

What is Parkinson Disease?

Parkinson Disease is a neurological illness named after Dr. James Parkinson, a London physician who was the first to describe it in 1817. Parkinson disease (or PD) is a disorder caused by the gradual loss of cells in a small part of the brain called the substantia nigra. The loss (death) of these cells produces a reduction in a vital chemical called "dopamine," which causes symptoms that may include shaking of hands, slowing down of movement, stiffness, and loss of balance. Other symptoms may include loss of facial expression, reduction in speech volume and clarity, difficulty swallowing, change in size of handwriting, dry skin, constipation, urinary difficulties, and depression. Because Parkinson disease is a progressive disorder, these symptoms worsen with time.

Who gets Parkinson Disease?

Estimates vary, but it is thought that about one million people in the United States have Parkinson disease. Although the illness most often affects older individuals, particularly those over the age of 55, Parkinson disease may also affect people in their 30's and 40's. PD appears to be slightly more common in men than in women. Various studies have suggested that PD may be more common in certain ethnic groups or in certain regions of the world, but these results are hard to interpret in light of regional and ethnic variations in mortality, perceptions of illness, and access to health care.

Parkinson disease has become one of the most common ailments in North America. There are several reasons for this:

- People are living longer. The average life span has increased from 50 years in 1900 to 75 years in 1986. As PD is generally an illness of middle and later years, it is not surprising that the number of older people with Parkinson is increasing. The longer you live, the greater your chances of developing PD.
- The "baby boomers" are aging. As the proportion of Americans over the age of 55 grows, so will the proportion of Americans with PD.

Although it causes disability, PD does not appear to significantly shorten the lifespan of its sufferers. PD can be thought of as an illness that people live with, rather than die from.

What causes Parkinson Disease?

The symptoms of Parkinson disease appear when the substantia nigra loses a large number of its dopamine-producing cells. But what causes the cells to die in the first place? This is a subject of current active research. While some diseases are known to be caused exclusively by genetic (inherited) factors, and other diseases by environmental toxins, most illnesses are thought to be due to a combination of these factors. Many researchers believe that Parkinson disease is such an example. There are very rare families (one in Italy, and one in Greece) where PD is clearly an

inherited disease. The genetic abnormality in these families has been identified on chromosome 4, and it codes for a protein called alpha synuclein. However, most people with PD do not have this same genetic abnormality. Similarly, there are very rare cases of individuals exposed (through "designer drug" use) to a toxin called MPTP, who subsequently developed an illness with striking similarities to PD. But most people with PD have no exposure to MPTP. It is possible that an unidentified gene (or, more likely, combination of genes) may predispose an individual to PD, perhaps by making that individual more vulnerable to an unidentified environmental toxin (or, more likely, combination of toxins). The Parkinson study group has a current research study investigating possible genetic factors in siblings with the illness.

Treatments For Parkinson Disease

Treatment options for patients with PD have expanded tremendously in recent years, and new treatments are becoming available every year, in part as a result of clinical trials conducted by the PSG (see "Completed Clinical Trials"). Therapeutic options can be divided into

- Non-pharmacological treatments
- Pharmacological treatments
- Surgical approaches

Non-pharmacological treatments

- Nutrition
- Education
- Support
- Exercise

Pharmacological treatments (medications)

Sinemet (Carbidopa/Levodopa)

This medication works by directly replacing dopamine, the brain chemical that is depleted in PD. The "levodopa" part is transformed into dopamine in the brain, and the "carbidopa" part prevents that transformation happening before the medication gets to the brain (which reduces effectiveness and causes side effects such as nausea). It is also available in a "controlled release" form (Sinemet CR). It is one of the most effective medications for relief of the symptoms of PD, bringing relief of stiffness, slowness and tremor for most patients. However, it may be associated with troublesome side effects (nausea, lightheadedness, extra movements called "dyskinesias", sleep disturbances, hallucinations and rarely delusions) in some patients, especially those in more advanced stages of the illness. An important question currently being investigated by the PSG is whether Sinemet should be given early in the course of the illness, or whether its use should be delayed.

Read about the ELLDOPA study.

Dopamine agonists

Dopamine agonists are chemicals with structures which allow them to mimic the effects of dopamine in the brain. Unlike levodopa, they do not require any metabolic transformation in the brain. They may be used alone, or in combination with Sinemet or other drugs. They provide relief from the symptoms of PD for many patients at all stages of the illness, and may be especially helpful in those patients who have developed "motor complications" on Sinemet therapy. Possible side effects include nausea, low blood pressure with dizziness, and confusion/hallucinations in a few patients.

Examples of dopamine agonists:

- Pramipexole (Mirapex®) CALM-PD study in *JAMA*
- Ropinirole (Requip®)
- Bromocriptine (Parlodel®)
- Pergolide (Permax®)
- Cabergoline (Dostinex®)

Anticholinergics

Dopamine acts in concert with another brain chemical, acetylcholine. Because a balance between these two chemicals is required for normal function, having too little dopamine throws things off balance, and so giving a drug that, in effect, dampens acetylcholine, can relieve some of the symptoms of PD. Possible side effects include dry mouth, constipation, urinary difficulties, mental confusion and sleepiness.

Examples of these medications:

- Trihexiphenidyl (Artane®)
- Benztropine (Cogentin®)
- Biperiden (Akineton®)
- Ethopropazine (Parsitan® - in Canada)

MAOB Inhibitors

Selegiline is one of a class of drugs called "MAO-B inhibitors". In animal experiments, it has been shown to prevent the development of the PD-like illness caused by the toxin MPTP. In an important PSG trial comparing vitamin E (tocopherol) and selegiline, (DATATOP study) the drug was shown to delay the need for Sinemet in newly-diagnosed PD patients. This might mean that the drug was preventing the loss of the dopamine-producing cells in the brain, or that it had a direct dopamine-like benefit. It is most commonly used early in the course of the illness but may also be helpful to patients in later stages whose Sinemet "wears off" too

quickly. It usually has few side effects, although some patients (especially elderly, and/or those also taking Sinemet) may become confused or even have hallucinations while taking selegiline. This class of drugs has the potential for serious drug and food interactions, but this is not a problem at the selegiline dose generally used in PD.

Rasagiline is another drug in this class. It has actions and benefits that are similar to selegiline. The TEMPO and PRESTO studies were performed using the drug rasagiline.

Amantadine (Symmetrel®)

This medication was originally used for the treatment of influenza, but was found to be useful in some patients with Parkinson's disease. How it works in PD is uncertain, but it seems to improve stiffness, tremor and walking in some PD patients. Possible side effects can include swelling of the ankles and a kind of rash called "livido reticularis", but usually, neither of these is severe enough to stop the medication. Some people taking amantadine get confused, and others have trouble sleeping, complaining of vivid dreams or nightmares. Some people have hallucinations. Any of these problems might prompt a reduction in the dose of amantadine, or discontinuation of the medication altogether.

COMT Inhibitors

COMT is a substance produced by the body that breaks down levodopa and dopamine, making them inactive. COMT inhibitors stop that breakdown process so that more levodopa can get into the brain where it is needed. Currently, these medications are used only in combination with Sinemet, and can be thought of as "Sinemet extenders". Patients taking one of these medications may find that they need less Sinemet, and/or that they have a smoother response to Sinemet. As a result, patients may find that they develop the extra movements called "dyskinesias" as the new medication is started (a sign that there is too much dopamine in their system). This side effect usually goes away as the dose of Sinemet is reduced. Another side effect that affects some people taking tolcapone (Tasmar®) is diarrhea. This may go away with time, but about one person in twenty stops taking the medication because of this. There have been rare cases of severe, life-threatening liver problems in some people taking tolcapone (Tasmar®) and this has led to a requirement for regular blood tests for anyone taking this medication. Diarrhea and liver problems have not been reported in the clinical trials of this medication so far.

Examples of COMT Inhibitors:

Tolcapone (Tasmar®)

- Entacapone (Comtan®)...see the SEESAW study

