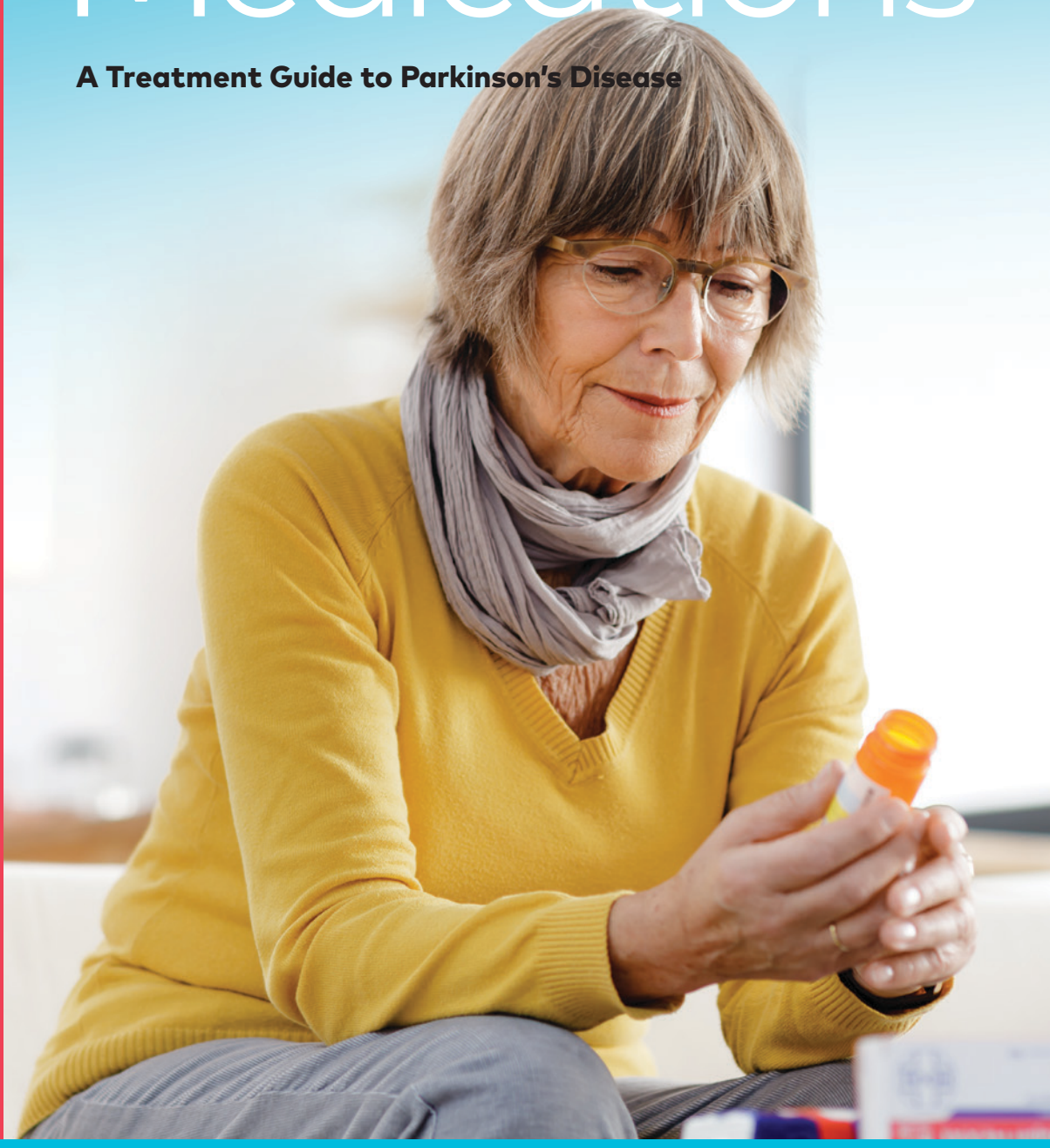
Medications

A Treatment Guide to Parkinson's Disease



Parkinson's Foundation

About this book

GLOSSARY

Definitions for all words underlined in blue can be found in the glossary starting on page 57. A comprehensive Parkinson's disease glossary can be found at Parkinson.org/Glossary.

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An index of key words and topics can be found on page 65.

PARKINSON'S FOUNDATION RESOURCES

Certain pages include tip sheets with practical pointers. You can find more helpful tips in the books, fact sheets, videos, webinars and podcasts in our PD library at Parkinson.org/Library.

There is no standard treatment for Parkinson's disease (PD). Treatment for each person with Parkinson's is based on his or her symptoms. There are many medications available to treat the Parkinson's symptoms, although none yet that reverse the effects of the disease.

It is common for people with PD to take a variety of these medications – all at different doses and at different times of day – to manage symptoms.

The information included here will explain the types of medications available to manage motor and non-motor symptoms in the hopes that it will help you to work with your Parkinson's specialist to find the right balance of medications to help you live well with Parkinson's.

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CHAPTER ONE

About Parkinson's Disease

If you're reading this book, you are probably already familiar with Parkinson's disease, but here are some basics: Parkinson's is a progressive neurodegenerative disorder that affects about one million people in the United States and 10 million people worldwide. It is called a movement disorder because of the tremors, slow movements, stiffness and muscle cramping it can cause. But its symptoms are diverse and usually develop slowly over time.

Parkinson's disease is not diagnosed with a test or a scan; instead it is diagnosed by a neurologist, who asks you questions about your health and medical history and observes your movement. Your doctor may want you to have some tests or imaging; some, like an MRI, can help rule out other conditions, while others, like DaTScan, may help confirm a Parkinson's diagnosis if there is uncertainty. The goal of treatment is to help you manage your symptoms. Good symptom management can help you to stay healthy, exercise, and keep yourself in the best possible shape. Although at this time there is no way to correct the brain changes that cause Parkinson's, we know that exercise can help you maintain your ability to fight the disease and that staying healthy can reduce setbacks that make PD progress faster. Great care is an important part of living your best life with Parkinson's.

Lack of dopamine in people with Parkinson's was first described in the 1960s. Dopamine is a type of neurotransmitter, or chemical messenger, one of several chemicals your brain cells use to send signals to one another. Soon after, dopamine-replacement therapy using levodopa became – and remains – the gold standard treatment. However, we know that the dopamine system is not the only one affected by Parkinson's. The disease process also disrupts other brain networks, including those linked to mood, behavior and thinking (cognition). You might also hear that Parkinson's is linked to a protein in the human brain called alpha-synuclein. Researchers continue to study how cells and brain networks are affected in Parkinson's to improve our understanding of the disease and potential for treatments.

You and your family may have questions or fears about Parkinson's and genetics. While there are several genetic mutations that can increase your risk, for the vast majority of people, Parkinson's is not inherited. There is no test that can accurately predict who will develop Parkinson's. Extensive gene and biomarker research is underway to uncover the possible factors involved in – not necessarily causes of – disease development.

CHAPTER TWO

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**
- **Adenosine A2a Antagonists**

The main goal of these medications is to lessen motor symptoms, or the symptoms that affect movement in people with Parkinson's disease. Since these symptoms are caused by changes in the amount of dopamine in the brain, most medications are used to replace, copy or enhance the effect of dopamine.

You can refer to the Medications for Motor Symptoms fact sheet included with this book for a summary of the medications used to treat the primary motor symptoms of Parkinson's disease (PD) including typical dosages, side effects and indications. Detailed discussions of the medications follow. Medications listed will follow the format of "general name (brand name)."

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, use of assistive devices and caregiver relief are all important aspects of the best treatment plan.

Pronunciation Key (accented syllable in bold)

NAME	PRONUNCIATION
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
Safinamide	Suh-**fin**-a-mide
Entacapone	En-**tak**-a-pone
Tolcapone	**Talk**-a-pone
Amantadine	A-man-**ta**-deen
Istradefylline	Iz-stra-da-**fi**-leen

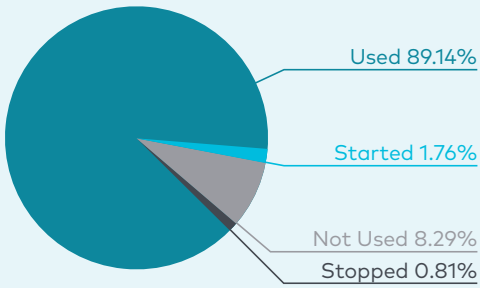
Levodopa

Through experimental trials in the 1950s, scientists discovered that depleting the dopamine in the brains of mice caused a condition that is similar to Parkinson's disease. Conversely, adding dopamine back into the brains of mice got rid of these symptoms. As they continued to experiment with these results, scientists successfully developed the medication known as levodopa in the 1960s.

Levodopa was the first medication proven effective for treating a chronic degenerative neurologic disease. When levodopa is in pill form, it is absorbed into the blood stream. It travels through the blood from the small intestine to the brain. Once it is in the brain, it is converted into dopamine. Levodopa that has not been converted into dopamine 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 screen that protects the brain by keeping out drugs and other chemicals that might be harmful.

LEVODPA USE IN PEOPLE WITH PARKINSON'S

As of November 2019, more than 35,000 evaluations had taken place on more than 13,000 people with Parkinson's. This chart shows the percentage of people using levodopa before and after visit and not using levodopa at each of those 35,000+ visits.



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 undesirable effect was the development of carbidopa, a drug that improves the effect of levodopa. Carbidopa does not enter the brain at usual dosages and prevents levodopa from being converted to dopamine outside the brain. When combined with levodopa, carbidopa allows an 80% decrease to the levodopa dose while maintaining the same benefits as a full dose.

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 major improvement to levodopa on its own, though nausea is a common side effect of carbidopa/levodopa.
The generic product is intended to be chemically the same as the name brand, and, for most people, works just as well. The rate of use for the generic brand in the body may be anywhere from 20% more to 20% less available than the name brand 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 make full use of your medication. Carbidopa/levodopa greatly reduces PD symptoms in the majority of persons with a clinical diagnosis of PD, although its effect on tremor may vary compared to its effect on other symptoms. Facial expression, posture, speech, gait and handwriting usually improves. Levodopa's half-life – a measure of how long a drug stays in the bloodstream before being broken down by the body – is relatively short, about 60–90 minutes. In early stages of the disease, considered the "honeymoon" period, people with Parkinson's may not take their levodopa consistently and still have no worsening of their PD symptoms. However, as the disease advances, Because levodopa has a short half-life, there may be fluctuations of blood and brain levels of dopamine, which is responsible for the motor fluctuations that people who have had PD longer may experience. Motor fluctuations result in "off" periods, which are times during the day when carbidopa/levodopa is not providing the optimal control in PD symptoms.

Levodopa is safe and effective for people with PD. There is no reliable data that levodopa speeds disease progression or produces damage to brain cells. Levodopa is extremely beneficial to people with PD, and can dramatically improve quality of life. Levodopa is effective throughout the disease course, however, due to disease progression, the dose of levodopa needs to be increased over time. There are certain symptoms that do not respond to levodopa, like falling, balance difficulty, speech, swallowing, or memory issues. Expert practitioners in the Parkinson's Foundation Parkinson's Outcomes Project report utilizing levodopa more than any other drug for Parkinson's therapy, and used levodopa more as the disease progressed.

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. It can be severe enough to interfere with activities of daily living and 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.

The likelihood of developing dyskinesia is low early in the disease, and – if it occurs – is usually mild. Most people with PD prefer some dyskinesia in order to get the most out of levodopa. Sometimes, the fear of dyskinesia leads to under treatment of PD symptoms. The ideal strategies for management of dyskinesia and the associated "wearing-off" are detailed below in discussing the adjunctive therapies to levodopa (dopamine agonists, MAO-B inhibitors, COMT-inhibitors, Amantadine and DBS).

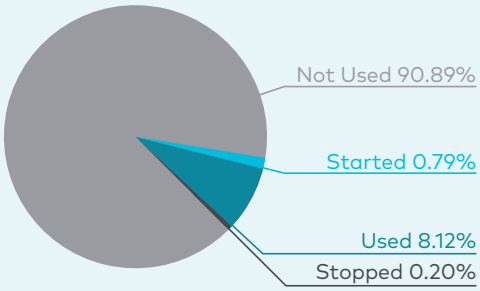
In 1988, the U.S. Food and Drug Administration (FDA) recommended that the daily dose of Sinemet should not exceed 800 mg per day, and as of 2013, this recommendation has not been revised. In 2018 the labeling of Sinemet recommends not exceeding a levodopa total daily dose of 2,000 mg per day. As movement disorder specialists, general neurologists and primary care doctors have learned, many people with Parkinson's can easily tolerate the higher doses used to minimize symptoms. Some people with PD encounter problems with insurance reimbursement of higher daily doses because of the FDA regulation. An insurance decision can be appealed if necessary.

A controlled release (CR) formulation was originally designed to enhance carbidopa/levodopa and possibly decrease "off" time and the number of pills needed per day. The CR pill is absorbed slower than regular carbidopa/levodopa. This may help people who need longer response times or overnight dosing. But, for others, this may be undesirable as there may be a delay in effect as only about 70% of the levodopa is usually absorbed before the pills pass through the intestinal tract.

Carbidopa/levodopa extended release (ER) capsules (Rytary), approved by the FDA in 2015, contain beads of carbidopa and levodopa that dissolve and are absorbed at different rates. Therapeutic levels are reached about an hour after taking it, similar to carbidopa/levodopa immediate release (IR). The levodopa levels in the blood are maintained for 4–5 hours before they decline. Clinical trials indicate that people who experience changes in motor symptoms throughout the day on other oral carbidopa/levodopa products may be able to switch to carbidopa/levodopa ER capsules and experience less "off" time while requiring fewer medication doses. **Dosages of carbidopa/levodopa ER capsules are not interchangeable with dosages of other carbidopa/levodopa products.** For prescribing and dosing information to share with your doctor, visit Parkinson.org/Rytary.

RYTARY USE IN PEOPLE WITH PARKINSON'S

This chart shows the percentage of people in the Parkinson's Outcomes Project using and not using Rytary. Out of 11,000+ visits tracked in the study (over 7,000 patients), doctors started a patient on Rytary at 88 (0.79%) of visits.



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

Another formulation is the orally dissolving carbidopa/levodopa (Parcopa). It's also useful for people who have difficulty swallowing or who don't have a liquid to wash down a dose of medication.

In 2018 the FDA approved INBRIJA™, a levodopa inhalation powder as a treatment for "off" periods in people with PD who are treated with carbidopa/levodopa. Powder from capsules is breathed in through an inhaler. It can be used up to five times a day as needed, improving "off" symptoms as soon as 10 minutes and lasting up to 60 minutes. This can improve symptoms for people with decreased gut movement while waiting for oral carbidopa/levodopa to take effect.

The most common side effects of carbidopa/levodopa are:

- Nausea
- Vomiting
- Loss of appetite
- Lightheadedness
- Lowered blood pressure
- Confusion

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

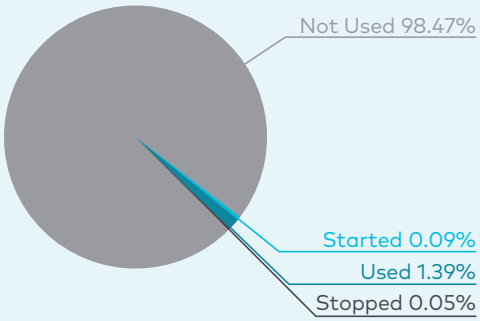
The stomach is an important route for carbidopa/levodopa, since levodopa is absorbed in the small intestine. People with Parkinson's often experience delays in the emptying of their stomach and a carbidopa/levodopa pill can sit in the stomach for a long time, causing a delay in the proper dosage. In addition, carbidopa/levodopa is absorbed into the bloodstream through a similar process that transports amino acids, the building blocks of proteins. As a result, some people 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, take carbidopa/levodopa one hour before a protein-rich meal or two hours afterwards. After several years of using carbidopa/levodopa, and alongside the development of motor fluctuations, many people with PD experience the benefits of a dose more quickly when the drug is taken on an empty stomach. Fortunately, most people with PD should have no problem with feeling "on" even if they take their medication with a meal.

Carbidopa/levodopa enteral suspension, known as Duopa in the United States, and Duodopa in other parts of the world, combines carbidopa/levodopa in a gel that is slowly and consistently pumped into the intestine through a surgically placed tube. 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 surgery to implant a small tube. The tube is inserted through the abdomen into the stomach and then into the small intestine. The surgery takes about 30 minutes. As with any surgery there are risks including infections and other complications. For more information on Duopa and the pump, download our book *Surgical Options* at Parkinson.org/Books, or call our Helpline at 1-800-4PD-INFO.

DUOPA USE IN PEOPLE WITH PARKINSON'S

This chart shows the percentage of people using and not using duopa before and after each of those 11,000+ visits. At 10 (0.09%) of the visits, doctors started a patient on duopa.



What are "on" and "off" times

"On-off" fluctuations, also called motor fluctuations, are changes in your ability to move. When levodopa begins to take effect, you experience periods of good symptom control ("on" time), when you can move and function well. As levodopa begins to lose its effect ("wearing off"), you may have periods in which symptoms are suddenly much more noticeable and movement becomes more difficult ("off" time). You might even have periods in which peak medication levels produce involuntary movements (dyskinesias). If you experience these various states throughout the day, you are said to have motor fluctuations.

Dopamine Agonists

A dopamine agonist (DA) is a chemical that acts like dopamine in the brain. Unlike levodopa, dopamine agonists are not converted into dopamine, they just act like it. There are multiple dopamine agonists available in the U.S. including:

- Ropinirole (Requip, Requip XL)
- Pramipexole (Mirapex, Mirapex ER)
- Rotigotine (Neupro skin patch)
- Apomorphine (Apokyn subcutaneous injection)

Bromocriptine (Parlodel) is also available but is not recommended, as it is a different type of Dopamine Agonist (ergo Dopamine Agonist) that is associated with a greater risk of heart and heart valve issues.

DAs improve the motor symptoms of PD, but they are less effective than levodopa. DAs 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, or longer duration of action, than levodopa and can be helpful in reducing "off" time or to generally enhance the benefits of levodopa.

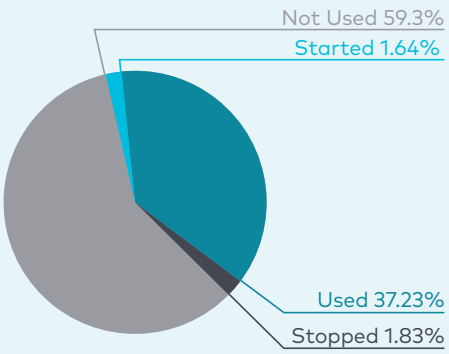
The negative effects of DAs are generally similar to those of carbidopa/levodopa. However, certain side effects, such as excessive daytime sleepiness, visual hallucinations, confusion and swelling of the legs, occur more commonly with dopamine agonists than with levodopa. Dyskinesia is rarely seen with the use of DAs when combined with levodopa.

One of the major issues with dopamine agonists are impulsive behaviors like uncontrolled gambling, sex, eating, shopping, etc. Those taking DAs 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 most likely related to overstimulation of dopamine receptors in the part of the brain responsible for instant gratification.

Data from the FDA and many other sources support the association of DAs and ICDs, though they can also be seen with the use of carbidopa/levodopa. Rotigotine, the DA patch, may have a lower incidence of impulse control issues, though it is unclear why. Older people with PD are more likely than younger people to have negative effects with using DAs.

DOPAMINE AGONIST

This chart shows the percentage of people using and not using dopamine agonists at each of the more than 35,000 evaluations for over 13,000 people with Parkinson's. At 1.64% of the visits, doctors started a patient on DAs. At 1.83% of visits, doctors took the patient off DAs.



People with PD should be aware of the risks before using dopamine agonists, and clinicians prescribing dopamine agonists should monitor for behavioral disorders. Remember that people suffering from impulse control issues may not have insight into the behavioral problems, and this lack of insight underscores the importance of involving care partners in monitoring plan.

Pramipexole (Mirapex) and Ropinirole (Requip) were approved by the FDA in 1997 and are currently the most commonly used DAs. They are both effective in the early treatment of motor symptoms of PD and in controlling motor fluctuations in later stages of the disease. Both these DAs are also available as once a day, long acting medications.

Rotigotine (Neupro) 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 oral DAs, such as pramipexole and ropinirole. The side effects are similar, with the addition of skin irritation under the patch in up to 40% of people with PD. Most people with PD have been able to tolerate the patch by rotating the sites of the patch on their bodies. Fewer than 5% of those studied in the clinical trials discontinued its use due to skin irritation. The patch can be helpful for people with PD who have stomach problems because the patch bypasses the stomach.

Apomorphine (Apokyn) was first used to treat PD in 1950, but was associated with many side effects, especially nausea and vomiting. It returned in the 1990s as a self-injectable "rescue" drug for people with PD who experience "off" episodes. When a person is having an "off" episode, a self-injected dose of Apokyn can reverse the "off" period within

minutes and bridge the gap until the dose of levodopa takes effect, which can be about 90 minutes. An anti-nausea medication, usually trimethobenzamide (Tigan) may be used (but is not required) prior to the first injection but can be discontinued after the first week or two if the person with PD does not experience nausea or vomiting. Apokyn can be used as many as five times per day.

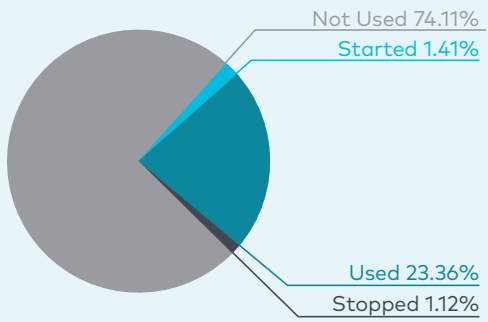
MAO-B Inhibitors

Monoamine Oxidase Type B (MAO-B) is an enzyme in our body that 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. This can modestly improve many motor symptoms of PD.

MAO-B inhibitors also provide some benefit for the motor symptoms of PD and are useful as early monotherapy or as an add-on to other medications, including levodopa. When used with other medications, MAO-B inhibitors may reduce "off" time and extend "on" time.

MAO-B INHIBITOR

This chart shows the percentage of people in the Parkinson's Outcomes Project using and not using MAO-B Inhibitors. More than 35,000 evaluations tracked in the study (over 13,000 patients), doctors started a patient on MAO-B inhibitors at 1.41% of visits.



In addition, animal studies showed that that MAO-B inhibitors might 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 this study was to determine if selegiline could delay the need for levodopa as PD symptoms worsened, compared to Vitamin E and a placebo. Selegiline was shown to delay the need for levodopa by nine months, suggesting neuroprotection. However, this benefit may simply have been from the antiparkinson symptom effect of selegiline. Vitamin E had no benefit in the clinical trial.

Selegiline is available in two formulations: standard oral (Eldepryl,) and orally disintegrating, or dissolving (Zelapar). Oral selegiline is taken twice a day and orally-disintegrating selegiline is taken once daily. Standard oral selegiline is changed into a stimulant, which can contribute to side effects of jitteriness and confusion.

Rasagiline (Azilect), is another MAO-B inhibitor and is structurally different from selegiline. It does not have an stimulant-like byproduct. 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 effectiveness, and there was also an hint of slowing disease progression. A worldwide study of rasagiline's potential for neuroprotection was published in 2008, and follow-up data from the original study. These results suggest that the use of rasagiline earlier in PD may offer the greatest long-term advantage and potentially manage symptoms over time, although true disease modification remains unproven.

Safinamide (Xadago) was approved by the FDA in 2017. This medication affects the dopaminergic system by blocking MAO-B, thereby blocking the breakdown of dopamine.

The most common side effects of MAO-B inhibitors include mild nausea, dry mouth, lightheadedness and constipation. Pharmacists routinely warn patients about interactions with other drugs, especially the antidepressants, when they start taking an MAO-B inhibitor, but negative side effects are very rare.

Any person with PD taking MAO-B inhibitors should review all medications and possible adverse interactions with their physician before starting any new medications. **The following medications should always be avoided by people taking MAO-B inhibitors:**

- Meperidine (Demerol)
- Tramadol (Rybix, Ryzolt, Ultram)
- Droperidol (Inapsine)
- Methadone (Dolophine, Methadose)
- Propoxyphene (Darvon, PP-Cap)
- Cyclobenzaprine (Amrix, Fexmid, Flexeril)
- Halothane (Fluothane)

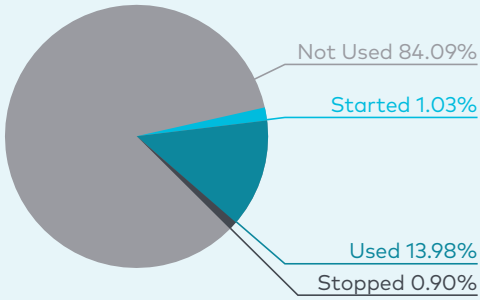
If it becomes necessary to take any of these medications for a planned surgery, consult with your Parkinson's neurologist and the anesthesiologist to decide whether to wean off of your MAO-B inhibitors ahead of the surgery.

COMT-Inhibitors

Catechol-O-methyl transferase (COMT) is an enzyme that deactivates levodopa in the body before it is absorbed in the bloodstream and taken to the brain. There are drugs that can block COMT, which makes levodopa more available to the brain, and they have been approved by the FDA for treating PD. The COMT-inhibitors increase the 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.

COMT-INHIBITORS

This chart shows the percentage of people in the Parkinson's Outcomes Project using and not using COMT-Inhibitors. Out of 35,000+ visits tracked in the study (over 13,000 patients), doctors started a patient on COMT-Inhibitors at 1.03% of visits.



Entacapone (Comtan), tolcapone (Tasmar), and newly approved opicapone (ONGENTYS®) are the three COMT-inhibitors approved by the FDA to treat PD. Opicapone is taken once daily and is only approved for those experiencing "off" episodes. Entacapone is prescribed with each dose of levodopa, and tolcapone is taken three times a day. COMT-inhibitors without levodopa have no effect on Parkinson's symptoms. There is no potential benefit from taking entacapone or tolcapone to try to extend the life of other PD medications. In fact, taking tolcapone without levodopa can lead to liver damage and can be potentially fatal. Hence, tolcapone should be used only after all other adjunct PD medications have been tried and should be discontinued if there is no benefit after three weeks. Before starting tolcapone, blood liver tests should be done and rechecked every two to four weeks for the first six months and periodically thereafter.

Carbidopa/levodopa/entacapone (Stalevo) is a combination drug which includes entacapone and levodopa in one pill. It is more convenient compared with carbidopa/levodopa + entacapone taken separately.

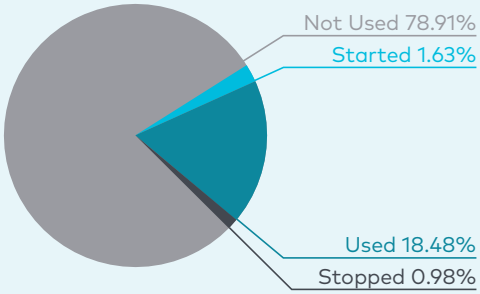
Amantadine

Amantadine (Symmetrel) was created as an anti-influenza medication in the 1960s, but its benefit in PD was first discovered in 1969, when observers noticed, by accident, that people with PD who took Amantadine to prevent influenza experienced less tremor. Amantadine often provides immediate benefit for most PD motor symptoms. It is unique 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 path through the brain is 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.

AMANTADINE

This chart shows the percentage of people in the Parkinson's Outcomes Project using and not using Amantadine. Out of 35,000+ visits tracked in the study (over 13,000 patients), doctors started a patient on Amantadine at 1.63% of visits.



Amantadine is most commonly available as a 100 mg capsule, although liquid and tablet forms are also available. 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, pedal edema and hallucinations. Urinary retention is another side effect, though it is rare. Another possible side effect is livedo reticularis, a web-like, purple discoloration of the skin, usually on the legs and with some accompanying leg swelling. This side effect is only experienced by 1% of Amantadine users. Stopping the drug will resolve this adverse effect, although if the drug is providing benefit there is no harm in continuing it. Amantadine should not be stopped suddenly, but rather slowly reduced, due to risk of a serious withdrawal syndrome.

Amantadine ER tablets (OSMOLEX ER™) is an extended release form of amantadine which is taken every day upon waking and can reduce "off" time of Parkinson's disease. The tablets should not be split, crushed, nor chewed as this could cause serious side effects by releasing all the medication at once, also known as "dose dumping."

Another amantadine-based medication, Amantadine ER capsules (GOCOVRI®) is the only medication to treat dyskinesia and "off" time in people with PD taking carbidopa/levodopa. It must be taken before bedtime and provides control of dyskinesia upon awakening and throughout the day. This medication is different from immediate-release amantadine and amantadine ER tablets (OSMOLEX ER™), which are not approved for dyskinesia or "off" time. GOCOVRI can start to reduce dyskinesia after 2 days, with most of the effect seen by 4 weeks. Some people may see additional benefit after 12 weeks. Reduced "off" time should be seen after about 2 weeks. For people with difficulty swallowing, the GOCOVRI capsules may be opened and contents sprinkled on small amount of soft food (teaspoon of applesauce) and swallowed. The capsule contents should not be crushed. Alcohol should be avoided when taking extended release amantadine (GOCOVRI or OSMOLEX ER), due to potential risk that this could break the extended release mechanism and cause "dose dumping."

Anticholinergics

The earliest medications used in PD blocked brain receptors for acetylcholine (a nervous system neurotransmitter) called anticholinergics. It is believed that acetylcholine and dopamine maintain a delicate balance in the normal brain, which is upset by the destruction of dopamine and the break down 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 mainly for tremor, 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 older persons with PD. As such, these medications are typically utilized in younger people.

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

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

Adenosine A2a Antagonists

Istradefylline (NOURIANZ™) is an adenosine receptor antagonist indicated as adjunctive treatment to carbidopa/levodopa in adult patients with Parkinson's experiencing "off" episodes. Since it is not dopaminergic, it can reduce "off" time by 30–60 minutes per day without worsening dyskinesia. However, dyskinesia can still be a side effect. Reduction in "off" time should be seen by 4 weeks. People with PD who smoke the equivalent of 20 cigarettes per day or more will require a higher dose (40mg) of medication. This is because the cigarettes cause the liver to increase the breakdown of (metabolize) Nourianz, making the medication less effective. It should be taken upon wakening to reduce the chance of causing insomnia.

CHAPTER THREE

Medications for Non-Motor Symptoms

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

- **Mood Disorders: Depression and Anxiety**
- **Impaired Thinking, Daytime Sleepiness and Sleep Disorders**
- **Dementia and Hallucinations**
- **Orthostasis (Low Blood Pressure Upon Standing)**
- **Gastrointestinal Symptoms: Nausea and Vomiting, Constipation, Early Satiety**
- **Drooling**
- **Urinary Symptoms**
- **Sexual Dysfunction**
- **Seborrheic Dermatitis and Excessive Sweating**
- **Pain**

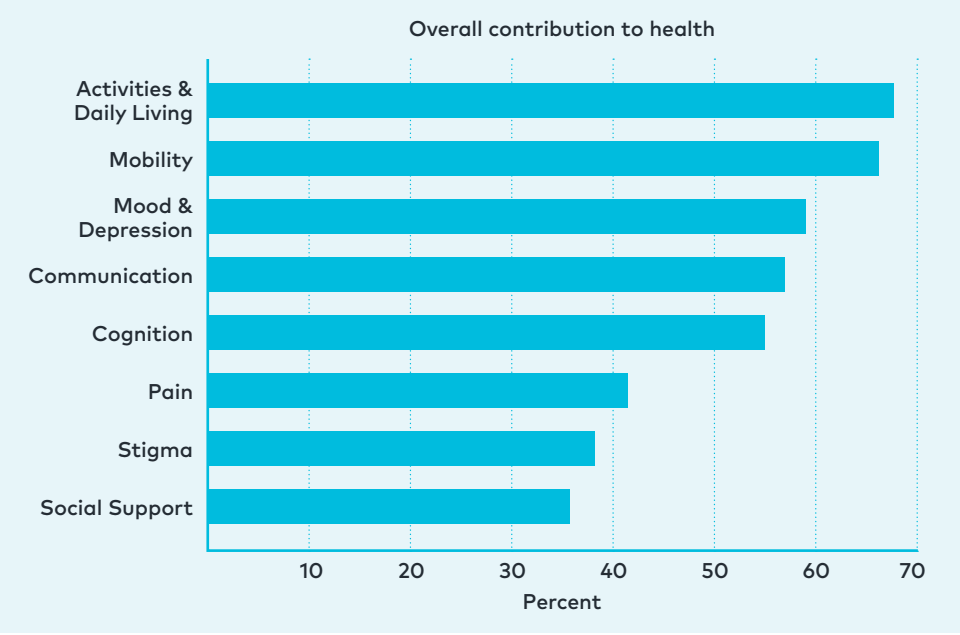
There is ever-growing recognition of the importance of "non-motor" symptoms of PD, which were identified as early as 1817 by James Parkinson. Although he didn't differentiate motor from non-motor symptoms, he observed that his patients experienced symptoms of fatigue, confusion, sleep disturbances, constipation, 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.

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!

Mood Disorders

The Parkinson's Outcomes Project was initiated in 2009 as a large, multicenter study partnering with many of the Parkinson's Foundations 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. Not surprisingly, being able to move and go about one's day are very important to quality of life. However, one of the first findings of the project was that, collectively, that mood and anxiety are the two PD symptoms that can have the largest impact on health status, and has consistently found Mood & Depression to be in the top 3 factors contributing to overall health.

A Parkinson's Foundation book specifically designed to address these issues, titled *Mood: A Mind Guide to Parkinson's*, is a comprehensive resource available online or in print. To request a free print copy, call our Helpline at 1-800-4PD-INFO (473-4636); online, go to 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. There is no specific timeframe for depression in PD; depression can occur before motor symptoms, when the diagnosis is first made or in advanced disease. 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 PD improve with adequate treatment of the most bothersome motor symptoms. However, many others require more aggressive management with psychotherapy and antidepressants.

Along with "feeling blue," symptoms of depression may include:

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

Antidepressants

Medications used to treat depression in general are also used to treat depression in PD. There is no specific medication approved to treat depression in PD. As detailed below, several different classes of medication may be helpful.

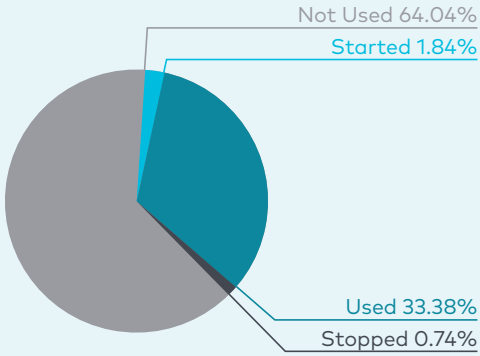
Most people with PD who are experiencing depression are treated with one of several common categories of antidepressants including the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). A large clinical trial published in 2012 confirmed the benefits of SSRIs and SNRIs for many people with PD. Occasionally, older tricyclic antidepressants (TCAs) are used, especially in younger people with PD with sleep difficulties. However, 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. The antidepressants buproprion and mirtazapine are also notable for their lack of sexual side effects. There is some evidence that pramipexole, a dopamine agonists may have antidepressant properties in people with PD.

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. The Medications for Non-Motor Symptoms fact sheet included with this book 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, or counseling in improving this non-motor symptom of PD. The importance of this is underscored by research from the Parkinson's Outcomes Project. Counseling plus medication was 25% more effective at resolving depression than medication alone for people with Parkinson's experiencing severe, long-term (at least two years) depression. So, while medication can be helpful, counseling is necessary to realize the full benefits of treatment. Cognitive-behavioral therapy, an approach that helps in developing the skills and actions to change patterns of thought and behavior related to depression, can be particularly helpful.

ANTIDEPRESSANT

As of May 2015, more than 35,000 evaluations had taken place on over 13,000 people with PD. This chart shows the percentage of people using and not using antidepressants at each of those 35,000+ visits. At 1.84% of the visits, doctors started a patient on antidepressants.



Counseling 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.

Mood may also change during "on-off" fluctuations. A general state of unease or dissatisfaction with life (dysphoria), irritability and anxiety are the most common mood changes in the "off" state. If you notice a relationship between mood changes and the timing of your PD medication, tell your neurologist. They might adjust your levodopa-replacement medications or dosing to reduce "off" time, which, in turn, may help your mood.

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 symptoms. 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, people 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.

Obsessive-compulsive disorder can become worse as a result of dopaminergic agents, particularly the dopamine agonists.

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

Anxiety can be part of non-motor fluctuations associated with levodopa. In such cases, working to optimize doses of levodopa may improve anxiety, 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 benefits may be achieved with clonazepam (Klonopin) than with alprazolam (Xanax) or lorazepam (Ativan). Common side effects of benzodiazepines include drowsiness, confusion, lethargy and imbalance when walking. People 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.

You are not alone. For more information on depression, anxiety and treatment, read the Parkinson's Foundation book, Mood: A Mind Guide to Parkinson's Disease or call the foundation's free Helpline at 1-800-4PD-INFO (473-4636) to speak with a Parkinson's specialist.

Impaired Thinking and Dementia

Cognitive impairment is when a person has trouble remembering, learning new things, concentrating, or making decisions that affect their everyday life. More than 30% of persons with PD may experience some degree of cognitive impairment at some point after a Parkinson's diagnosis. These alterations 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. However, 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 possibly permanent compromise in lifestyle and quality of life.

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 cognitive impairment associated with PD is not Alzheimer's disease, and the severity of the cognitive deficits and the effect of those deficits on day-to-day functioning are not as disabling.

Parkinson's disease dementia (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 on a daily basis.

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 one's thinking in relation to motor symptoms. If cognitive impairment begins before or within one year of motor symptoms, 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. 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).

Evaluation for change in cognitive function in persons with PD should be part of a complete medical workup for other causes of cognitive impairment, some of which may be treatable. If the change in cognitive ability is sudden, severe, and accompanied by significant alteration in consciousness, an underlying cause aside from PD should be considered. This could mean infection (usually of lungs or bladder), vitamin depletion, dehydration, thyroid disease, intoxication by drugs, constipation, sleep deprivation or head injury from falls.

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 likely. Many of the anti-PD medications and other drugs (for example narcotic pain killers) can cause confusion mimicking dementia, particularly in elderly PD persons. A careful evaluation of current medications is always important, paying particular attention to PD medications like anticholinergics, amantadine and dopamine agonists.

Medications that are approved for people with PD dementia are rivastigmine or Exelon. Other medications approved by the FDA for the treatment of memory disorder in Alzheimer's disease are donepezil (Aricept), galantamine (Razadyne) and memantine (Namenda).

Acetylcholinesterase Inhibitors
Rivastigmine (Exelon) was approved by the FDA in 2006 for treatment of dementia in PD. Donepezil (Aricept), and galantamine (Razadyne) are the next most frequently prescribed medications to address symptoms of cognitive impairment in PD. Originally approved by the FDA for the treatment of Alzheimer's disease, donepezil and rivastigmine have been effective for some people with PD, though benefits are sporadic and modest. Most common side effects include tremor, drooling and bladder issues. Rivastigmine has been shown to help with apathy that can happen in PD Dementia.

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 that are activated by the neurotransmitter glutamate. It is commonly used in combination with donepezil, although the results of treatment are often disappointing in PD dementia.

Other stimulants, such as methylphenidate (Ritalin), and medications used for excessive daytime sleepiness, such as modafinil (Provigil), are sometimes used in PD for fighting fatigue and improving alertness. They are not specifically used for cognitive issues.

PD Psychosis

People with PD psychosis (PDP) may experience visual hallucinations, illusions, or delusions. These are more commonly seen in people with PD who develop dementia in the late stages of disease.

- A hallucination occurs when a person believes they see, smell, hear or feel something that **is not** actually there.
- An illusion is a misperception or misleading view of reality – that is, a misperception of something that **is** actually there. For example, a belt may appear to be a snake.
- A delusion is a form of self-deception in which the person develops a false belief despite strong evidence that the belief is false. For example, that someone is stealing from them despite reassurance from family that no one is stealing anything.

Feeling a "sense of presence" is also fairly common, when they feel like someone else in the room with them when no one else is present.

PDP can occur in people with Parkinson's, whether or not they take medications. It can also occur with or without underlying dementia.

Visual hallucinations are the most common form of hallucination in PD psychosis. They often involve seeing little people, animals or insects. The most common delusions are paranoid delusions. This means that the person with PD may suspect that someone is plotting to do something harmful, most commonly believing that spouse is being unfaithful. Delusions are difficult to manage and should be urgently treated. Often those with PDP, especially with dementia, have hallucinations and agitation at the end of the day after sundown, when darkness can be disorienting. The term "sundowning" is named after this inopportune time of day. Fatigue after the day's activities can also cause collapse of a stable mental status.

Additionally, if the person with PD moves to an unfamiliar environment, such as a hospital, vacation site or new home, the stress of geographical disorientation can sometimes lead to the development or return of hallucinations, delusions and confusion. Fortunately, many people with PD retain insight, understanding that the hallucination is not real and that their mind is "playing tricks" on them. Others react by becoming extremely troubled and frightened.

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 rapid eye movement (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?

2. **Identify any other medical problems you are experiencing.** Other medical problems could trigger a decline in cognitive 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 that require attention (e.g., disorders of the heart, liver or kidneys; dehydration)?

3. **Review the list of all PD medications you are taking, paying special attention to any recent medication changes.** Your healthcare team can evaluate if the mental changes you are experiencing are related to 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.

   If your doctor recommends medication changes, they may decrease or stop Amantadine and anticholinergics first, because the risk of psychosis usually outweighs the modest benefit that these medications provide.

   In practice, the risk of cognitive and psychiatric complication is higher with dopamine agonists than with levodopa. Thus, when the symptoms of psychosis require action to help someone who is on a combination of levodopa and dopamine agonists, doctors will typically taper off of and eventually stop the agonist. Levodopa then becomes the only dopaminergic medication the individual is taking. The risk of psychosis usually outweighs the benefit that these medications provide. 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 narcotic pain medications like Percocet], antibiotics, steroids, anti-anxiety or anti-depressant medications)? Consider over-the-counter medications too. Could illicit drugs, marijuana or alcohol be involved?

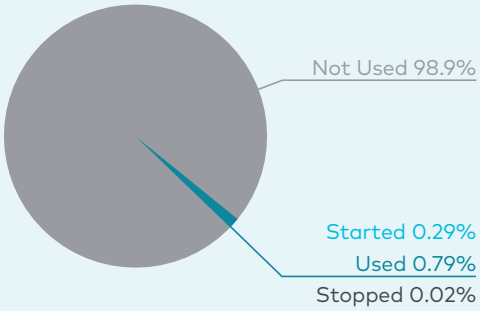
Based on the findings in the four steps above, your physician and healthcare team will be able to suggest the best course of treatment.

In 2016, the FDA approved pimavanserin (Nuplazid) as the first and only drug specifically designed to treat Parkinson's disease psychosis. Pimavanserin is not a dopamine-blocking drug like clozapine and quetiapine. In fact, it acts on serotonin receptors just like antidepressants. It is the safest choice when treating people with PD who are experiencing psychosis. There are fewer side effects with this medication than other antipsychotics because it only targets serotonin. Unlike dopamine-blocking drugs, it does not typically worsen motor symptoms, cause

excessive sleepiness, start fluctuations in blood pressure, or affect drooling and bladder function. However, common side effects are confusion, leg swelling, and worsening hallucinations. It should be noted that it can take up to three weeks for this medication to provide full benefits. It is extremely important that you find the right antipsychotic drug for you. In addition to pimavanserin, there are currently two antipsychotic medications that are suitable for use in people with PD: clozapine and quetiapine.

PIMAVANSERIN

This chart shows the percentage of people in the Parkinson's Outcomes Project using and not using Pimavanserin. Out of 11,000+ visits tracked in the study (over 7,000 patients), doctors started a patient on Pimavanserin at 32 (0.29%) of visits.

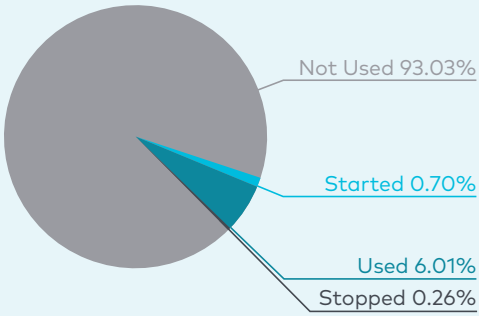


Clozapine (Clozaril) can be used effectively, especially at low doses, in people with PD without a risk of worsening Parkinson's symptoms. In 1990, the FDA approved clozapine for use in the treatment of schizophrenia as long as the patient completes weekly blood counts for the first six months (then every 2 weeks for 6 months if stable, and then monthly if stable thereafter). For those on hospice, the blood counts can be reduced to once every 6 months. This is so that your healthcare provider can monitor the low, but significant, risk that clozapine can depress your white blood count and increase the risk of serious infection. This requirement has made the use of clozapine inconvenient, but safe. Experience has shown that low dose clozapine has an important place in the management of the psychosis that can occur in persons with PD. Additional risks with clozapine include seizures, heart inflammation, low blood pressure and fainting.

Quetiapine (Seroquel) had been widely used for people with PDP before pimavanserin was approved. It has the advantage of not requiring frequent blood counts. Common side effects include dizziness, dry mouth and weight gain. Although clinical trials did not report clinical success with quitepine, physicians in general have had positive experiences with it in treating hallucinations and other symptoms of psychosis. Occasionally people with PD may require a combination of therapy with pimavanserin or quetiapine.

ANTIPSYCHOTIC

This chart shows the percentage of people in the Parkinson's Outcomes Project using and not using antipsychotics. Out of 35,000+ visits tracked in the study (over 13,000 patients), doctors started a patient on antipsychotics at 0.70% of visits.



Sleep Disorders

Disturbed sleep is so common among people 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)

Difficulty controlling tremor, stiffness and poor bed mobility can account for an inability to sleep at night. Excessive daytime sleepiness (EDS) can also account for difficulty sleeping, due to the possible reversal of the sleep cycle. 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 your healthcare team with the most accurate medical history, it is useful for the spouse, partner, housemate or professional caregiver to help describe your nighttime activities. An Epworth Sleepiness Scale (see Appendix C) can help identify daytime sleepiness and provide clues to disruption of sleep at night. This questionnaire (given in the office or completed at home) examines a person's tendencies to fall asleep during the day during daily activities, such as driving or watching television. An overnight evaluation by a trained specialist (often a neurologist) can provide even more information. This can be helpful especially **if co-existing obstructive sleep apnea (OSA) is suspected, a breathing disorder that flares up during sleep that**

affects, and can even stop, breathing. The evaluation typically will include monitoring heart rate, breathing activity, snoring, involuntary movements and quality of sleep. Treatment of OSA which can include a using a CPAP (Continuous Positive Airway Pressure) breathing machine at night can improve daytime sleepiness.

Restless leg syndrome (RLS) is a common disorder characterized by unpleasant sensations in the legs at rest and an uncontrollable urge to move the legs in order to relieve these feelings. RLS sensations are often described as burning, creeping, tugging or like "insects crawling inside the legs." Often called paresthesia (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. These symptoms occur after prolonged sitting or laying in bed. When experiencing symptoms of RLS, sleep can be significantly disrupted, which can cause daytime sleepiness or 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 sleep disorders, the bed partner is more aware of the involuntary movements than the person with the symptom. RLS and PLMS often occur together in people with PD.

Diagnosis can be fairly simple when the symptoms are obvious, but your physician or provider may recommend an overnight sleep study. Additionally, it may be recommended that blood ferritin levels be tested. If ferritin levels are low, iron replacement therapy may be recommended. Extra nighttime doses of Parkinson's medications may bring relief. Your healthcare provider may also consider gabapentin, benzodiazepines (like clonazepam) or low-dose opiates.

REM-sleep behavior disorder (RBD) is characterized by acting out dreams during the REM sleep phase. It involves active behaviors (e.g., kicking, fighting, yelling or thrashing) during the phase of sleep when dreaming normally occurs. The person experiencing RBD may even walk or fall out of bed during REM sleep. The history provided by the person with PD, their care partner 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 be a symptom of Parkinson's or can result from disruption of nighttime sleep, sleep apnea and PD medications, especially dopamine agonists. It is most problematic for the person with PD who is experiencing cognitive decline. People with PD may even suffer "sleep attacks" during the day, which are described as the sudden and irresistible urge to sleep or the sudden and unwarned onset of sleep, not preceded by sleepiness. This happens significantly more often in people with PD who take moderate to high doses of the dopamine agonists.

Insomnia is an inability to fall asleep or, more commonly, to stay asleep. Itis more complicated in PD because there are extra factors that might contribute, including normal nighttime awakening, wearing-off of anti-Parkinson medication, depression, anxiety and a change in circadian rhythm.

Treatment of EDS and insomnia can be challenging and usually requires a multi-faceted approach. Discuss with your healthcare provider whether to reduce dosage, change medication timing, or even eliminate dopamine agonists. Cognitive behavioral therapy (CBT) provided by a psychologist or other trained health care provider can help with insomnia. Medications such as melatonin, eszopiclone, or low-dose doxepin (1–3 mg) may help with staying asleep. Other options for EDS include CNS stimulant medications like Ritalin, modafinil, or Nuvigil.

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 daytime naps
- Avoiding food and drink within several hours of bedtime

It is recommended that you avoid use the bed for non-sleeping tasks such as reading, doing work or watching television, as these activities can condition the body for wakefulness. Once you've improved your sleep hygiene, a helpful look to over the counter supplements, like melatonin, before prescription medications. Doses as high as 10–15mg can be used for better sleep.

Some antidepressant drugs, such as amitriptyline (Elavil), trazodone (Desyrel) or mirtazapine (Remeron), can 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 anti-tremor drug because of its anticholinergic properties. Amitriptyline and diphenhydramine should be avoided by older people with Parkinson's because they can worsen cognition, cause constipation, dry mouth and increase risk of arrhythmias. If motor symptoms such as stiffness and tremor interrupt sleep because of the gap between night and morning doses, an extra dose of carbidopa/levodopa may be taken late in the evening or during the night upon awakening. Some people with PD use controlled-release carbidopa/levodopa or carbidopa/levodopa extended capsules (Rytary) at bedtime.

Other sleeping medications can be beneficial such as hydroxyzine, Ambien, Lunesta, Sonata, Rozerem, quetiapine, clonazepam and others.If nighttime sleeping problems are controlled but excessive daytime sleepiness persists, increased coffee intake in the morning is also worth a try.

Stimulants such as methylphenidate (Ritalin) and mixed amphetamine salts (Adderall) can be tried. Indicated for narcolepsy and attention-deficit disorder, they can be used carefully 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.

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 may not cover them.

Orthostasis

The terms orthostasis or orthostatic hypotension describes the drop of blood pressure when a person with PD rises from being seated or lying down. Normally when a person rises, blood pressure drops but is maintained in a small range by protective reflexes in the body's blood vessels that are controlled by the body's autonomic nervous system (ANS). When a person with PD stands, the normal reflexes that protect against a drop in blood pressure are impaired. The result, typically within 1–3 minutes of standing, is lightheadedness, dizziness and fainting — symptoms that reflect a lack of blood flow to the brain.

Since the ANS is often impaired in PD, autonomic functions such as blood pressure regulation, gastrointestinal motility and sweating can be affected. When orthostasis is related to a disease of the nervous system, like in PD, it is called neurogenic orthostatic hypotension (NOH).

NOH in PD can be brought on by anti-Parkinson medications, especially the dopamine agonists amantadine 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.

People with PD often assume, mistakenly, that any symptom in any organ system is caused by PD. It is good to remember that having PD doesn't protect you from getting unrelated medical problems. A good example of a frequent parallel problem is back, neck and limb pain due to degenerative arthritis of the spine. Pain caused by PD symptoms certainly occurs, but it is usually an aching discomfort and feeling of heaviness of the large muscles of the legs, which often occurs 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 involving the heart or lungs must be explored. In addition, other medications prescribed, particularly medications for high blood pressure, should be closely examined. The overlap of multiple health issues in people with PD underscores the need for the PD specialist to communicate regularly with the primary care physician, other specialists and/or healthcare team members.

For a person with Parkinson's experiencing orthostasis and high blood pressure, their blood pressure may be high while sitting but normal when standing, so they should always have their BP checked both in a sitting and standing position even at a primary care office or a visit to the emergency

room. If you experience dizziness or lightheadedness, your doctor may also check your blood pressure in a lying position and then a standing position one hour later, preferably after breakfast or lunch.

If a person with PD experiences orthostasis, it is appropriate for the physician or healthcare provider to consider decreasing the dosages of medications that may cause this problem, such as dopamine agonists, amantadine and carbidopa/levodopa. If drugs for hypertension are being used, the doses should be reduced or even discontinued.

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 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 this doesn't help, ask your physician or healthcare provider if medications to raise blood pressure would be appropriate. For more information on NOH, visit nohmatters.com.

Fludrocortisone (Florinef) will increase blood pressure by increasing retention of salt and blood volume. Increased dietary salt will enhance its effect. Fludrocortisone 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. Drinking plenty of water, about 8–10 glasses per day, will also help improve this condition.

Midodrine (Proamatine) increases blood pressure by stimulating the norepinephrine receptors and is dosed three times per day. There is an higher chance of developing high blood pressure while lying flat (supine hypertension) with midodrine than fludrocortisone, so if midodrine is prescribed this should be carefully monitored.

Pyridostigmine (Mestinon) can be used either as monotherapy or as an adjunctive drug to enhance the blood pressure raising effect of fludrocortisone and midodrine. Ordinarily used to treat the neuromuscular disease myasthenia gravis, pyridostigmine might have a small, but significant, increase in diastolic blood pressure.

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 is approved for the treatment of orthostatic dizziness, lightheadedness, or the feeling that you may pass out in adult patients NOH. Similar to midodrine and fludrocortisone, there is potential for the development of high blood pressure when lying flat, which should be monitored carefully.

Some drugs for orthostasis increase blood pressure when lying down (supine position). To avoid supine hypertension (high of blood pressure spikes), the last dose midodrine and droxidopa should be taken no later than 3–4 hours before bedtime. If you are on these medications and taking a nap during the day, use a recliner instead of lying down to avoid supine hypertension.

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 caused by the same system that is responsible for neurodegeneration in the brain. In this case, the disease process affects the autonomic nervous system (ANS), which controls the normal movements 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.

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 mixture of carbidopa/levodopa (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 the brain, they should be avoided because they can worsen the symptoms of PD.

Domperidone (Motilium) is a good choice for treating nausea and vomiting associated with the use of any of the dopaminergic anti-Parkinson 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. There is, however, a risk of cardiac issues with this medication.

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 been 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. Ondansetron or other antinausea medications in the same family (5HT3 Receptor blocker) should not be combined with apomorphine as it can cause lowering of blood pressure. Often times, ginger capsules (or ginger tea, a less expensive option) may be helpful.

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.
- Regular exercise
- 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), or stimulant laxatives, such as senna/sennosides (Senokot) or bisacodyl (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 the Medications for Non-motor Symptoms Fact Sheet included with this book.

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 which can cause stains on clothing, wet the floor and can even cause aspiration. For example, this can happen when the head is down and 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. 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).** These medications 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. These medications should be avoided in older people with Parkinson's.
- **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 (wide spread) side effects are much less likely with this local treatment.

There are two botulinum toxins approved for drooling, botulinum toxin A (Xeomin) and botulinum toxin B (Myobloc). Botulinum toxin injections into the salivary glands of the cheek and below the jaw decreases production

of saliva, and hence helps decrease drooling. These injections are required approximately every 3 months.

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 messages from the brain to the spinal cord tell the bladder to empty prematurely in PD. Urinary frequency and urgency can lead to incontinence. This can be an issue for those who experience motor fluctuations and who need to get to a toilet quickly when there is a sudden urge to empty the bladder. As with other nonmotor complaints, it is important to rule out other possible causes of urinary frequency, including urinary tract infection and enlarged prostate. Managing urinary problems with a urologist is important.

Medications that can help re-establish bladder control:

- Anticholinergic medications can relax the overactive muscles of the bladder, which allows the bladder to fill to greater capacity. There are several available by prescription.
- The alpha-adrenergic receptor blockers prazosin and tamsulosin (Flomax) relax the detrusor and make it easier for the bladder to empty. These drugs may also be used for men if an enlarged prostate is the reason for the symptoms.
- 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.

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 about this topic. It remains underdiagnosed 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. Depression, often present in PD, can decrease sexual desire, and some antidepressants can affect sexual response. The motor symptoms of PD can impact both the fine motor skills of touch and the mobility that contributes to 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 at its best, such as when you are rested and medications are maximized, this could be a good time to express yourself with a loved one.

In addition to the neurologist, other members of the healthcare team that might address sexual functioning include the psychologist, 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, which is responsible for delivering 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 which 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 and other disorders listed above. A complete physical examination should be conducted by the general physician and urologist.

There are a variety of medication options to treat ED. Some can be injected into the penis and others are taken orally. Oral medications for ED include sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis).

Mechanical treatments include vacuum pumps, constriction rings and penile implants. Injectable medications include papaverine HCl (Papaverine vials for injection), phentolamine (Regitine vials for injection) and alprostadil (Caverject).

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 seeing a dermatologist.

Some people observe that they sweat profusely in the "off" state of motor fluctuations or when dyskinesia is severe enough to increase body heat. Many people report sudden and unexplained drenching sweat, often awakening them from sleep and creating a need to change bedclothes. Levodopa can also cause severe episodes of sweating. Sweating disorders in PD can be associated with other autonomic abnormalities, such as constipation and orthostasis.

For adults with facial and body presentation of Seborrheic dermatitis, medications are typically topical ketoconazole 1%–2% shampoo or other topical antifungals (such as ciclopriox); short term use of topical corticosteroids (hydrocortisone, betamethasone valerate, etc.); topical calcineurin inhibitors (pimecroliums 1% cream, tacroliums 0.1% ointment).

Thermoregulatory Functions

This inability to regulate body temperature can manifest as excessive sweating, or a drastic rise or drop in body temperature. Excessive sweating (hyperhidrosis), experienced by more than 50 percent of people with PD, consists of sudden, drenching sweats of the head and neck. Though it may occur in people taking no PD medications, it often occurs as prescriptions wear off or during episodes of dyskinesia. Adjusting dopaminergic therapy can help, and neurologists may consider reducing/removing patient's anticholingeric medications, especially in warmer weather, as Anticholinergics can block sweat secretion and add to overheating.

Conversely if patients are sweating excessively, consider reducing cholinergic medications (such as donepezil).

Pain

Almost half of people with Parkinson's experience pain during their PD experience, and it can become more common as the disease progresses. 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) central "parkinsonian" pain. There may be a pattern between discomfort and PD medication schedule. For some people, being in the "off" state can increase a sensation of pain, adjusting medication dosage and timing will help.

The most common cause of pain in PD is related to dystonia, which is a sustained 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 spasms. Depending on the timing of dystonic pain, multiple different approaches may be 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 an injection of apomorphine. If dystonia occurs as a wearing-off symptom, minimizing the "off" period with dopaminergic therapy can be beneficial. Botulinum toxin injections can also be helpful in treating localized dystonia.

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.

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

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 traditional anti-inflammatories, muscle relaxants, gabapentin, tricyclic antidepressants and additional PD medications. 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.

Anti-inflammatory medications include steroids and non-steroidal anti-inflammatory drugs (NSAIDs) and can help with musculoskeletal pain. NSAIDs are available both over-the-counter (OTC) and prescription. Some common NSAIDs include ibuprofen (Advil, Motrin), naproxen (Aleve), meloxicam (Mobic), and diclofenac (Voltaren). Oral NSAIDs should be taken with food. Common side effects of NSAIDs include nausea, stomach ulcers, and swelling/fluid retention. Steroids can have similar side effects to NSAIDs and long-term use can cause changes such as high blood sugar and high blood pressure.

Muscle relaxants may be used on an as needed basis for muscle spasms but are typically not long term solutions. Common muscle relaxants that have shown to be more effective for spasms include cyclobenzaprine (Flexeril), tizanidine (Zanaflex), and baclofen. Common side effects include dizziness, drowsiness, confusion and low blood pressure.

If pain is thought to be related to nerve pain or "neuropathic", medications such as gabapentin, serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), or opioid medications may be used. Gabapentin (Neurontin) and pregabalin (Lyrica) are commonly dosed two to three times a day but may be dosed at bedtime for restless leg. These medications must be increased gradually over several weeks to avoid side effects and reach an effective dose. Many people with PD may need 600–900 mg of gabapentin per dose to notice benefit. Common side effects include dizziness, sleepiness, blurry vision, and changes in gait/walking. Duloxetine (Cymbalta) is an SNRI can lessen nerve pain at 30–60 mg per day.

TCAs, such as amitriptyline and nortriptyline, can be effective for nerve pain but have many drug interactions and side effects that include confusion, forgetfulness, hallucinations, light-headedness, blurry vision, urinary retention, dry mouth. The mechanism of how acetaminophen (Tylenol) works is not completely understood, however it may also be helpful for neuropathic pain. It commonly comes in combination with other medications for pain. To prevent serious liver damage, for most people with PD, the total daily dose of acetaminophen should not exceed 3,000 mg per day from all sources. For some, it is advised not to exceed 2,000 mg per day due to liver disease or alcohol use.

Opioid medications such as tramadol (Ultram) or oxycodone (Oxycontin) may be used for nerve pain but is typically a last resort. This is due to many drug interactions and side effects of opioids that include drowsiness, decreased breathing, confusion, and constipation. Opioid medications can lose their effect over time requiring higher doses and higher risk of serious side effects. These medications can be addictive and some patients have accidently overdosed which lead to serious injury or death at doses commonly prescribed. Long-term use and high doses of opioids can cause a worsening of pain. This phenomenon is called "hyperalgesia ". Hyper meaning more and algesia meaning pain. Long-term use of opioids is typically reserved for cancer pain. If you are on long-term or high dose opioids, ask your doctor if you should receive a "rescue" medication called naloxone (Narcan) which can be administered by a bystander or caregiver in the event of an accidental overdose.

Involving Your Team

When pain lasts longer than two weeks, interferes with sleep, or intensifies, it's time to involve your team. Keep track of WHEN the pain started, WHERE it hurts, HOW long it lasts and WHAT it feels like (achy, sharp). It will be useful to also track when the pain starts in relation to when you take your medication. This information will help your healthcare team work more efficiently with you in designing a treatment plan.

CHAPTER FOUR

Development of New Drugs

Drugs and devices have to go through a process of clinical trials before the U.S. Food and Drug Administration (FDA) can consider approving a new therapy. A clinical trial, also called a clinical study or clinical research, is research conducted with people to answer scientific questions. Clinical trials determine if scientific concepts can be turned into safe and effective therapies that make life better for people with Parkinson's.

Phases of Clinical Research For Drug and Device Research

- **Phase I.** Tests potential treatment for the first time in a small group of people to evaluate safety, determine the safe dosage and identify side effects.
- **Phase II.** Further evaluates the safety of the treatment being tested and provides preliminary measures of effectiveness.
- **Phase III.** Determines if the treatment benefits participants and if its benefits outweigh its risks.
- **Phase IV.** After a drug or device is approved, this final phase of research can be conducted. Collects and looks over additional information about a treatment, including risks, benefits and optimal use, after FDA approval.

The entire process of bringing a new medication to the pharmacy can take up to 10 years from the time it is tested in a laboratory to the time that the doctor prescribes it as a treatment.

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 come from. Since the approval of Sinemet (carbidopa-levodopa) in the 1970s, research has led to many life-changing treatments for Parkinson's. Looking at research breakthroughs in our understanding of medications, therapies and devices to treat Parkinson's, today's best care provides a different disease journey than a generation ago. Today's focus on non-motor symptoms is largely a consequence of how effective treatments are for motor symptoms.

Today, the biggest research challenge is slowing the disease 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:

- **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.

- **Slowing disease progression.** If we could make the diagnosis of the disease earlier and slow its progression, people may take a long time to experience troublesome symptoms. 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 potentially get better and start to work again, resulting in an improvement in symptoms. This would be the first step in curing Parkinson's – 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.
- **Diagnosing Parkinson's and measuring progression.** Most people with Parkinson's can be 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. Some medications, essential tremor or small strokes can mimic Parkinson symptoms. Further, figuring out how far Parkinson's has progressed since the last evaluation is difficult, as it may depend on fluctuating medication effect, level of fatigue and external stress factors. A better measure for progression would help with clinical trials of treatments to slow the disease.
- **Replacing lost function.** It is a goal to create therapies that help the brain function like a healthy, normal brain. 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 does restore lost function. However, not all of these changes with Parkinson's can 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 hard task. There is not much evidence that this can be successful with surgical approaches, such as transplants of brain cells failing to be effective in well-designed trials.

  There are always ongoing studies, such as the current test of whether or not gene therapy in the brain will improve its ability to produce dopamine.

- **New symptomatic treatments.** Research is ongoing in many areas, including helping people who experience fluctuating medication effects ("on-off" fluctuations), reducing dyskinesia, achieving better motor control, and managing a range of symptoms, whether it be mood and psychiatric symptoms or 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 clinical trials, including drugs and other therapies on the horizon that are likely to help people with PD in the near future. However, these change frequently as studies show effects of particular treatments. Please visit the Parkinson's Foundation website, Parkinson.org, to find information and resources on the newest research and treatment options. You can also contact our Helpline at 1-800-4PD-INFO (473-4636) or helpline@parkinson.org for help finding a clinical trial near you, so that you can help scientists find the next breakthrough therapy!

- **The role of exercise.** While treating the symptoms of the disease is not the same as slowing its progression, the Parkinson's Outcomes Project shows that people with PD who start exercising earlier and a minimum of 2.5 hours a week, experience a slowed decline in quality of life compared to those who start later. Establishing early exercise habits is essential to overall disease management.

APPENDIX A

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 B

Evaluating Research Reports

New drugs and other PD treatments often gain attention from the popular media. Publicly traded companies have to report their study results as soon as they are available and before they are presented at scientific meetings. This is usually done in form of a press release. 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 trustworthy scientific meeting? Or is the information derived from unscientific, and possibly incorrect, 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 and be more accurate.
- How was the study designed: (1) Were the subjects randomized to equal treatment groups? (2) Was the study double-blind? (3) 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 three of these elements.

APPENDIX C

Medication and Hospitalization

When hospitalized, your healthcare team may not recognize some of your PD symptoms, why they fluctuate so drastically and/or may not know that treating them requires careful medication management. They will naturally be focused on treating the condition that brought you to the hospital, which may be unrelated to PD. This lack of understanding can seriously affect your quality of life, both in the hospital and after you are discharged.

To avoid serious side effects, people with PD need their medication on time, every time – do not let the hospital staff skip or postpone doses. People with PD often have complex and precisely timed medication regimens, which can be difficult to maintain. Nurses are accustomed to dispensing medications on certain schedules and likely have an hour window to distribute medications within that schedule. They may not realize that even a 15-minute delay can make the difference between independent function and poor mobility. Additionally, hospital pharmacies may not keep your specific PD medications in stock.

To help your nurses understand, make sure that the drug schedule, with specific times, is written into the doctor's orders. It is important for you or your advocate to double check the drugs and schedules in your medical chart. If the hospital pharmacy does not stock your medications, ask to use your own. If you are told that you cannot take your own medications, ask your neurologist to write a letter or call the hospital to assure them your own medications are best. Keeping a set of your medications in their original bottles in your Aware in Care kit will help make this possible. Emphasize to the medical staff that delaying or stopping PD medications will not only affect your symptoms, but can also be dangerous. For example, missing the dose of a dopamine agonist may lead to withdrawal symptoms such as anxiety or pain.

The Parkinson's Foundation Aware in Care kit contains information to give to hospital providers about Parkinson's and what medications are safe for people with PD. Call our Helpline at 1-800-4PD-INFO (473-4636) to request your free Aware in Care kit, or order one online at Parkinson.org/Store. Review the materials when you receive the kit, so you will be ready to advocate for yourself or your loved one if he or she is hospitalized or in another in-patient setting, whether it's a planned visit or an emergency.

Glossary

Glossary terms are identified with a blue underline the first time they appear in this book.

A **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.

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

C **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.

Chronic degenerative neurologic disease A disease characterized by the loss of cells of the brain or spinal cord, which over time leads to dysfunction and disability.

Clinical Trials A research study in humans that aims to test a new intervention – this could be a drug, surgery or therapy like exercise or diet guidelines – to make sure it is effective and safe.

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.

Controlled release formulation A type medication that is released or activated at predetermined intervals or gradually over a period of time.

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.

D

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.

Detrusor A muscle that forms a layer of the wall of the bladder, responsible for allowing the bladder to store and release urine.

Diastolic blood pressure Part of the measure of blood pressure, which measures the time between beats and indicates the time that the coronary artery is able to supply blood to the heart.

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.

E

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

Enteral suspension A method of medication distribution through the gastrointestinal tract through the use of a liquid or gel-like mixture of liquids and solids.

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 release (ER) formulation A type of medication designed to slowly release over an extended period of time, especially to reduce dosing frequency.

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

F

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.

G

Gabapentin An anticonvulsant, or anti-epileptic, medication also used in adults to treat neuropathic pain and restless leg syndrome

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

H

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.

Holistic practices An approach to care that looks beyond standard medical care, as complementary therapies (use with standard medical treatments) or Alternative therapies (used instead of standard medical treatments).

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.

I

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

Immediate release (IR) A Type of medication that disintegrates or dissolves rapidly with no special rate controlling features.

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.

L

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."

M

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.

Musculoskeletal The combined network or muscles, bones, ligaments, tendons and nerves

Myasthenia gravis A chronic autoimmune, neuromuscular disease that impacts the muscles responsible for functions involving breathing and movement.

N

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).

Non-pharmacologic Interventions that do not involve medications

Norepinephrine A chemical messenger (neurotransmitter) that plays a role in mood disorders and is released in response to stress.

Nutritional consultation The process of seeking professional guidance on how nutrition can benefit overall well-being.

Occupational therapy A type of therapy that helps maintain or develop daily living or occupational skills in times of physical change.

"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.

Pedal edema The accumulation of fluid in the feet or lower legs

Peripheral neuropathy Conditions that result when nerves carrying messages from the brain and spinal cord to the rest of the body, including muscles, skin and internal organs, are damaged, resulting in weakness, numbness, and/or pain, usually in the hands or feet.

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.

Physical therapy A type of therapy that maintains and strengthens parts of the body related to movement.

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.

Psychological counseling A broad term used to refer to the many varieties of counseling or talk therapy available today. Also called Psychotherapy or "talk therapy."

S

Seborrheic Dermatitis A common skin condition that causes redness (on light skin) or light patches (on darker skin) and an itchy rash with flaky scales. Also called dandruff, cradle cap, seborrhea, sebhorrheic exzema and seborrheic psoriasis.

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.

Speech therapy A type of therapy that evaluates speech changes and creates solutions and improvements to help with speech issues.

Spinal stenosis A condition in which your spinal canal starts to narrow, which can punch the spinal cord or the nerves around it causing pain, tingling or numbness in your legs, arms or torso.

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

Supine hypertension See Orthostatic Hypotension

T **Therapeutic levels** The range in which the amount of medication in your blood that is effective without causing serious problems

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.

U **Use of assistive devices** Using adaptive equipment to help one engage in daily activities such as a shower chair, elevated toilet seat or replacing buttons with Velcro.

V **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.

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