Parkinson disease

What is Parkinson's disease?
Parkinson's disease belongs to a group of conditions called movement disorders. The four main symptoms are tremor, or trembling in hands, arms, legs, jaw, or head; rigidity, or stiffness of the limbs and trunk; bradykinesia, or slowness of movement; and postural instability, or impaired balance. These symptoms usually begin gradually and worsen with time. As they become more pronounced, patients may have difficulty walking, talking, or completing other simple tasks. Not everyone with one or more of these symptoms has PD, as the symptoms sometimes appear in other diseases as well.

PD is both chronic, meaning it persists over a long period of time, and progressive, meaning its symptoms grow worse over time. It is not contagious. Although some PD cases appear to be hereditary, and a few can be traced to specific genetic mutations, most cases are sporadic — that is, the disease does not seem to run in families. Many researchers now believe that PD results from a combination of genetic susceptibility and exposure to one or more environmental factors that trigger the disease.

PD is the most common form of parkinsonism, the name for a group of disorders with similar features and symptoms. PD is also called idiopathic PD. The term idiopathic means a disorder for which no cause has been found. While most forms of parkinsonism are idiopathic, there are some cases where the cause is known or suspected or where the symptoms result from another disorder.

What causes the disease?
Parkinson's disease occurs when nerve cells, or neurons, in the brain die or become impaired. The main area affected is an area near the base of the brain called the substantia nigra. Normally, the neurons in this area produce an important brain chemical known as dopamine. Dopamine is a chemical messenger responsible for transmitting signals between the substantia nigra and the next "relay station" of the brain, the corpus striatum, to produce smooth, purposeful movement. Loss of dopamine results in abnormal nerve firing patterns within the brain that cause impaired movement. Studies have shown that most people with Parkinson's have lost 60 to 80 percent or more of the dopamine-producing cells in the substantia nigra by the time symptoms appear, and that people with PD also have loss of the nerve endings that produce the neurotransmitter norepinephrine. Norepinephrine, which is closely related to dopamine, is the main chemical messenger of the sympathetic nervous system, the part of the nervous system that controls many automatic functions of the body, such as pulse and blood pressure. The loss of norepinephrine might explain several of the non-motor features seen in PD, including fatigue and abnormalities of blood pressure regulation.

Many brain cells of people with PD contain Lewy bodies—deposits of the protein alpha-synuclein. Researchers do not yet know why Lewy bodies form or what role they play in the disease. Some research suggests that the cell’s protein disposal system may fail in people with PD, causing proteins to build up to harmful levels and trigger cell death. Additional studies have found evidence that clumps of protein that develop inside brain cells of people with PD may contribute to the death of neurons. However, the precise role of the protein deposits remains unknown. Some researchers even speculate that this protein buildup is part of an unsuccessful attempt to protect the cell.

Scientists have identified several genetic mutations associated with PD, and many more genes have been tentatively linked to the disorder. Studying the genes responsible for inherited cases of PD can help researchers understand both inherited and sporadic cases. The same genes and proteins that are altered in inherited cases may also be altered in sporadic cases by environmental toxins or other factors. Researchers also hope that discovering genes will help identify new ways of treating PD.

In addition to genetics, environmental exposures may increase a person's risk of developing the disease. Even in familial cases, exposure to toxins or other environmental factors may influence when symptoms of the disease appear or how the disease progresses. There are a number of toxins that can cause parkinsonian symptoms in humans. Other,
still-unidentified environmental factors also may cause PD in genetically susceptible individuals. Inflammation or overstimulation of cells (because of toxins or other factors) may play a role in the disease.

Several lines of research suggest that mitochondria may play a role in the development of PD. Mitochondria are the energy-producing components of the cell and abnormalities in the mitochondria are major sources of free radicals—molecules that damage membranes, proteins, DNA, and other parts of the cell. This damage is often referred to as oxidative stress. Oxidative stress-related changes, including free radical damage to DNA, proteins, and fats, have been detected in brains of PD patients.

While mitochondrial dysfunction, oxidative stress, inflammation, and many other cellular processes may contribute to PD, the actual initial cause of the dopamine cell death is still undetermined.

Who gets Parkinson's disease?
About 50,000 Americans are diagnosed with PD each year, but getting an accurate count of the number of cases is difficult because many people in the early stages of the disease may assume their symptoms are the result of normal aging and do not seek medical attention. Also, diagnosis is sometimes difficult and uncertain because other conditions may produce symptoms of PD and there is no definitive test for the disease. People with PD may sometimes be told by their doctors that they have other disorders, and people with PD-like diseases may be incorrectly diagnosed as having PD.

PD affects about 50 percent more men than women, and the reasons for this discrepancy are unclear. While it occurs in people throughout the world, a number of studies have found a higher incidence in developed countries. Other studies have found an increased risk in people who live in rural areas and in those who work in certain professions, although apparent risks are not fully characterized.

One clear risk factor for PD is age. The average age of onset is 60 years, and the incidence rises significantly with increasing age. However, about 5 to 10 percent of people with PD have "early-onset" disease that begins before the age of 50. Some early onset cases are linked to specific gene mutations such as parkin. People with one or more close relatives who have PD have an increased risk of developing the disease themselves, but the total risk is still about 2 to 5 percent unless the family has a known gene mutation for the disease. An estimated 15 to 25 percent of people with PD have a known relative with the disease.

In very rare cases, parkinsonian symptoms may appear in people before the age of 20. This condition is called juvenile parkinsonism. It often begins with dystonia and bradykinesia, and the symptoms often improve with levodopa medication.

What are the symptoms of the disease?
Early symptoms of PD may be subtle and occur gradually. Affected people may feel mild tremors or have difficulty getting out of a chair. Activities may take longer to complete than in the past and individuals may note some stiffness in addition to slowness. They may notice that they speak too softly or that their handwriting looks cramped or small. This very early period may last a long time before the more classical and obvious motor symptoms—shaking (tremor), stiffness (rigidity), slowness of movement (bradykinesia) and unsteadiness (postural instability)—appear.

Friends or family members may be the first to notice changes in someone with early PD. They may see that the person's face lacks expression and animation (known as "masked face") or that the person moves more slowly.

As the disease progresses, the symptoms of Parkinson's disease may begin to interfere with daily activities. Affected individuals may not be able to hold utensils steady or they may find that the shaking makes reading a newspaper difficult. Tremor is usually the symptom that causes people to seek medical help.

People with PD often develop a so-called parkinsonian gait that includes a tendency to lean forward, small quick steps as if hurrying (called festination), and reduced swinging of the arms. They also may have trouble initiating movement (start hesitation), and they may stop suddenly as they walk (freezing).

PD does not affect everyone the same way, and the rate of progression and the particular symptoms may differ among individuals.

PD symptoms typically begin on one side of the body. However, the disease eventually affects both sides. Even after
the disease involves both sides of the body, the symptoms are often less severe on one side than on the other. The four primary symptoms of PD are:

**Tremor.** The tremor associated with Parkinson's disease has a characteristic appearance. Typically, the tremor takes the form of a rhythmic back-and-forth motion of the thumb and forefinger at three beats per second. This is sometimes called "pill rolling." Tremor usually begins in a hand, although sometimes a foot or the jaw is affected first. It is most obvious when the hand is at rest or when a person is under stress. In three out of four patients, the tremor may affect only one part or side of the body, especially during the early stages of the disease. Later it may become more general. Tremor is rarely disabling and it usually disappears during sleep or improves with intentional movement.

**Rigidity.** Rigidity, or a resistance to movement, affects most parkinsonian patients. A major principle of body movement is that all muscles have an opposing muscle. Movement is possible not just because one muscle becomes more active, but because the opposing muscle relaxes. In Parkinson's disease, rigidity comes about when, in response to signals from the brain, the delicate balance of opposing muscles is disturbed. The muscles remain constantly tensed and contracted so that the person aches or feels stiff or weak. The rigidity becomes obvious when another person tries to move the patient's arm, which will move only in ratchet-like or short, jerky movements known as "cogwheel" rigidity.

**Bradykinesia.** Bradykinesia, or the slowing down and loss of spontaneous and automatic movement, is particularly frustrating because it is unpredictable. One moment the patient can move easily. The next moment he or she may need help. This may well be the most disabling and distressing symptom of the disease because the patient cannot rapidly perform routine movements. Activities once performed quickly and easily — such as washing or dressing — may take much longer.

**Postural instability.** Postural instability, or impaired balance, causes affected individuals to fall easily.

A number of other symptoms may accompany PD, and some can be treated with medication or physical therapy.

**Depression.** This is a common problem and may appear early in the course of the disease, even before other symptoms are noticed. Depression may not be severe, but it may be intensified by the drugs used to treat other symptoms of Parkinson's disease. Fortunately, depression can be successfully treated with antidepressant medications.

**Emotional changes.** Some people with Parkinson's disease become fearful and insecure. Perhaps they fear they cannot cope with new situations. They may not want to travel, go to parties, or socialize with friends. Some lose their motivation and become dependent on family members. Others may become irritable or uncharacteristically pessimistic.

**Difficulty in swallowing and chewing.** Muscles used in swallowing may work less efficiently in later stages of the disease. In these cases, food and saliva may collect in the mouth and back of the throat, which can result in choking or drooling. Medications can often alleviate these problems.

**Speech changes.** About half of all parkinsonian patients have problems with speech. They may speak too softly or in a monotone, hesitate before speaking, slur or repeat their words, or speak too fast. A speech therapist may be able to help patients reduce some of these problems.

**Urinary problems or constipation.** In some people with PD, bladder and bowel problems can occur due to the improper functioning of the autonomic nervous system, which is responsible for regulating smooth muscle activity. Medications can effectively treat some of these symptoms.

**Skin problems.** In PD, the skin on the face may become oily, particularly on the forehead and at the sides of the nose. The scalp may become oily too, resulting in dandruff. In other cases, the skin can become very dry. Standard treatments for skin problems can help.

**Sleep problems.** Sleep problems are common in PD and include difficulty staying asleep at night, restless sleep, nightmares and emotional dreams, and drowsiness or sudden sleep onset during the day. Another common problem is "REM behavior disorder," or RBD, in which people act out their dreams, potentially resulting in injury to themselves or their bed partners. The medications used to treat PD may contribute to some of these sleep issues. Many of these
problems respond to specific therapies.

- **Dementia or other cognitive problems.** Some people with PD may develop memory problems and slow thinking. Cognitive problems become more severe in late stages of PD, and a diagnosis of Parkinson’s disease dementia (PDD) may be given. Memory, social judgment, language, reasoning, or other mental skills may be affected. There is currently no way to halt PD dementia, but some drugs like rivastigmine, donepezil, or memantine can help.

- **Orthostatic hypotension.** Orthostatic hypotension is a sudden drop in blood pressure when a person stands up from a lying-down or seated position. This may cause dizziness, lightheadedness, and, in extreme cases, loss of balance or fainting. Studies have suggested that, in PD, this problem results from a loss of nerve endings in the sympathetic nervous system that controls heart rate, blood pressure, and other automatic functions in the body. The medications used to treat PD also may contribute to this symptom. There are both non-pharmacologic (lifestyle) measures and medications that can be used to address this.

- **Muscle cramps and dystonia.** The rigidity and lack of normal movement associated with PD often causes muscle cramps, especially in the legs and toes. Massage, stretching, and applying heat may help with these cramps. PD also can be associated with dystonia — sustained muscle contractions that cause forced or twisted positions. Dystonia in PD is often caused by fluctuations in the body’s level of dopamine. It can usually be relieved or reduced by adjusting the person’s medications.

- **Pain.** Many people with PD develop aching muscles and joints because of the rigidity and abnormal postures often associated with the disease. Treatment with levodopa and other dopaminergic drugs often alleviates these pains to some extent. Certain exercises also may help.

- **Fatigue and loss of energy.** The unusual demands of living with PD often lead to problems with fatigue, especially late in the day. Fatigue may be associated with depression or sleep disorders, but it also may result from muscle stress or from overdoing activity when the person feels well. Fatigue also may result from akinesia - trouble initiating or carrying out movement. Exercise, good sleep habits, staying mentally active, and not forcing too many activities in a short time may help to alleviate fatigue.

- **Sexual dysfunction.** Men with PD may have erectile dysfunction because of its effects on nerve signals from the brain. PD-related depression or use of certain medications also may cause decreased sex drive and other problems. People should discuss these issues with their physician as they may be treatable.

What other diseases resemble Parkinson disease?

A number of disorders can cause symptoms similar to those of PD. People with symptoms that resemble PD but that result from other causes are considered to have parkinsonism. Some of these disorders include:

- **Multiple system atrophy.** Multiple system atrophy (MSA) refers to a set of slowly progressive disorders that affect the central and autonomic nervous systems. MSA is one of a group of neurodegenerative disorders (including Parkinson’s disease and Dementia with Lewy Bodies) in which the protein alpha-synuclein forms harmful filament-like aggregates in certain neurons and supporting cells in the brain. MSA may have symptoms that resemble PD. It also may take a form that primarily produces poor coordination and slurred speech, or it may have a mixture of these symptoms. Other symptoms may include swallowing difficulties, male impotence, constipation, and urinary difficulties. The disorder previously called Shy-Drager syndrome refers to MSA with prominent orthostatic hypotension—a fall in blood pressure every time the person stands up. MSA with parkinsonian symptoms is sometimes referred to as MSA-P (or striatonigral degeneration), while MSA with poor coordination and slurred speech is sometimes called MSA-C (or olivopontocerebellar atrophy).

- **Dementia with Lewy bodies.** Dementia with Lewy bodies is a neurodegenerative disorder associated with abnormal protein deposits (Lewy bodies) found in certain areas of the brain. Symptoms may include traditional parkinsonian symptoms such as bradykinesia, rigidity, tremor, and shuffling walk, to symptoms similar to those of Alzheimer's disease (memory loss, poor judgment, and confusion). These symptoms may fluctuate, or wax and wane dramatically. Visual hallucinations may be one of the first symptoms, and individuals may suffer from other psychiatric disturbances such as delusions and depression. Cognitive problems also occur early in the course of the disease. Levodopa and other antiparkinsonian medications can help with the motor symptoms of Dementia with Lewy bodies, but they may make hallucinations and delusions worse.
Progressive supranuclear palsy. Progressive supranuclear palsy (PSP) is a rare, progressive brain disorder that causes problems with control of gait and balance. People often tend to fall early in the course of PSP. One of the characteristic features of the disease is an inability to move the eyes properly. Some people describe this effect as a blurring. People with PSP often show alterations of mood and behavior, including depression and apathy as well as mild dementia. The symptoms of PSP are caused by a gradual deterioration of brain cells in the brain stem. It is often misdiagnosed because some of its symptoms are very much like those of PD, Alzheimer's disease, and other brain disorders. PSP symptoms usually do not respond to medication.

Corticobasal degeneration. Corticobasal degeneration results from atrophy 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 some of the features found in PD, including rigidity, impaired balance, and problems with coordination. Often there is dystonia affecting one side of the body. Other symptoms may include cognitive and visual-spatial impairments, apraxia (loss of the ability to make familiar, purposeful movements), hesitating and halting speech, myoclonus (muscular jerks), and dysphagia (difficulty swallowing). Unlike PD, corticobasal degeneration usually does not respond to medication.

Several diseases, including MSA, corticobasal degeneration, and progressive supranuclear palsy, are sometimes referred to as "Parkinson's-plus" diseases because they have the symptoms of PD plus additional features.

Parkinsonism resulting from neurologic disorders

Arteriosclerotic parkinsonism. Sometimes known as pseudoparkinsonism, vascular parkinsonism, or atherosclerotic parkinsonism, arteriosclerotic parkinsonism involves damage to the brain due to multiple strokes. Tremor is rare in this type of parkinsonism, while dementia—the loss of mental skills and abilities—and difficulties with gait are common. Antiparkinsonian drugs are of little help to people with this form of parkinsonism.

Post-traumatic parkinsonism. Also known as post-traumatic encephalopathy or "punch-drunk syndrome," parkinsonian symptoms can sometimes develop after a severe head injury or frequent head trauma that results from boxing or other activities. This type of trauma also can cause a form of dementia called chronic traumatic encephalopathy, or dementia pugilistica.

Essential tremor. Sometimes called benign essential tremor or familial tremor, is a common condition that tends to run in families and progresses slowly over time. The tremor is usually equal in both hands and increases when the hands are moving. It may involve the head but usually spares the legs. Essential tremor is not the same as Parkinson's disease and does not usually lead to it, although in some cases the two conditions may overlap in one person. People with essential tremor have no other parkinsonian features. Essential tremor does not respond to levodopa or most other PD drugs, but it can be treated with other medications.

Normal pressure hydrocephalus. Normal pressure hydrocephalus (NPH) is an abnormal increase of cerebrospinal fluid (CSF) in the brain's ventricles, or cavities. This causes the ventricles to enlarge, putting pressure on the brain. Symptoms include problems with walking, impaired bladder control leading to urinary frequency or incontinence, and progressive mental impairment and dementia. The person also may have a general slowing of movements or may complain that his or her feet feel "stuck." These symptoms may sometimes be mistaken for PD. Brain scans, intracranial pressure monitoring, and other tests can help to distinguish NPH from PD and other disorders. NPH can sometimes be treated by surgically implanting a CSF shunt that drains excess cerebrospinal fluid into the abdomen, where it is absorbed.

Parkinsonism accompanying other conditions. Parkinsonian symptoms may also appear in individuals with other, clearly distinct neurological disorders such as Wilson's disease, Huntington's disease, Alzheimer's disease, spinocerebellar ataxias, and Creutzfeldt-Jakob disease. Each of these disorders has specific features that help to distinguish them from PD.

Environmental causes

Postencephalitic parkinsonism. Just after the first World War, the viral disease encephalitis lethargica attacked almost 5 million people throughout the world, and then suddenly disappeared in the 1920s. Known as sleeping sickness in the United States, this disease killed one-third of its victims and led to post-encephalitic parkinsonism in many others. This resulted in a movement disorder that appeared sometimes years after the initial illness. (In 1973, neurologist Oliver Sacks published Awakenings, an account of his work in the late 1960s with surviving post-
encephalitic patients in a New York hospital. Using the then-experimental drug levodopa, Dr. Sacks was able to temporarily "awaken" these individuals from their statue-like state). In rare cases, other viral infections, including western equine encephalomyelitis, eastern equine encephalomyelitis, and Japanese B encephalitis, have caused parkinsonian symptoms.

**Drug-induced parkinsonism.** A reversible form of parkinsonism sometimes results from use of certain drugs, such as chlorpromazine and haloperidol, which are typically prescribed for patients with psychiatric disorders. Some drugs used for stomach disorders (metoclopramide), high blood pressure (reserpine), and others such as valproate can cause tremor. Stopping the medication or lowering the dosage of these medications usually causes the symptoms to go away.

**Toxin-induced parkinsonism.** Some toxins can cause parkinsonism by various mechanisms. The chemical MPTP also causes a permanent form of parkinsonism that closely resembles PD. Investigators discovered this reaction in the 1980s when heroin addicts in California who had taken an illicit street drug contaminated with MPTP began to develop severe parkinsonism. This discovery, which showed that a toxic substance could damage the brain and produce parkinsonian symptoms, caused a dramatic breakthrough in Parkinson's research.

**Parkinsonism-dementia complex of Guam.** This disease occurs among the Chamorro populations of Guam and the Mariana Islands and may be accompanied by a motor neuron disease resembling amyotrophic lateral sclerosis (Lou Gehrig's disease). The course of the disease is rapid, with death typically occurring within 5 years.

**How is Parkinson disease diagnosed?**
There are currently no blood or laboratory tests that have been proven to help in diagnosing sporadic PD. Therefore the diagnosis is based on medical history and a neurological examination. The disease can be difficult to diagnose accurately. Early signs and symptoms of PD may sometimes be dismissed as the effects of normal aging. The physician may need to observe the person for some time until it is apparent that the symptoms are consistently present. Doctors may sometimes request brain scans or laboratory tests in order to rule out other diseases. However, CT and MRI brain scans of people with PD usually appear normal. Since many other diseases have similar features but require different treatments, making a precise diagnosis as soon as possible is essential so that patients can receive the proper treatment.

**How is the disease treated?**
At present, there is no cure for Parkinson's disease. But a variety of medications provide dramatic relief from the symptoms.

**Drug treatments**
Medications for PD fall into three categories. The first category includes drugs that work directly or indirectly to increase the level of dopamine in the brain. The most common drugs for PD are dopamine precursors – substances such as levodopa that cross the blood-brain barrier and are then changed into dopamine. Other drugs mimic dopamine or prevent or slow its breakdown.

The second category of PD drugs affects other neurotransmitters in the body in order to ease some of the symptoms of the disease. For example, anticholinergic drugs interfere with production or uptake of the neurotransmitter acetylcholine. These drugs help to reduce tremors and muscle stiffness, which can result from having more acetylcholine than dopamine.

The third category of drugs prescribed for PD includes medications that help control the non-motor symptoms of the disease, that is, the symptoms that don't affect movement. For example, people with PD-related depression may be prescribed antidepressants.

- **Levodopa.** The cornerstone of therapy for PD is the drug levodopa (also called L-dopa). Levodopa (from the full name L-3,4-dihydroxyphenylalanine) is a simple chemical found naturally in plants and animals. Levodopa is the generic name used for this chemical when it is formulated for drug use in patients. Nerve cells can use levodopa to make dopamine and replenish the brain's dwindling supply. People cannot simply take dopamine pills because dopamine does not easily pass through the blood-brain barrier, a lining of cells inside blood vessels that regulates the transport of oxygen, glucose, and other substances into the brain. Usually, patients are given levodopa combined with another substance called carbidopa. When added to levodopa, carbidopa delays the conversion of levodopa into
dopamine until it reaches the brain, preventing or diminishing some of the side effects that often accompany levodopa therapy. Carbidopa also reduces the amount of levodopa needed.

Levodopa is very successful at reducing the tremors and other symptoms of PD during the early stages of the disease. It allows the majority of people with PD to extend the period of time in which they can lead relatively normal, productive lives.

Although levodopa helps most people with PD, not all symptoms respond equally to the drug. Levodopa usually helps most with bradykinesia and rigidity. Problems with balance and other non-motor symptoms may not be alleviated at all.

People often see noticeable improvement in their symptoms after starting levodopa therapy. However, they may need to increase the dose gradually for maximum benefit. Proteins can interfere with the absorption of levodopa from the stomach, so it may sometimes be necessary to avoid taking the medication close to a meal. Levodopa is often so effective that some people may temporarily forget they have PD during the early stages of the disease. But levodopa is not a cure. Although it can reduce the symptoms of PD, it does not replace lost nerve cells and it does not stop the progression of the disease.

Levodopa can have a variety of side effects. The most common initial side effects include nausea, low blood pressure, and restlessness. The drug also can cause drowsiness or sudden sleep onset, which can make driving and other activities dangerous. Long-term use of levodopa sometimes causes hallucinations and psychosis. The nausea and vomiting caused by levodopa are greatly reduced by combining levodopa and carbidopa.

**Dyskinesias**, or involuntary movements such as twitching, twisting, and writhing, commonly develop in people who take large doses of levodopa over an extended period. These movements may be either mild or severe and either very rapid or very slow. The dose of levodopa is often reduced in order to lessen these drug-induced movements. However, the PD symptoms often reappear even with lower doses of medication. Doctors and patients must work together closely to find a tolerable balance between the drug's benefits and side effects. If dyskinesias are severe, surgical treatment may be considered. Because dyskinesias tend to occur with long-term use of levodopa, doctors often start younger PD patients on other dopamine-increasing drugs and switch to levodopa only when those drugs become ineffective.

Other difficulties may be encountered later in the disease course. Patients may begin to notice more pronounced symptoms before their first dose of medication in the morning and between doses as the period of effectiveness after each dose may begin to shorten, called the wearing-off effect. People may also experience sudden, unpredictable “off periods,” where the medications do not seem to be working. One approach to alleviating these side effects is to take levodopa more often and in smaller amounts. People with PD should never stop taking levodopa without their physician's input, because rapidly withdrawing the drug can have potentially serious side effects.

In addition to levodopa-carbidopa, there are other available treatments:

- **Dopamine agonists.** These drugs, which include apomorphine, pramipexole, ropinirole, and rotigotine, mimic the role of dopamine in the brain. They can be given alone or with levodopa. They are somewhat less effective than levodopa in treating PD symptoms. Many of the potential side effects are similar to those associated with the use of levodopa, including drowsiness, sudden sleep onset, hallucinations, confusion, dyskinesias, edema (swelling due to excess fluid in body tissues), nightmares, and vomiting. In rare cases, they can cause an uncontrollable desire to gamble, hypersexuality, or compulsive shopping.

- **MAO-B inhibitors.** These drugs inhibit the enzyme monoamine oxidase B, or MAO-B, which breaks down dopamine in the brain. MAO-B inhibitors cause dopamine to accumulate in surviving nerve cells and reduce the symptoms of PD. Studies supported by the NINDS have shown that selegiline (also called deprenyl) can delay the need for levodopa therapy by up to a year or more. When selegiline is given with levodopa, it appears to enhance and prolong the response to levodopa and thus may reduce wearing-off. Selegiline is usually well-tolerated, although side effects may include nausea, orthostatic hypotension, or insomnia. It should not be taken with the antidepressant fluoxetine or the sedative meperidine, because combining selegiline with these drugs can be harmful. Another MAO-B inhibitor, rasagiline, was approved by the FDA in May 2006 for use in treating the motor symptoms of PD with or without levodopa. Study results announced in 2013 showed people with Parkinson’s disease who took rasagiline as an add-on...
treatment to dopamine agonists showed a slower rate of disease worsening and less worsening between baselines than in individuals who took a placebo.

• **COMT inhibitors.** COMT stands for catechol-O-methyltransferase, another enzyme that breaks down dopamine. The drug entacapone and tolcapone prolong the effects of levodopa by preventing the breakdown of dopamine. COMT inhibitors can decrease the duration of “off periods” of one’s dose of levodopa. The most common side effect is diarrhea. The drugs may also cause nausea, sleep disturbances, dizziness, urine discoloration, abdominal pain, low blood pressure, or hallucinations. In a few rare cases, tolcapone has caused severe liver disease, and people taking tolcapone need regular monitoring of their liver function.

• **Amantadine.** An antiviral drug, amantadine, can help reduce symptoms of PD and levodopa-induced dyskinesia. It is often used alone in the early stages of the disease. It also may be used with an anticholinergic drug or levodopa. After several months, amantadine’s effectiveness wears off in up to half of the patients taking it. Amantadine’s side effects may include insomnia, mottled skin, edema, agitation, or hallucinations. Researchers are not certain how amantadine works in PD, but it may increase the effects of dopamine.

• **Anticholinergics.** These drugs, which include trihexyphenidyl, benztropine, and ethopropazine, decrease the activity of the neurotransmitter acetylcholine and help to reduce tremors and muscle rigidity. Only about half the patients who receive anticholinergics are helped by it, usually for a brief period and with only a 30 percent improvement. Side effects may include dry mouth, constipation, urinary retention, hallucinations, memory loss, blurred vision, and confusion.

When recommending a course of treatment, a doctor will assess how much the symptoms disrupt the patient’s life and then tailor therapy to the person’s particular condition. Since no two patients will react the same way to a given drug, it may take time and patience to get the dose just right. Even then, symptoms may not be completely alleviated.

**Medications to treat the motor symptoms of Parkinson disease**

Drugs that increase brain levels of dopamine
- Levodopa-carbidopa

Drugs that mimic dopamine (dopamine agonists)
- Apomorphine
- Bromocriptine
- Pramipexole
- Ropinirole

Drugs that inhibit dopamine breakdown (MAO-B inhibitors)
- Rasagiline
- Selegiline (deprenyl)

Drugs that inhibit dopamine breakdown (COMT inhibitors)
- Entacapone
- Tolcapone

Drugs that decrease the action of acetylcholine (anticholinergics)
- Benztropine
- Ethopropazine
- Trihexyphenidyl

Drugs with an unknown mechanism of action for PD
- Amantadine

**Medications for non-motor symptoms.** Doctors may prescribe a variety of medications to treat the non-motor symptoms of PD, such as depression and anxiety. For example, depression can be treated with standard antidepressant drugs such as amitriptyline or fluoxetine (however, as stated earlier, fluoxetine should not be combined with MAO-B inhibitors). Anxiety can sometimes be treated with drugs called benzodiazepines. Orthostatic hypotension may be helped by increasing salt intake, reducing antihypertension drugs, or prescribing medications such as fludrocortisone.

Hallucinations, delusions, and other psychotic symptoms are often caused by the drugs prescribed for PD. Therefore reducing or stopping PD medications may alleviate psychosis. If such measures are not effective, doctors sometimes
prescribe drugs called atypical antipsychotics, which include clozapine and quetiapine. Clozapine also may help to control dyskinesias. However, clozapine also can cause a serious blood disorder called agranulocytosis, so people who take it must have their blood monitored frequently.

**Surgery**

Before the discovery of levodopa, surgery was a common option to treating PD. Studies in the past few decades have led to great improvements in surgical techniques, and surgery is again considered for people with PD for whom drug therapy is no longer sufficient.

**Pallidotomy and thalamotomy.** The earliest types of surgery for PD involved selectively destroying specific parts of the brain that contribute to the symptoms of the disease. Investigators have now greatly refined the use of these procedures. The most common of these procedures is called pallidotomy. In this procedure, a surgeon selectively destroys a portion of the brain called the globus pallidus. Pallidotomy can improve symptoms of tremor, rigidity, and bradykinesia, possibly by interrupting the connections between the globus pallidus and the striatum or thalamus. Some studies have also found that pallidotomy can improve gait and balance and reduce the amount of levodopa patients require, thus reducing drug-induced dyskinesias and dystonia. A related procedure, called thalamotomy, involves surgically destroying part of the brain's thalamus. Thalamotomy is useful primarily to reduce tremor.

Because these procedures cause permanent destruction of brain tissue, they have largely been replaced by deep brain stimulation for treatment of PD.

**Deep brain stimulation.** Deep brain stimulation, or DBS, uses an electrode surgically implanted into part of the brain. The electrodes are connected by a wire under the skin to a small electrical device called a pulse generator that is implanted in the chest beneath the collarbone. The pulse generator and electrodes painlessly stimulate the brain in a way that helps to stop many of the symptoms of PD. DBS has now been approved by the U.S. Food and Drug Administration, and it is widely used as a treatment for PD.

DBS can be used on one or both sides of the brain. If it is used on just one side, it will affect symptoms on the opposite side of the body. DBS is primarily used to stimulate one of three brain regions: the subthalamic nucleus, the globus pallidus, or the thalamus. However, the subthalamic nucleus, a tiny area located beneath the thalamus, is the most common target. Stimulation of either the globus pallidus or the subthalamic nucleus can reduce tremor, bradykinesia, and rigidity. Stimulation of the thalamus is useful primarily for reducing tremor.

People who initially responded well to treatment with levodopa tend to respond well to DBS. While the motor function benefits of DBS can be substantial, it usually does not help with speech problems, “freezing,” posture, balance, anxiety, depression, or dementia.

One advantage of DBS compared to pallidotomy and thalamotomy is that the electrical current can be turned off using a handheld device. The pulse generator also can be externally programmed.

Individuals must return to the medical center frequently for several months after DBS surgery in order to have the stimulation adjusted by trained doctors or other medical professionals. The pulse generator must be programmed very carefully to give the best results. Doctors also must supervise reductions in medications. After a few months, the number of medical visits usually decreases significantly, though individuals may occasionally need to return to the center to have their stimulator checked. Also, the battery for the pulse generator must be surgically replaced every three to five years, though externally rechargeable batteries may eventually become available. DBS does not stop PD from progressing, and some problems may gradually return. DBS is not a good option for everyone. It is generally appropriate for people with levodopa-responsive PD who have developed dyskinesias or other disabling "off" symptoms despite drug therapy. It is not generally an option for people with memory problems, hallucinations, severe depression, poor health, or a poor response to levodopa. DBS has not been demonstrated to be of benefit for "atypical" parkinsonian syndromes such as multiple system atrophy, progressive supranuclear palsy, or post-traumatic Parkinsonism.

As with any brain surgery, DBS has potential complications, including stroke or brain hemorrhage. These complications are rare, however. There is also a risk of infection, which may require antibiotics or even replacement of parts of the DBS system. Researchers are continuing to study DBS and to develop ways of improving it. A two-part study funded by the NINDS and the Department of Veterans Affairs first compared bilateral DBS to best medical therapy, including
medication adjustment and physical therapy. Bilateral DBS showed overall superiority to best medical therapy at improving motor symptoms and quality of life. The second part of the study, involving nearly 300 patients, compared subthalamic nucleus (STN) DBS to globus pallidus interna (GPI) DBS. The two groups reported similar improvements in motor control and quality of life in scores on the Unified Parkinson’s Disease Rating Scale. On a variety of neuropsychological tests, there were no significant differences between the two groups. However, the STN DBS group experienced a greater decline on a test of visuomotor processing speed, which measures how quickly someone thinks and acts on information. Also, the STN DBS group had slight worsening on a standard assessment of depression, while the GPI DBS group had slight improvement on the same test. The importance of these two differences is not clear, and will be scrutinized in follow-up research, the investigators say. Other clinical studies hope to determine the best part of the brain to receive stimulation and to determine the long-term effects of this therapy. They also are working to improve the technology used in DBS.

**Complementary and supportive therapies**

A wide variety of complementary and supportive therapies may be used for PD. Among these therapies are standard physical, occupational, and speech therapy techniques, which can help with such problems as gait and voice disorders, tremors and rigidity, and cognitive decline. Other types of supportive therapies include the following:

**Diet.** At this time there are no specific vitamins, minerals, or other nutrients that have any proven therapeutic value in PD. A NINDS clinical study of the dietary supplement coenzyme Q10 was stopped in 2011 when results from an interim analysis showed active treatment with the supplement was unlikely to demonstrate a statistically significant difference than from a placebo. The NINDS and other components of the National Institutes of Health are funding research to determine if caffeine, antioxidants, and other dietary factors may be beneficial for preventing or treating PD. While there is currently no proof that any specific dietary factor is beneficial, a normal, healthy diet can promote overall well-being for people with PD just as it would for anyone else. Eating a fiber-rich diet and drinking plenty of fluids also can help alleviate constipation. A high protein diet, however, may limit levodopa's absorption, highlighting the importance of the timing of medications.

**Exercise.** Exercise can help people with PD improve their mobility and flexibility. Some doctors prescribe physical therapy or muscle-strengthening exercises to tone muscles and to put underused and rigid muscles through a full range of motion. Exercises will not stop disease progression, but they may improve body strength so that the person is less disabled. Exercises also improve balance, helping people minimize gait problems, and can strengthen certain muscles so that people can speak and swallow better. Exercise can also improve the emotional well-being of people with PD, and it may improve the brain's dopamine synthesis or increase levels of beneficial compounds called neurotrophic factors in the brain. Although structured exercise programs help many patients, more general physical activity, such as walking, gardening, swimming, calisthenics, and using exercise machines, also is beneficial. People with PD should always check with their doctors before beginning a new exercise program.

Other complementary therapies that are used by some individuals with PD include massage therapy, yoga, tai chi, hypnosis, acupuncture, and the Alexander technique, which optimizes posture and muscle activity.

Another important therapeutic approach involves speech and swallowing evaluation and therapy. Certain techniques can help with the low voice volume that patients with Parkinson’s often experience.

**How can people cope with Parkinson disease?**

While PD usually progresses slowly, eventually the most basic daily routines may be affected — from socializing with friends and enjoying normal relationships with family members to earning a living and taking care of a home. These changes can be difficult to accept. Support groups can help people cope with the disease emotionally. These groups can also provide valuable information, advice, and experience to help people with PD, their families, and their caregivers deal with a wide range of issues, including locating doctors familiar with the disease and coping with physical limitations. A list of national organizations that can help patients locate support groups in their communities appears at the end of this brochure. Individual or family counseling also may help people find ways to cope with PD.

People with PD also can benefit from being proactive and finding out as much as possible about the disease in order to alleviate fear of the unknown and to take a positive role in maintaining their health. Many people with PD continue to work either full- or part-time, although eventually they may need to adjust their schedule and working environment to accomodate their symptoms.
Can scientists predict or prevent Parkinson disease?
In most cases, there is no way to predict or prevent sporadic PD. However, researchers are looking for a biomarker — a biochemical abnormality that all patients with PD might share — that could be picked up by screening techniques or by a simple chemical test given to people who do not have any parkinsonian symptoms. This could help doctors identify people at risk of the disease. It also might allow them to find treatments that will stop the disease process in the early stages.

One important area of research in this domain involves imaging techniques, such as special MRI techniques or nuclear imaging techniques currently under study at the National Institutes of Health and elsewhere.

In rare cases, where people have a clearly inherited form of PD, researchers can test for known gene mutations as a way of determining an individual's risk of the disease. However, this genetic testing can have far-reaching implications and people should carefully consider whether they want to know the results of such tests.

Where can I get more information?
For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
(800) 352-9424
www.ninds.nih.gov

Information also is available from the following organizations:
American Parkinson Disease Association
135 Parkinson Avenue
Staten Island, NY 10305-1425
http://www.apdaparkinson.org
718-981-8001, 800-223-2732 Calif: 800-908-2732

Michael J. Fox Foundation for Parkinson's Research
Grand Central Station
P.O. Box 4777
New York, NY 10163
http://www.michaeljfox.org
212-509-0995

National Parkinson Foundation
1501 N.W. 9th Avenue
Bob Hope Road
Miami, FL 33136-1494
http://www.parkinson.org/
305-243-6666, 800-473-4636

Parkinson Alliance
P.O. Box 308
Kingston, NJ 08528-0308
http://www.parkinsonalliance.org
609-688-0870, 800-579-8440

Parkinson's Action Network (PAN)
1025 Vermont Ave. N.W., Suite 1120
Washington, DC 20005
http://www.parkinsonsaction.org
800-850-4726, 202-638-4101

Parkinson's Disease Foundation (PDF)
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