formulations: standard oral (Eldepryl®, l-deprenyl) and orally-disintegrating (Zelapar®). Both oral and orally-disintegrating selegiline are taken once daily. Standard oral selegiline is converted to an amphetamine like by-product which may contribute to side effects of jitteriness and confusion. Conversely, Zelapar® is
dissolved in the mouth and absorbed directly into the bloodstream (no byproduct) without these side effects. Because of Zelapar®’s absorption in the mouth, it may be preferred for convenience or out of necessity for the person who has difficulty swallowing.

**Rasagiline** (Azilect®), the newest MAO-B inhibitor, is structurally different from selegiline and does not have an amphetamine-like byproduct that can cause jitteriness. Taken once each day, rasagiline came to the U.S. market in late 2006. Clinical trials of Azilect® as monotherapy or adjunctive therapy showed mild but definite efficacy, and there was also an unproven hint of slowing disease progression. A worldwide, multi-institutional clinical trial of rasagiline’s potential for neuroprotection was published in 2008 and follow-up data from the original studies has also been examined closely. These results suggest that the use of rasagiline earlier in PD may offer the greatest long-term advantage and modify the symptomatology over time, although true disease modification remains unproven. Even with this new data, the FDA indication for rasagiline remains for early monotherapy and later add-on therapy.

The most common side effects of MAO-B inhibitors include mild nausea, dry mouth, lightheadedness and constipation. It is usually well-tolerated even in the more aged patient. Special mention should be made of a unique and rare adverse effect of the MAO-B inhibitors called the “wine and cheese effect.” Taking MAO-B inhibitors with the heavy consumption of aged cheeses or wines high in tyramine may theoretically raise blood pressure to dangerous levels. Also, pharmacists routinely warn patients about interactions with other drugs, especially the antidepressants, when they start an MAO-B inhibitor, but the occurrence of an adverse reaction in this setting remains very rare (this side effect is usually from MAO-A inhibitors and not MAO-B inhibitors). A study was published in 2011 that fortunately found no cases of dangerous blood pressure shifts in over 2000 patients taking rasagiline in combination with many of the anti-depressant medications on the market today. Still, it is appropriate for any person with PD to review all medications and possible adverse interactions with their treating physician before starting anything new.

**COMT-Inhibitors**

Catechol-O-methyl transferase (COMT) is an enzyme that inactivates levodopa in the body before it is transported in the bloodstream to the brain. Two drugs that block this enzyme, thereby making levodopa more available to the brain, have been approved by the FDA for treating PD. The COMT-blocking drugs or inhibitors extend the clinical benefit of levodopa, reducing “off” time and lengthening “on” time. COMT-inhibitors are generally well-tolerated, though they may exaggerate some levodopa-related side effects, particularly dyskinesia. Additional side effects include confusion, hallucinations, discoloration of urine (reddish-brown or rust-colored) and diarrhea.

**KEY POINT:** COMT-inhibitors extend the benefit of levodopa by reducing “off” symptoms between doses. Without levodopa, COMT-inhibitors have no effect on Parkinson’s symptoms.
Entacapone (Comtan®) and Tolcapone (Tasmar®) are the two COMT-inhibitors approved by the FDA to treat PD. Entacapone is prescribed with each dose of levodopa, whereas tolcapone is taken three times a day, no matter how many doses of levodopa are prescribed. COMT-inhibitors without levodopa have no effect on Parkinson’s symptoms. There is no potential benefit to be gained from taking Entacapone or Tolcapone to try to extend the life of other PD medications. Tolcapone was removed from the American market in the early 2000s because of a few instances of liver toxicity in people who used it. During clinical trials before FDA approval in 1999, transient, mild abnormalities of liver function tests were documented in 1-2% of patients and were considered to be inconsequential. Tolcapone is currently available with the condition that blood tests of liver function be conducted every two to four weeks for the first six months after beginning treatment, then periodically thereafter.

Carbidopa/levodopa/entacapone (Stalevo®) is a combination drug useful in people with advanced PD who experience motor fluctuations. It works by providing relief for the motor symptoms as well as reducing “off” time. By combining the two drugs into one tablet, the manufacturer has made pill-taking a little more convenient compared with carbidopa/levodopa + entacapone taken separately. In addition, there are more dosing options (see table) to better tailor the medication needs to an individual patient. In 2012 this combination pill entered the generic market in the U.S.

Amantadine

Amantadine (Symmetrel®) was created as an anti-influenza medication in the 1960s, but its benefit in PD was first described in 1969, when astute observers noticed, quite by accident, that people with PD who took Amantadine to prevent influenza had much better control over tremor. Amantadine often provides immediate benefit for most PD motor symptoms, but its effect frequently wanes after a few weeks or months. It is unique, however, in that it can also reduce levodopa-induced dyskinesia.

Amantadine has become a useful adjunctive medication in people with advanced PD and motor fluctuations. Its mechanisms of action are not fully known, but it is likely that it interacts with multiple receptors at various sites in the brain to achieve its positive effect. Amantadine is cleared from the body by the kidneys, so a person with kidney problems may require a lower dose.

KEY POINT: Amantadine may be particularly beneficial in people with PD who have prominent tremor or bothersome levodopa-induced dyskinesia.

Amantadine is most commonly available as a 100 mg capsule, although liquid and tablet forms can also be obtained. If the person with PD requires lower doses or has difficulty swallowing, the liquid or tablet formulations would be preferred.

The most frequent side effects of Amantadine are nausea, dry mouth, lightheadedness, insomnia, confusion and hallucinations. Urinary retention is another, rare, side effect. In less than 1% of people with PD who take this medication, another side effect is a
mottled, lacey, reddish-purple discoloration of the skin, usually on the legs and with some accompanying leg swelling, known as **livedo reticularis**. Stopping the drug will resolve this adverse effect, although if the drug is providing good benefit there is no harm in continuing it.

**Anticholinergics**

The earliest medications used in PD were those that blocked brain receptors for acetylcholine, called anticholinergics. It is believed that acetylcholine and dopamine maintain a delicate equilibrium in the normal brain, which is upset by the depletion of dopamine and the degeneration of dopamine-producing cells. Drugs that block the effect of acetylcholine have the potential for restoring the normal balance of these two chemicals, thereby reducing the symptoms of PD.

The anticholinergics can provide modest benefit for the motor symptoms of PD, but they can also cause significant mental and physical side effects. Confusion, hallucinations, decreased short-term memory, dry mouth, blurry vision and urinary retention are potential side effects, particularly in the older person with PD. As such, these medications are typically utilized in younger people. Experience has shown that the anticholinergics work best against tremor.

Additionally, research from the NPF Parkinson’s Outcomes Project has supported the finding that cognitive slowing is a side effect of anticholinergics.

**KEY POINT:** Anticholinergics are most useful in young people with tremor-predominant PD, though side effects may limit their usefulness.

**Trihexyphenidyl** (formerly available as Artane®) and **Benztropine** (Cogentin®) are the two most common anticholinergics prescribed in PD. Dosing is usually two to three times a day. The common antihistamine and sleeping agent diphenhydramine (Benadryl®) also has anti-tremor properties.

**Ethopropazine**, an anticholinergic and an antihistamine, may have fewer side effects but is not available in most U.S. pharmacies.
Chapter 3
Medications for Non-Motor Symptoms

The following non-motor symptoms and their treatments are discussed in this chapter:

- Disorders of mind and mood
  - Depression
  - Anxiety
  - Impaired thinking and dementia
  - Hallucinations and psychosis
- Sleep disorders
- Orthostasis (low blood pressure upon standing)
- Gastrointestinal symptoms: nausea, constipation, early satiety
- Drooling
- Urinary symptoms
- Sexual dysfunction
- Seborrheic dermatitis and excessive sweating
- Pain

There is ever-growing recognition of the importance of “non-motor” symptoms of PD, which were identified as early as 1817 by James Parkinson in his essay. Although he didn’t differentiate motor from non-motor symptoms, he observed that his patients experienced symptoms of fatigue, confusion, sleep disturbances, constipation, drooling and disturbances of speech and swallowing. Speech, swallowing and drooling are included among non-motor symptoms although the root cause is in part motor: decreased coordination of the muscles of the mouth and throat.

**KEY POINT:** Non-motor symptoms may cause more disability for the person with PD than the classic motor features. Make sure your healthcare provider is aware of any non-motor symptoms you are experiencing!

Non-motor symptoms are very common in PD. In one recent study, 90% of people with PD reported experiencing at least one of the non-motor symptoms listed in Table 1. Unfortunately, it has also been shown that physicians and healthcare team members do not recognize these symptoms in their patients up to 50% of the time. Just as physicians assess complaints of slowness, stiffness or tremor, they should also address issues related to sleep, memory, mood, etc. People with PD are encouraged to be proactive in discussing these issues with their doctor. Don’t wait to be asked!
Disorders of Mind and Mood

The Parkinson’s Outcomes Project (POP) was initiated in 2009 as a large, multicenter study partnering with many of the NPF Centers of Excellence. This research collaborative is helping to define the symptoms and treatments that have the greatest impact on PD patients and their quality of life. One of the first findings of the POP is that, collectively, mood and anxiety exact the greatest toll on health status, causing even more burden than the well-recognized motor symptoms of slowness, stiffness and tremor.

An NPF book specifically designed to address these issues, entitled *Mind, Mood, and Memory*, is a comprehensive resource available online or in print from the National Parkinson Foundation. To request a free print copy, call the NPF Helpline at 1-800-4PD-INFO (1-800-473-4636); online, go to www.parkinson.org/books. What follows is a brief summary of some important features of mind and mood disorders in PD with emphasis on the medications used for treatment.

**Depression**

Depression is a common but under-recognized symptom, affecting up to 50% of people with PD at some point during the course of the disease, often in its earliest stages. The definitive cause is not completely understood but it is likely related to an imbalance of chemicals in the brain (including dopamine, serotonin and norepinephrine). Some people who report depression related to their disability improve with adequate treatment of the most bothersome motor symptoms. However, many others require more aggressive management with psychotherapy and antidepressants.

**KEY POINT:** Depression is very common in PD, affecting up to 50% of people with PD at some point during the course of their illness. Recognition and treatment are important.

Along with “feeling blue,” symptoms of depression may include:

- Insomnia or excessive sleeping
- Loss of interest or pleasure in social or recreational activities
- Sexual dysfunction
- Feelings of guilt and self-pity
- Loss or reduction of energy levels
- Diminished attention and concentration
- Loss or gain of appetite and weight
- Thoughts of death or suicide

**Antidepressants**

Numerous medications are now available to treat depression in PD. Several trials have been published comparing one or more antidepressants to placebo. As detailed below, several different classes of medication may be helpful.
Most persons with PD who are experiencing depression are treated with one of several common categories of antidepressants including the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and other similar neurotransmitter reuptake inhibitors. A recent large clinical trial published in 2012 confirmed the benefits of SSRIs and SNRIs for many PD patients. Occasionally, older tricyclic antidepressants (TCAs) are used, and another trial in 2009 noted the benefits of this class of medication for depression in PD. But TCAs tend to cause more side effects than the SSRIs, including confusion, forgetfulness, hallucinations, lightheadedness, blurry vision, urinary retention and dry mouth. SSRIs are generally better tolerated by people with PD, though loss of libido is a relatively common adverse effect, and recent research suggests that QTc prolongation (a potentially serious irregular heartbeat) can occur with certain SSRIs. The antidepressants buproprion and mirtazapine are notable for their lack of sexual side effects. There is preliminary evidence from a clinical trial published in 2010 that dopamine agonists have antidepressant properties in PD patients, and a controlled study of cognitive-behavioral therapy in 2011 for depression in PD was also positive.

Recognizing a medication’s side effects can be used to the advantage of the person with PD. For example, more sedating medications may be appropriate for nighttime dosing in the PD person with insomnia. Or a TCA that causes dry mouth may help to reduce the severity of drooling. Table 3 reviews the antidepressants commonly used in treating people with PD.

While many individuals improve with antidepressants, the person with PD and his or her physician, psychologist, social worker and other healthcare team members should also recognize the value of psychotherapy in improving non-motor symptoms of PD. Psychotherapy can be offered in an individual or a group setting. Therapeutic exercise such as physical workouts, yoga, tai chi, massage and meditation also may help to improve mood in PD. Electroconvulsive therapy can be a consideration of last resort for people with severe depression who do not respond to drugs. It is effective and safe when managed by experts, and may also temporarily improve motor symptoms.

**KEY POINT:** The combination of psychotherapy, antidepressants and therapeutic physical and mental exercise offers the best approach to the treatment of depression in PD.
Anxiety

Often seen in combination with depression, anxiety can also appear early in the course of PD. People with PD may describe feelings of unease, jitteriness, worry and panic. Anxiety may also cause physical symptoms such as difficulty breathing or swallowing, heart fluttering, shaking and “cold sweats.”

Feelings of anxiety can be related to motor features. For example, the appearance of tremor or freezing during an “off” period or during social situations may cause anxiety or embarrassment. This anxiety can worsen the intensity of the symptoms, creating a vicious cycle and possibly leading to a panic attack.

Along with specific feelings of anxiety as described above, persons with PD may also experience the following:

- Generalized anxiety involves features of excessive worry throughout most of the day without dramatic fluctuation.
- Obsessive-compulsive disorder refers to repetitive thoughts/ideas that cause anxiety (obsessions) and behaviors that relieve those feelings (compulsions).
- Social avoidance, which can be especially troubling to someone whose personality is normally outgoing, involves avoiding social situations and opportunities to interact with friends and others as a result of anxiety or embarrassment.

Both generalized anxiety and obsessive-compulsive disorder can become worse as a result of dopaminergic agents, particularly the dopamine agonists.

**KEY POINT:** Anxiety in PD may manifest as panic attacks, generalized anxiety, obsessive-compulsive disorder or social avoidance.

There are many options for treating anxiety in PD, including medications, traditional psychotherapy and cognitive behavior therapy (CBT). It is important for persons with PD to inquire about the services of a psychologist, counselor, social worker and/or other appropriate members of the healthcare treatment team.

**Levodopa** optimization may improve anxiety in PD, and decreasing the intervals between levodopa doses may relieve the sense of anxiety that occurs as part of the “off” phase. Of course, adjusting your medication schedule should always be discussed with your physician.

**SSRIs and related medications** are commonly used for depression, but some of the SSRIs (listed in Table 3) may also improve anxiety. It may take several weeks of taking an SSRI for the person with PD to realize its full benefit. Buspirone (Buspar®) is also particularly effective in treating generalized anxiety.
Benzodiazepines are a popular and effective class of anti-anxiety drugs that can be potent in reducing symptoms of panic and worry. At times they can even help to control tremor in anxious patients by reversing the negative effects of anxiety that can cause tremor to worsen. Each of the approved benzodiazepines has different practical advantages, including duration of action, so the appropriate medication should be chosen based on frequency and severity of symptoms. For example, longer-acting benefit may be achieved with clonazepam (Klonopin®) or lorazepam (Ativan®) than with alprazolam (Xanax®).

Common side effects of benzodiazepines include drowsiness, confusion, lethargy and imbalance when walking. Persons with PD may develop a tolerance to the benzodiazepines over time, and discontinuation must be done gradually to avoid withdrawal symptoms.

A host of effective, non-pharmacologic techniques are readily available for treating anxiety including psychotherapy, behavior modification, biofeedback, meditation, massage, yoga, exercise, acupuncture and more.

### Table 3. Summary of Medications for Depression and Anxiety in PD

<table>
<thead>
<tr>
<th>Medication (product name in parenthesis)</th>
<th>Dosages in Milligrams (mg); tablets unless otherwise noted</th>
<th>Typical Treatment Regimens*</th>
<th>Potential Side Effects</th>
<th>Indications for Usage (italics = approved by FDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective Serotonin Reuptake Inhibitors (SSRIs)</td>
<td></td>
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<td></td>
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<tr>
<td>Citalopram (Celexa®)</td>
<td>10, 20, 40 mg tablets; 10 mg/2 ml solution</td>
<td>10–40 mg daily</td>
<td>Headache, nausea, insomnia, vivid dreams, sedation, jitteriness, diminished sexual libido, weight gain</td>
<td>Depression, anxiety/panic, obsessive – compulsive disorder (OCD)</td>
</tr>
<tr>
<td>Escitalopram (Lexapro®)</td>
<td>5, 10, 20 mg tablets; 5 mg/5 ml solution</td>
<td>5–20 mg daily</td>
<td>Same as above but weight neutral</td>
<td>Depression, anxiety/panic, OCD</td>
</tr>
<tr>
<td>Fluoxetine (Prozac®)</td>
<td>10, 20, 40, 90</td>
<td>10–40 mg daily</td>
<td>Same as above</td>
<td>Depression, anxiety/panic, OCD</td>
</tr>
<tr>
<td>Fluvoxamine (generic, Luvox CR®)</td>
<td>25, 50, 100 CR 100, 150</td>
<td>25–100 mg daily/nightly (may be different for extended-release)</td>
<td>Headache, nausea, insomnia, vivid dreams, sedation, jitteriness, diminished sexual libido, weight gain</td>
<td>Depression, anxiety/panic, OCD</td>
</tr>
<tr>
<td>Paroxetine (Paxil®, Paxil CR®, Pexeva®)</td>
<td>10, 12.5, 20, 25, 30, 37.5, 40 mg tablets; 10 mg/5 ml suspension CR 12.5, 25, 37.5</td>
<td>10–40 mg daily (may be different for extended-release)</td>
<td>Same as above</td>
<td>Depression, anxiety/panic, OCD</td>
</tr>
</tbody>
</table>
### Table 3, continued. Summary of Medications for Depression and Anxiety in PD

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosages in Milligrams (mg); tablets unless otherwise noted</th>
<th>Typical Treatment Regimens*</th>
<th>Potential Side Effects</th>
<th>Indications for Usage (italics = approved by FDA)</th>
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<tr>
<td><strong>Selective Serotonin Reuptake Inhibitors (SSRIs), continued</strong></td>
<td></td>
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<tr>
<td>Sertraline (Zoloft®)</td>
<td>25, 50, 100 mg tablets; 20 mg/ml concentrate</td>
<td>25–100 mg daily</td>
<td>Headache, nausea, insomnia, vivid dreams, sedation, jitteriness, diminished sexual libido, weight gain</td>
<td>Depression, anxiety/panic, OCD</td>
</tr>
<tr>
<td>Vilazadone (Viibryd®)</td>
<td>10, 20, 40</td>
<td>10–40 daily</td>
<td>Diarrhea, nausea, dizziness, dry mouth, insomnia, vomiting, vivid dreams</td>
<td>Depression, anxiety/panic, OCD</td>
</tr>
<tr>
<td><strong>Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desvenlafaxine (Pristiq®)</td>
<td>50, 100</td>
<td>50 mg daily</td>
<td>Nausea, headache, insomnia, vivid dreams, sedation, jittery, dry mouth, constipation, diminished libido</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Duloxetine (Cymbalta®)</td>
<td>20, 30, 60</td>
<td>10–30 mg twice a day</td>
<td>Same as above</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Milnacipran (Savella®)</td>
<td>12.5, 25, 50, 100</td>
<td>50 mg twice a day</td>
<td>Same as above</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Nefazodone (Serzone®)</td>
<td>50, 100, 150, 200, 250</td>
<td>25–100 mg twice a day</td>
<td>Same as above, plus requires monitoring for liver function</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Venlafaxine (Effexor®, Effexor XR®)</td>
<td>25, 37.5, 50, 75, 100, 150, 225 XR 37.5, 75, 150</td>
<td>25–75 mg twice a day (may be different for extended-release)</td>
<td>Nausea, headache, insomnia, vivid dreams, sedation, jittery, dry mouth, constipation, diminished libido</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td><strong>Tricyclic and Related Compounds</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline (Elavil®)</td>
<td>10, 25, 50, 75, 100, 150</td>
<td>10–50 mg nightly</td>
<td>Confusion, forgetfulness, hallucinations, light-headedness, blurry vision, urinary retention, dry mouth</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Imipramine (Tofranil®, Tofranil PM®)</td>
<td>10, 25, 50 PM 75, 100, 125, 150</td>
<td>10–50 mg nightly; PM 100 mg max in elderly</td>
<td>Same as above</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Nortriptyline (Pamelor®)</td>
<td>10, 25, 50, 75 mg capsules; 10 mg/5 ml solution</td>
<td>10–50 mg nightly</td>
<td>Same as above</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Trazodone (Desyrel®, Oleptro®) also a serotonin modulator</td>
<td>50, 150, 300</td>
<td>75–300 mg daily (divided)</td>
<td>Same as above</td>
<td>Depression, anxiety</td>
</tr>
</tbody>
</table>
### Other Antidepressants

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Dose Range</th>
<th>Side Effects</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>75, 100 SR 100, 150, 200 XL 150, 300</td>
<td>75–150 mg 1–2 times daily (may be different for extended-release)</td>
<td>Dry mouth, insomnia, headache, nausea, constipation, weight neutral, lack of sexual side effects, lowers seizure threshold</td>
<td>Depression</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>7.5, 15, 30, 45 Regular or orally disintegrating tablets</td>
<td>15–30 mg daily</td>
<td>Drowsiness, increased appetite, headache, vivid dreams, lack of sexual side effects</td>
<td>Same as above. Also available in orally disintegrating form.</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.25, 0.5, 1, 2, 3 mg tablets; 1 mg/ml solution XR 0.5, 1, 2, 3</td>
<td>0.25-1 mg 3–4 times daily (may be different for extended-release)</td>
<td>Drowsiness, light-headedness, depression, headache, confusion, dizziness, fatigue, constipation, blurred vision</td>
<td>Anxiety/panic. Also available in orally disintegrating form.</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.125, 0.25, 0.5, 1, 2</td>
<td>0.25–2 mg up to 3 times daily</td>
<td>Same as above</td>
<td>Anxiety/panic. Also available in orally disintegrating form.</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.5, 1, 2 mg tablets; 2 mg/ml concentrate</td>
<td>0.5–2 mg up to 3 times daily</td>
<td>Same as above</td>
<td>Anxiety/panic</td>
</tr>
</tbody>
</table>

**Other Anti-anxiety Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Dose Range</th>
<th>Side Effects</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buspirone</td>
<td>5, 7.5, 10, 15, 30</td>
<td>5–15 mg twice a day</td>
<td>Dizziness, drowsiness, dry mouth, nausea, headache</td>
<td>Generalized anxiety disorder</td>
</tr>
<tr>
<td>Propranolol</td>
<td>10, 20, 40, 60, 80 mg tablets; 20 mg/5 ml &amp; 40 mg/5 ml solution LA 60, 80, 120, 160 XL 80, 120</td>
<td>10–40 mg up to 3 times daily (may be different for extended-release)</td>
<td>Decreased heart rate, depression, exacerbation of pre-existing asthma</td>
<td>Anxiety/panic – can suppress outward signs (like racing heartbeat and shakiness)</td>
</tr>
</tbody>
</table>

* “Typical treatment regimens” should act only as a guide. The prescribed dosage by your doctor and your effective dose may vary from dosages listed.

## Impaired Thinking and Dementia

Over time, more than 50% of persons with PD may experience some degree of impaired thinking. These alterations in thinking ability fall on a broad spectrum from mild cognitive impairment to severe dementia. Mild cognitive impairment occurring early in the course of illness may be a nuisance to the person with PD and his or her loved ones, especially if he or she is still working, but it usually will not affect routine activities of...
daily living. Progression to dementia is the greatest worry for many people with PD, as this usually implies a significant and perhaps permanent compromise in lifestyle and quality of life. While the majority of people with PD will develop some degree of cognitive impairment, many will not progress to severe disability.

People with PD may experience difficulty with:

- Speed of mental processing
- Attention/concentration — losing their train of thought in conversation
- Problem solving, decision-making, multi-tasking and planning
- Short-term memory
- Language production

In most cases, the impaired thinking associated with PD is not Alzheimer’s disease, so the severity of the cognitive or thinking deficits and the effect of those deficits on day-to-day functioning are not as disabling.

Dementia in Parkinson’s disease (PDD) occurs when the specific deficits in attention/concentration, problem-solving and memory are severe enough to interfere with the person’s ability to function appropriately at work and/or in social situations. PDD is differentiated from other forms of dementia by additional distinguishing characteristics such as fluctuating awareness and attention span, visual hallucinations and altered spatial orientation. Fluctuating awareness refers to periods of mental clarity alternating with periods of confusion, distractibility, sleepiness and psychosis (usually visual hallucinations).

A closely related parkinsonian disorder — dementia with Lewy bodies (DLB) — is similar but different from PDD in important ways. The main difference in making the diagnosis is the timing of significant impairments in thinking in relation to the motor symptoms. If cognitive impairment begins before or within one year of the motor symptoms of PD, the diagnosis is DLB; if cognitive impairment follows the appearance of motor parkinsonian symptoms by more than one year, the diagnosis can be classified as PDD.

Evaluation for change in cognitive function in persons with PD should be part of a complete medical workup for other causes of impaired thinking, all of which may be treatable. If the change in thinking ability is sudden, severe, and accompanied by significant alteration in consciousness, an underlying cause separate from PD should be sought, such as infection (usually of lungs or bladder), vitamin depletion, dehydration, thyroid disease, intoxication by drugs, constipation, sleep deprivation or head injury (from tendency to fall).

A similar evaluation should be done if the change is more gradual and chronic, but the likelihood of finding a reversible cause of dementia is less than in the acute setting. Many of the anti-PD medications and other drugs (for example strong pain killers like narcotics) can cause confusion mimicking dementia, particularly as the person with PD ages. A careful evaluation of current medications is always important, paying particular attention to the anticholinergics, amantadine and dopamine agonists.
Medications that may improve thinking ability in people with PD are available. Originally approved by the FDA for the treatment of memory disorder in Alzheimer’s disease, one of these — rivastigmine or Exelon® — is also approved for treating cognitive impairment in PD.

**Acetylcholinesterase Inhibitors**

**Donepezil** (Aricept®), **rivastigmine** (Exelon®) and **galantamine** (Razadyne®) are the medications most frequently prescribed to address symptoms of cognitive impairment in PD. Originally approved by the FDA for the treatment of Alzheimer’s disease, donepezil and rivastigmine have recently been shown to be well-tolerated and effective for some people with PD, though benefits are sporadic and modest. Rivastigmine was approved by the FDA in 2006 for treatment of dementia in PD. This group of drugs is usually well tolerated by persons with PD, although tremor can become more pronounced in some people.

**Glutamate Antagonists**

**Memantine** (Namenda®) is approved for moderate-to-severe Alzheimer’s disease in the U.S. It may help cognitive symptoms in PD by blocking the brain’s receptors activated by the neurotransmitter glutamate. It is commonly used in combination with donepezil, although the results of treatment are often disappointing. Glutamate is a natural brain chemical essential for normal function but it can worsen some of the PD symptoms.

**Other medications** such as methylphenidate (Ritalin®), a stimulant, and medications for excessive daytime sleepiness, such as modafinil (Provigil®), are occasionally used for decreasing fatigue and improving alertness in PD. They are not specifically indicated for cognitive impairment.

**Hallucinations and Psychosis**

People with PD may experience visual hallucinations, illusions, delusions, agitation and other symptoms of psychosis. These are more commonly seen in patients who develop dementia in the late stages of disease.

- A **hallucination** occurs when a person believes he sees or hears something that isn’t actually there.
- An **illusion** is a misperception or misleading view of reality — that is, a misperception of something that is actually there.
- A **delusion** is a form of self-deception in which the person develops a false belief despite strong evidence that the belief is false.

Visual hallucinations often involve scenes of people, animals or insects, while people with paranoid delusions may suspect that someone is plotting to do something harmful or that their spouse is unfaithful. Hallucinations are more common at the end of the day after sundown, when darkness can be disorienting, hence the term “sundowning.” Fatigue after the day’s activities can also cause collapse of a stable but fragile mental status.

Additionally, if the person with PD moves from a familiar to an unfamiliar environment, such as a hospital, vacation site or new home, the stress of geographical disorientation
can sometimes lead to the emergence or reemergence of hallucinations, delusions and confusion. Fortunately, many people with PD retain insight and quickly realize that the hallucination is not real and that their mind is “playing tricks” on them. Others react by becoming extremely troubled and frightened. The emergence of psychosis in the person with PD, in conjunction with fluctuating attention and personality, may signify the transition to Parkinson’s disease with dementia (PDD).

Many people with PD also experience vivid dreams at night, which some experts believe may be “precursors” to hallucinations. Others never progress to having waking visions or delusional thoughts. Vivid dreams can be due to other sleep disorders, such as REM behavioral disorder (discussed later in this chapter).

Your healthcare team will want to assess and treat hallucinations and psychosis using the following guidelines:

1) **Fully characterize the behavior.** How frequent and severe are your hallucinations? Do they occur day and night? Do you retain insight during hallucinations? Does the problem pose a physical, emotional or financial threat to you or your family? Has your memory, personality and/or concentration been changing (implying worsening dementia in addition to the psychosis)?

2) **Identify any other medical problems you are experiencing.** Other medical problems could possibly trigger a decline in thinking ability. For example, are there any signs of infection such as fever, cough, painful urination or diarrhea? Are there symptoms of underlying depression? Are there other medical conditions (e.g., disorders of the heart, liver or kidneys; dehydration)?

3) **Review the list of all PD medications you are taking.** Your healthcare team can evaluate whether the mental changes you are experiencing are related to the use of exacerbating PD medications. Virtually all of the anti-PD medications have the potential to cause mental clouding and hallucinations, especially at high doses or in combination with other risk factors. Amantadine and anticholinergics should be tapered and stopped first (one at a time if you are taking both), as the risk of psychosis usually outweighs the modest benefit that these medications provide. Levodopa and the dopamine agonists are the other classic offenders, since high levels of dopamine in certain areas of the brain are associated with psychosis.

In practice, the risk of cognitive and psychiatric complications is higher with the dopamine agonists than with levodopa. Thus, when the symptoms of psychosis demand immediate action to rescue someone who is on a combination of levodopa and dopamine agonists, the first step is usually to taper and eventually stop the agonist. Levodopa becomes the only dopaminergic medication the individual is taking. Not only is levodopa the best drug for treating PD, it also has the best “therapeutic margin,” or highest ratio of benefit to side effects.

4) **Discuss medications you may be taking for other illnesses.** Your physician or healthcare team will want to assess whether any non-PD medications or other substances are impacting your mental changes. Have any new medications been started or doses
changed (e.g., sleep aids, narcotics [especially codeine derivatives like percocet],
antibiotics, steroids, anti-anxiety or anti-depressant medications)? Could illicit drugs or
alcohol be involved?

Based on the findings in the four steps above, your physician and healthcare team members
will be able to suggest the best course of treatment, including any appropriate anti-psychotic
medications. Psychosis and dopamine excess can be remedied by the use of drugs, known
as neuroleptics, which block the receptors activated by dopamine. These drugs have been
used for over 50 years to treat severe mental illness, particularly schizophrenia. However,
most of the dopamine-blocking drugs can cause serious problems in the person with
PD, leading to worsening of the motor symptoms and loss of effectiveness of the other
dopaminergic medications. Therefore, it is extremely important that the right neuroleptic or
anti-psychotic drug be chosen. There are only two drugs in this class of medications that are
suitable for use in persons with PD: clozapine and quetiapine.

**Clozapine** (Clozaril®) is one of the two antipsychotic medications that can be used
effectively, especially at low doses, in persons with PD without a risk of worsening
Parkinson’s symptoms. The FDA approved clozapine for use in the treatment of
schizophrenia in 1990 with the condition that weekly blood counts be completed. This is
so that your healthcare provider can monitor the low but significant risk that clozapine
can depress your white blood count and thereby increase the risk of serious infection. This
requirement has made the use of clozapine inconvenient but safe, and experience has shown
that low dose clozapine has an important place in the management of the psychosis that can
sometimes occur in persons with PD. Clozapine is the only antipsychotic drug that has been
shown in a randomized clinical trial to be effective against psychotic behavior in PD.

**Quetiapine** (Seroquel®) is the other useful antipsychotic and has the advantage over
clozapine of not adversely affecting blood counts. It is usually the drug of first choice in
treating symptoms of psychosis in the person with PD because there are no major side effects
and it does not require blood count monitoring. While many PD physicians have had positive
individual experiences with quetiapine in treating hallucinations and other symptoms of
psychosis in PD, a few small clinical trials to date have not confirmed its overall efficacy.

This chart shows the percentage of people in the Parkinson’s Outcomes Project (the largest clinical study of Parkinson’s in
the world) using and not using antipsychotics. Out of 19,000+
visits tracked in the study (almost 8,000 patients), doctors
started a patient on antipsychotics at 1% of visits.
Table 4. Summary of Medications for Dementia and Hallucinations in PD

<table>
<thead>
<tr>
<th>Medication (product name in parenthesis)</th>
<th>Dosages in Milligrams (mg); tablets unless otherwise noted</th>
<th>Typical Treatment Regimens*</th>
<th>Potential Side Effects</th>
<th>Indications for Usage (italics = approved by FDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholinesterase Inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donepezil (Aricept®) 5, 10, 23</td>
<td>5–23 mg nightly</td>
<td>Nausea, headache, diarrhea, pain, insomnia, dizziness, muscle cramps, fatigue</td>
<td>Parkinson’s disease dementia</td>
<td></td>
</tr>
<tr>
<td>Galantamine (Razadyne®, Razadyne ER®) 4, 8, 12 mg tablets; 4 mg/ml solution ER: 8, 16, 24</td>
<td>8–12 mg, twice a day (may be different for extended-release)</td>
<td>Nausea, vomiting, diarrhea, loss of appetite, dizziness, headache, UTI, weight loss</td>
<td>Parkinson’s disease dementia</td>
<td></td>
</tr>
<tr>
<td>Rivastigmine (Exelon®, Exelon Patch®) 1.5, 3, 4.5, 6 mg capsules; 2 mg/ml solution Patch 4.6, 9.5 mg</td>
<td>1.5–6 mg, twice a day Patch 4.6–9.5 mg once/day</td>
<td>Nausea, vomiting, diarrhea, loss of appetite, abdominal pain, indigestion, dizziness, fatigue</td>
<td>Parkinson’s disease dementia</td>
<td></td>
</tr>
<tr>
<td>Other Medications to Improve Thinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memantine (Namenda®) 5, 10 mg tablets; 2 mg/ml solution</td>
<td>5–20 mg/day. If more than 5 mg/day, give twice a day</td>
<td>Dizziness, headache, confusion, constipation, high blood pressure, cough, pain</td>
<td>Parkinson’s disease dementia</td>
<td></td>
</tr>
<tr>
<td>Methylphenidate (Ritalin®, Ritalin LA®, Ritalin SR®, Concerta®, Metadate CD®, Methylin®, Daytrana® patch) 5, 10, 20 mg tablets; 10mg/5 ml solution; LA 10, 20, 30, 40; SR 20; Concerta® 18, 27, 36, 54 ER; Metadate® CD 10, 20, 30, 40, 50, 60 ER; Methylin® 2.5, 5, 10; Daytrana® 10, 15, 20, 30</td>
<td>5–15 mg two or three times a day (may be different for extended-release and patch)</td>
<td>Palpitations, high blood pressure, confusion, psychosis, insomnia (if taken too late in day)</td>
<td>Inattentiveness, excessive daytime sleepiness, fatigue</td>
<td></td>
</tr>
<tr>
<td>Modafinil (Provigil®) 100, 200</td>
<td>200 mg in the morning</td>
<td>Headache, nausea, nervousness, rhinitis, diarrhea, anxiety, insomnia, dizziness, dyspepsia</td>
<td>Inattentiveness, excessive daytime sleepiness, fatigue</td>
<td></td>
</tr>
</tbody>
</table>
## Sleep Disorders

Disturbed sleep is so common among persons with PD that it has become a major focus of therapeutic interest and research. The specific disorders include:

- Restless leg syndrome (RLS)
- Periodic limb movements of sleep (PLMS)
- Rapid eye movement (REM)-sleep behavior disorder (RBD)
- Excessive daytime sleepiness (EDS)
- Insomnia
- Co-existing obstructive sleep apnea (OSA)

Inadequate tremor control, stiffness in the late evening and poor bed mobility can account for an inability to sleep at night as can reversal of the sleep cycle because of excessive daytime sleepiness (EDS). Each of these issues is briefly reviewed below. For more information on medical causes of disrupted sleep, including obstructive sleep apnea and congestive heart failure, please check with your physician or healthcare provider.

To provide your physician and members of your healthcare team with the most accurate history, it is useful for the spouse, partner, housemate or professional caregiver to help describe the person with PD’s nighttime activities. An Epworth Sleepiness Scale (see Appendix D) can help identify the circumstances that cause daytime sleepiness and provide clues to disruption of sleep at night. This questionnaire (given in the office or completed at home) concerns a person’s tendencies to fall asleep during the day in various real life situations such as driving or watching television. A formal overnight

### For Hallucinations and Psychosis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Frequency</th>
<th>Side Effects</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine (Clozaril®, FazaClo®)</td>
<td>12.5, 25, 50, 100, 200</td>
<td>50–300 mg twice a day</td>
<td>Requires weekly blood tests for low white blood cell counts. Drowsiness, drooling, tachycardia, dizziness, constipation, low blood pressure, headache</td>
<td>Hallucinations and psychosis</td>
</tr>
<tr>
<td>Quetiapine (Seroquel®, Seroquel SR®)</td>
<td>25, 50, 100, 150, 200, 300, 400 SR 50, 150, 200, 300, 400</td>
<td>12.5–100 mg divided daily (may be different for extended-release)</td>
<td>Sleepiness, dry mouth, dizziness, orthostatic hypotension, tachycardia, low blood pressure, constipation, increased appetite</td>
<td>Hallucinations and psychosis</td>
</tr>
</tbody>
</table>

* “Typical treatment regimens” should act only as a guide. The prescribed dosage by your doctor and your effective dose may vary from dosages listed.*
evaluation in a sleep laboratory by a trained specialist (often a neurologist) can provide even more information, especially if OSA is suspected. The evaluation typically will include observations during sleep of heart rate, breathing activity, snoring, involuntary movements and quality of sleep.

**KEY POINT:** Sleep disruption related to PD may be caused by restless leg syndrome (RLS), periodic limb movements of sleep (PLMS), REM-sleep behavior disorder (RBD), excessive daytime sleepiness (EDS), insomnia or increased Parkinson’s symptoms in bed.

**Restless leg syndrome (RLS)** is a common disorder of the general population characterized by unpleasant sensations in the legs at rest (without associated movement) and an uncontrollable urge to move the legs to relieve these feelings. RLS sensations are often described by those who experience them as burning, creeping, tugging or “like insects crawling inside the legs.” Often called paresthesias (numbness and tingling) or dysesthesias (unpleasant numbness and tingling), the sensations range in severity from uncomfortable and irritating to painful. Voluntary movement of the legs, particularly walking, relieves the uncomfortable urge at least temporarily. When symptoms of RLS are unrelieved, sleep can be disrupted sufficiently to cause serious daytime fatigue from sleep deprivation. Some people with PD confuse RLS, an abnormal sensory perception, with levodopa-induced dyskinesia, an overt involuntary movement of the legs.

**Periodic limb movements of sleep (PLMS)** describes episodes of repetitive, jerky involuntary leg movements during sleep. Like many of the in-sleep disorders, the bed partner is more aware of the involuntary movements than the person with the symptom. RLS and PLMS are common in persons with PD, probably because of the involvement of dopamine in causing them. Diagnostic evaluation can be fairly simple when the symptoms are obvious, but your physician or provider may prescribe an overnight sleep study to help determine a clear diagnosis. Also, the level of iron in your blood should be tested, since iron deficiency has been associated with RLS, although iron replacement therapy usually has little effect on the symptoms of RLS.

The most common medications for RLS and PLMS are the dopamine agonists and, in the person with PD, extra nighttime doses of the agonists or levodopa may bring relief. Your healthcare provider may also want to consider benzodiazepines (clonazepam), gabapentin or low-dose opiates.

**REM-sleep behavior disorder (RBD)** describes active behaviors (e.g., kicking, fighting, yelling or thrashing) during the phase of sleep when dreaming normally occurs (without such accompanying movements). The person experiencing RBD may even walk or fall out of bed during REM sleep. The history provided by the person with PD or their care partner or housemate may be sufficient for a presumed diagnosis, but an overnight sleep study can confirm it. RBD is often present for months or years before the onset of the motor symptoms of PD.
Anticholinergics, selegiline and dopaminergic drugs can all worsen the RBD behaviors. For treatment of RBD, low-dose benzodiazepines (e.g., clonazepam) or melatonin at bedtime may help.

**Excessive daytime sleepiness** (EDS) is very common in PD. It may result from disruption of nighttime sleep, and it is most problematic for the person with PD who is experiencing progressive decline in thinking ability. People with PD may even suffer “sleep attacks” during the day, which are described as the sudden, irresistible urge to sleep or the sudden, unwarned onset of sleep not preceded by sleepiness. This phenomenon is significantly increased in persons with PD who take moderate to high doses of the dopamine agonists or levodopa.

**Insomnia** is an inability to fall asleep or, more commonly, to stay asleep. It is more complicated in PD because of many factors that may contribute, including “normal” nighttime awakening associated with aging, wearing off of antiparkinson medication effect during sleep, depression and anxiety.

Treatment of EDS and insomnia can be challenging and usually requires a multi-pronged approach. Discuss with your healthcare provider whether to reduce, rearrange or even eliminate daytime dopamine agonists.

A contributing factor to insomnia might be drug-induced loss of impulse control. In these cases, the person with PD may develop some obsessive compulsive behaviors as a side effect of the dopamine agonists. Examples of these behaviors may include obsession with shopping, sexual activity, eating and gambling, all of which can interfere with sleep. If you experience any of these behaviors, be sure to speak with your healthcare provider.

Every attempt should be made to normalize the sleep-wake cycle and to improve sleep hygiene. This means:

- Establishing regular bedtimes and rising times
- Reducing caffeine and alcohol intake
- Limiting naps
- Avoiding food and drink within several hours of bedtime

Also, you should not use the bed as a site for non-sleeping tasks, such as reading, doing work or watching television, as these activities can condition the body for wakefulness. Sleep hygiene can be further improved by the prudent use of physician-supervised sleeping medications such as quetiapine, clonazepam and others.

Some antidepressant drugs, such as trazodone (Desyrel®) or mirtazapine (Remeron®), can also promote sleep due to their sedative properties. Most over-the-counter preparations are not suggested for use unless recommended by a physician, although the antihistamine diphenhydramine (Benadryl®) may double as a sleeping pill and an antitremor drug because of its anticholinergic properties. If motor symptoms such as stiffness and tremor interrupt sleep because of the long gap between the last dose of antiparkinson medication in the evening and the first dose the following day, an extra dose of carbidopa/levodopa.
may be taken late in the evening or during the night on awakening. Some people with PD use controlled-release carbidopa/levodopa (Sinemet CR®) at bedtime for this purpose, although the amount of the drug that can be absorbed by the body is limited and its half-life is not much greater than immediate-release formulations.

If nighttime sleeping problems are controlled but excessive daytime sleepiness persists, increased coffee intake in the morning is also worth a try. There has been much interest in the interplay between caffeine and PD. Increased caffeine intake in young adults may lower the risk of developing PD. A recent study highlighted the possibility of caffeine improving some of the slowness and stiffness of PD when consumed judiciously (about 1-2 cups of coffee per day).

Stimulants such as methylphenidate (Ritalin®) and mixed amphetamine salts (Adderall®) can be tried. Indicated for narcolepsy and attention-deficit disorder, they could be used carefully in the person with PD to increase daytime wakefulness and alertness. They should be given in low doses and taken in the morning initially, preferably before 8 a.m. If additional amounts of the drug are needed, they should be taken before noon. Side effects include palpitations, high blood pressure, confusion, psychosis and insomnia (if the dose is too high or taken too late in the day).

The non-stimulant modafinil (Provigil®), approved only for treatment of narcolepsy, also is potentially useful. Its mode of action in the brain is unknown, but it has a good track record of reducing daytime sleepiness with fewer side effects because it is not a stimulant like methylphenidate and the amphetamines.

It should be noted that the use of methylphenidate, amphetamine and modafinil for the treatment of EDS in PD is not approved by the FDA (“off label” use), which means that most health insurance plans will not cover them.

**Orthostasis**

The terms orthostasis or orthostatic hypotension describe the tendency for blood pressure to decrease significantly when a patient rises from seated or lying to standing, causing dizziness, lightheadedness, headache, blurred or dimmed vision or fainting. Normally, blood pressure is maintained in a narrow range and is protected against major fluctuations that are too high or too low by protective reflexes in the body’s blood vessels that are controlled by the body’s autonomic nervous system (ANS). Since the ANS is often impaired in PD, autonomic functions such as blood pressure regulation, gastrointestinal motility, sweating, etc. can be affected. When a person with PD stands too quickly, and the normal reflexes that protect against a drop in blood pressure upon changing the body’s position against gravity are impaired, the result is lightheadedness, dizziness and fainting — symptoms that reflect a lack of blood flow to the brain. This tendency in PD can be aggravated by the antiparkinson medications, especially the dopamine agonists and carbidopa/levodopa. In addition, the drugs commonly used to treat high blood pressure can make orthostasis worse. Any person who experiences orthostatic symptoms should inform all healthcare providers involved with their care.
Persons with PD often assume, mistakenly, that any symptom in any organ system is caused by PD. Therefore, it is good to remember that having PD doesn’t protect you from getting other, unrelated medical problems. A good example of a frequent and straightforward parallel problem (or comorbidity) is back, neck and limb pain due almost always to degenerative arthritis of the spine. Pain attributable to PD certainly occurs, but it is usually an aching discomfort and feeling of heaviness of the large muscles of the legs, often during an “off” period. The same thing can be said of light-headedness or dizziness. Orthostatic hypotension is usually the primary reason for the symptom, but general medical causes, especially involving the heart or lungs, must be explored. In addition, other medications prescribed by other physicians and healthcare providers, particularly medications for high blood pressure, should be thoroughly considered. The coincidence of multiple problems in many persons with PD underscores the need for the PD specialist to communicate frequently with the primary care physician, other specialists and/or healthcare team members who treat the patient as this will lead to a comprehensive treatment approach.

**KEY POINT:** Make certain that all healthcare providers consider causes for orthostasis and that an appropriate evaluation is completed.

If a person with PD experiences orthostasis, it is appropriate for the physician or healthcare provider to consider decreasing the dosages of potentially offending drugs such as dopamine agonists and carbidopa/levodopa to a lower level that is still compatible with control of the Parkinson’s symptoms. If drugs for hypertension are being used, the doses should be adjusted. Communication between all treating physicians and members of the healthcare team is mandatory in these matters.

Drugs are not the only remedy for orthostasis. The following non-pharmacologic techniques are important:

- Change positions slowly, particularly when rising from a seated to a standing position. Pause for several seconds between each move. Walking with an assisted device (cane or walker) may also be helpful.
- Increase fluids, salt and caffeine in the diet.
- Wear support stockings and elevate legs periodically during the day.

If the foregoing measures are not effective, then ask your physician or healthcare provider if medications to raise blood pressure would be appropriate in your case.

**Fludrocortisone** (Florinef®) will increase blood pressure by increasing retention of salt and blood volume. Increased dietary salt will enhance the effect. Florinef® should be started at once a day dosing of 0.1 mg. Dosing higher than three times a day should be avoided. Leg edema (swelling) and high blood pressure when lying flat are potential adverse effects.
Midodrine (Proamatine®) increases blood pressure by stimulating the autonomic nervous system directly and is dosed three times per day. The development of high blood pressure when lying flat is greater with midodrine than fludrocortisone and should be carefully monitored.

Pyridostigmine (Mestinon®) can be used either as monotherapy or as an adjunctive drug to augment the blood pressure raising effect of fludrocortisone and midodrine. Ordinarily used to treat the neuromuscular disease myasthenia gravis, Mestinon® has been evaluated in two single dose clinical trials (one open-label and one placebo-controlled), both of which showed a small but statistically significant elevating effect on diastolic blood pressure. Only one study, an open-label survey, has examined the long-term effect of using Mestinon® for orthostatic hypotension. It, too, showed that patients were satisfied with its benefit.

Droxidopa (NortheraTM) was approved by the FDA in 2014 for the treatment of symptomatic neurogenic orthostatic hypotension in PD. The drug has been promising in multiple system atrophy (MSA) and in cases of pure autonomic failure. Several recent studies report its usefulness in PD, but we do not have enough data to know if it will be effective. The studies leading to the FDA approval were only conducted for two weeks, and the approval was offered as part of the FDA’s new accelerated approval process. The one side effect that is potentially worrisome is skyrocketing blood pressure when laying down (supine hypertension). NortheraTM is available only through specialty pharmacies; your doctor has to complete a special form to prescribe it.

Gastrointestinal Symptoms

Nausea, constipation and early satiety (feeling full after eating less than a full meal) are common problems throughout the course of PD and are attributable to the same pathology that is responsible for neurodegeneration in the brain. In this case, the disease process affects the autonomic nervous system (ANS), which controls the normal contractions of the gastrointestinal tract. In PD the contractions of the stomach are slowed, and everything that is swallowed, including medications, stays in the stomach longer than it should because of delayed emptying. Slowed gastric emptying translates into gas and bloating, nausea, loss of appetite and pain. In addition, constipation occurs early in the evolution of PD, and it often but not always increases in severity and frequency as PD progresses. All of these symptoms vary in their responses to treatment with antiparkinson drugs, but usually improve with the use of drugs that specifically speed gastrointestinal movement.

Nausea

The management of gastrointestinal disorders in PD can be complicated. Dopaminergic medications can worsen nausea, but the addition of extra carbidopa (Lodosyn®) to the prefixed mixture of carbidopa/levodopa in Sinemet® usually helps to prevent or lessen this side effect. However, Lodosyn® does not work if the nausea is caused by dopamine agonists.

Other medications, specifically metoclopramide (Reglan®), prochlorperazine (Compazine®) and promethazine (Phenergan®), are available for treating nausea, but because they work by blocking dopamine receptors in the intestinal tract and in the brain, they should be avoided because they can worsen the symptoms of PD.
**KEY POINT:** Dopamine-blocking medications for GI symptoms (Reglan®, Compazine®, and Phenergan®) should be avoided in persons with PD.

**Domperidone** (Motilium®) is a good choice for treating nausea and vomiting associated with the use of any of the dopaminergic antiparkinson drugs (levodopa and the dopamine agonists) because it does not cross the blood brain barrier and does not worsen PD symptoms. However, it is available only from sources outside the U.S. because it hasn’t been submitted to the FDA for approval by the manufacturer. Trimethobenzamide (Tigan®) is another available medication to treat nausea in PD. Simple antacids (i.e., simethicone) are less effective but worth trying because they are inexpensive and do not require a prescription. Another medication that was initially approved for chemotherapy and radiation therapy-induced nausea and vomiting, and has proven useful for nausea in PD is ondansetron (Zofran®). Since it does not block dopamine in the brain ondansetron is safe for patients with PD, and it probably helps block nausea both in the brain and in the gut. It should not be combined with apomorphine as it can cause lowering of blood pressure.

**Constipation**

This is another example of the effect of PD on the ANS and is a major nuisance for many people with PD. Fortunately, good dietary management and the prudent use of stool softeners, laxatives and other bowel modulators are usually helpful. There are several steps to good dietary management and preventive maintenance:

- Drink plenty of water and fluids.
- Consume lots of dietary fiber in the form of fruits, fruit juices, vegetables and cereals.
- Use appropriate fiber additives, such as Metamucil, the stool softeners lactulose and polyethylene glycol (Miralax®), and the stimulant laxatives, such as dulcolax.

Another option for the treatment of constipation is lubiprostone (Amitiza®) which increases the secretion of fluid in your intestines to help make it easier to pass stools (bowel movements). Lubiprostone is used to treat chronic constipation in adults.

Guidance from the neurologist, primary care doctor or healthcare provider on how to use and combine these agents is essential. A review of GI medications can be found in Table 5.

**Drooling (Sialorrhea)**

Drooling in PD can be defined as an inability to manage the flow of the saliva in and around the mouth as it is being produced by the salivary glands. It results not from overproduction of saliva but from slowing of the automatic swallowing reflex that normally clears saliva from the mouth. Drooling is common in PD, and it ranges from mild wetting of the pillow during sleep to embarrassing outpourings of saliva during unguarded moments. For example, this can happen when the head is down, the mouth is held open...
involuntarily (as happens in advanced PD) or when a person is engaged in an activity and is distracted from the need to swallow automatically. When severe, drooling is an indicator of more serious difficulty with swallowing (also known as dysphagia), which can cause the person to choke on food and liquids, or can lead to aspiration pneumonia.

Treatment of drooling is not always effective, but the list of therapies includes:

• Glycopyrrolate and other oral anticholinergic medications (trihexyphenidyl, benztropine, hycosamine). Oral anticholinergic medications, as a class, decrease the production of saliva. Usually this is perceived as a side effect (dry mouth), but in this case it is an advantage. Other anticholinergic side effects may be seen, including drowsiness, confusion, vomiting, dizziness, blurred vision, constipation, flushing, headache and urinary retention.

• Scopolamine patch. This patch offers anticholinergic medicine that slows production of saliva as it is absorbed into the entire bloodstream, and anticholinergic side effects similar to oral agents may be seen.

• 1% atropine eye drops (an anticholinergic), given as 1-2 drops under the tongue per day to dry the mouth. Systemic side effects are much less likely with this local treatment.

• Botulinum toxin A. Injection of botulinum toxin A (Botox®) into the salivary glands of the cheek and jaw decreases production of saliva without side effects, except for thickening of oral mucus secretion. Botox is not always effective, but when it works the benefit can last for several months before it wears off and re-injection is necessary. Botulinum toxin should probably be avoided when secretions are deep and thick. Also, botulinum toxin B (Myobloc®) causes dry mouth when used for dystonia but it is not approved by the FDA for drooling.

• Chewing gum. Gum activates the jaw and the automatic swallowing muscles reflex and can help clear saliva.

**KEY POINT:** Botulinum toxin A can be an effective treatment for severe drooling, although pills, the patch and mouth drops should be tried first in the interest of cost saving.
Table 5. Summary of Medications for Gastrointestinal (GI) Symptoms and Drooling in PD

<table>
<thead>
<tr>
<th>Medication (product name in parentheses)</th>
<th>Dosages in Milligrams (mg); tablets unless otherwise noted</th>
<th>Typical Treatment Regimens*</th>
<th>Potential Side Effects</th>
<th>Indications for Usage (italics = approved by FDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medications for Nausea and Vomiting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbidopa (Lodosyn®)</td>
<td>25</td>
<td>Adding 25–50 mg to each dose of carbidopa/levodopa</td>
<td>Could worsen dyskinesia</td>
<td>Reduce levodopa-induced nausea &amp; vomiting</td>
</tr>
<tr>
<td>Domperidone (Motilium®)</td>
<td><strong>10</strong></td>
<td>10 mg up to four times daily, 15–30 minutes prior to meals</td>
<td>Headache, hives, hot flashes, itching of skin; itching, redness, pain, or swelling of eye;</td>
<td>Treat nausea, vomiting, and constipation with increasing emptying of stomach</td>
</tr>
<tr>
<td>NOTE: not available in the U.S. at this time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ondansetron (Zofran®)</td>
<td><strong>4, 8</strong></td>
<td>4 mg up to three times daily as needed</td>
<td>Headache, malaise/fatigue, constipation, diarrhea</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Trimethobenzamide (Tigan®)</td>
<td></td>
<td>300 mg capsule; 200 mg suppositories</td>
<td>300 mg up to four times daily</td>
<td>Blurry vision, depression, diarrhea, confusion, dizziness, headache, drowsiness, cramps</td>
</tr>
<tr>
<td>Metoclopramide (Reglan®)</td>
<td><strong>5, 10</strong></td>
<td>Worsens PD symptoms: dystonic reaction, confusion, dizziness, headache, drowsiness</td>
<td>Treat or prevent nausea and vomiting, and constipation with increasing emptying of stomach</td>
<td></td>
</tr>
<tr>
<td>Prochlorperazine (Compazine®)</td>
<td><strong>5, 10</strong></td>
<td>Same as above</td>
<td></td>
<td>Treat nausea and vomiting</td>
</tr>
<tr>
<td>Promethazine (Phenergan®)</td>
<td><strong>12.5, 25, 50</strong></td>
<td>Same as above</td>
<td></td>
<td>Treat nausea and vomiting</td>
</tr>
<tr>
<td><strong>Medications for Constipation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lubiprostone (Amitiza®)</td>
<td><strong>8, 24 mcg</strong></td>
<td>8–24 mcg twice daily</td>
<td>Bloating, gas, upset stomach, dizziness, chest pain</td>
<td>Constipation</td>
</tr>
<tr>
<td>Polyethylene glycol 3350 (MiraLax®)</td>
<td></td>
<td>Every day if necessary, may use lower doses for maintenance</td>
<td>Bloating, gas, upset stomach, dizziness, increased sweating</td>
<td>Constipation</td>
</tr>
</tbody>
</table>
**Urinary Symptoms**

Urinary frequency, urinary urgency and loss of bladder control (urge incontinence) are common complaints in PD. The urinary bladder loses its capacity to hold normal amounts of urine because the neural impulses descending from the brain to the spinal cord tell the bladder to empty prematurely in PD. Urinary frequency and urgency can lead to urge incontinence more often in those people who are too slowed down by PD to get to a toilet quickly when the urge to empty the bladder suddenly presents itself. As with other non-motor complaints, it is important to exclude other possible causes of urinary frequency, including urinary tract infection and enlarged prostate. Co-management of urinary problems by a urologist is important.

Medications that can help re-establish bladder control:

- Anticholinergic medications can relax the overactive muscular wall of the bladder and allow the bladder to fill to greater capacity without suddenly emptying. There are several available by prescription.
- The alpha-adrenergic receptor blockers prazosin and tamsulosin (Flomax®) relax the detrusor muscle at the outlet of the bladder and make it easier for the bladder to empty. These drugs may also be indicated in men if an enlarged prostate is found to be a reason for the symptom.
The tricyclic antidepressants nortriptyline and imipramine have anticholinergic properties in addition to other, healthful pharmacologic effects. Your physician or healthcare provider can assess which is most appropriate for your situation.

**KEY POINT:** Urinary frequency, urinary urgency and urge incontinence are common complaints in PD. They typically are not responsive to dopaminergic medications but can be remedied by the use of drugs that relax the bladder and allow it to fill to a greater capacity.

### Sexual Dysfunction

Sexual dysfunction in PD is common for many reasons including dysfunction of the ANS. It affects men more often than women, though little has been published in the research literature about this topic. It remains underappreciated as patients, partners and healthcare providers may not be comfortable with a frank discussion of sex. This topic certainly deserves attention, so you and/or your partner may need to initiate a conversation with someone on your healthcare team.

Many factors contribute to good sexual health for both women and men, and certain symptoms of PD can impact sexual functioning and response. Gila Bronner, a sex therapist in Israel who works with people with Parkinson’s, offers the following observations. Depression, often present in the context of PD, can decrease sexual desire, and some antidepressants affect sexual response. The motor symptoms of PD can impact both the fine motor skills of touch and the mobility that contributes to satisfying sexual activity. The expressiveness that can be an important part of non-verbal communication is often affected in PD as both facial expression and volume of voice may decrease. If there are times of the day when your functioning is optimal, such as when you are rested and medications are minimizing symptoms, this could be a good time to express yourself with a loved one.

Other members of the healthcare team that might address sexual functioning include the PD nurse, primary care physician and/or nurse practitioner, gynecologist for women and urologist for men.

In PD, sexual dysfunction may arise as a primary symptom resulting from the loss of dopamine, the principal neurochemical mediator of reward and pleasure in the brain. As with other non-motor symptoms, the doctor or other healthcare provider should consider other causes of impotence and decreased libido. These include poor circulation to the genitals that commonly occurs in diabetes and peripheral vascular disease, enlarged prostate, depression and other medical conditions. Various medications, including antihistamines, antidepressants, benzodiazepines, and drugs for high blood pressure and excessive alcohol or tobacco use can also contribute to sexual dysfunction. Fortunately, most anti-PD drugs are not associated with impotency or loss of libido, with the exception of the anticholinergics. To the contrary, the dopamine agonists have been associated with disorders of impulse control, including uncontrolled sexual urges.
Male impotence, otherwise known as erectile dysfunction (ED), refers to difficulty with achieving and maintaining an adequate erection. Erectile dysfunction warrants a thorough evaluation so the physician or other healthcare provider can look for all possible causes, especially diabetes (which can cause autonomic neuropathy) and other disorders listed above. A complete physical examination should be conducted by the general physician and urologist.

The list of treatments available to treat ED has been upgraded in the last decade from those that must be injected into the penis to oral preparations. Oral medications for ED include sildenafil (Viagra®), vardenafil (Levitra®), tadalafil (Cialis®) and yohimbine (Yocor®). Mechanical treatments include vacuum pumps, constriction rings and penile implants, while injectable medications include papaverine HCl (Papaverine® vials for injection), phentolamine (Regitine® vials for injection) and alprostadil (Caverject®).

**KEY POINT:** Sexual health and sexual dysfunction should be as much a part of the conversation between the person with PD and his or her healthcare team as any other health matter.

**Seborrheic Dermatitis and Excessive Sweating**

Many persons with PD will develop skin-related symptoms including seborrheic dermatitis (SD) and excessive sweating. SD is a disorder of the oil-producing glands of the skin, which can become infected with a particular yeast in patients with neurologic disease. It occurs mostly around the face and scalp in people with PD. In seborrheic dermatitis the skin is oily, reddened and scaly. Treatment of mild SD can be accomplished by the frequent use (two to three times a week) of a good dandruff shampoo. More severe cases require consultation with a dermatologist.

Excessive sweating (hyperhidrosis) has been known to be a peculiar feature of PD for over a century. The cause is often unknown, but some individuals observe that they sweat profusely in the “off” state of motor fluctuations or when dyskinesia is severe enough to generate significant body heat. Many people report spontaneous and unexplained drenching sweat, often awakening them from sleep and creating a need to change bedclothes. Levodopa can also cause severe, episodic sweating. A recent study showed that sweating disorders in PD are often associated with other autonomic abnormalities such as constipation and orthostasis. Botulinum toxin A can be effective in small injections for hyperhidrosis of the palms and armpits.

**Pain**

Almost half of patients with Parkinson’s disease experience pain or unpleasant sensations as a symptom of their PD, and it can become more common with disease progression. Other painful conditions may coexist with PD, including arthritis, peripheral neuropathy, spinal stenosis, and musculoskeletal strains and sprains. These alternative causes of discomfort should always be considered before assuming that pain is due to PD.
Pain in PD can be related to (1) dystonia, (2) muscles and joints, (3) nerves or nerve roots, (4) akathisia (restlessness) and/or (5) primary, central “parkinsonian” pain. There may be a pattern between the experience of pain or discomfort and one’s PD medication schedule. For some people, being in the “off” state can increase a sensation of pain, and adjusting medication dosage and intervals will lead to improvement.

The most common cause of pain in PD is related to **dystonia**, which is a patterned posture of the neck, arms, legs or feet. Camptocormia is an example of dystonia characterized by severe bending at the waist, causing back pain or spasm. Depending on the timing of dystonic pain, several different approaches may prove helpful. Early morning dystonia often improves with movement and/or the first dose of dopaminergic medication. In some cases, the severity of morning dystonia merits a subcutaneous injection of apomorphine. If dystonia occurs as a wearing-off phenomenon, minimizing the “off” period with dopaminergic therapy is the goal of treatment. Botulinum toxin injections can also be helpful in treating focal dystonias.

**Musculoskeletal pain** may be related to rigidity and decreased movement/mobility. Adjustments of the PD medication schedule and physical therapy can help in these cases. **Radicular**, or nerve root, pain should be evaluated for a compressed root or nerve lesion. If these causes are eliminated and the radicular pain is thought to be related to Parkinson’s disease, physical and/or occupational therapy may be helpful.

**Akathitic discomfort** is an inner restlessness that makes it difficult for one to sit still and is different from dyskinesias or anxiety. In about half the reported cases, additional dopaminergic therapy is helpful. **Central pain** in PD is different than dystonia, rigidity or musculoskeletal pain. It is likely caused by the PD itself, and it may feel like stabbing, burning, scalding or insects crawling on the skin.

Non-motor painful sensations, such as abdominal bloating or chest wall tightening, may be related to PD in some patients. These symptoms should be addressed by the physician to rule out other primary causes of abdominal and chest pain.

Depression, which is common in PD, can heighten an individual’s experience of pain. This highlights the importance of identifying and treating depression in Parkinson’s disease.

Treatment of the pain in PD can be challenging. Some options include conventional anti-inflammatory, muscle relaxants, gabapentin, tricyclic antidepressants and additional dopaminergic doses. Opiates should be used only in severe cases, and referral to a pain specialist is recommended. Several non-pharmacologic techniques include regular exercise, heating pads, ice packs and massage.

**KEY POINT:** Pain in PD can be related to (1) dystonia, (2) muscles and joints, (3) nerves or nerve roots, (4) akathisia (restlessness) and/or (5) primary, central “parkinsonian” pain. It also may be related to other medical conditions such as arthritis or neuropathy.
Our understanding of Parkinson’s disease has evolved from one in which the motor symptoms were the primary focus of treatment to one where the broader effects of the disease process are more likely to be acknowledged and treated as well. Persons with PD who are seeking relief from their symptoms may decide to explore complementary therapies which can support or complement Western or traditional medicine. The delineation between medications and supplements has never been very well-defined and, as more substances derived from foods, herbs, spices, etc. are studied for their potential therapeutic and/or neuroprotective properties, the distinction becomes even less apparent. This chapter will explore some of the promising agents in that group, but it is important to realize that most of them have not been extensively studied in humans. We will also review some of the other products that seem to be commonly used by patients with PD, sometimes without the approval of their doctors, who may be uncomfortable with the lack of data as to their safety or effectiveness.

Herbs and Supplements

There is genuine interest in, and some concern about, which herbal and nutritional supplements can be used to treat various health complaints and how to obtain optimal benefit with the fewest risks. One concern is that herbal supplements in the U.S. are not regulated by the FDA, so there can be tremendous variations in potency and purity of these over-the-counter supplements. Those considering taking herbs or supplements not regulated by the FDA should take the following precautions:

• Look for standardized products and supplements labeled with the U.S. Pharmacopeia USP Dietary Supplement Verified seal. This indicates that the product in question has met established manufacturing standards.

• Know the manufacturing company. A large, well-known company interested in preserving a good reputation may be more likely to offer a good quality product.

• European herbs and supplements are subject to standards and regulations. Supplements from other areas and some U.S. companies may be contaminated with harmful substances. For example, in 1998 the California Department of Health reported that 32% of Chinese patent supplements contained undeclared chemicals such as lead, mercury and arsenic.

• The Dietary Supplement Health and Education Act of 1994 does not require manufacturers to submit information about the safety of supplements (vitamins, minerals, enzymes, herbs, amino acids). Reputable manufacturers will provide an address and sometimes a phone number or website on the product label although this is not a guarantee of content, safety or purity.

• Check the label for exact contents and listed side effects. If a product does not contain a detailed label, consider not taking it.
• Check to see if the package is sealed. If the package is not sealed, don’t purchase the product.

• Contact reliable resources such as The American Academy of Family Physicians and The National Institute of Health’s National Center for Complementary and Alternative Medicine. Such organizations provide fact sheets that list harmful interactions if certain supplements and prescription drugs are taken together.

• Consult with a licensed herbalist, naturopath, nutritionist or DOM (Doctor of Oriental Medicine). These practitioners have specialized training in herbs and supplements for promotion of health and treatment of disease.

Some authors in the resource list at the end of this chapter offer guidelines to help consumers judge the quality of herbal remedies. Some of the products discussed in this chapter are commonly recommended and considered safe for persons who have Parkinson’s disease, but others are not. The information provided should not be taken as recommendations for these substances, but should be used as discussion points when consulting with your licensed healthcare professional.

**Research and Medical Education**

In Chapter 5, the importance given to double-blind, placebo-controlled studies and their role in modern science will be briefly described. Physicians’ training leads them to respect this vigorous scientific method, which is a context in which few supplements have been studied. The fact that most physicians trained in Western medicine do not have formal training in complementary therapies also makes them cautious, and perhaps uncomfortable, with the use of herbs and supplements.

Other supplements are used despite lack of any clear evidence of effectiveness.

When treatments continue to be used without measurable benefit, this may be due to the placebo effect, a well-recognized factor when assessing any PD treatment. The placebo effect refers to the commonly observed phenomenon that people in PD drug studies tend to have improvement in their symptoms even when they are receiving the placebo or sugar pill instead of the actual study medication. This spills over into other situations in which a person with PD may expect to get better, such as consuming a special juice touted to improve PD symptoms or trying some other treatment expected to result in improvement. The reason most drug studies are conducted with a control or placebo group is so that the difference between the placebo and treatment groups will be considered effective. Most doctors are quite skeptical of treatments that have not been subjected to this kind of study.

Fortunately, a growing number of U.S. medical schools now offer courses in complementary medicine, combining the best of Western tradition with other treatment modalities. The National Institutes of Health has also been instrumental in disseminating research data to practicing healthcare professionals through the National Center for Complementary and Alternative Medicine.
If you are considering complementary therapies, we strongly urge you to investigate the credentials and experience of anyone offering advice or product recommendations regarding such therapies.

**KEY POINTS**

- Most herbs and supplements have not been rigorously studied as safe and effective treatments for Parkinson’s disease.
- The FDA does not strictly regulate herbs and supplements.
- There is no guarantee of safety, strength or purity of supplements not monitored by the FDA.
- Beware of unproven treatments on internet websites—check everything with your doctor.

**Ginger (zingiber officinalis)** in almost any form is excellent for nausea and vomiting, whether the nausea stems from something as simple as motion sickness or as a side effect of medications.

Fresh ginger root, available in the produce section of grocery stores and markets, can be prepared in liquid form. Cover a 1-inch slice in water, bring to a boil, and simmer for 30 minutes. Ginger is also available in health food stores as a liquid; a drop or two can be added to tea or other beverages.

Crystallized ginger, available as a cooking spice, is another option. A small piece can be nibbled at the first sign of queasiness, offering an easy and convenient dose form.

Zingerone, a compound found in ginger root, seemed to have a protective effect on dopamine-containing neurons in a study done in Japan using a mouse model of PD.

**St. John’s wort (hypericum perforatum)**, an herbal supplement, is a popular antidepressant, working in a pharmacologic manner similar to the prescription selective serotonin reuptake inhibitors (SSRIs). It may be effective in mild to moderate depression but two studies reported no benefit in major depression. In one study of hypericum perforatum in a mouse model of PD, there appeared to be some inhibition of the effect of the toxin (MPTP) used to cause parkinsonism.

**Caution:**

- St. John’s wort should not be used concurrently with other antidepressant medications. People taking Prozac®, Zoloft®, Paxil® or other SSRIs risk serious overdose effects by using Hypericum.
- St. John’s wort should not replace traditional prescription medicine for the treatment of a serious or major depressive episode.
- Those who take blood thinners such as aspirin, heparin or warfarin (Coumadin®) should not take St. John’s wort.
• St. John’s wort should not be taken with MAO-B Inhibitors.
• People with PD who also take asthma medications, steroids or birth control pills should consult their physicians or healthcare providers before taking St. John’s wort.

**Ginkgo biloba** research in the U.S. has been limited to stroke recovery and Alzheimer’s disease, but Dr. James A. Duke, author of *The Green Pharmacy*, suggests that it might be helpful in PD because it improves blood circulation through the brain, possibly delivering more levodopa to its target. No clinical trials have been conducted to verify this claim. It is important not to confuse ginkgo biloba with ginseng, which may be over-stimulating in some older adults.

**Caution:**
Ginkgo may raise blood pressure when taken with a thiazide diuretic such as hydrochlorothiazide. In addition, it tends to have an anti-clotting effect. Therefore, if you are taking any other anti-clotting medication such as aspirin or warfarin (Coumadin®), you should not take Ginkgo without consulting your healthcare provider.

**Milk thistle (silybum marianum)** has been used to treat disorders of the liver and gallbladder for at least 2,000 years, as many drugs and environmental toxins are processed through the liver. Research shows that the silymarin in milk thistle helps protect the liver from many industrial toxins such as carbon tetrachloride. The compound appears to be safe, although more testing is needed to determine if there are any negative long-term effects. There are not currently any published studies of milk thistle in the treatment of PD.

**Glutathione** is an important brain antioxidant that is generally decreased in PD. Intravenous administration of glutathione has been proposed as a treatment for PD and has been used by many patients over the last decade or so, despite a lack of evidence as to the safety and efficacy of this therapy. In 2009, a placebo-controlled study was finally published but it demonstrated no statistically significant improvement in PD signs and symptoms.

**Vitamin B12** is an important factor in brain and nerve health, especially memory. Dietary vitamin B12 is found in animal protein sources such as meat, eggs, fish and dairy products. As people age, they may develop difficulty absorbing B12 from the gut, even if the amount in their food sources is adequate. Oral supplements (usually 1000 mcg) may help, although persons with severe B12 absorption problems or deficiencies may require injections. Vegetarians may also develop a B12 deficiency. A chemical called homocysteine sometimes becomes elevated in persons with PD, often in conjunction with levodopa therapy. Elevation of homocysteine may be related to memory loss in some patients, although this is unproven. Increasing B12 and folic acid will often result in a decrease in homocysteine levels, though it is not yet known whether this will improve memory.
Folate (folic acid, vitamin B9) is another vitamin that is important for brain health and good memory. It is vital for the development of the nervous system and ensuring adequate amounts during pregnancy can prevent certain types of birth defects. Folic acid, along with B12 and possibly B6, can decrease levels of homocysteine, which may prevent strokes and heart attacks, and may help memory as well.

Vitamins C and E are antioxidants that fight free radicals and may protect brain cells. Free radicals are toxic molecules produced by virtually every cell in the body, usually in response to stress or injury. For example, sunlight exposure, cigarette smoking and infection can generate free radical formation in some cell types. These particles are thought to be particularly toxic to brain cells. Antioxidants “soak up” or scavenge free radicals.

The DATATOP study (see page 57) failed to demonstrate a neuroprotective effect of vitamin E in patients with early Parkinson’s disease. Some concerns have been raised about possible side effects of vitamin E supplements; this may result from the form of vitamin E commonly available, alpha-tocopherol. A “mixed” supplement, containing multiple forms of vitamin E, may turn out to be safer or more effective. More research is needed; meanwhile dietary sources include whole grains, wheat germ, avocados, nuts and vegetable oils.

Vitamin D has become an important focus in PD research in recent years as several studies have suggested that deficiencies may lead to an increased risk of Parkinson’s disease. The mechanism for this relationship is not known. However, the substantia nigra has a large number of vitamin D receptors. It is thought that occupation of these receptors by vitamin D could have a neuroprotective effect.

Vitamin D is manufactured in the skin from direct exposure to sunlight and may also be obtained from supplements. It is important for bone health, a vital concern for people with PD as osteoporosis can contribute to fractures if balance declines and falls occur.

Calcium comes from a variety of foods including milk and other dairy products. While calcium and vitamin D supplementation is recommended as a treatment for osteoporosis, it is not clear whether it is valuable for prevention of bone loss. There was one study that suggested that supplementation might help with fall prevention.

Polyphenols are compounds widely found in plants. Many have been found to have antioxidant, anti-inflammatory and other potentially beneficial effects. Polyphenols are found in many foods, green tea, coffee and curries.

Green tea polyphenols (GTPs) have antioxidant and free radical scavenging activities. There have been some studies suggesting that these compounds could have a neuroprotective effect and possibly even a treatment effect in PD. However, a study conducted in China to determine whether GTPs can slow the progression of PD failed to reach statistical significance. Green tea products do contain caffeine, which should be taken into consideration when using them.

Curcumin, a polyphenol which is a chemical component of the spice turmeric, has anti-inflammatory and antioxidant properties and is able to cross the blood-brain barrier, unlike many substances. Curcumin and related molecules may help prevent the
aggregation of alpha-synuclein, which appears to have a central role in the pathology of PD. A similar compound is being studied in animal models of PD and several other neurodegenerative diseases.

**Ginsenosides (ginseng)** are phytoestrogen compounds extracted from the root of the ginseng plant. Estrogen or estrogen derivatives may have neuroprotective effects and could account for the lower incidence of PD in women. Ginseng may be over-stimulating in some older adults.

**Resveratrol** and **oxyresveratrol** are stilbene polyphenols. Resveratrol appears to have powerful antioxidant effects, including effects in preventing MPTP-induced damage. MPTP is a chemical that has been found to selectively kill dopamine neurons and is used to produce animal models of PD. Resveratrol is found in grapes and several other plants and may be responsible for some of the health benefits of red wine. Oxyresveratrol is found in various tree fruits, including mulberries, and may have even more powerful antioxidant properties.

**Natural sources of levodopa** are abundant and include fava beans and mucuna pruriens. Studies done with the latter suggested that mucuna could be used safely in the treatment of PD, and that this treatment may have a lower incidence of causing dyskinesia compared to current pharmaceutical levodopa preparations. However, the purity and safety of currently available preparations are not routinely assessed by the FDA at present.

**Ganoderma lucidum** is a Chinese herb that has been studied in patients with PD in China. The results of this study have not yet been published. There is some evidence that ganoderma could protect degeneration of dopamine neurons. As with most of the treatments discussed in this section, further studies are needed.

**Other Neutraceuticals**

**Sulforaphane** is a potent antioxidant found in cruciferous vegetables. In studies with mouse models of PD, it appeared to have some neuroprotective activity.

**Coconut oil** has been touted as a possible treatment for PD because of some anecdotal reports of benefits in a patient with Alzheimer’s disease. There are no published studies of coconut oil in PD patients.

**Creatine** is a commonly used dietary supplement that may protect brain cells. One of the first compounds deemed “non-futile” (worth studying further), Creatine was investigated in NET-PD LS1, a multi-center, placebo-controlled clinical trial that was halted in 2013 because it did not demonstrate any protective or disease modifying benefits. However, there maybe other symptomatic benefits such as muscle mass increase.

**Coenzyme Q10** is an antioxidant involved in mitochondrial energy production. The mitochondria are tiny units (organelles) within cells that supply energy for various cell functions. Mitochondrial dysfunction is thought to be one aspect of PD pathology. While a small pilot study in PD patients had suggested a possible disease-modifying effect, a large, multi-center study using very large doses of CoQ10 failed to show any benefit. The study was stopped early.
Mitoquinone is an analogue of coenzyme Q10 and may also have beneficial effects on mitochondrial function. It may mimic the effect of CoQ10 while greatly enhancing the antioxidant properties.

Alpha-lipoic acid and acetyl-L-carnitine in combination has been shown to have beneficial effects in several studies of animal models of PD. No studies in PD patients have been published.

**Summary of Herbs and Nutritional Supplements**

It is important for persons with Parkinson’s disease to let their healthcare providers know of any herbal products, vitamins and over-the-counter medications they are using on a regular basis. In addition to important safety concerns if there are interactions between prescribed medicines and supplements, this encourages open communication toward the goal of achieving optimal control of symptoms with minimal risk of side effects.

Resources for further study are included at the end of this chapter. Persons with Parkinson’s disease and family members are encouraged to research books, journals and the internet and to seek out the assistance of a licensed holistic healthcare professional. A personalized integrative therapy program can help to optimize health!

**Exercise**

While thinking about your medications, therapies and treatment plan, it is important to consider exercise. Many movement disorder specialists now say that exercise is as important as your medications to minimize symptoms and enhance quality of life. There are research studies ongoing to examine whether exercise may actually be disease-modifying. Recent studies confirm that those with mild to moderate PD who exercise vigorously experience less pain and have improved balance and quality of life.

There are many options for exercise at any level of PD. Patients who are still quite fit and active may be able to maintain vigorous activities such as running and skiing for years. Patients with moderate disease may find yoga, Pilates, hiking (often helped by trekking poles), dancing or brisk walking quite helpful. Even patients with more advanced motor symptoms can benefit from chair exercises or appropriate gait and balance classes. It is important to find something relatively enjoyable as this will be easier to stick with. Having a knowledgeable trainer, exercise buddy or a congenial group to work out with may also help with motivation. Consultation with a physical therapist experienced with PD can also enhance the exercise experience at all stages.

Two examples of therapeutic exercise regimens include tai chi and LSVT-BIG. Tai chi is a Chinese martial art and form of exercise with very slow, deliberate movements. A recently completed study concluded that tai chi improves balance in mild to moderate PD. LSVT-BIG is a program that focuses on intensive exercising with high amplitude (exaggerated) movements. Research has shown that those with mild to moderate PD have improved motor scores after participating in a 4-week, 4 sessions per week LSVT-BIG program.
Recent studies show that exercise in PD:

- Improves posture
- Improves strength
- Improves balance
- Improves walking ability
- Prevents falls
- Can limit physical decline
- Can restore functional ability
- Reduces some symptoms

Please refer to NPF’s book *Fitness Counts*, which can be ordered by calling the NPF Helpline at 1-800-473-4636, to read more about the benefits of exercise. You can also download the book online at www.parkinson.org.

**Further Reading on Herbs and Supplements**

*The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines* (Integrative Medicine Communications, 1998) is a translation of guidelines for the use of herbal medicines developed by an expert committee appointed by the German government. It contains reviews published between 1983 and 1995, covering 254 approved and 126 unapproved herbal products. Information from 81 more recently revised monographs is included in the U.S. publication.

*PDR® for Herbal Medicines, 4th Edition* (Thomson Healthcare Inc., 2007) provides physicians and healthcare professionals with an updated reference so they can better advise patients who ask about specific herbal remedies; it also provides the latest scientific data, including Commission E indications.

*The Green Pharmacy: The Ultimate Compendium of Natural Remedies from the World’s Foremost Authority on Healing Herbs* (St. Martin’s Paperbacks, 1998) leads you through the vast world of natural remedies; it also includes findings from the Commission E monographs.

*This chapter was updated and edited by guest author, Melanie Brandabur, MD.*

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Chapter 5
Research and Future Developments: Symptomatic Treatment, Neuroprotection and Neurorestoration

The discussion in this chapter addresses:

- The development of new drugs
- Evaluating research reports
- Symptomatic treatment
- Neuroprotective treatment
- Neurorestorative treatment

Drugs for Parkinson’s disease that are currently being investigated in clinical trials will be reviewed in this chapter. Most of these compounds are not yet available for prescription use. You may wish to periodically check with your healthcare providers to see if certain agents are close to release by the FDA or to inquire about participating in a clinical trial.

There are several places where up-to-date information is available for those who would like to know more about participating in research studies:

- Your PD healthcare provider may have current research listings.
- www.clinicaltrials.gov, a website sponsored by the National Institutes of Health (NIH), offers information on clinical trials.
- Fox Trial Finder (www.foxtrialfinder.michaeljfox.org) will generate a listing of possible trial matches from the Fox Trial Finder database of recruiting Parkinson’s disease trials. To find potential trial matches, you create a profile with information such as location, gender, date of birth and brief medical history.

Development of New Drugs

Here is a brief tutorial on the multi-year process by which pharmaceutical research brings new drugs to your local pharmacy. Most drugs are studied in animals before they are tested in humans. Each drug must then progress through the following series of research studies in humans before it can be approved for use by the FDA.

**Phase I** studies are typically conducted with healthy volunteers. The drug is tested in a small group of 20-80 people while researchers observe side effects, judge the safety of the drug and determine safe dosage ranges.

**Phase II** studies are conducted in a larger group of people who have the symptoms or illness that the drug is designed to treat, such as Parkinson’s disease. The goal of Phase II research is to evaluate the drug’s effectiveness as well as to gather more information about safety and tolerability.
Phase III studies are conducted with a much larger group of at least 1,000 people with a particular disease. In addition to testing the drug’s effectiveness and cataloging possible adverse effects, Phase III testing seeks to compare the drug to other similar approved drugs or to placebo (also known as a sugar pill or dummy pill).

The two most important characteristics of a Phase III trial are:

1) **Randomization** of subjects to receive the experimental drug or placebo, which means that study participants are assigned to a treatment group using a method based on chance; it is meant to minimize the differences between groups so that study results will be unbiased and reliable. If more than one dose of a drug is being evaluated, more subjects are needed to give the study enough statistical power to reach a valid conclusion about the drug’s effect on the disease being observed.

2) **Double-blind**, meaning that neither patient nor investigator knows which drug a patient is taking. This is another way to prevent observer bias in evaluating the effect of the drug.

Once a drug has successfully completed Phase I, II and III testing, it may be submitted to the FDA for approval. Once approved, the medication can be prescribed by physicians and other licensed healthcare providers.

**Phase IV** studies test the new, approved drug for additional benefits that may not have been studied in earlier phases. Phase IV studies also gather information regarding long term use and safety of the drug.

The entire process of bringing a new medication to the pharmacy can take up to ten years from the time that it is tested in a laboratory to the time that the doctor prescribes the drug for a person with disease.

**Evaluating Research Reports**

New drugs and other PD treatments often garner attention from the popular media, especially televised advertisements. While headlines may make it sound like new drugs are available, a closer look often reveals that the new drug is only in the early stages of research and years away from becoming an available treatment. Taking some time to evaluate the research behind the headlines can help determine the best way to use the new information.

Following are some questions to ask when evaluating clinical studies of new medications and treatments for PD:

- **What is the source of the information?** Has the information been published or presented at a reputable scientific meeting? Or is the information derived from unscientific opinion? Check with a member of your healthcare team to determine if the source is reliable.

- **How many people participated in the study?** The higher the number of participants, the more likely the results will achieve statistical significance.
• How was the study designed? Were the subjects randomized to equal treatment groups? Was the study double-blind? Was a placebo group incorporated into the study’s design? The gold standard for the most valid clinical trial is one that includes all of these elements.

New Drugs on the Horizon

To fully appreciate where we are going with Parkinson’s disease treatment, it is important to realize where we have been. Since the advent of the levodopa era in the 1950s, pharmaceutical research has yielded many symptomatic treatments. But many other medications have been tried with less success, particularly those with potential neuroprotective properties (to slow disease progression). Levodopa, dopamine agonists, MAO-B inhibitors, antioxidants and others have all been studied for neuroprotection. There remains limited evidence that any of the currently available group of medications can slow disease progression (as mentioned in Chapter 2), but science is hopeful.

Symptomatic Treatment

Pharmaceutical research continues to seek options to add to the medicine cabinet for treating the motor symptoms in PD. The key to limiting motor fluctuations and dyskinesia appears to be “continuous dopaminergic stimulation.” New delivery systems and new drugs in existing classes of medications are in development. Carbidopa/levodopa gel infusion (Duodopa®) and extended release (IPX066®), alternative dopamine agonists (Pardoprunox®, Aplindore®), novel COMT inhibitors (Nebicapone®, Opicapone®), new glutamate antagonists (perampanel (Fycompa®), mavoglurant (AFQ056), and dipraglurant) and a new MAO-B inhibitor (Safinamide®) are currently at various stages of testing for PD. Other novel therapeutics are discussed below.

Adenosine A(2A) receptor antagonists block unwanted activity of receptors in the basal ganglia of the brain and have been proposed to improve motor symptoms in PD. These medications have been evaluated in Phase II and III studies with mixed results. The study of preladenant by Merck was recently stopped for lack of efficacy. Two additional compounds are still being investigated, and it is possible that istradefylline and/or tozadenant may prove effective for monotherapy or combination therapy in PD.

Zonisamide is an anti-seizure drug that was evaluated in a Japanese study as an additional medication for those people with PD with insufficient response to levodopa. Additional study was initiated in January 2013 to investigate its ability to treat early PD.

Alpha-adrenergic receptor antagonists help balance the activity of GABA in the basal ganglia in hopes of reducing motor fluctuations and dyskinesia. Fipamezole has shown particular benefit in a U.S. population of PD patients, though it must be noted that other larger populations have not shown the same efficacy. The direction of study for this class of drug is not clear at this time.

Serotonergic agonists act to enhance transmission of serotonin, one of many neurotransmitters that may be affected in progressive PD. Sarizotan and piclozotan have been studied in Phase II trials, and the potential for serotonergic agonists to offer neuroprotection has been proposed.
Neuroprotective Treatment

The NIH Exploratory Trials in Parkinson’s Disease (NET-PD) was created to efficiently screen and study candidate drugs for neuroprotection. A total of 59 potential agents were reviewed by a team of 42 international experts. These include caffeine, coenzyme Q10, creatine, two dopamine agonists, estrogen, GM-1 ganglioside, GPI-1485, two MAO-B inhibitors, minocycline and nicotine. Many of these were evaluated by a series of “futility studies” to see if it was worthwhile to continue with more advanced studies. Several of these medications – old and new – deserve special mention.

DATATOP was the first randomized, double-blind, placebo-controlled clinical trial to explore the neuroprotective potential of an antiparkinson drug. The results suggested, but did not prove, that the MAO-B inhibitor selegiline postponed the time when the subjects with new onset PD in the treatment group needed levodopa compared with the placebo group. Unfortunately, later analysis of the DATATOP reached a different conclusion, that selegiline’s benefit was more likely due to a subtle symptomatic effect rather than a neuroprotective effect.

Rasagiline (Azilect®), another MAO-B inhibitor, has been the subject of additional study for its disease-modifying effects. The TEMPO studies and the ADAGIO study compared patients who started the drug at the beginning of the trials with others who delayed their initiation for six months (TEMPO) or nine months (ADAGIO). At the 18-month conclusion of ADAGIO, the patients taking the 1mg dose of rasagiline at the beginning of the trial maintained greater benefits in motor performance compared to those who delayed the start of medication. The TEMPO study has also been extended beyond 6 years and the early group still showed motor improvement over the delayed start group. But overall results with rasagiline are inconclusive. In both studies, the benefits were quite small, and similar improvements were not seen in the higher dosed 2 mg group of the ADAGIO trial. To date, rasagiline is still used predominantly for its symptomatic benefits, and further neuroprotective effects remain unclear.

While dopamine agonists are available for symptomatic relief of tremor, slowness and stiffness, some research trials using advanced brain imaging suggest they may protect against loss of brain cells in PD. This did not confirm neuroprotection and an additional trial utilizing a “delayed start” design was completed. This also did not find any additional compelling evidence for disease modification by the dopamine agonists.

As mentioned earlier, both creatine and coenzyme Q10 were studied in large, multi-center trials but failed to show any benefit.

Other Medications

Pioglitazone. Animal studies and cell culture analyses have shown the potential for a diabetes drug, pioglitazone (Actos®), to protect brain cells that are showing early signs of PD. Pioglitazone is now being tested in patients already treated with rasagiline or selegine in the FS-ZONE study. It is hopeful that its anti-inflammatory and cellular stabilizing properties will slow progression of the disease.
**Isradipine.** This drug is in a class that is traditionally used for blood pressure control, but early population-based studies suggested people on this drug were less likely to develop PD. Isradipine (Dynacirc®) may block some chemical stressors on the brain cells that are at-risk in PD, which might slow or stop disease progression. An early study did confirm that isradipine is well-tolerated in PD patients, and further studies are planned (STEADY-PD).

**Glutathione.** Glutathione (GSH) levels may be lower in some patients with PD, and increasing them has been proposed to allow greater antioxidant protection. One strategy suggests optimizing the delivery of GSH (i.e., intranasal, intravenous, etc.). Another strategy uses n-acetylcysteine (NAC), which may increase GSH levels in the brain.

Green tea polyphenol, iron chelators, deep brain stimulation and exercise protocols are also being studied for their impact on disease progression.

**Neurorestorative Treatment**

Recent advances in technology allow for the possibility of treatments to restore function – or even to reverse disease – in PD. Clinical trials have been initiated, and some completed, that assess whether the infusion of growth factors, genes or other brain cells (i.e., pluripotent stem cells) into the brain may help reverse some of the dysfunction in PD. Some examples follow.

**Genes and growth factor** therapies are implemented by injecting bits of DNA (the genetic material that guides the formation of all of the body’s essential proteins) in microscopic packages into carefully targeted cells of the brain, usually in the basal ganglia. This DNA can direct the cell to produce growth factors or other proteins to help protect dying neurons and to encourage re-growth of healthy neurons. Neurturin is a growth factor that has shown mixed results in previous trials. In the CERE-120 Neuturin trial the primary outcome of improved Parkinson’s disease motor scores was not achieved. Cogane, a plant-based growth factor that can be taken orally, failed in a human trial including Parkinson’s disease patients.

Several clinical trials have also evaluated the potential of a surgically implanted substance called GDNF (or glial-derived neurotrophic factor) into the basal ganglia to improve PD symptoms. Several open-label studies (not blinded and without a placebo group) showed some benefit, but a later double-blinded, placebo-controlled study did not replicate those positive results.

**Cell implantation** utilizing pluripotent stem cells remains a relatively new scientific discipline, embroiled in religious and political controversy. The surgical placement of dopamine-producing fetal cells into the basal ganglia of patients with advanced PD initially yielded disappointing results in trials conducted over the last two decades. However, there was a “silver lining” to these efforts, as scientists were successful in having the cells graft into the recipient’s brain. Additional cell-replacement strategies are being devised, but the future remains unclear regarding these possibilities.
Appendix A
Glossary

**Acetylcholine** – A chemical messenger released by cholinergic nerves; involved in many brain functions, such as memory and control of motor activity. There appears to be an interplay between the actions of acetylcholine and dopamine.

**Adjunctive** – Supplemental or secondary to (but not essential to) the primary agent (i.e., medications used to enhance levodopa therapy).

**Ancillary** – That which serves as an aid; auxiliary.

**Anxiolytic** – An agent, usually referring to a class of medications that reduces anxiety.

**Autonomic Neuropathy** – Damage to the autonomic nerves which affect involuntary body functions, including heart rate, blood pressure, perspiration, digestion and other processes. Signals between the brain and portions of the autonomic system are disrupted. Symptoms vary widely, depending on which parts of the autonomic nervous system are affected. They may include dizziness and fainting upon standing (orthostatic hypotension); urinary problems including difficulty starting urination, overflow incontinence and inability to empty your bladder completely; sexual difficulties including erectile dysfunction or ejaculation problems in men, and vaginal dryness and difficulties with arousal and orgasm in women; difficulty digesting food (gastroparesis); sweating abnormalities including decreased or excessive sweating.

**Corticobasal Degeneration (CBD)** – A progressive neurological disorder characterized by nerve cell loss and atrophy, or shrinkage, of multiple areas of the brain including the cerebral cortex and the basal ganglia. Initial symptoms may first appear on one side of the body, but eventually affect both sides. Symptoms are similar to those in PD, such as poor coordination, absence of movements, rigidity, impaired balance and abnormal muscle postures. Other symptoms may include cognitive and visual-spatial impairments, loss of the ability to make familiar, purposeful movements, hesitant and halting speech, muscular jerks and difficulty swallowing. An individual with corticobasal degeneration eventually becomes unable to walk.

**Delusion** – False, fixed, idiosyncratic belief, not substantiated by sensory or objective evidence.

**Dementia** – Not a diagnosis, but descriptive of a broad symptom complex that can arise from a variety of causes. Symptoms can include disorientation, confusion, memory loss, impaired judgment and alterations in mood and personality.

**Dementia with Lewy Bodies (DLB)** – A progressive degenerative disease or syndrome of the brain that shares symptoms of both Alzheimer’s and Parkinson’s disease and is characterized by fluctuating cognition, hallucinations and parkinsonism.
**DNA** – Deoxyribonucleic acid; the basic chemical substance that makes up a gene.

**Dyskinesia** – Abnormal involuntary movement of muscles. Dystonia, athetosis and chorea are forms of dyskinesias.

**Dystonia** – Involuntary spasms of muscle contraction that cause abnormal movements and postures.

**Endogenous** – Originating internally; developing from within (e.g., an endogenous depression is not caused by external circumstances).

**Etiology** – The science of causes or origins of a disease; the etiology of Parkinson’s disease is unknown.

**Exogenous** – Originating externally; relating to external factors (i.e., an exogenous depression might arise following a major life crisis).

**Futility Studies** – A drug trial design that tests whether a drug is ineffective rather than the traditional study of whether it is effective. Relatively short futility studies allow for multiple drugs to be tested more quickly and easily, and further efficacy trials are offered for drugs that “pass” the futility trial.

**Glutamate** – A salt or ester of glutamic acid related to the hydrolysis of proteins.

**Half-life** – The time taken for the concentration of a drug in the bloodstream to decrease by one half; drugs with a shorter half-life must be taken more frequently.

**Hallucinosis** – A state of experiencing hallucinations. In PD, hallucinations are usually visual in nature and insight into reality may or may not be retained.

**Hydrophilic** – Capable of uniting with or taking up water.

**Idiopathic** – An adjective meaning unknown; the most common form of PD is idiopathic Parkinson’s disease.

**Mild Cognitive Impairment** – A transition stage between the cognitive changes of normal aging and the more serious problems of dementia. Mild cognitive impairment can affect many areas of cognition such as memory, language, attention, reasoning, judgment, reading and/or writing. Mild cognitive impairment may be irritating but it does not typically change how a person lives their life.

**Multiple System Atrophy (MSA)** – A progressive neurodegenerative disorder characterized by symptoms of autonomic nervous system failure (such as lightheadedness or fainting spells, constipation, erectile failure in men and urinary retention) combined with tremor and rigidity, slurred speech or loss of muscle coordination.

**Neurons** – The structural and functional unit of the nervous system, consisting of the nerve cell body and all its processes, including an axon and one or more dendrites.

**Neurodegeneration** – Loss of cells of the brain or spinal cord. Over time, it leads to dysfunction and disability.
Neurotransmitter – A biochemical substance, such as dopamine, acetylcholine or norepinephrine, that transmits nerve impulses from one nerve cell to another at a synapse (connection point).

Nutraceutical – A substance that is a food or a part of a food and may provide medical or health benefits including the prevention and treatment of disease.

“Off-On” Effect – Sudden or varying changes in motor performance and other Parkinson’s symptoms. It may correlate with effects of medication wearing off.

Open-Label – When both the researcher and the participant in a research study know the treatment that the participant is receiving. Open-label is the opposite of double-blind when neither the researcher nor the participant knows what treatment the participant is receiving. Open-label studies should be interpreted with caution because of the potential for biased conclusions.

Pathogenesis – The production or development of a disease.

Pharmacodynamics – The study of the relationship of drug concentration to drug effect; essentially what the drug does to the body.

Pharmacokinetics – The study of the absorption, distribution, metabolism and excretion of drugs; essentially what the body does to the drug.

Placebo – A substance containing no medication; an inactive substance or preparation used as a control in an experiment or test to determine the effectiveness of a medicinal drug.

Progressive Supranuclear Palsy (PSP) – A Parkinson’s-like, degenerative brain disorder that causes progressive problems with gait and balance. There is an inability to aim the eyes properly, and persons often show alterations of mood and behavior, including depression and apathy as well as progressive mild dementia. Because some symptoms are similar, PSP is often misdiagnosed as Parkinson’s or Alzheimer’s disease. The hallmark distinguishing factor of PSP is early gait instability and difficulty moving the eyes. PSP, like MSA and CBD, does not respond very well to levodopa therapy.

Sham surgery – A surgery performed as a control in research; similar to the real procedure but omits the key therapeutic element (“fake” surgery).

Substantia Nigra – The area deep within the brain where dopamine is produced.

Tyramine – An amine that causes elevated blood pressure and increased heart rate by displacing the chemical norepinephrine from storage in the body. Tyramine is generally produced by fermentation of food products.
To order your free Medical Alert Card, call the NPF Helpline at 1-800-4PD-INFO (473-4636). You can also download the card at www.parkinson.org/books.

### Medical Alert Card

**I have Parkinson’s Disease** which could make me move slowly and have difficulty standing or speaking.

**I am not intoxicated.** Please call my family or physician for help.

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**Important Medical Information for Health Care Professionals**

- To avoid serious side effects, Parkinson’s patients need their medication on time, every time – do not skip or postpone doses.
- Do not stop levodopa therapy abruptly.
- If an antiparkinson drug is necessary, use quetiapine (Seroquel®) or clozapine (Clozaril®).

**Special Alert**

- Drugs such as benzodiazepines, muscle relaxants, bladder control medications and other medications used for sleep and pain may lead to confusion, hallucinations and other symptoms.
- Use this card over for a list of contraindicated medications & important considerations if the patient has a brain device & needs an MRI/EEG.

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**Medical Alert Card**

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**Allergies/Other Medical Conditions**

**Medications that may be Contraindicated in Parkinson’s Disease**

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<td>Antipsychotics</td>
<td>quetiapine (Seroquel®), clozapine (Clozaril®) avoid all other typical and atypical antipsychotics</td>
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<td>Pain Medication</td>
<td>mild analgesics, but narcotic medications may cause confusion/psychosis and constipation if patient is taking MAO inhibitor such as selegiline or rasagiline (Azilect®), avoid meperidine (Demerol®)</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>request a consult with the anesthesiologist, surgeon and Parkinson’s doctor to determine best anesthetic given your Parkinson’s symptoms and medications if patient is taking MAO inhibitor such as selegiline or rasagiline (Azilect®), avoid meperidine (Demerol®), tramadol (Ultram®), droperidol (Inapsine®), methadone (Dolophine®), Meadadusa), propylene (Daran®, PP-Prop®), cyclobenzaprine (Amrix®, Flexeril®, Flexeril®), halothane (Fluothane®)</td>
</tr>
<tr>
<td>Nausea/Drugs</td>
<td>domperidone (Motilium®), trimethobenzamide (Tigan®), ondansetron (Zofran®), dolasetron (Anzemet®), granisetron (Kytril®), prochlorperazine (Compazine®), metoclopramide (Reglan®), promethazine (Phenergan®), droperidol (Inapsine®)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>amoxapine (Asendin®)</td>
</tr>
</tbody>
</table>

**Share this with your doctor**

- If you have a Deep Brain Stimulation device (DBS):
  - MRI Warning: MRI should not be performed unless the hospital has MRI experience imaging a DBS device safely and the DBS device is turned off. MRI should not be performed if the pacemaker is placed in the abdomen or below and MRI should not be used to change structures of the body lower than the head (neck, abdomen, arms, legs or below) as dangerous heating of the lead could occur. EEG and ECG Warning:
    - Turn off the DBS device before conducting EEG or ECG.
    - Diathermy should be avoided.
### Appendix C

**Formula for Liquid Sinemet®**

**Formula for Liquid Sinemet® - 1 mg levodopa per 1 ml solution**

- Sinemet® 25/100 tablets 10 tablets (1,000 mg levodopa)  
  (do not use Sinemet CR®)
- Ascorbic acid (Vitamin C) crystals ½ tsp. (approx. 2 gms)
- Tap water or distilled water 1 liter or 1 quart

1) Mix the above ingredients in a liter/quart plastic container with lid (do not use metal).
2) Rotate or shake gently until tablets dissolve (no need to crush tablets). Tablets may not go completely into solution.
3) Formula will maintain full strength and purity for 24 to 48 hours in refrigerator.

### Dosing Recommendations

(Always establish a dosing plan with your physician or healthcare provider first!)

1) **Morning (“Jump Start”) dose:**
   - 60 ml of the formula (60 mg or a little more than ½ of a 25/100 tablet of carbidopa/levodopa), or may use amount comparable to usual tablet dose.
   - Adjust dose 5-10 ml up or down every three to five days until you achieve the best “on” response with the least dyskinesia.

2) **Hourly dosing:**
   - 30 ml of the formula on the hour while awake, or hourly proportion of usual tablet dose. (For instance, a person with PD taking one carbidopa/levodopa 25/100 tablet every two hours might try 50 ml per hour of the liquid.)
   - Adjust dose 5-10 ml up or down every three to five days until “on” periods are smoother.

For the best overall result, it is strongly recommended that you adjust the morning jump start dose prior to adjusting the hourly doses. Accuracy of the dose and exact hourly timing between doses is critical for optimal benefit. Optimal dosing can vary tremendously from one person to another.
Appendix D
Epworth Sleepiness Scale

The Epworth Sleepiness Scale is used to determine the level of daytime sleepiness. A score of 10 or more is considered sleepy. A score of 18 or more is very sleepy. If you score 10 or more on this test, you should consider whether you are obtaining adequate sleep, need to improve your sleep hygiene and/or need to see a sleep specialist. These issues should be discussed with your personal physician.

Use the following scale to choose the most appropriate number for each situation:

0 = would never doze or sleep.
1 = slight chance of dozing or sleeping
2 = moderate chance of dozing or sleeping
3 = high chance of dozing or sleeping

Fill in your answers and see where you stand.

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of Dozing or Sleeping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td></td>
</tr>
<tr>
<td>Watching TV</td>
<td></td>
</tr>
<tr>
<td>Sitting inactive in a public place</td>
<td></td>
</tr>
<tr>
<td>Being a passenger in a motor vehicle for an hour or more</td>
<td></td>
</tr>
<tr>
<td>Lying down in the afternoon</td>
<td></td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td></td>
</tr>
<tr>
<td>Sitting quietly after lunch (no alcohol)</td>
<td></td>
</tr>
<tr>
<td>Stopped for a few minutes in traffic while driving</td>
<td></td>
</tr>
</tbody>
</table>

Total score (add the scores up)
(This is your Epworth score)
Listed below is a brief selection of books currently available as general resources for Parkinson’s disease. As new resources continuously become available, please check our website, www.parkinson.org, for the most recent titles.

The Parkinson’s Disease Treatment Book: Partnering with Your Doctor to Get the Most from Your Medications
J. Eric Ahlskog, MD, 2005.

Parkinson’s Disease for Dummies
Michele Tagliati, MD, Gary Guten and Jo Horne, 2007.

Parkinson’s Treatment: 10 Secrets to a Happier Life
Michael S. Okun, MD, 2013.

The First Year – Parkinson’s Disease: An Essential Guide for the Newly Diagnosed
Jackie Hunt Christensen, 2005.

Living Well with Parkinson’s Disease: What Your Doctor Doesn’t Tell You… That You Need to Know
Acknowledgments

The first *Medications* manual was written by Jean Pintar Hubble, MD, and Richard C. Berchou, PharmD.

Jill Marjama-Lyons, MD, and Gale Kittle, RN, MPH, updated the second and third editions.

David Houghton, MD, MPH, Howard Hurtig, MD, Sharon Metz, RN, MPH, and guest author Melanie Brandabur, MD, updated the fourth edition.
About the Authors

**David Houghton, MD, MPH**, received his medical degree from the Medical College of Georgia in Augusta, Georgia and his master’s in public health in epidemiology at the Rollins School of Public Health at Emory University in Atlanta. He completed his internship and residency in neurology at the Hospital of the University of Pennsylvania, followed by fellowship training in movement disorders at Pennsylvania Hospital in Philadelphia. Dr. Houghton began his clinical and academic pursuits at the University of Louisville as an assistant professor and clinical director of the Movement Disorder Surgical Program. He joined the Ochsner Health System in New Orleans, Louisiana, in 2012 as Chief of the Division of Movement and Memory Disorders.

**Howard Hurtig, MD**, graduated from Tulane University (BA ’62, MD ’66) and received training in internal medicine at Cornell-New York Hospital Medical Center (’66-’68) and neurology at the Hospital of the University of Pennsylvania (’70-’73). In 1982, he and Matthew Stern, MD, founded the Parkinson’s Disease and Movement Disorders Center at the University of Pennsylvania, an NPF Center of Excellence, where he is the Frank Gladys Elliott Professor of Neurology. In addition to his interest in patient care, Dr. Hurtig has conducted clinical research in experimental therapeutics, clinical-pathological correlations of Parkinson’s disease and other parkinsonian syndromes and neuroimaging.

**Sharon Metz, RN, MPH**, received her nursing degree from the University of Vermont and her master’s in public health from the Johns Hopkins University. Before joining the National Parkinson Foundation staff, she worked in intensive care nursing at the George Washington University Medical Center and in an AIDS research study at Johns Hopkins. She has worked with the National Parkinson Foundation since 1999, working closely with persons with PD and center coordinators in a variety of contexts, most recently on the NPF Helpline.

**Melanie Brandabur, MD**, received her BA degree from the University of Illinois in Urbana and her MD degree from Rush Medical College in Chicago. She completed her neurology residency at Rush-Presbyterian-St. Luke’s Medical Center in Chicago. While there, she completed a Fellowship in Movement Disorders and Pharmacology. This was followed by a post-doctoral basic sciences Fellowship in Neurodegenerative Diseases.

Dr. Brandabur has over 20 years of experience caring for patients with PD and related disorders. Her philosophy of patient care arises from her strong beliefs in patient education and a multidisciplinary approach to PD treatment. In addition, she has participated as an investigator in over 40 clinical trials. In July of 2006, she joined the faculty at The Parkinson’s Institute in Sunnyvale, California, as the director of the outpatient clinic for Parkinson’s disease and other movement disorders. Dr. Brandabur is Board Certified in Neurology, and is a member of the American Academy of Neurology, the Movement Disorders Society, and the Santa Clara County Medical Society.
National Parkinson Foundation
Educational Books

This book is part of the National Parkinson Foundation’s Educational Book Series, which addresses important topics for people with Parkinson’s disease. All topics and titles in the series are listed below. To request a free copy of any book(s) in the series, contact the NPF Helpline at 1-800-4PD-INFO (800-473-4636) or visit www.parkinson.org/books.

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Managing Advanced Parkinson’s Disease

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(1 = not easy at all; 5 = very easy)

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