

Parkinson's Disease

Overview

Parkinson's disease (PD) is a progressive disorder that affects nerve cells in the brain responsible for body movement. When dopamine-producing neurons die, symptoms such as tremor, slowness, stiffness, and balance problems occur. Treatments focus on reducing symptoms to enable a more active lifestyle and include medication, diet, exercise, and deep brain stimulation surgery.

The nervous system & dopamine

To understand Parkinson's, it is helpful to understand how neurons work and how PD affects the brain.

Nerve cells, or neurons, are responsible for sending and receiving nerve impulses or messages between the body and the brain. Try to picture electrical wiring in your home. An electrical circuit is made up of numerous wires connected in such a way that when a light switch is turned on, a light bulb will beam. Similarly, a neuron that is excited will transmit its energy to neurons that are next to it.

Neurons have a cell body with branching arms, called dendrites, which act like antennae and pick up messages. Axons carry messages away from the cell body. Impulses travel from neuron to neuron, from the axon of one cell to the dendrites of another, by crossing over a tiny gap between the two nerve cells called a synapse. Chemical messengers called neurotransmitters allow the electrical impulse to cross the gap.

Neurons talk to each other in the following manner (Fig 1):

1. Incoming messages from the dendrites are passed to the end of the axon where sacs containing neurotransmitters open into the synapse.
2. The neurotransmitters cross the synapse and fit into special receptors on the receiving cell.
3. That cell is stimulated to pass the message on.
4. After the message is passed on, the receptors release the neurotransmitters back into the synapse where they are "taken up" or recycled within the releasing neuron.
5. Chemicals called MAO-B and COMT break down any remaining neurotransmitters so that the synapse area is "clean" and ready for the next message.

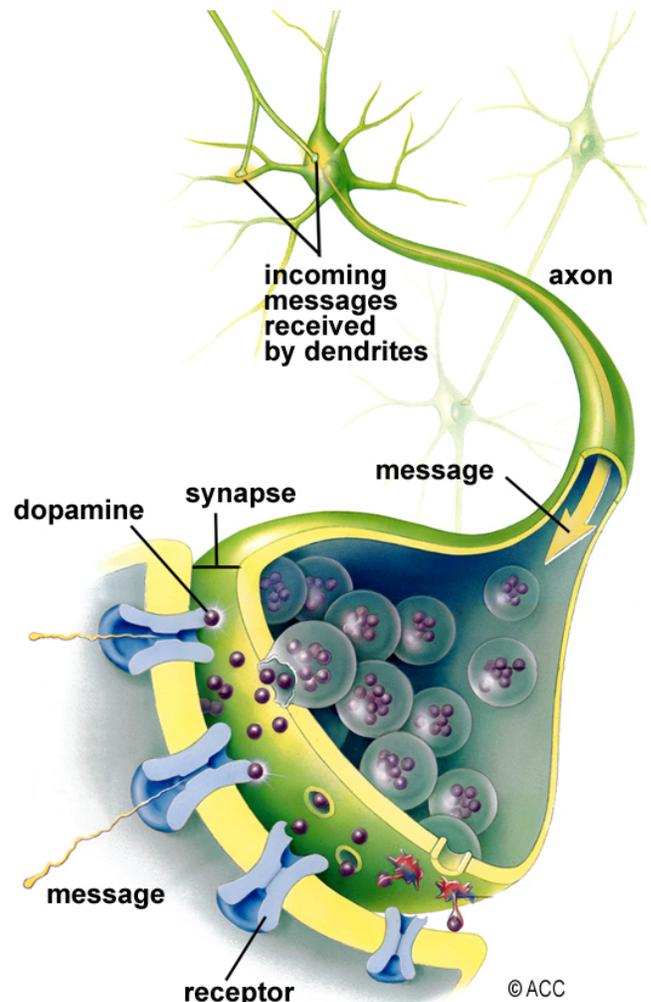


Figure 1. Neurons communicate with each other across a tiny gap called a synapse. Incoming messages from the dendrites are passed to the axon where the nerve cell is stimulated to release neurotransmitters into the synapse. The neighboring nerve cell receptors pick up these chemical messengers and effectively transmit the message onto the next nerve cell.

What is Parkinson's disease?

Parkinson's Disease (PD) is a degenerative, progressive disorder that affects nerve cells in deep parts of the brain called the basal ganglia and the substantia nigra. Nerve cells in the substantia nigra produce the neurotransmitter dopamine and are responsible for relaying messages that plan and control body movement. For reasons not yet understood, the dopamine-producing nerve cells of the substantia nigra begin to die off in some individuals. When 80% of dopamine is lost, PD symptoms such as tremor, slowness of movement, stiffness, and balance problems occur.

Body movement is controlled by a complex chain of decisions involving interconnected groups of nerve cells called ganglia. Information comes to a central area of the brain called the striatum, which works with the substantia nigra to send impulses back and forth from the spinal cord to the brain. The basal ganglia and cerebellum are responsible for ensuring that movement is carried out in a smooth, fluid manner (Fig 2).

Impulses are passed from neuron to neuron, moving quickly from your brain to your spinal cord and, finally, to your muscles. When dopamine receptors in the striatum are not adequately stimulated, parts of the basal ganglia are either under- or over-stimulated. In particular, the subthalamic nucleus (STN) becomes overactive and acts as a brake on the globus pallidus interna (GPI) causing shutdown of motion and rigidity. When the GPI is overstimulated it has an over-inhibitory effect on the thalamus, which in turn decreases thalamus output and causes tremor (Fig 3).

The action of dopamine is opposed by another neurotransmitter called acetylcholine. In PD the nerve cells that produce dopamine are dying. The symptoms of tremor and stiffness occur when the nerve cells fire and there isn't enough dopamine to transmit messages. High levels of glutamate, another neurotransmitter, also appear in PD as the body tries to compensate for the lack of dopamine.

What are the symptoms?

Symptoms of PD vary from person to person, as does the rate of progression. A person who has Parkinson's may experience some of these more common "hallmark" symptoms:

- **Bradykinesia** - slowness of movement, impaired dexterity, decreased blinking, drooling, expressionless face.
- **Tremor at rest** - involuntary shaking that decreases with purposeful movement. Typically starts on one side of the body, usually the hand.
- **Rigidity** - stiffness caused by involuntary increase in muscle tone.
- **Postural instability** - sense of imbalance. Patients often compensate by lowering their center of gravity, which results in a stooped posture.

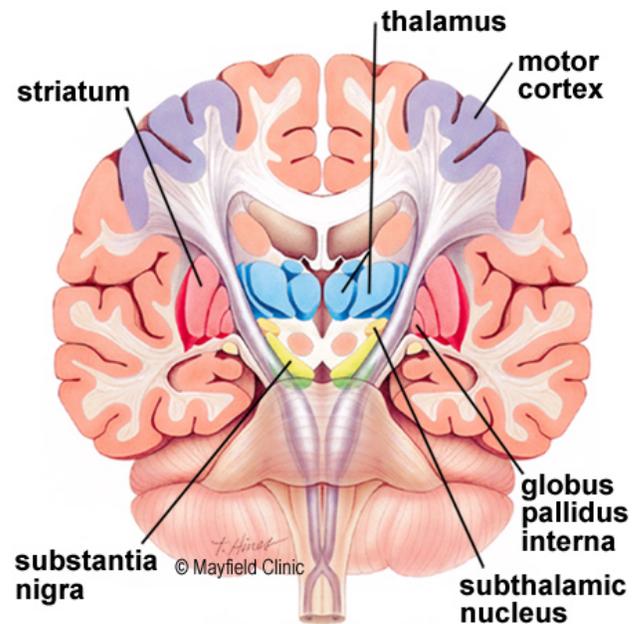


Figure 2. A cross section of the brain. The impulse for body movement begins in the motor cortex of the brain. The basal ganglia are responsible for activating and inhibiting specific circuits or feedback loops.



Figure 3. When the basal ganglia are over-stimulated or under-stimulated the symptoms of tremor, rigidity and slowness of movement occur.

Other symptoms that may or may not occur:

- Freezing or being stuck in place
- Shuffling gait or dragging of one foot
- Stooped posture
- Small, cramped handwriting
- Sleep problems, insomnia
- Apathy, depression
- Lowered voice volume or tremor when speaking
- Difficulty swallowing
- Constipation
- Cognitive impairment

What are the causes?

The cause of Parkinson's is largely unknown. Scientists are currently investigating the role that genetics, environmental factors, and the natural process of aging have on cell death and PD.

There are also secondary forms of PD that are caused by medications such as haloperidol (a drug used to treat confusion and hallucinations), reserpine (an ingredient in some anti-hypertension drugs), and metoclopramide (an anti-nausea drug).

Who is affected?

More than 1.5 million Americans have PD. It typically occurs in men and women around age 60. Early-onset Parkinson's occurs around age 40.

How is a diagnosis made?

Because other conditions and medications mimic the symptoms of PD, getting an accurate diagnosis is important. No single test can confirm a diagnosis of PD because the symptoms vary from person to person. A thorough history and physical exam should be enough for a diagnosis to be made. Other conditions that have Parkinson's-like symptoms include Parkinson's plus, essential tremor, progressive supranuclear palsy, multi-system atrophy, dystonia, and normal pressure hydrocephalus.

What treatments are available?

Many people with Parkinson's enjoy an active lifestyle and a normal life expectancy. Maintaining a healthy lifestyle by eating a balanced diet and staying physically active contributes to overall health and well-being. Parkinson's disease can be managed with self-care, medication, and surgery.

Self care

Exercise is as important as medication in the treatment of PD. It helps maintain flexibility and improves balance and range of motion. Patients may want to join a support group and continue enjoyable activities to improve their quality of life. Equally important is the health and well being of the family and caregivers who are also coping with PD. For additional pointers, see Coping With Parkinson's Disease.

These are some practical tips patients can use:

- Exercise to maintain strength and flexibility. Maintain a healthy diet. Consult your physician before initiating a new diet or exercise plan.
- Don't overdo physical activities; know your limits and stay within them.
- Remove throw rugs and low-lying obstacles from pathways inside and outside your home.
- Replace clothes that have complicated fasteners with those you can slip on easily, such as sweatpants, sweatshirts, or pants with elastic waistbands.
- Tile flooring in the bathroom can become slippery and dangerous when wet. Consider replacing it with wall-to-wall carpeting.
- Exaggerate lifting your feet and swinging your arms. With each step, pretend you are stepping over a log.
- Take extra-small bites of food, chew thoroughly, and swallow carefully.
- Take a breath before you start to speak, and pause between every few words or even between each word.
- Instead of writing by hand, use a computer.

Medications

There are several types of medications used to manage Parkinson's. These medications may be used alone or in combination with each other depending if your symptoms are mild or advanced.

1. Conserve dopamine in the brain by blocking the breakdown action of MAO-B. These drugs are selegiline (Eldepryl, Zelapar) and rasagiline (Azilect), which are also neuroprotective and can slow disease progression.
2. Block the action of the neurotransmitter glutamate, which allows for an increase in dopamine release. This drug is amantadine (Symmetrel) and used to help tremor.
3. Introduce agents that mimic dopamine and bind to the receptors in the neuron's synapse. These drugs include pramipexole (Mirapex), ropinirole (Requip), and apomorphine (Apokyn).
4. Replace missing dopamine in the brain. The drug levodopa helps with movement problems of tremor, stiffness, slowness and walking. Levodopa is combined with carbidopa (Sinemet) to reduce nausea side effects and to ensure that levodopa is converted to dopamine in the brain and not in the intestine or blood.
5. Optimize delivery of Levodopa to the brain by blocking COMT, which breaks down dopamine in the digestive system, allowing a steady supply of Levodopa to reach the bloodstream. These drugs include tolcapone (Tasmar) and entacapone (Comtan).

- Reduce activity of the neurotransmitter acetylcholine. These drugs reduce tremor and include trihexyphenidyl (Artane) and benztropine (Cogentin).

After a time on medication, patients may notice that each dose wears off before the next dose can be taken (wearing-off effect) or erratic fluctuations in dose effect (on-off effect). Anti-Parkinson's drugs can cause dyskinesia, which are involuntary jerking or swaying movements that typically occur at peak dosage and are caused by an overload of dopamine medication. Sometimes dyskinesia can be more troublesome than the Parkinson's symptoms.

A new method to take medication is through a **drug pump** that delivers a carbidopa/levodopa gel (Duopa) directly into the intestines. Surgery is required to place a small hole (stoma) in the stomach through which a tube is connected to a portable pump worn on your belt. It is designed to deliver the medicine continuously, a little at a time, to improve absorption and reduce off-times. Duopa is similar to insulin pumps used by diabetics.

Surgery

When medications fail to control symptoms because of severe "on-off" fluctuations, lack of effectiveness, or intolerable side effects, surgery should be considered.

- Deep brain stimulation (DBS)** is a surgical procedure to implant a pacemaker-like device that sends electrical signals to brain areas responsible for body movement. Electrodes are placed in a specific area of the brain (usually the subthalamic nucleus) depending on the symptoms being treated. The electrodes are placed on both the left and right sides of the brain through small holes made at the top of the skull. The electrodes are connected by long extension wires that are passed under the skin and down the neck to a battery-powered stimulator under the skin of the chest (Fig. 4). When turned on, the stimulator sends electrical pulses to block the faulty nerve signals causing tremors, rigidity, and other symptoms.

The stimulator settings are programmable and can be adjusted as your symptoms change over time. DBS improves the symptoms of slowness, tremor, and rigidity. Most people are able to reduce their medications and lessen their side effects, including dyskinesias. Furthermore, DBS does not damage the brain tissue. Thus, if better treatments develop in the future, the DBS procedure can be reversed.

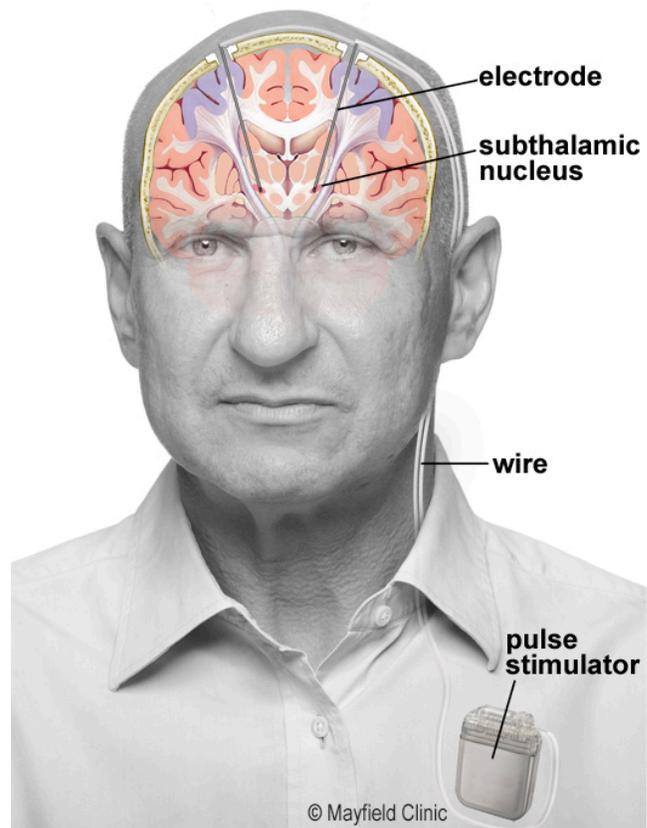


Figure 4. Overview of a deep brain stimulator (DBS). Electrodes are placed deep within the brain through small holes in the skull. The electrodes are connected by an extension wire to a battery-powered stimulator placed under the skin of the chest. Because the left side of the brain controls the right side of the body and vice versa, DBS is commonly performed on both sides of the brain. The patient is able to turn the stimulator off and on with a handheld controller.

- Other surgical procedures include pallidotomy and thalamotomy, which target specific brain areas. But instead of stimulation, a high-frequency energy current is used to permanently destroy the cells. These procedures are not reversible and are only used in special cases when a DBS is not feasible.

Patients with severe depression, advanced dementia, or an unstable medical condition may not be candidates for surgery. Also, patients who have symptoms similar to PD but who have been diagnosed with a different disorder, such as multiple system atrophy, progressive supranuclear palsy, or cortical basal degeneration, should not consider surgery.

Clinical trials

Clinical trials are research studies in which new treatments—drugs, diagnostics, procedures, and other therapies—are tested in people to see if they are safe and effective. Research is always being conducted to improve the standard of medical care. Information about current clinical trials, including eligibility, protocol, and locations, are found on the Web. Studies can be sponsored by the National Institutes of Health (see www.clinicaltrials.gov) as well as private industry and pharmaceutical companies (see www.centerwatch.com).

Sources & links

If you have questions, please contact Semmes Murphey at 901-522-7700.

Support

Through the American Parkinson Disease Association 800-223-2732, local support groups are available. The support group provides an opportunity for patients and their families to share experiences, receive support, and learn about advances in treatments, and medications.

Links

Parkinson's Foundation
www.parkinson.org

Awakenings www.parkinsonsdisease.com

American Parkinson Disease Association
www.apdaparkinson.com

Parkinson & Movement Disorder Society
www.movementdisorders.org

Michael J. Fox Foundation www.michaeljfox.org

Glossary

axon: a long process of the nerve cell (neuron) that carries nerve impulses away from the cell body to other nerve cells.

acetylcholine: a neurotransmitter that allows messages to be passed from neuron to neuron across a synapse; released by cholinergic nerves.

basal ganglia: a mass of nerve cell bodies (gray matter) located deep within the white matter of the cerebrum.

bradykinesia: slowness of movement, impaired dexterity, decreased blinking, drooling, expressionless face.

dendrite: the “arms” of a nerve cell that connect with the axons to transmit impulses toward the cell body.

dopamine: a neurotransmitter that allows messages to be passed from neuron to neuron across a synapse.

dystonia: a movement disorder that causes sustained muscle contraction producing repetitive movements or abnormal postures. Spasms can often be controlled with sensory tricks.

essential tremor: involuntary rhythmic tremors of the hands and arms. Tremors occur both at rest and during purposeful movement. Also affects the head in a “no-no” motion; often an inherited condition.

globus pallidus interna (GPi): nuclei in the brain that regulate muscle tone; part of the basal ganglia.

glutamate: a neurotransmitter that allows messages to be passed from neuron to neuron across a synapse.

micrographia: small handwriting.

neuron: basic unit of the nervous system, composed of a cell body, dendrites, and axon; also called a nerve cell.

neurotransmitter: a chemical substance that allows for the transmission of electrical impulses from one nerve cell to another across synapses.

progressive supranuclear palsy: a degenerative neurologic disorder that causes motor disturbances similar to Parkinson's. Notable symptom is the loss of ability to move the eyes to look downward.

striatum (corpus striatum): part of the basal ganglia involved with the subconscious regulation of movement.

substantia nigra: a group of cells in the brain where dopamine is produced.

synapse: the tiny gap between two nerve cells; across which impulses pass by release of neurotransmitters.

thalamus: a relay station for all sensory messages that enter the brain; part of the basal ganglia.



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