



Parkinson's Disease Medications

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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 | Exercise Is Medicine | 46 |
| Chapter 5 | Integrative Medicine | 49 |
| Chapter 6 | Research and Future Developments | 63 |

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..... | 40 |

| | | |
|------------|-----------------------------------|----|
| Appendix A | Glossary | 67 |
| Appendix B | Medical Alert Card..... | 72 |
| Appendix C | Formula for Liquid Sinemet® | 73 |
| Appendix D | Epworth Sleepiness Scale | 74 |
| Appendix E | Selected Readings..... | 75 |

| | |
|------------------------|----|
| About the Authors..... | 76 |
|------------------------|----|

| | |
|-------------|----|
| Index | 78 |
|-------------|----|

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.

Chapter 1

Introduction to Parkinson's Disease

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

| |
|--|
| <p>MOTOR SYMPTOMS</p> <ul style="list-style-type: none"> • Bradykinesia (slowness of movement) • Rigidity (stiffness of movement) • Tremor (involuntary shaking of the hands, feet, arms, legs, jaw or tongue; usually more prominent at rest) • Postural instability (tendency to fall, usually when pivoting) |
| <p>NON-MOTOR SYMPTOMS</p> <ul style="list-style-type: none"> • Mood changes (depression, anxiety, irritability) • Cognitive changes (memory problems, personality changes, psychosis/hallucinations) • Orthostatic hypotension (lightheadedness and low blood pressure when standing) • Constipation and early satiety (a feeling of fullness after eating small amounts) • Hyperhidrosis (excessive sweating) • Seborrhea (oily skin) • Urinary urgency and incontinence • Sexual dysfunction • Loss of sense of smell • Sleep disorders • 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) • Fatigue • Sensory problems (pain, tightness, tingling, burning) |
| <p>MIXED MOTOR AND NON-MOTOR SYMPTOMS</p> <ul style="list-style-type: none"> • Drooling due to slowed swallowing (sialorrhea) • Speech and swallowing problems |

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**)

| | |
|-------------|----------------------------|
| Levodopa | Lee-voe- doe -pa |
| Carbidopa | Car-bee- doe -pa |
| Ropinirole | Row- pin -er-ole |
| Pramipexole | Pram-i- pex -ole |
| Rotigotine | Row- tig -oh-teen |
| Apomorphine | Ae-poe- more -feen |
| Selegiline | Sell- edge -ah-leen |
| Rasagiline | Rah- saj -ah-leen |

Table 2. Summary of Medications for Motor Symptoms in PD

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

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

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

Key: *monotherapy* = medication used alone

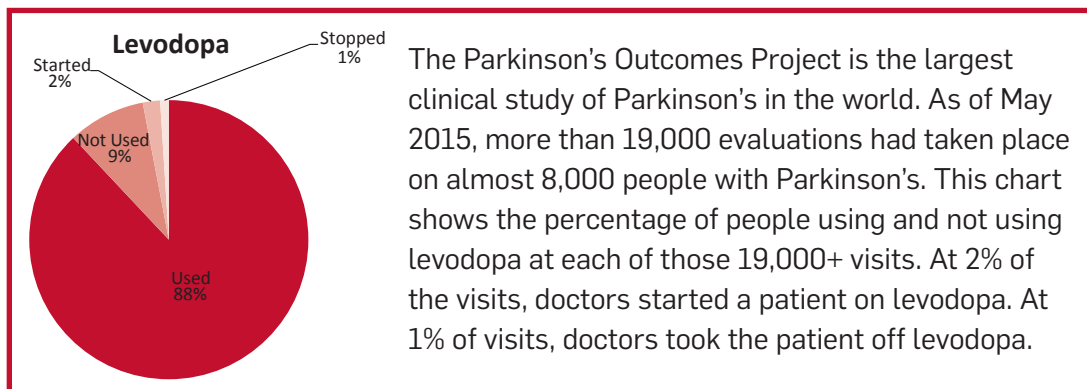
combination or adjunct therapy = medication added to other medications

* “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.

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 www.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
- Lightheadedness
- Vomiting
- Lowered blood pressure
- Loss of appetite
- 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. Carbidopa/levodopa enteral solution, or 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. Below you will find information every patient interested in the pump should be familiar with. For more information on Duopa, including information on support services, visit www.duopa.com.

- 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)

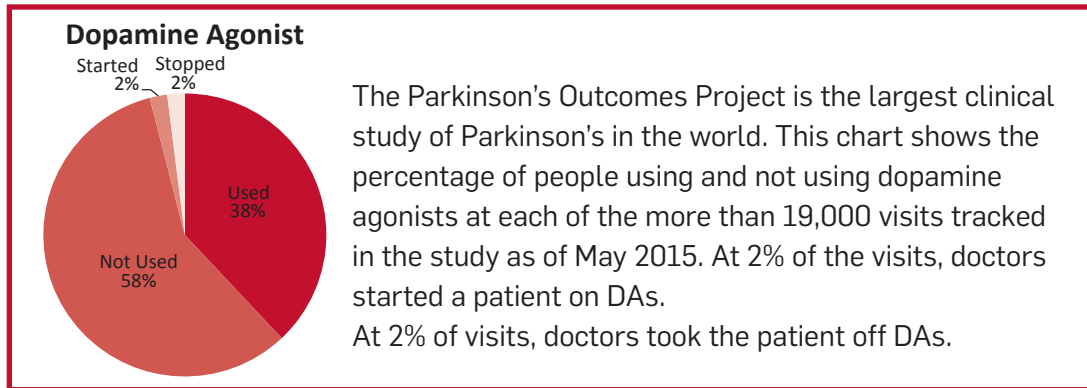
Generally DAs effectively improve the motor symptoms of PD, but they are less potent than levodopa. A DA can be used early in the course of PD as a single drug (monotherapy) or later in combination with carbidopa/levodopa (combination or adjunct therapy). Dopamine agonists have longer half-lives (longer 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.

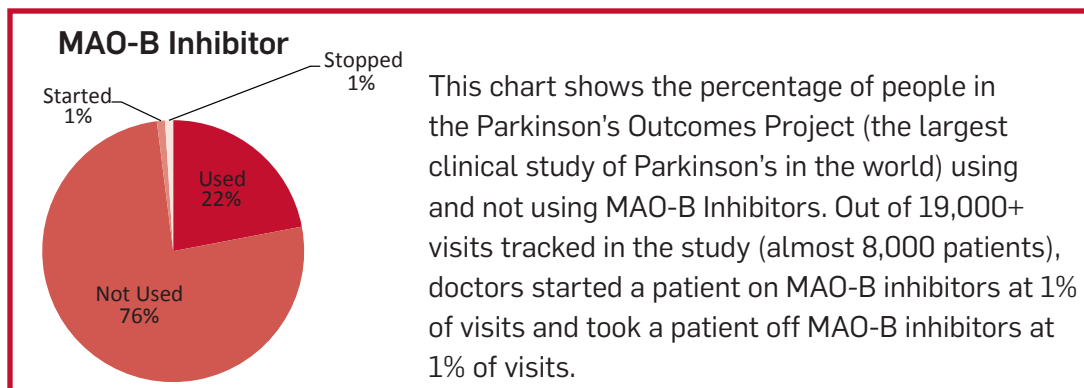
Pramipexole (Mirapex®) and **Ropinirole** (Requip®) were approved by the FDA in 1997 and are currently the most commonly used DAs. Neither of these dopamine agonists is ergot-derived, nor have they been associated with abnormalities of the heart valves. They are both effective in the early treatment 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 **Benzotropine** (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](http://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:

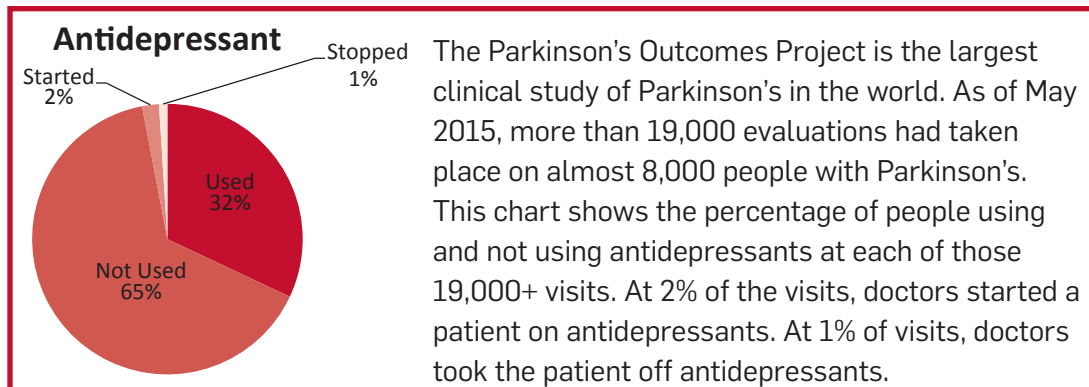
- Insomnia or excessive sleeping
- Loss of interest or pleasure in social or recreational activities
- Sexual dysfunction
- Feelings of guilt and self-pity
- Loss or reduction of energy levels
- Diminished attention and concentration
- Loss or gain of appetite and weight
- Thoughts of death or suicide

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 bupropion 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

| Medication (product name in parenthesis) | Dosages in Milligrams (mg); tablets unless otherwise noted | Typical Treatment Regimens* | Potential Side Effects | Indications for Usage (<i>italics = approved by FDA</i>) |
|--|---|--|--|---|
| REMEMBER TO DISCUSS THE RISKS OF COMBINED USAGE OF ANTI-DEPRESSANTS AND THE MAO-B INHIBITORS (SELEGILINE OR RASAGILINE) WITH YOUR DOCTOR | | | | |
| Selective Serotonin Reuptake Inhibitors (SSRIs) | | | | |
| Citalopram (Celexa®) | 10, 20, 40 mg tablets; 10 mg/2 ml solution | 10–40 mg daily | Headache, nausea, insomnia, vivid dreams, sedation, jitteriness, diminished sexual libido, weight gain | <i>Depression, anxiety/panic, obsessive – compulsive disorder (OCD)</i> |
| Escitalopram (Lexapro®) | 5, 10, 20 mg tablets; 5 mg/5 ml solution | 5–20 mg daily | Same as above but weight neutral | <i>Depression, anxiety/panic, OCD</i> |
| Fluoxetine (Prozac®) | 10, 20, 40, 90 | 10–40 mg daily | Same as above | <i>Depression, anxiety/panic, OCD</i> |
| Fluvoxamine (generic, Luvox CR®) | 25, 50, 100 CR 100, 150 | 25–100 mg daily/nightly (<i>may be different for extended-release</i>) | Headache, nausea, insomnia, vivid dreams, sedation, jitteriness, diminished sexual libido, weight gain | <i>Depression, anxiety/panic, OCD</i> |
| Paroxetine (Paxil®, Paxil CR®, Pexeva®) | 10, 12.5, 20, 25, 30, 37.5, 40 mg tablets; 10 mg/5 ml suspension CR 12.5, 25, 37.5 | 10–40 mg daily (<i>may be different for extended-release</i>) | Same as above | <i>Depression, anxiety/panic, OCD</i> |
| Selective Serotonin Reuptake Inhibitors (SSRIs), continued | | | | |
| Sertraline (Zoloft®) | 25, 50, 100 mg tablets; 20 mg/ml concentrate | 25–100 mg daily | Headache, nausea, insomnia, vivid dreams, sedation, jitteriness, diminished sexual libido, weight gain | <i>Depression, anxiety/panic, OCD</i> |
| Vilazodone (Viibryd®) | 10, 20, 40 | 10–40 daily | Diarrhea, nausea, dizziness, dry mouth, insomnia, vomiting, vivid dreams | <i>Depression, anxiety/panic, OCD</i> |

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

| Medication (product name in parenthesis) | Dosages in Milligrams (mg); tablets unless otherwise noted | Typical Treatment Regimens* | Potential Side Effects | Indications for Usage (<i>italics</i> = approved by FDA) |
|---|--|--|---|--|
| Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs) | | | | |
| Desvenlafaxine (Pristiq®) | 50, 100 | 50 mg daily | Nausea, headache, insomnia, vivid dreams, sedation, jittery, dry mouth, constipation, diminished libido | <i>Depression, anxiety</i> |
| Duloxetine (Cymbalta®) | 20, 30, 60 | 10–30 mg twice a day | Same as above | <i>Depression, anxiety</i> |
| Milnacipran (Savella®) | 12.5, 25, 50, 100 | 50 mg twice a day | Same as above | Depression, anxiety |
| Nefazodone (Serzone®) | 50, 100, 150, 200, 250 | 25–100 mg twice a day | Same as above, plus requires monitoring for liver function | <i>Depression, anxiety</i> |
| Venlafaxine (Effexor®, Effexor XR®) | 25, 37.5, 50, 75, 100, 150, 225 XR 37.5, 75, 150 | 25–75 mg twice a day (<i>may be different for extended-release</i>) | Nausea, headache, insomnia, vivid dreams, sedation, jittery, dry mouth, constipation, diminished libido | <i>Depression, anxiety</i> |
| Tricyclic and Related Compounds | | | | |
| Amitriptyline (Elavil®) | 10, 25, 50, 75, 100, 150 | 10–50 mg nightly | Confusion, forgetfulness, hallucinations, light-headedness, blurry vision, urinary retention, dry mouth | <i>Depression, anxiety</i> |
| Imipramine (Tofranil®, Tofranil PM®) | 10, 25, 50 PM 75, 100, 125, 150 | 10–50 mg nightly; PM 100 mg max in elderly | Same as above | <i>Depression, anxiety</i> |
| Nortriptyline (Pamelor®) | 10, 25, 50, 75 mg capsules; 10 mg/5 ml solution | 10–50 mg nightly | Same as above | <i>Depression, anxiety</i> |
| Trazodone (Desyrel®, Oleptro®) <i>also a serotonin modulator</i> | 50, 150, 300 | 75–300 mg daily (divided) | Same as above | <i>Depression, anxiety</i> |

| Other Antidepressants | | | | |
|---|--|--|--|--|
| Bupropion (Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®, Budeprion SR®, Budeprion XL®, Zyban®) | 75, 100 SR 100, 150, 200 XL 150, 300 | 75–150 mg 1–2 times daily (<i>may be different for extended-release</i>) | Dry mouth, insomnia, headache, nausea, constipation, weight neutral, lack of sexual side effects, lowers seizure threshold | <i>Depression</i> |
| Mirtazapine (Remeron®, Remeron SolTab®) | 7.5, 15, 30, 45 Regular or orally disintegrating tablets | 15–30 mg daily | Drowsiness, increased appetite, headache, vivid dreams, lack of sexual side effects | Same as above. Also available in orally disintegrating form. |
| Benzodiazepines | | | | |
| Alprazolam (Xanax®, Xanax XR®, Niravam®) | 0.25, 0.5, 1, 2, 3 mg tablets; 1 mg/ml solution XR 0.5, 1, 2, 3 | 0.25–1 mg 3–4 times daily (<i>may be different for extended-release</i>) | Drowsiness, light-headedness, depression, headache, confusion, dizziness, fatigue, constipation, blurred vision | <i>Anxiety/panic.</i> Also available in orally disintegrating form. |
| Clonazepam (Klonopin®) | 0.125, 0.25, 0.5, 1, 2 | 0.25–2 mg up to 3 times daily | Same as above | <i>Anxiety/panic.</i> Also available in orally disintegrating form. |
| Diazepam (Valium®) | 2, 5, 10 mg tablets; 5 mg/5 ml solution | 1–5 mg up to 4 times daily | Same as above | <i>Anxiety/panic</i> |
| Lorazepam (Ativan®) | 0.5, 1, 2 mg tablets; 2 mg/ml concentrate | 0.5–2 mg up to 3 times daily | Same as above | <i>Anxiety/panic</i> |
| Other Anti-anxiety Medications | | | | |
| Buspirone (BuSpar®) | 5, 7.5, 10, 15, 30 | 5–15 mg twice a day | Dizziness, drowsiness, dry mouth, nausea, headache | Generalized <i>anxiety</i> disorder |
| Propranolol (Inderal®, Inderal LA®, InnoPran XL®) | 10, 20, 40, 60, 80 mg tablets; 20 mg/5 ml & 40 mg/5 ml solution LA 60, 80, 120, 160 XL 80, 120 | 10–40 mg up to 3 times daily (<i>may be different for extended-release</i>) | Decreased heart rate, depression, exacerbation of pre-existing asthma | Anxiety/panic – can suppress outward signs (like racing heartbeat and shakiness) |

* “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.

In 2016, the FDA approved **pimavanserin** (Nuplazid™) as the first drug specifically designed to treat Parkinson's disease psychosis. Pimavanserin is not a dopamine-blocking drug like clozapine and quetiapine. It is a selective serotonin inverse agonist. This means it targets serotonin receptors. It is a safer choice when treating people with PD that are experiencing psychoses because it can reduce hallucinations without disrupting motor performance.

Clozapine (Clozaril®) 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 was shown in a randomized clinical trial to be effective against psychotic behavior in PD.

Until pimavanserin was approved in 2016, **quetiapine** (Seroquel®) had become the drug of choice to treat psychosis in PD; it has the advantage over clozapine of not adversely affecting blood counts. 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.

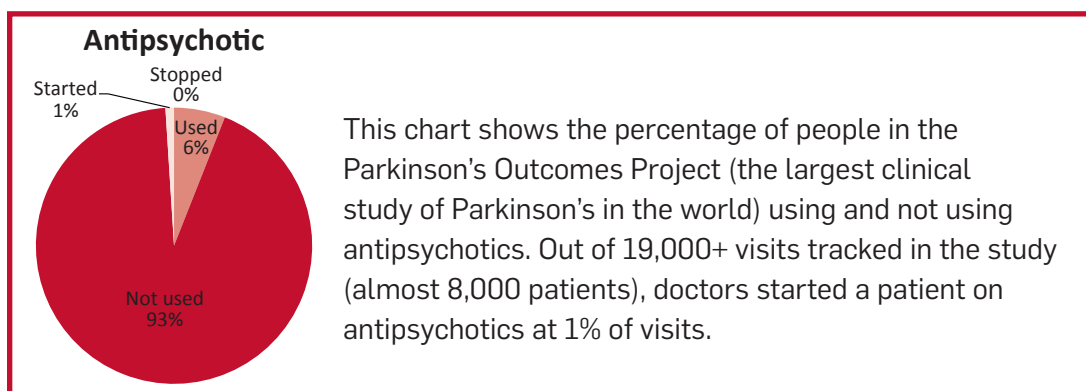


Table 4. Summary of Medications for Dementia and Hallucinations in PD

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

| For Hallucinations and Psychosis | | | | |
|--------------------------------------|--|---|--|-------------------------------------|
| Pimavanserin (Nuplazid™) | 34 | 34 mg/day, taken as two 17 mg tablets once daily | Swelling of limbs, nausea, confusion, constipation, gait disturbance | <i>Hallucinations and psychosis</i> |
| Clozapine (Clozaril®, FazaClo®) | 12.5, 25, 50, 100, 200 | 50–300 mg twice a day | Requires weekly blood tests for low white blood cell counts. Drowsiness, drooling, tachycardia, dizziness, constipation, low blood pressure, headache | <i>Hallucinations and psychosis</i> |
| Quetiapine (Seroquel®, Seroquel SR®) | 25, 50, 100, 150, 200, 300, 400 SR 50, 150, 200, 300, 400 | 12.5–100 mg divided daily (may be different for extended-release) | Sleepiness, dry mouth, dizziness, orthostatic hypotension, tachycardia, low blood pressure, constipation, increased appetite | <i>Hallucinations and psychosis</i> |

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

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 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 orthostasis is related to a disease of the nervous system, like PD or multiple system atrophy, it is called neurogenic orthostatic hypotension, or nOH.

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. For more information on nOH, visit www.nohmatters.com.

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 (Northera®) is believed to work by increasing standing blood pressure through elevating levels of norepinephrine, a chemical in the body that helps regulate blood pressure. Northera was approved by the FDA in 2014 for the treatment of orthostatic dizziness, lightheadedness, or the “feeling that you are about to black out” in adult patients with symptomatic neurogenic orthostatic hypotension (nOH) caused by primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy. The studies leading to the FDA approval were short-term (10 weeks or less) and effectiveness beyond two weeks of treatment has not been demonstrated. Therefore, the continued effectiveness of Northera should be assessed periodically by your doctor. Similar to midodrine and fludrocortisone, there is potential for the development of high blood pressure when lying flat (supine hypertension) that should be monitored carefully. Northera is only available through specialty pharmacies; your doctor has to complete a treatment form and fax it to the Northera Support Center to prescribe it. For more information, visit www.northera.com.

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

| Medication (product name in parentheses) | Dosages in Milligrams (mg); tablets unless otherwise noted) | Typical Treatment Regimens* | Potential Side Effects | Indications for Usage (<i>italics = approved by FDA</i>) |
|--|---|--|--|--|
| Medications for Nausea and Vomiting | | | | |
| Carbidopa (Lodosyn®) | 25 | Adding 25–50 mg to each dose of carbidopa/levodopa | Could worsen dyskinesia | <i>Reduce levodopa-induced nausea & vomiting</i> |
| Domperidone (Motilium®) <i>NOTE: not available in the U.S. at this time</i> | 10 | 10 mg up to four times daily, 15–30 minutes prior to meals | Headache, hives, hot flashes, itching of skin; itching, redness, pain, or swelling of eye; | Treat nausea, vomiting, and constipation with increasing emptying of stomach |
| Ondansetron (Zofran®) | 4, 8 | 4 mg up to three times daily as needed | Headache, malaise/fatigue, constipation, diarrhea | Nausea and vomiting |
| Trimethobenzamide (Tigan®) | 300 mg capsule; 200 mg suppositories | 300 mg up to four times daily | Blurry vision, depression, diarrhea, confusion, dizziness, headache, drowsiness, cramps | <i>Treat nausea and vomiting, premedication for Apokyn®</i> |

| Medication (product name in parentheses) | Dosages in Milligrams (mg); tablets unless otherwise noted) | Typical Treatment Regimens* | Potential Side Effects | Indications for Usage (<i>italics = approved by FDA</i>) |
|---|---|--|--|---|
|  Metoclopramide (Reglan®) | 5, 10 | | Worsens PD symptoms: dystonic reaction, confusion, dizziness, headache, drowsiness | <i>Treat or prevent nausea and vomiting, and constipation with increasing emptying of stomach</i> |
|  Prochlorperazine (Compazine®) | 5, 10 | | Same as above | <i>Treat nausea and vomiting</i> |
|  Promethazine (Phenergan®) | 12.5, 25, 50 | | Same as above | <i>Treat nausea and vomiting</i> |
| Medications for Constipation | | | | |
| Lubiprostone (Amitiza®) | 8, 24 mcg | 8–24 mcg twice daily | Bloating, gas, upset stomach, dizziness, chest pain | <i>Constipation</i> |
| Polyethylene glycol 3350 (MiraLax®) | 1 capful (17 grams) in 4–8 ozs. water or liquid | Every day if necessary, may use lower doses for maintenance | Bloating, gas, upset stomach, dizziness, increased sweating | <i>Constipation</i> |
| Medications for Excessive Drooling | | | | |
| Atropine drops | 1% ophthalmic solution | Only 1–2 drops under the tongue twice a day | Dry mouth | Excessive drooling |
| Glycopyrrolate | 1, 2 | 1–2 mg two or three times daily as needed | Dry mouth, drowsiness, confusion, vomiting, dizziness, blurred vision, constipation, flushing, headache, urinary retention | Excessive drooling |
| Scopolamine patch | 1.5 mg patch | Apply patch every 3 days as needed | Same as above | Excessive drooling |
| Botulinum toxin A (Botox®) | 100 unit vials | 10–100 units injected into parotid and/or submandibular glands | Dry mouth | Excessive drooling |

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

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 (Yocon®). 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-inflammatories, 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.

Chapter 4

Exercise Is Medicine

The symptoms of Parkinson's disease include more than just what doctors call the motor features – the slowness, stiffness and tremor that characterize the disease. Parkinson's impacts thinking: the disease can affect working memory, decision-making, staying attentive and concentration. Parkinson's also affects behavior; PD is linked to depression and anxiety, and it can disturb sleep.

From a biological perspective, Parkinson's results in low levels of the brain chemical dopamine, and this leads to the loss of effective communication between the higher brain structures on the surface of the brain (called the cortex) and the deep part of the brain that manages more basic functions (called the basal ganglia). The higher brain structures are where you think, and the deep structures are where those thoughts are translated into actions, particularly movement. The loss of these connections is also linked to the behavioral changes observed in Parkinson's.

In the last decade, studies and ongoing research have clearly shown us that exercise and physical therapy can help restore lost behaviors and function in people with Parkinson's. In total these studies have shown that physical therapy and exercise can improve many diverse aspects of Parkinson's by incorporating feedback, repetition, challenge, problem solving, engagement and motivation. In addition to improving symptoms, scientists are increasingly convinced that exercise may slow disease progression.

Reported benefits of exercise include:

- Improved gait and balance
- Reduced falls
- Increased flexibility and posture
- Improved endurance
- Reduced freezing of gait
- Improved working memory and decision making
- Improved attention/concentration
- Reduced depression and anxiety
- Improved quality of sleep

KEY POINT: Based on findings from the National Parkinson Foundation's Parkinson's Outcomes Project, the largest-ever clinical study of Parkinson's, it is recommended that people with PD engage in at least 2.5 hours of exercise a week for a better quality of life. Establishing early exercise habits is an essential part of overall disease management.

EXERCISE EFFECTS ON COGNITION

Across medicine, researchers have long linked exercise to cognitive function or thinking. More recently, researchers are finding that exercise seems to improve aspects of how you think that are frequently affected in Parkinson's. About half of people with Parkinson's experience challenges with what doctors call *executive functioning*, which involves planning activities, keeping a schedule, organizing things on your desk or in your house and similar tasks. Executive function can be impaired by problems with working memory (measured by how many things you can keep track of simultaneously), problems with keeping focused on a task and responding to changes.

The parts of the brain that perform executive function tasks are the same ones that help you to apply motor learning in changing environments. For example, you use these executive function centers when you go from walking inside the house to walking outside. You also use your executive function centers when you think about how to improve a motor skill – how to do a task you know how to do better or faster.

Today, we have ideas about how to exercise better. In the past, when scientists studied how exercise affected the brain they always studied basic aerobic training such as biking or walking on a treadmill, track or around the community. When you exercise aerobically, you make your heart healthier and you improve how your body uses oxygen. Studies of aerobic exercise have shown that it can help improve age-related changes in executive function. Scientists are now working to determine how well aerobic exercise works to slow Parkinson's disease. They are studying what is the right "dose" of exercise to get the best benefits, including looking at how to balance the benefits of exercise versus the risk that exercising too much might increase your risk of falls or injury.

Studies of Parkinson's have already shown that exercise helps. Studies of skill-based exercise have been shown to improve motor function, too. So far, we don't know which is better. In fact, the answer may be both: doing skill-based exercise *and* aerobic exercise may work best of all, in particular for targeting cognition. Your physical therapist may incorporate skills and aerobic training by having you do exercises with set goals. A goal might be to stay at a certain speed or finish a task at a certain time.

How can you try to do both skill-based exercise and aerobic exercise together?

- Learn to play tennis
- Spin training
- Walk a course (through your neighborhood) with the goal of finishing in a pre-set time

KEY POINT: Mixing up exercises that are skills-based and/or aerobic offers the opportunity to get both motor and cognitive benefits.

EXERCISE AND NEUROPLASTICITY

We've known for years that exercise improves muscle strength, flexibility, bone density and cardiovascular health. However, new research is showing us that the brain isn't just a passive beneficiary of these health benefits. When you take up a new sport, you *learn* it, and that is about your brain – not just your muscles – learning the movements. This process of teaching your brain a new pattern (whether it is a movement, being comfortable in a new place, or even learning a way to think) is called *neuroplasticity*. We have actually measured in animals that exercise leads to the following Parkinson's-fighting changes:

- Exercise changes how your brain uses the chemicals that signal from one cell to the next (*neurotransmitters*). Exercise actually made brain cells use dopamine more effectively.
- Exercise caused the animals to grow new blood vessels, helping brain cells to get the oxygen and nutrients they need to stay healthy and participate in the activities of thinking.
- Exercise changes brain circuits by changing the way the network of brain cells are connected. Exercise helps neurons grow new connections – synapses – and grow new neurons that become part of a more efficient brain network by releasing brain growth factors and other effects.
- Exercise helps the body's immune system to work more effectively, and recent research has suggested that the immune system may be a part of PD, too.

It really is amazing that by doing something enjoyable to make your body healthier, you are making your brain healthier, too.

KEY POINTS: Benefits of exercise include the following:

- Increased blood flow to the brain
- Increased expression of growth factors that strengthen brain connections
- Optimized use of energy by brain cells (improved metabolism)
- Reduced potentially harmful effects of the immune system (inflammation)
- Even better effects of the medicines you take to fight Parkinson's

Overall Key Points

- When you learn a new exercise skill (like tai chi, boxing or yoga) it helps both how you move and how you think.
- There is not just one best exercise – you should do aerobic, strength and skills exercises to get the best benefits.
- Doing a variety of different exercises, as well as pushing yourself to get better at the ones you do helps your neurons to grow new connections, resulting in learning.
- Exercise is a LIFELONG COMMITMENT.
- Exercise is medicine, and we don't see any signs that there ever will be a pill to replace it.

Chapter 5

Integrative Medicine

Thanks to advances in our ability to manage motor symptoms, 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 have become the key to successful treatment. Indeed, health is promoted and disease is best treated with a balanced, holistic approach that embraces engagement in care, positive lifestyle change, and complementary as well as conventional medicine. In this section you will expand your knowledge of available treatments to include integrative therapies. An integrative approach does not differentiate between lifestyle, complementary, and traditional medical therapies; instead, it promotes the idea that lifestyle and complementary therapies work synergistically to enhance healing, emotional wellbeing, and resilience.

Complementary therapies are increasingly popular: people in the U.S. spend over three billion dollars a year on them, and acceptance of such therapies in mainstream medicine is also growing. Exercise, once considered complementary, is now standard of care for PD. The same is true for diet and stress management. One study suggests that more than three-quarters of people with PD are turning to and embracing complementary therapies in an effort to feel better, reduce symptoms, and promote healing. Their reasons for use are varied and include the desire for control, distrust of mainstream health care, perceived safety, belief in natural products, fear of medicine side effects or toxicity, limited access to traditional treatment, cultural beliefs, marketing influences, and the belief in personal or innate healing.

There are multiple proposed mechanisms for how integrative therapies may help people with PD, including the following:

- *Cellular health:* Your body's cells, like your body itself, need to be healthy. Your cells need a healthy environment, oxygen and nutrition; they need to get rid of waste; and they even have cell-scale organs that have to work properly. For example, mitochondria are like the digestive system of the cell, turning sugars from the blood into energy the cell can use. Oxidative stress – a toxic byproduct of this cell metabolism – is like pollution in the cell's environment. Similarly, stress or injury cause inflammation, which is a warning sign, like a fire alarm, in the body. Each of these can be involved in PD and other neurodegenerative diseases. Researchers are actively studying supplements and natural therapies that can reduce or reverse these problems.
- *Neuroplasticity and neuroprotection:* Neuroplasticity refers to the brain's ability to reorganize itself by forming new connections. This allows the brain to compensate for injury and disease and to respond to new situations and changes in the environment. Neuroprotection means saving neurons from damage caused by Parkinson's. This could be stopping or even reversing the course of the disease, the holy grail of Parkinson's research (there is more information about this in the next chapter). Our brains change subtly all the time – influenced by our daily actions, activities, and thoughts. Stress causes

the body to release chemicals that can harm the brain, which is why stress often leads to fatigue, inactivity and even isolation. Therefore, learning to manage stress and participating in creative and emotionally- and spiritually-rich activities can help protect the brain from harm. Even better, exercise – involving the coordinated motion of the whole body – is good for both body AND brain. Exercise can strengthen brain networks and improve the health of brain cells that have been weakened by Parkinson's.

- *Stress reduction*: Stress harms the brain, but this can be offset by activities that help you relax. Many mind-body therapies work in part by enhancing relaxation. These strategies engage the parasympathetic nervous system, the “rest and digest” response that slows many high-energy body functions, as opposed to the “fight or flight” response of the sympathetic nervous system, which increase heart rate, blood pressure, and other reflexes in response to a perceived threat.
- *Placebo and “nocebo”*: Any treatment you believe will help you will give you a placebo effect – a benefit above and beyond any actual biochemical or biological benefit due to the belief that the treatment will work. Some treatments may even work entirely through this process. The strength of placebo effect depends on the expectations you have for a treatment, your prior experience with a similar treatment, and how much you value a treatment. If you fear or don't want a treatment, it can give you a “nocebo” effect – a negative effect that you experience because of fear or rejection of the treatment.

SAFE AND WISE SELECTION

Evidence-based medicine is the practice of integrating individual clinical expertise, best external evidence (research), and patient values and expectations into care decisions, and these principles are regularly applied to the safe use and promotion of traditional medical and surgical therapies. Researchers perform blinded placebo-controlled studies to insure that treatment results are due to the biological effects of the treatment rather than the psychological effects of being involved in a study. A study is blinded when neither the doctor nor the patients know who is getting the drug or treatment being studied or a dummy treatment such as a sugar pill (placebo). If a new treatment is better than the dummy treatment in the study, then health care providers can choose that treatment to help their patients. In Chapter 6, the importance of 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.

Unfortunately, this level of evidence showing both safety and efficacy does not exist for many integrative therapies. With drugs, regulators monitor claims made about how effective they are. On the other hand, because they are often based on natural products, exercise, or therapies, integrative treatments tend not to be so strictly regulated. Without regulation, these treatments can be marketed based on exaggerated claims. Many products are promoted as able to treat symptoms and even cure disease, without the evidence to support these claims. Anecdotal reports and passionate personal stories are used in place of carefully conducted scientific research.

Many clinicians are skeptical of integrative therapies because there is no objective scientific research to support their use. 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 such products and techniques. This is understandable; however, a treatment can be helpful even if it has not been studied. Some treatments just do not lend themselves to placebo-controlled studies or are too difficult or too expensive to study. For example, supplements can be studied in a controlled manner, similar to prescription medication, but such a trial can be expensive. Massage, another example, is difficult to study, as it is difficult to find an effective placebo treatment.

How to Evaluate and Incorporate Integrative Therapies

- Discuss therapies with your medical provider. See helpful talking points in the section “How to Talk to Your Neurologist about Integrative Therapies” on page 52.
- Use the therapy or treatment to support and enhance traditional therapies treatments that have scientific proof for benefit rather than in place of these treatments.
- When possible, look for therapies with placebo-controlled research studies to support their use in people with PD.
- If there is no or limited research for the use of a desired therapy in people with PD, look for studies that evaluate the effect of these therapies in people with other chronic or neurologic conditions.
- Practice a healthy sense of skepticism when evaluating therapies based on individual stories, strong marketing campaigns, and promises.
- Don't expect vitamins and supplements to substitute for healthy nutrition or replace your medications.
- Check the label for exact contents and listed side effects. If a product does not contain a detailed label, consider not taking it.
- Analyze the risks and benefits of a treatment. If you determine that a treatment is high risk, you should not try it unless you find scientific evidence supporting its benefit.
- Broaden your definition of risk and benefit to include *extended risk* and *extended benefit*:
 - *Extended benefit* includes unanticipated or potentially unexplained results of using a therapy or treatment. For example:
 - ▶ There is no clear scientific explanation for the effects of Reiki therapy, yet there are measurable physiologic changes to suggest that Reiki can enhance the relaxation response important for health and healing.
 - ▶ You may change your behavior to focus on more positive activities or habits, such as diet and exercise, if you have less pain, more energy, and a greater focus on health.
 - *Extended risk* refers to activities you are not doing or thoughts you may have because of the treatment that can be detrimental to your health. For example:

- ▶ You choose not to go to the gym because you receive massage therapy.
- ▶ You do not improve your diet because you take vitamins.
- ▶ You do not think appropriate medicine is needed since you take supplements.

Another example of extended risk is cost. If the cost of a therapy could otherwise be used for an activity with proven benefit, such as exercise, healthy diet, or mindfulness classes, then it might not be money well spent.

- Look for products with the designation “USP Verified.” The U.S. Pharmacopeial Convention (USP) is a scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements. The “USP Verified” label ensures that supplements and natural therapies are produced, labelled, and stored according to accepted guidelines and Good Manufacturing Practices (GMP).
- 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.
- Choose a balance of activities: your treatment plan could include a combination of therapies that focus on nutrition, physical and muscular health, and emotional wellbeing.
- Choose a balance of active and passive therapies. Active therapies require work and focus; examples include mindfulness meditation and maintaining a healthy diet. Passive therapies do not require such focus and include massage therapy and vitamins.
- Seek out therapists and practitioners that hold specific credentials and certification or structured training in their field.

HOW TO TALK TO YOUR NEUROLOGIST ABOUT INTEGRATIVE THERAPIES

Adapted from Optimal Health with Parkinson's Disease. A Guide to Integrating Lifestyle Alternative and Conventional Medicine by Dr. Monique L. Giroux, page 47.

Estimates suggest that less than half of people with PD talk to their health care provider about the complementary therapies they use. Some people do not bring it up because they don't want their providers to know, or because they don't think it's important. Other people wait for providers to ask, but many do not. This might be because they lack knowledge of these therapies or are skeptical of – and therefore hesitant to discuss or promote – them.

Fortunately, a growing number of U.S. medical schools now offer courses in complementary medicine, combining the best of Western science with other treatment modalities. The National Institutes of Health has also been instrumental in disseminating research data to practicing health care professionals through the National Center for Complementary and Integrative Health (NCCIH).

The following tips and examples can help you talk to your doctor even if he or she is skeptical of integrative therapies.

- Begin with a discussion of your goal for treatment before discussion of a specific treatment option: "I am interested in finding non-medical ways to treat my back pain. My goal is to reduce pain so that I can reduce reliance on pain medicine."
- Reinforce your self-care values and priorities: "I have always been interested in personal healing and believe that certain non-traditional therapies can be helpful. Trying these therapies also gives me a sense of hope and control, which is important to me."
- Describe the mechanism by which you believe a certain therapy may help: "Research supports the use of acupuncture for pain."
- Reinforce the fact that you would like to begin this therapy for your own self-care and not to replace appropriate traditional therapies they may prescribe: "I know this is not the only solution, so I will continue to take my medicines and see the physical therapist prescribed to help my back."
- Discuss the potential risk of the treatment and what you will measure as a sign of progress as well as reason to continue, limit, or stop treatment: "According to my research, the risk of acupuncture is low. I will be sure to find an acupuncturist that is trained and certified. There is cost associated with this treatment, so I will discuss my pain control goals with the therapist before starting and agree on a specific number of treatments before re-evaluating benefit. I will also be sure not to change any medicines without discussing with you [neurologist] first."

KEY POINT: Complementary therapies can be used to ease medication burden, but should not replace Parkinson's medications or the treatments recommended by your neurologist.

INTEGRATIVE THERAPIES

The National Center for Complementary and Integrative Health (NCCIH) categorizes integrative therapies as generally falling into one of two subgroups:

1. *Natural products* include plant-derived chemicals and products, vitamins and minerals, and probiotics. They are widely marketed and available and are often sold as nutritional supplements.
2. *Mind and body practices* include a range of procedures and techniques administered by someone who is trained in that method. The focus is on the interaction between mind, body, social, mental, and spiritual factors, and include yoga, chiropractic manipulation, meditation, massage, and acupuncture.

While not a complete list, the following section describes therapies studied for use in PD as well as some common therapies used by people with PD. The information provided should not be taken as recommendations for these substances, but should be used as discussion points when consulting with your licensed health care professional.

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 integrative therapies.
- There is no guarantee of safety, strength, or purity of supplements not monitored by the FDA.
- Beware of unproven treatments or websites – check everything with your health care team.

Natural Therapies

Natural therapies – plant-derived chemicals and products, vitamins, and supplements – are used by people who believe they will promote cell health and healing, control symptoms, and improve emotional wellbeing.

Vitamins and Minerals

Vitamins and minerals are not produced by the body, but they are needed in small amounts for cell growth and development. Vitamins are complex organic chemicals, meaning they can be broken down by chemical reaction; minerals are inorganic compounds, which cannot be broken down by chemical reaction. Both vitamins and minerals are found in foods and also can be taken as supplement pills. Research across many different disease states has indicated that people benefit more when they get their vitamins and minerals primarily from foods, rather than pills. This is based in part on the concept of food synergy: vitamins in their natural form are better absorbed and work together for benefits compared with the artificial ratios and chemical derivatives found in many vitamin supplements. Furthermore, there is no data to suggest that taking vitamin supplements when you are not actually deficient in those vitamins will improve health or symptoms. In other words, if you have regular levels of vitamin D, for example, you are not likely to receive benefits from taking extra vitamin D pills.

Calcium and Vitamin D

Ninety-nine percent of calcium is stored in bones. It improves bone strength and protects against osteoporosis (low bone density) and fractures from falls. Most men need 1000 to 1200mg of calcium daily, and women need about 1200mg daily. Research cautions that calcium in supplement form carries some risk not present with food sources of calcium. When researchers analyzed data from 8,000 people in 15 studies, they found that if 1,000 people were given calcium supplements for five years, they would experience 14 heart attacks, 10 strokes, and 13 deaths, in exchange for preventing just 26 fractures.

Vitamin D is the “sunshine vitamin”: it is produced by the body when ultraviolet rays from sunlight hit the skin. It plays an important role in bone health by increasing how much calcium your bones can absorb. Low vitamin D levels are associated with an increased risk of developing PD, as well as depression, cognitive impairment, and falls. However, there is no data that shows treatment with vitamin D slows the progression of PD or alters symptoms after diagnosis.

Vitamin D is fat-soluble (stored in body fat), so it can be dangerous if taken in high doses. The U.S. Institute of Medicine recommends that a vitamin D level of 20 ng/mL (50 nmol/liter) or above is adequate for bone health. A simple blood test can determine if your vitamin D level is low or if you’ve had too much.

Food sources

- Calcium is found in many foods.
 - Milk, yogurt, and cheese are the main sources of calcium for most people in the U.S.
 - Kale and broccoli are vegetable sources of calcium.
- Few foods in nature contain vitamin D.
 - Fatty fish like tuna, mackerel, and salmon are some of the best sources of vitamin D.
 - Most milk sold in the U.S. is fortified with vitamin D.

B Vitamins

Diets low in B vitamins are linked with various negative effects, while diets high in B vitamins can lower risk for some conditions. For example:

- Low vitamin B12 is linked to cognitive difficulties and peripheral neuropathy (loss of sensation in feet that can worsen balance).
- Folate deficiency is linked to depression.
- People with diets high in B6 have lower risk of PD.

Furthermore, vitamins B6, B12, and folate can reduce excessive levels of homocysteine produced when levodopa is metabolized. This is beneficial, as elevated levels of homocysteine can cause blood clots, heart disease, and stroke.

Repeated studies show strongest benefits when B vitamins are ingested from foods and fail to show a consistent benefit of taking vitamin B pills in the absence of vitamin B deficiency. Vitamin B6 dose should be less than 100mg daily, as higher levels can cause nerve toxicity, interact with the PD medicines MAO inhibitors (rasagiline and selegiline), and block the absorption of levodopa.

Food sources

- Vitamin B6 is found in poultry, fish, and organ meats, as well as potatoes and other starchy vegetables.
- Beef liver and clams are the best sources of vitamin B12. It is also found in fish, meat, poultry, eggs, milk, and other dairy products.
- Plant foods have no B12.

Vitamins A and E

Vitamins A and E have strong antioxidant properties (see below). Diets high in carotenoids (natural vitamin A) and vitamin E are associated with lower risk of PD, though there is no evidence that taking these vitamins treats PD once diagnosed. In fact, taking high-dose vitamin E is linked to premature death, underscoring that it is preferable to consume vitamins from food rather than in pill form.

Food sources

- Vitamin A is found in beef liver and organ meats, but these are high in cholesterol, so limit their intake.
- Green leafy vegetables and colorful vegetables such as broccoli, carrots, and squash are good sources of vitamin A.
- Nuts, seeds, and vegetable oils are among the best sources of vitamin E.

Antioxidants

Antioxidants are compounds that reduce the cell-damaging effect of oxidative stress, a toxic byproduct of cell metabolism that is thought to cause nerve cell death when left unchecked in PD and other neurodegenerative disorders. Similar to vitamins and minerals, antioxidants from foods display stronger disease-fighting capacity than pill-based antioxidants. Colorful fruits and vegetables, legumes, green tea, coffee, whole grains, and many seeds and nuts are food sources of antioxidants.

Glutathione and N-Acetyl Cysteine

Glutathione is a powerful antioxidant, but its levels decline as we age. It decreases in the substantia nigra of people with PD long before symptoms are significant. Glutathione is composed of three amino acids (building blocks of protein), so it is digested in the gastrointestinal tract (similar to proteins). This means it is not effective if taken in pill form, as most pills are digested in the stomach. Despite this fact, glutathione is sometimes advertised in pill form, reminding us that supplements and their marketing are not strictly regulated. N-acetyl cysteine is an alternative pill option, since it is converted to glutathione in the body.

Intravenous (IV) glutathione has been studied but has failed to show a benefit over placebo. In addition, IV therapy is expensive and comes with risk, such as pain and infection at the IV insertion site. Current studies using a glutathione nasal spray are showing some promise.

Inosine and Uric Acid

Inosine and uric acid are powerful antioxidant and anti-inflammatory agents. Inosine is metabolized to uric acid in the body. People with PD tend to have lower uric acid levels, while higher levels of uric acid correlate with a slower decline in PD motor symptoms. At the same time, high uric acid levels can cause a painful form of arthritis called gout, as well as kidney stones and high blood pressure. A phase 3 clinical trial is underway to test whether inosine is an effective therapy in PD (see Chapter 6 for more information on the research process).

Anti-inflammatory Agents

Anti-inflammatory agents reduce cellular inflammation, which is a proposed cause of ongoing nerve cell death in PD.

Omega-3 Fatty Acids (Fish and Krill Oil)

Diets high in omega-3 are associated with a lower risk of arthritis, stroke, depression, cognitive decline, and Alzheimer's disease. There is no direct connection between PD and omega-3 fatty acids, but studies remain limited.

Fish oil is derived from the tissues of oily fish, while krill oil is obtained from small sea-living crustaceans. Fish oil pills are the most commonly used omega-3 supplement. Typical doses of fish oil are 1000 to 1500mg daily combined DHA and EPA (two types of fish-derived omega-3 fatty acids). In a placebo-controlled study, fish oil with and without antidepressants improved PD depression.

Food sources

- Cold water oily fish such as salmon, mackerel, sardines, herring, halibut, and tuna are natural sources of omega-3 fatty acids.
- Vegetarian sources include flax seed, purslane, pumpkin, and walnuts, but these are less potent.

Curcumin

Curcumin is a polyphenol with strong anti-inflammatory and antioxidant properties. It is found in the turmeric root, which is an important ingredient in Indian cooking (responsible for the yellow color of curries). Turmeric is under study for its use in PD, dementia, cancer, and brain injury.

Bioenergetics

This category includes compounds that enhance cell energy production or serve as a brain or muscle energy source.

Coenzyme Q10

Coenzyme Q10 (CoQ10) is an antioxidant that assists in the mitochondrial energy production that is necessary for cell life. (Mitochondria are small, energy-producing structures inside cells – the “power plants” of cells.) Interest in CoQ10 stems from the finding that PD is associated with mitochondrial dysfunction and impaired energy production. People with a specific mitochondrial disease can be treated with CoQ10, however a large, multicenter study using large doses of CoQ10 failed to show any benefit and was halted early.

Furthermore, CoQ10 can be expensive, and what you get differs from one commercial product to the next. This supplement is fat-soluble, so absorption can vary based on foods eaten, time of day taken, other supplements taken at the same time, and the type of CoQ10 used.

Coconut Oil and Medium Chain Fatty Acids

Coconut oil contains an abundance of medium-chain fatty acids (defined by the number of carbon molecules in the chemical structure), which are a good energy source. Medium-chain fatty acids are metabolized to ketone bodies, and the brain actually uses ketones preferentially and more efficiently than glucose. There is longstanding interest in diets high in medium-chain fatty acids for Alzheimer's disease, and there have been some reports of improvement in measures of cognitive function. However, there are no published studies of coconut oil in people with PD.

Hydroxybutyrate is a ketone body under study for potential neuroprotective effects in PD.

Creatine

Creatine is a naturally occurring amino acid found in foods (especially meat); in the human body, its greatest concentration is in our muscles. Interest in creatine for use in PD is based on its role in improving mitochondrial energy production, muscle mass, and strength. A large, multicenter trial on the effects of creatine on people with PD was stopped early when analysis showed no difference between supplement and placebo.

Neurochemicals and Neuromodulators

Some practitioners are attempting to help their patients by using drugs or supplements that are classified as either neuromodulators – which they believe will interact with our brain's immune health and circadian body rhythms or neurochemicals – which activate or inhibit nerve cell activity.

Melatonin

Melatonin is a powerful antioxidant that is responsible for regulation of circadian rhythms, sleep, and wakefulness, so it is sometimes used to help people sleep. In a small study in people with PD who were carefully monitored, modest improvements in sleep quality were experienced with 5mg and 50mg, with the 50mg showing more favorable results. Melatonin 3 to 12mg can also reduce REM sleep behavior disorder. However, the safety of doses higher than 3mg is not established, so use with caution. Early morning sedation, depression, and vivid dreaming are experienced by some people who take melatonin; it can also alter blood sugar levels in people with diabetes and influence the immune system.

Naltrexone

Naltrexone is traditionally used to treat alcohol and narcotic (opioid) addiction or overdose, as it blocks opioid receptors in the brain and spinal cord (this system plays an important role in regulating pain). Naltrexone at lower doses (4.5mg) is used in multiple neurologic conditions including PD, multiple sclerosis, and impulse control disorders, but reports of benefit in PD are based on anecdotal or individual experiences that do not control for diagnosis, symptoms studied, or placebo effect, and overall research suggests that naltrexone does not improve motor symptoms. Despite this lack of evidence, this supplement continues to gain a significant following based on individual reports and strong marketing.

Botanicals

These are herbs or chemical derivatives of plants or plant-based agents used for their medicinal properties.

Marijuana

Marijuana refers to the dried leaves, flowers, stems, and seeds from the hemp plant *Cannabis sativa*. Although there are many chemicals with biologic activity in the plant, tetrahydrocannabinol (THC) and cannabidiol (CBD) carry the greatest medicinal interest. THC is the chemical known for its mood-altering effects, and CBD is a powerful antioxidant that has shown neuroprotective effects in research models of head injury and neurodegenerative disease. The latter holds promise for medical use since it does not have the psychoactive effects described with the marijuana plant or THC compound. People with PD have self-reported that use of marijuana helps manage nausea, loss of appetite, muscle spasm and spasticity, pain, and anxiety. A recent study showed improved sleep, pain, tremor and bradykinesia (motor slowness) 30 minutes after smoking marijuana in clinic.

However, it is not clear whether these benefits are from a direct effect of marijuana on PD brain chemistry or physiology. Marijuana has psychoactive, behavioral, and motor effects, which can all impact tremor and movement. For example, tremor will increase with stress and improve with treatments known to enhance relaxation. Marijuana's behavioral effects may lead to greater relaxation or euphoric mood, or may mitigate the stress response, and this alone could reduce tremor. As with any drug, there are pros and cons to using marijuana, and it is important to review these with your healthcare provider. In particular, the lack of regulation and the potential addictive and psychoactive consequences (including psychosis and apathy) are potential concerns. For more information on marijuana and PD, visit www.parkinson.org/marijuana.

Mucuna Pruriens

Mucuna pruriens, or cowhage seeds, have been used in India and Ayurvedic medicine for the treatment of PD for thousands of years because they contain 3-4% levodopa. Because of this, *mucuna pruriens* is often referred to as natural dopamine.

A small, controlled study comparing the effect of carbidopa/levodopa and *mucuna pruriens* in patients with motor fluctuations and dyskinesia showed faster and longer "on" time, without dyskinesia, after *mucuna* treatment. The authors propose that benefits from *mucuna pruriens* may be due to more than just levodopa.

Mucuna pruriens contains levodopa and therefore carries the same potential risks and side effects of levodopa. A greater concern is the lack of information about purity, strength, contamination, and toxins such as pesticides when purchased as a supplement.

Mind-Body Therapies

Mind-body therapies work on the premise that the mind, body, and spirit do not exist in isolation and that disease and/or symptoms change when these are out of balance. Many people feel these therapies make a difference for them. Practitioners believe that these therapies help by:

- Improving emotional wellbeing
- Enhancing cellular healing
- Improving physical or cognitive performance and symptom control
- Enhancing resiliency
- Promoting inner peace, acceptance, and relaxation
- Increasing positivity

Body Therapies

The following therapies use movement of the physical body for benefit.

Feldenkrais Method and Alexander Technique

The Feldenkrais Method and Alexander Technique are ways of learning how to reduce tension in the body through exercises that improve coordination, agility, and balance. These methods help participants learn and habituate new movements that studies have indicated may help reduce falls. The focus is on mind-body awareness, rather than exertion and fitness like traditional exercise, and they also offer benefits to individual feelings of comfort and body image.

The Alexander Technique and Feldenkrais Method have many similarities and some subtle differences. Alexander Technique uses a structured hands-on approach for awareness of alignment and body position, while the Feldenkrais Method focuses on practitioner guidance and spontaneous and self-generated expression to increase ease and range of motion. Feldenkrais improved PD-associated balance problems, and the Alexander Technique improved measures of disability, depression, and attitudes toward self-care compared to a group getting massage or no treatment, and this effect seemed to persist after active training ended. In addition, the focus of the Alexander Technique on upper body postures and voice suggest that this may be of help for speech problems associated with PD, but no studies have yet tested this hypothesis.

Massage

There are many different types of massage and massage techniques. Some, such as medical massage, focus on relaxation, while others focus on muscle and deep tissue relaxation/release. Clinical studies investigating the benefits of massage in PD have shown improvement in self-reported daily activities and self-confidence. Avoid massage over DBS batteries, wires and scalp. Aggressive massage can exacerbate spasm associated with dystonia.

Music Therapy

Music therapy uses components of sound such as beat, melody, tone, and lyrics to promote healing. Research suggests that music therapy can reduce bradykinesia (slow movement)

and rhythmic sound can help freezing of gait. Music and sound can be used to improve many symptoms, including speech, apathy, low energy, and mood. A music therapist is certified by the Certification Board for Music Therapists (www.cbmt.org).

Tai Chi and Qigong

Tai chi is both an ancient martial art and an exercise. Characterized by gentle, flowing movement couple with breathing, it is becoming increasingly popular due to its low impact on joints. Qigong combines the breath with subtle, flowing movement along with focused attention to release life energy (chi) and reach a calm state of mind. Both tai chi and qigong have been shown to improve in people with PD.

Yoga and Therapeutic Yoga

Yoga unites the mind and body through physical postures, use of the breath, and meditation to bring awareness to sensations of the body, thoughts, and emotions. Hatha yoga uses physical postures (poses) to join the mind and body. Therapeutic yoga blends traditional yoga with gentle postures, breathwork, meditation, and guided imagery to promote physical health, relaxation, and emotional healing. Therapeutic yoga programs are often designed to promote relaxation, reduce pain, enhance mood and relaxation, and support healing in the setting of chronic illness. It is best to look for a teacher who has experience working with people with Parkinson's.

Mindful Therapies

These therapies use the mind to influence thoughts, stress, emotional responses, and physical and sensory awareness. Examples of mindful therapies include biofeedback, guided imagery, hypnosis, guided breathwork, and meditation. Mindfulness meditation is reviewed below.

Mindfulness Meditation

Meditation is a broad term defining many practices designed to focus the mind to enhance relaxation, gain insight and control over emotional and physical responses to daily experiences, and improve compassion as well as mental or physical performance. Meditation can be performed both informally and formally. There are many formal meditation practices, including concentrative, heart-centered, mindfulness-based, reflective, creative, and visualization-based practices, but it can also be done informally. There are many apps for that!

Mindfulness-based meditation involves bringing attention or awareness to the moment without judgment. Focus is on observation, insight, and letting go. Mindfulness is particularly helpful for living with chronic illness: it increases resiliency by encouraging living life to the fullest despite, in response to, or as a result of difficulties. This is done through understanding that each moment is impermanent, change is part of life, and you have control of your thoughts, all of which helps prevent the downward spiral that can accompany distress.

Numerous studies across multiple conditions show that mindfulness meditation improves quality of life, sleep, and mental function and decreases depression, anxiety, fatigue, and pain. Studies examining the effect of this therapy on PD are underway. Brain MRI studies in people with PD practicing mindfulness meditation showed changes in brain activity and size in the amygdala, hippocampus, thalamus, and caudate nucleus, all important brain structures for control of movement, learning, and stress.

Energy Therapy

Energy medicine is a unique form of mind-body therapy based on the premise that energy is an important part of health and balance. Practitioners believe that systems of energy exist within our body, between individuals, and in the environment. They believe that balance of these energy systems affects health, and blockage or disequilibrium impacts disease. Practitioners of energy therapies use sound and heat as well as visual, electromagnetic, tactile, and emotional energy to heal.

Acupuncture

Acupuncture is an ancient treatment originating over 2500 years ago. Different forms or styles of acupuncture are performed in the U.S., influenced by Chinese, Japanese, or Korean medicine. An acupuncturist inserts tiny needles into specific body areas that they believe will change the flow of energy or Qi. According to these practices, health is associated with unobstructed energy flow, and disease is associated with blocked Qi. They believe that energy flows through the body along channels or meridians. Acupuncture points are locations where they believe these meridians are close to the skin's surface. While some studies have found a benefit from acupuncture, other studies have found that "sham acupuncture" (where a practitioner applies the acupuncture needles into places on the body that are not acupuncture points) is as good as true acupuncture.

Reiki

Reiki is a Japanese technique for healing and stress reduction that adherents believe works on the premise that an unseen energy or life force flows within our bodies and between individuals. Through placement of hands on or over different areas of the body, the Reiki practitioner is believed to transfer, guide, and direct flow of energy. Like many mind-body therapies, there are no objective controlled studies evaluating the effect of Reiki on PD, and benefits rely on personal stories and experiences. Nonetheless, there is much interest in Reiki therapy in the PD community. Meta-analysis of multiple studies suggests that Reiki may have positive effects on pain and anxiety.

USE TECHNIQUES THAT WORK FOR YOU

Many people enjoy benefits from these techniques even though some have no scientific foundations and some have been tested scientifically and have failed. If integrating one or more of these alternative techniques into your care helps you feel better and more in control of your life and symptoms, there is no reason to wait for science to validate your choices. While scientists may have found no evidence that Qi exists and that acupuncture changes it, several studies have found that, for example, acupuncture does help patients who have chronic pain. If something helps you to live your best life, you don't need scientists to figure out how it works before you take advantage of that benefit!

Chapter 6

Research and Future Developments

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. You can also visit www.clinicaltrials.gov, a website sponsored by the National Institutes of Health (NIH), which offers information on clinical trials.

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 THERAPIES 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 approval of Sinemet (carbidopa-levodopa) in the 1970s, research has yielded many life-changing treatments for Parkinson's. Taking together research breakthroughs in our understanding of medications, therapies and devices to treat Parkinson's, today's best care yields a very different disease journey than was experienced a generation ago. Today's focus on non-motor symptoms is largely a consequence of how effective treatments for motor symptoms are.

Today, the biggest research challenge is slowing progression. It has been demonstrated that today's best treatment plan – which involves expert medication, therapy, exercise and sometimes surgery – slows your experience of Parkinson's progression and may actually be helping your brain fight the disease.

New research is investigating opportunities in several areas:

- **Slowing disease progression.** The holy grail of Parkinson's research is to slow the progression of the disease. If we could diagnosis the disease earlier and slow its progression, people might never actually experience troublesome symptoms, effectively getting a "vaccination" effect. Also, people with Parkinson's often have a combination of brain cells that die and others that get "sick" so that they don't work as well. If we could make a treatment that would slow the disease progression, some of these brain cells could get better and start to work again, resulting in a moderate improvement in status.
- **Replacing lost function.** For people who have Parkinson's, it would be great if we could come up with therapies that would help the brain to function more like it does in people without Parkinson's. To date, there is not much evidence that this can be successful, with surgical approaches like transplants of brain cells failing to be effective in well-designed trials. However, there are scientists who are still working on studying therapies to replace lost cells in the brain, and there have been some promising developments.
- **Preventing Parkinson's.** Many researchers are looking at genetic and environmental causes of Parkinson's to see if they can identify targets for drugs that would help brain cells to fight the changes that cause Parkinson's. If we could do this, then our children could be tested for risk factors, and people with a high risk for Parkinson's could receive treatments to prevent it. Such a treatment might also slow Parkinson's disease in people who already had the disease, but it might not.
- **Diagnosing Parkinson's and measuring progression.** Most people with Parkinson's can be easily diagnosed by a neurologist using standard clinical tests. However, sometimes it can be difficult to tell the difference between Parkinson's disease and other conditions that mimic it, like when you experience Parkinson's-like symptoms because of other medications, essential tremor or a small stroke. Further, figuring out how far Parkinson's has progressed or your progression since your last evaluation is also difficult, as it may depend on where you are in terms of fluctuating medication effect, your level of fatigue and whether or not you got stuck in traffic on your way to the clinic. A better measure for progression would help with clinical trials of treatments to slow the disease.
- **New symptomatic treatments.** While treating the symptoms of the disease is not the same as slowing its progression, we are quite confident that exercising at least 2.5 hours a week does slow your experience of disease progression. In order to exercise, you need to have your symptoms optimally in control. Research is ongoing in many areas, including helping people who experience fluctuating medication effects (i.e., "on-off fluctuations"); reducing dyskinesia; achieving better motor control; and managing a range of symptoms, from mood and psychiatric symptoms to autonomic symptoms like lightheadedness on standing (orthostatic hypotension), constipation and others.

Parkinson's research has made amazing progress in the last two decades, and all the signs suggest that progress will continue unabated. There are trials, drugs and therapies on the horizon that are likely to help people with PD in the next few years, but these change frequently as studies show effects or no effects of a particular treatment. Please visit the NPF website, www.parkinson.org, to find information and resources on the newest research and treatment options. You can also contact the NPF Helpline at 1-800-4PD-INFO or helpline@parkinson.org for help finding a clinical trial near you, so that you can help scientists find the next breakthrough therapy!

WHAT DO WE MEAN BY CURE?

People often talk about how we need a *cure* for Parkinson's disease. What does that really mean?

- The first step in curing Parkinson's would be **stopping the disease progression**, or slowing it enough that we can't tell the difference between Parkinson's and the changes people experience naturally from aging. There are a number of ways in which scientists are working to help brain cells fight the effects of Parkinson's. Most of this work is looking at drugs that people with PD could take or have administered at a hospital or clinic. Scientists have some good leads that they are following with the hope of slowing the disease.
- The second step would be **restoring lost function**. To some extent, we do this every day through interventions like exercise, physical therapy, occupational therapy and speech therapy, where clinicians help you compensate for the changes caused by Parkinson's. All of us have to compensate for changes in our bodies and brains as we age, and so good therapy really does restore lost function. However, we would like to gain this benefit faster, and some of the changes with Parkinson's can't be corrected with therapy, so there is research into ways to restore cells that have been lost. Scientists call this neurorestoration. Unfortunately, unlike bones and skin, the brain doesn't have systems to automatically repair itself or to integrate a graft or transplant to replace cells that have been lost. So far, neurorestoration has turned out to be a very hard task.

A **cure for Parkinson's** would ideally offer both of these benefits. However, if we had a treatment that could dramatically slow or stop disease progression, with early diagnosis we could hold people in the earliest stages of Parkinson's for a long time.

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).

Antihistamine – A drug normally used to control allergies or as a sleep aid; some (like Benadryl) are anticholinergic drugs, with anti-tremor properties.

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); and sweating abnormalities including decreased or excessive sweating.

Benzodiazepines – A popular and effective class of anti-anxiety drugs.

Catechol-o-methyl transferase (COMT) – An enzyme that inactivates levodopa in the body before it gets to the brain. COMT inhibitors block the work of the enzyme, so more levodopa is available to the brain.

Compulsive behaviors – Performing an act persistently and repetitively without it necessarily leading to an actual reward or pleasure; in Parkinson's, this can be a side effect of dopamine agonists and usually takes the form of uncontrolled shopping, gambling, eating, or sexual urges. If you experience this symptom, tell your doctor immediately.

Confusion – The state of being unclear, with lack of understanding of situation and/or surroundings; a symptom of many medications for Parkinson's motor and non-motor symptoms.

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.

Diminished/decreased libido – Decreased sexual urges; a symptom of many medications for depression and anxiety.

DNA – Deoxyribonucleic acid; the basic chemical substance that makes up a gene.

Double-blind study – A study in which neither the participants nor the investigators know which drug a patient is taking; designed to prevent observer bias in evaluating the effect of a drug.

Dry mouth – Usually from decreased saliva production; a side effect of many medications for motor and non-motor symptoms.

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).

Extended benefit – Unanticipated or potentially unexplained results of using a therapy or treatment.

Extended risk – Activities you are not doing or thoughts you may have because of a treatment that can be detrimental to your health.

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.

Hallucinations – Something you see, hear, smell, taste, or feel that is not actually there; can be a side effect of anticholinergics and some medications for depression and anxiety.

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

Holistic – Characterized by the treatment of the whole person, taking into account social and other factors, not just symptoms of disease.

Homocysteine – An amino acid that occurs in the body and is produced when levodopa is metabolized; elevated levels of homocysteine can cause blood clots, heart disease, and stroke.

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.

Integrative medicine – Involves bringing together conventional and complementary approaches in a coordinated way. The National Center for Complementary and Integrative Health uses the term "complementary health approaches" when discussing practices and products of non-mainstream origin, and the term "integrative health" when talking about incorporating complementary approaches into mainstream health care.

Low blood pressure – When blood pressure is below normal (normal range is usually between 90/60 mmHg and 120/80 mmHg); the medical name for low blood pressure is hypotension; common side effect of levodopa and dopamine agonists. *See also "neurogenic orthostatic hypotension."*

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.

Mind-body therapies – Therapies that work on the premise that the mind, body, and spirit do not exist in isolation and that disease and/or symptoms change when these are out of balance.

Monoamine oxidase type B (MAO-B) – An enzyme in our body that breaks down dopamine; MAO-B inhibitors block the work of the enzyme, so there is more dopamine available in the brain.

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.

Natural therapies – Plant-derived chemicals and products, vitamins and minerals, probiotics, and nutritional supplements used to promote cell health and healing, control symptoms, and improve emotional wellbeing.

Nausea – A feeling of sickness with an inclination to vomit; common side effect of many medications for Parkinson's symptoms.

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.

Neuroplasticity – The brain's ability to reorganize itself by forming new connections. This allows the brain to compensate for injury and disease and to respond to new situations and changes in the environment.

Neurogenic orthostatic hypotension (nOH) – Orthostatic hypotension (OH) is a drop in blood pressure that happens within a few minutes of standing up. Parkinson's disease and some other diseases can cause OH – in this case, it is called neurogenic OH, since it is related to dysfunction of the nervous system.

Neuroprotection – An effect that results in recovery, repair, or regeneration of nervous system structure and function.

Neurorestoration – Repair, replacement, or regeneration of brain cells.

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).

"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.

Oxidative stress – A toxic byproduct of cell metabolism that is thought to cause nerve cell death when left unchecked in PD and other neurodegenerative disorders.

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.

Placebo effect – The commonly observed phenomenon that people in drug studies tend to have improvement in their symptoms even when they are not receiving the actual study medication or therapy. This benefit above and beyond any actual biological benefit is due instead to the belief that the treatment will work.

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).

Sialorrhea – Increased amount of saliva in the mouth, either from excessive production of saliva or decreased swallowing.

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.

Vivid dream – A dream that is very realistic and can be caused by awakening during the dream; common side effect of medications for depression and anxiety.

Appendix B

Medical Alert Card

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

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.



NATIONAL PARKINSON FOUNDATION

1.800.4PD.INFO (473-4636)
www.parkinson.org

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 antipsychotic 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.

Turn this card over for a list of contraindicated medications & important considerations if the patient has a brain device & needs a MRI/EKG/EEG.

MY NAME _____

HOME ADDRESS _____

PERSON TO CALL _____ PHONE _____

PHYSICIAN _____ PHONE _____

ALLERGIES/OTHER MEDICAL CONDITIONS

Medications that may be Contraindicated in Parkinson's Disease

| Safe Medications: | Medications to Avoid: |
|--|--|
| ANTIPSYCHOTICS quetiapine (Seroquel®), clozapine (Clozaril®) | avoid all other typical and atypical anti-psychotics |

| | |
|---|--|
| PAIN MEDICATION most are safe to use, but narcotic medications may cause confusion/psychosis and constipation | if patient is taking MAOB inhibitor such as selegiline or rasagiline (Azilect®), avoid meperidine (Demerol®) |
|---|--|

| | |
|---|---|
| ANESTHESIA request a consult with the anesthesiologist, surgeon and Parkinson's doctor to determine best anesthesia given your Parkinson's symptoms and medications | if patient is taking MAOB inhibitor such as selegiline or rasagiline (Azilect®), avoid: meperidine (Demerol®), tramadol (Rybit®), Ryzolt®, Ultram®, droperidol (Inapsine®), methadone (Dolophine®, Methadose®), propoxyphene (Darvon®, PP-Cap®), cyclobenzaprine (Amrix®, Fexmid®, Flexeril®), halothane (Fluothane®) |
|---|---|

| | |
|---|--|
| NAUSEA/GI DRUGS domperidone (Motilium®), trimethoprim (Tigan®), ondansetron (Zofran®), dolasetron (Anzemet®), granisetron (Kytril®) | prochlorperazine (Compazine®), metoclopramide (Reglan®), promethazine (Phenergan®), droperidol (Inapsine®) |
|---|--|

| | |
|--|----------------------|
| ANTIDEPRESSANTS fluoxetine (Prozac®), sertraline (Zoloft®), paroxetine (Paxil®), citalopram (Celexa®), escitalopram (Lexapro®), venlafaxine (Effexor®) | amoxapine (Asendin®) |
|--|----------------------|

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 to 0.0 volts.
 - MRI should never be performed if the pacemaker is placed in

the abdomen or below and MRI should not be used to image structures of the body lower than the head (neck, abdomen, arms, legs or below) as dangerous heating of the lead could occur.

- EKG and EEG Warning**
- Turn off the DBS device before conducting EKG or EEG.
 - 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.

| Situation | Chance of Dozing or Sleeping |
|--|------------------------------|
| Sitting and reading | |
| Watching TV | |
| Sitting inactive in a public place | |
| Being a passenger in a motor vehicle for an hour or more | |
| Lying down in the afternoon | |
| Sitting and talking to someone | |
| Sitting quietly after lunch (no alcohol) | |
| Stopped for a few minutes in traffic while driving | |
| Total score (add the scores up) (This is your Epworth score) | |

Appendix E

Selected Readings

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

Gretchen Garie and Michael Church with Winifred Conkling, 2007.

10 Breakthrough Therapies for Parkinson's Disease

Michael S. Okun, MD, 2015.

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.

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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. 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.

Your generosity makes this publication possible.

The National Parkinson Foundation is proud to provide these educational materials at no cost to individuals around the globe. If you find these materials helpful, please consider a gift so that we may continue to fight Parkinson's on all fronts: funding innovative research, providing support services and offering educational materials such as this publication. Thank you for your support.

| | |
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Index

- Acetylcholine 7, 20, 29, 32, 67
 Acetylcholinesterase inhibitors 29, 32
 Acupuncture 25, 53, 62
 Adderall 36
 Alexander Technique 60
 Alprazolam 24, 27
 Alprostadil 43
 Amantadine 8, 10, 14, 19, 20, 29, 30
 Amitriptyline 26
 Amitiza 39, 41
 Anticholinergics 8, 10, 20, 29, 30, 35, 39, 40, 42, 43, 67, 69
 Antioxidants 56-59
 Antipsychotics 31, 33
 Apokyn 10, 15, 17, 40
 Apomorphine 8, 10, 15, 17, 39, 44
 Aricept 29, 32
 Artane 10, 20
 Ativan 24, 27
 Atropine eye drops 40, 41
 Azilect 10, 18
 Benadryl 20, 35, 67
 Benzodiazepines 24, 25, 27, 34, 35, 43, 67
 Benztropine 10, 20, 39
 Botox 40, 41
 Botulinum toxin A 40, 41, 44
 Botulinum toxin B 40
 Bromocriptine 15, 16
 Budeprion SR 27
 Budeprion XL 27
 Bupropion 27
 Buspar 24, 27
 Bupirone 24, 27
 Calcium 54, 55
 Carbidopa-levodopa enteral solution 9, 13
 Carbidopa-levodopa extended-release 9, 12, 35
 Carbidopa-levodopa extended-release capsules 9, 12
 Carbidopa-levodopa immediate release 9, 12, 35
 Carbidopa-levodopa oral disintegrating 9, 12
 Carbidopa-levodopa-entacapone 9, 19
 Caverject 43
 Celexa 25
 Cialis 43
 Citalopram 25
 Clonazepam 24, 27, 34, 35
 Clozapine 31, 33
 Clozaril See clozapine
 Coconut oil 58
 Coenzyme Q10 57
 Cogentin 10, 20
 Cognition 28, 29, 32, 46, 47, 68, 69
 Compazine 38, 41
 COMT inhibitors 8, 10, 14, 19, 67
 Comtan 10, 19
 Concerta 32
 Creatine 58
 Curcumin 57
 Cymbalta 26
 DaTscan 7
 Daytrana patch 32
 Deep brain stimulation (DBS) 7, 14, 60
 Delusion 29, 30, 68
 Dementia with Lewy bodies 5, 28, 68
 Desvenlafaxine 26
 Desyrel 26, 35
 Diazepam 27
 Diphenhydramine 20, 35
 Domperidone 38, 40
 Donepezil 29, 32
 Dopamine agonists 8-10, 14-17, 23, 24, 29, 30, 34-38, 43, 67
 Drooling 6, 21, 23, 33, 39, 40, 41
 Droxidopa 38
 Duloxetine 26
 Duopa 9, 13
 Dyskinesia 9, 10, 13-15, 19, 20, 34, 40, 44, 59, 65, 68, 73
 Dystonia 40, 44, 45, 60, 68
 Effexor 26
 Effexor XR 26
 Elavil 26
 Eldepryl 10, 18
 Entacapone 9, 10, 19
 Erectile dysfunction 43, 67, 70
 Escitalopram 25
 Ethopropazine 20
 Excessive daytime sleepiness 6, 15, 29, 32-36
 Excessive sweating 6, 21, 36, 41, 43, 44
 Executive function 28, 47
 Exelon 29, 32
 Exercise 7, 8, 23, 25, 45-52, 60, 61, 65, 66

| | | | |
|--|---|---|--|
| FazaClo | 33 | Motor fluctuations | 9, 10, 13, 14, 17, 19, 20, 44, 59, 65 |
| Feldenkrais Method | 60 | Mucuna pruriens | 59 |
| Fish oil | 57 | Music therapy | 60 |
| Flomax | 42 | Myobloc | 40 |
| Florinef | 37 | N-acetyl cysteine | 56 |
| Fludrocortisone | 37, 38 | Naltrexone | 58 |
| Fluoxetine | 25 | Namenda | 29, 32 |
| Fluvoxamine | 25 | Nausea | 9-12, 17, 18, 20, 21, 25-27, 32, 33, 38-41, 59, 70 |
| Galantamine | 29, 32 | Nefazodone | 26 |
| Glutathione | 56 | Neupro | 9, 15, 17 |
| Glycopyrrolate | 39, 41 | Neurogenic orthostatic hypotension | 6, 36-38, 65, 67 |
| Hallucination | 6, 10, 15, 19-21, 23, 26, 28-33, 68, 69 | Neuroplasticity | 48, 49, 70 |
| Hycosamine | 39 | Neuroprotection | 4, 18, 49, 58, 59, 63, 70 |
| Imipramine | 26, 42 | Neurorestoration | 63, 66, 70 |
| Impulse control disorders (ICDs) | 16, 35, 43, 58 | Niravam | 27 |
| Inderal | 27 | Northera | 38 |
| Inderal LA | 27 | Nortriptyline | 26, 42 |
| InnoPran XL | 27 | Nuplazid | 31, 33 |
| Inosine | 56 | Oleptro | 26 |
| Insomnia | 6, 20, 22, 23, 25-27, 32-36 | Omega-3 fatty acids | 57 |
| Integrative medicine | 49, 69 | Ondansetron | 39, 40 |
| Klonopin | 24, 27 | Pain | 6, 21, 32, 36, 38, 40, 41, 44, 45, 51, 53, 56, 58, 59, 61, 62 |
| L-deprenyl | 10, 18 | Pamelor | 26 |
| Levitra | 43 | Papaverine | 43 |
| Lexapro | 25 | Parcopa | 9, 12 |
| Lodosyn | 12, 38, 40 | Parkinson's Outcomes Project | 11, 14, 16, 17, 20, 22, 23, 31, 46 |
| Lorazepam | 24, 27 | Parlodel | 15, 16 |
| Low blood pressure | 6, 9, 21, 33, 36, 37, 69 | Paroxetine | 25 |
| Lubiprostone | 39, 41 | Paxil | 25 |
| Luvox CR | 25 | Paxil CR | 25 |
| MAO-B inhibitors | 8, 10, 14, 17, 18, 25, 69 | Pergolide | 15, 16 |
| Marijuana | 59 | Periodic limb movements of sleep (PLMS) | 6, 33, 34 |
| Massage | 23, 25, 45, 51-53, 60 | Permax | 15, 16 |
| Meditation | 23, 25, 52, 53, 61 | Pexeva | 25 |
| Medium-chain fatty acids | 58 | Phenergan | 38, 41 |
| Melatonin | 35, 58 | Phentolamine | 43 |
| Memantine | 29, 32 | Pimavanserin | 31, 33 |
| Mestinon | 37 | Placebo | 18, 22, 37, 50, 51, 56-58, 63, 64, 70, 71 |
| Metadate CD | 32 | Polyethylene glycol | 39, 41 |
| Methylin | 32 | Pramipexole | 8, 9, 15, 17 |
| Methylphenidate | 29, 32, 36 | Pramipexole ER | 9, 15 |
| Metoclopramide | 38, 41 | Pristiq | 26 |
| Midodrine | 37, 38 | Proamatine | 37 |
| Milnacipran | 26 | Prochlorperazine | 38, 41 |
| Mindfulness | 52, 61 | Promethazine | 38, 41 |
| MiraLax | 39, 41 | Propranolol | 27 |
| Mirapex | 9, 15, 17 | Provigil | 29, 32, 36 |
| Mirapex ER | 9, 15 | Prozac | 25 |
| Mirtazapine | 23, 27, 35 | | |
| Modafinil | 29, 32, 36 | | |
| Motilium | 38, 40 | | |

| | | | |
|--|-------------------------------|---|--|
| Pyridostigmine | 37 | Tricyclic antidepressant | 23, 26, 42, 45 |
| Qigong..... | 61 | Trihexyphenidyl | 10, 20, 39 |
| Quetiapine | 31, 33, 35 | Trimethobenzamide | 17, 39, 40 |
| Rasagiline | 8, 10, 18, 19, 25, 55 | Uric acid | 56 |
| Razadyne | 29, 32 | Urinary symptoms..... | 6, 10, 20, 21, 23, 26, 39, 41, 42, 67, 70 |
| Razadyne ER..... | 32 | Valium..... | 27 |
| Regitine | 43 | Vardenafil..... | 43 |
| Reglan..... | 38, 41 | Venlafaxine | 26 |
| Reiki..... | 51, 62 | Viagra | 43 |
| REM sleep behavior disorder | 33, 34, 58 | Viibryd..... | 25 |
| Remeron..... | 27, 35 | Vilazadone..... | 25 |
| Remeron SolTab..... | 27 | Vitamin A | 56 |
| Requip..... | 9, 15, 17 | Vitamin B | 55 |
| Requip XL..... | 9, 15 | Vitamin D | 54, 55 |
| Restless leg syndrome | 6, 33, 34 | Vitamin E | 18, 56 |
| Ritalin | 29, 32, 36 | Vivid dreams | 7, 25-27, 30, 58, 71 |
| Ritalin LA | 32 | Wearing off | 10, 13-15, 35, 44, 70 |
| Ritalin SR | 32 | Wellbutrin | 27 |
| Rivastigmine | 29, 32 | Wellbutrin SR | 27 |
| Ropinirole..... | 8, 9, 15, 17 | Wellbutrin XL | 27 |
| Ropinirole XL..... | 9, 15 | Xanax | 24, 27 |
| Rotigotine..... | 8, 9, 15, 17 | Xanax XR | 27 |
| Rytary..... | 9, 12 | Yocon | 43 |
| Savella | 26 | Yoga..... | 23, 25, 48, 53, 61 |
| Scopolamine patch | 40, 41 | Yohimbine | 43 |
| Seborrheic dermatitis..... | 6, 21, 43 | Zelapar..... | 10, 18 |
| Selective serotonin reuptake inhibitor (SSRI) ... | 22-25 | Zofran | 39, 40 |
| Selegiline..... | 8, 10, 18, 25, 35, 55 | Zoloft..... | 25 |
| Seroquel..... | 31, 33 | Zyban | 27 |
| Seroquel SR..... | 33 | Zydis selegiline HCL oral disintegrating..... | 10 |
| Serotonin-norepinephrine reuptake inhibitor (SNRI)..... | 22, 23, 26 | | |
| Sertraline..... | 25 | | |
| Serzone | 26 | | |
| Sexual dysfunction | 6, 21, 22, 25, 42, 43, 67, 68 | | |
| Sialorrhea | 6, 39, 71 | | |
| Sildenafil | 43 | | |
| Sinemet | 9, 11-13, 15, 38, 64, 73 | | |
| Sinemet CR | 9, 12, 35, 73 | | |
| Sleep apnea..... | 33 | | |
| Stalevo | 9, 19 | | |
| Symmetrel..... | 10, 19 | | |
| Tadalafil | 43 | | |
| Tai chi | 23, 48, 61 | | |
| Tamsulosin | 42 | | |
| Tasmar..... | 10, 19 | | |
| Tigan..... | 17, 39, 40 | | |
| Tofranil..... | 26 | | |
| Tofranil PM | 26 | | |
| Tolcapone | 10, 19 | | |
| Trazodone | 26, 35 | | |



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