Parkinson's Disease

Diagnosis

Parkinson's disease (PD) is a common neurodegenerative disorder, affecting about one percent of the population over the age of 60 years. While the typical age at onset is in the sixth decade of life (average 55 years), about five percent of patients with PD have onset of their symptoms before age 40. Parkinson’s disease is twice as common in men as in women in most populations. It is a chronic, progressive disorder of the nervous system that affects movement. It develops gradually and can commonly cause tremor, stiffness, and slowness of movement. The symptoms of Parkinson’s disease worsen as the condition progresses over time. Although there is no cure for Parkinson’s disease, medications may markedly improve the symptoms of the disease.

The signs of symptoms of Parkinson's disease vary from person to person. Early signs may be mild and go unnoticed. The symptoms commonly begin on one side of the body and usually remain worse on that side when the symptoms begin to affect both sides. There are a variety of symptoms that can be described as motor (pertaining to movement) and non-motor that will be described below.

Motor Symptoms:

- Tremor
- Slowed movements (bradykinesia)
- Rigid muscles
- Impaired posture and balance
- Reduced automatic movements (blinking, smiling, arm swing with walking)
- Writing changes
- Speech changes
Neurologists examine for the “cardinal features” of PD when the concern for the disease exists. These cardinal features include tremor, slowness of movement (bradykinesia), muscle stiffness (rigidity), and loss of balance (postural instability). One of the most common presenting features of Parkinson’s disease is the presence of an asymmetric tremor that is present with the limb is at rest. Other typical symptoms of PD include loss of normal facial expression (hypomimia), low volume of speech (hypophonia), and slurred speech (dysarthria). Walking can become problematic for Parkinson’s disease patients and may involve shuffling, using short steps, and difficulty initiating gait or feeling as if the feet are glued to the floor (freezing). One’s posture may become stooped and problems with balance (loss of postural reflexes) may lead to increased risk for falls. It may also become difficult to write and handwriting may become smaller (micrographia).

Non-motor symptoms:

It is now well recognized that PD is a complex disorder with a diverse range of symptoms that include cognitive, psychiatric and non-motor features in addition to the motor symptoms described above. Some of these non-motor symptoms can occur years, or even decades, before the classic motor symptoms become noticeable. Non-motor symptoms become more prominent as the course of Parkinson’s disease progresses and can be a major quality of life determinant.

These symptoms may include the following:

- Sleep disturbances
- Fatigue
- Loss of sense of smell
- Loss of sense of taste
- Constipation
- Urinary dysfunction
- Orthostatic hypotension (lightheadedness with standing due to a drop in blood pressure)
• Excessive sweating
• Excessive salivation
• Pain and sensory symptoms
• Mood disorders (depression, anxiety and apathy)
• Psychosis and hallucinations
• Cognitive dysfunction and dementia.

Sleep difficulty can be particularly problematic. Patients may experience insomnia, daytime sleepiness, restless leg syndrome (RLS), and rapid eye movement sleep behavior disorder (RBD). Common causes of frequent awakenings during sleep in PD include increased urinary frequency, cramps, vivid dreams or nightmares and pain, and difficulty turning in bed. RLS is a movement disorder characterized by an urge to move the limbs that is associated with an unpleasant sensation that improves with movement, especially walking. It occurs mainly at night time and emerges or worsens with rest. RBD is also commonly seen in PD. Patients with RBD act out their dreams and may scream out and flail their arms and legs in punching and kicking motions.

A variety of "autonomic" nervous system problems can become affected. The autonomic nervous system is the part of the nervous system that helps regulate the internal organs, including the blood vessels, heart, stomach, bladder, genitals, and the sweat, salivary, and digestive glands. Symptoms that can arise from autonomic nervous system dysfunction include orthostatic hypotension (lightheadedness when standing due to a drop in blood pressure upon standing), urinary dysfunction such as urinating more frequently, sudden strong urges to urinate, and urinary incontinence, constipation, swallowing difficulty (dysphagia), excessive sweating, and erectile dysfunction.

Painful sensory symptoms can be one of the most troublesome non-motor symptoms in patients with both early and late stage PD. The pain can be burning, lancinating, or tingling and can be localized to different body areas including the
face, joints, abdomen, and genitals. Mood can become adversely affected and it is important to monitor for signs of depression and anxiety. Depression is the most common psychiatric disturbance seen in PD and about 50% of PD patients endorse depressive symptoms. Although it is generally mild to moderate in severity, depressive symptoms may have a negative impact on motor disability and lead to reduced quality of life. Anxiety is the next most frequent mood disturbance in PD and may occur in about 30% of patients. Depression and anxiety may occur together and may also fluctuate in severity depending on “on-off” fluctuations (described in more detail in the therapy section).

Cognitive dysfunction and dementia are common in PD. As the disease gets worse with time, many people develop dementia. Older age and severity of motor symptoms in PD are associated with an increased risk of developing dementia. Dementia usually occurs late in the course of the disease. PD dementia may cause problems with speaking and communicating, problem-solving, forgetfulness, and paying attention. Clinically, a diagnosis of PD dementia is made if the illness begins with PD and then the dementia develops at least one year of the onset of PD motor symptoms. In time, patients with PD dementia likely will not be able to live independently, because it affects the ability to take care of oneself.

Motor Complications of PD:

As PD progresses, the symptoms typically worsen and will require increasing doses of medications or adding additional medications to help appropriately treat symptoms. Over time it will take higher doses of levodopa to obtain the same therapeutic benefit. As time progresses, it may also take lower doses of levodopa to cause abnormal involuntary movements called, “dyskinesias.”

Dyskinesias can manifest as a variety of movements but commonly occur as head bobbing, body swaying, writhing limb movements, and abnormal muscle posturing called dystonia. When dyskinesias occur, they commonly begin when levodopa levels are higher and then resolve when levodopa wears off. Not all patients
develop dyskinesias with levodopa therapy. Risk factors for levodopa-induced dyskinesias include earlier age of onset of PD, longer duration of disease, longer duration of levodopa treatment, female sex, and possibly genetic factors.

Patients may begin to appreciate a “wearing off” effect of medication. The PD symptoms experienced when the medication is worn off is often referred to as the “OFF” symptoms. When the medication “kicks in” and patients appreciate the symptomatic benefit of the medication, it is referred to as the “ON” period. As PD progresses, patients may experience less ON time and more OFF time, referred to as “motor fluctuations,” which can usually be addressed with medication adjustments.

Because of concerns about experiencing these motor fluctuations and dyskinesias as a possible complication of levodopa therapy, some clinicians have advocated delaying the onset of levodopa therapy until such time when the symptoms of PD begin to interfere with performance of activities of daily living or work.

In most cases, the diagnosis is based on the clinical features and examination by an experienced clinician. There is no blood test for PD, although some genetic forms of parkinsonism can be diagnosed by a DNA test. Sometimes, a dopamine transporter scan (DaTscan) is ordered which can help show a loss of dopamine in the deeper structures of the brain. This can help differentiate between PD and other diseases that can resemble Parkinson’s disease. This test, however, is usually not needed, as the diagnosis can be made based on the clinical features and physical examination. Although PD is a progressive disease, it does not significantly alter life expectancy. Even though the symptoms can affect activities of daily living, interfere with work, and may adversely impact the quality of life, the prognosis varies markedly from one individual to another. The presence of tremor, rather than gait and balance problems, as the initial or dominant symptom suggests a favorable prognosis indicating a slowly progressive course.
Cause

Although the cause of PD is still not completely understood, remarkable progress has been made in our knowledge about the mechanisms of neuronal cell loss (neurodegeneration). Many of the symptoms of PD are due to the reduction of a chemical in the brain called dopamine. The symptoms of PD start when there is about 60 percent loss of dopamine-producing neurons in the uppermost part of the brainstem called the midbrain, more specifically, the substantia nigra. There is a growing body of evidence that show these neurons die, in part, as a result of an abnormal accumulation of cellular proteins that damage neurons and impair their ability to produce dopamine. Dopamine is needed to act on other deep brain structures ("basal ganglia") to facilitate normal motor function. The basal ganglia is a group of structures deeper in the brain that work together to promote "wanted" movements and to prevent "unwanted" movements. The presence of dopamine is critical for the basal ganglia to function properly. Thus, it is the loss of dopamine that underlies many of the signs and symptoms experienced by PD patients and is the basis for many of the medications used to treat the symptoms of PD.

The current scientific evidence supports the notion that neurodegeneration associated with PD results from a complex interaction between genetic and environmental factors. Although only about 20 percent of patients have another family member with PD, genetic causes of PD are supported by the increasing number of mutated genes identified in PD patients with or without family history. The vast majority of patients with PD, however, have no identifiable gene mutation. Many epidemiological studies have suggested that certain environmental toxins, such as pesticides, may increase the risk of PD while others, such as smoking and caffeine, have been associated with lower risk of PD. No specific dietary, occupational or other environmental causative factors, however, can be identified as risk factors in most cases.

Treatment
The treatment of PD has improved dramatically since the introduction of anticholinergic drugs such as trihexyphenidyl (Artane) and amantadine (Symmetrel) in the 1950s. Levodopa was introduced in the 1960s and, when combined with carbidopa (levodopa-carbidopa or Sinemet), it has remained the most effective drug for the treatment of motor symptoms of PD.

**Levodopa:**

Levodopa (L-dopa) is well established as the most effective drug for the symptomatic treatment of PD. Levodopa replaces the dopamine that is reduced in patients with PD. Carbidopa is combined with levodopa to help prevent nausea as a side effect of levodopa therapy. Carbidopa/levodopa is marketed in both immediate release (Sinemet and generics) and extended release (Sinemet CR and generic carbidopa/levodopa ER) formulations. A pre-bedtime dose of Sinemet CR may allow the patient some improved mobility overnight. It should be kept in mind that the response to individual doses of Sinemet CR is less predictable than the response to standard Sinemet because not all of the medication may get absorbed by the time it reaches the large intestine. Rytary is another extended release formulation of carbidopa/levodopa that obtained FDA approval for the treatment of Parkinson’s disease in 2015.

Duopa is another formulation of carbidopa/levodopa that is delivered as an enteral suspension that allows continuous infusion of levodopa into the small intestine, which can be used in patients with advanced Parkinson’s disease with motor fluctuations. Duopa requires placement of a PEG-J (Percutaneous Endoscopic Gastrostomy with Jejunal Extension) that is placed a part of the small intestines called the jejunum. This procedure is performed by a gastroenterologist.

**Dopamine agonists**

Dopamine agonists are a group of drugs that directly stimulate dopamine receptors, thus they mimic the effect of dopamine. Dopamine agonists, such as pramipexole (Mirapex), ropinirole (Requip), and rotigotine (Neupro patch), are often prescribed
as the initial dopaminergic therapy. Apomorphine, which is also a dopamine agonist and is administered subcutaneously (under the skin), may be used in select patients with severe motor fluctuations.

**Monamine oxidase type B inhibitors (MAO-I)**

MAO-I inhibitors prevent the break-down of dopamine and thus help to prolong the effect of dopamine made naturally in the body as well as prolong the effects of levodopa therapy. In the early stages of PD, before PD symptoms become troublesome, monoamine oxidase type B inhibitors (MAOB-I), such as selegiline (Eldepryl, Deprenyl), a sublingual preparation of selegiline (Zelapar), or rasagiline (Azilect), may be appropriate as these MAOB-I not only provide symptomatic relief in mild, early cases, but also delay the need for levodopa. Safinamide was approved for marketing in the United States in March 2017. This medication was approved for use as an adjunct to levodopa in patients with PD to help reduce wearing OFF effects.

**COMT inhibitors**

The catechol-o-methyl transferase (COMT) inhibitors also prevent the break-down of dopamine and thus help to prolong the effect of dopamine made naturally in the body as well as prolong the effects of levodopa therapy. COMT inhibitors such as entacapone (Comtan) are never used alone, but rather added as an additional medication to carbidopa/levodopa and are typically taken at the same time as each dose of carbidopa/levodopa to help prolong its effects. Alternatively, patients can be switched to a combination medication, levodopa-carbidopa-entacapone (Stalevo).

**Anticholinergics**

Trihexyphenidyl (Artane) can be useful as the sole medication for younger patients with PD who have bothersome tremor and without significant slowing or
walking problems. This medication is usually prescribed specifically to help with tremor when tremor is the predominant symptom. Caution must be used in the elderly with this medication because older patients may be more susceptible to side effects of memory problems, confusion, and hallucinations. Other potential side effects include dry mouth, blurred vision, constipation, nausea, and urinary retention.

Amantadine is an antiviral agent that has mild antiparkinsonian activity. Although its exact mechanism of action is uncertain, it is known to increase dopamine release and to have anticholinergic effects. It is also the only drug known to help treat levodopa-induced dyskinesias. An extended release formulation of amantadine (Gocovri) has recently obtained FDA approval in 2017 for the treatment of levodopa-induced dyskinesias.

Medication Effects

When the dosage is optimized most patients can tolerate these medications well, but some side effects may occur such as nausea, lightheadedness, drowsiness, hallucinations, dyskinesias, ankle swelling, and other adverse effects. If any of these, or other, adverse events occur, the patients should notify their physicians. Usually, appropriate adjustments can be made to improve the tolerability of anti-PD medications. For example, initiating the medication at the lowest possible dose and increasing it slowly or taking it with meals improves tolerability.

Patients who experience motor fluctuations should generally avoid taking medications after eating protein-rich meals as the amino acids can interfere with the absorption of levodopa in the small intestine. Taking additional carbidopa (Lodosyn) or adding anti-nausea medications, such as hydroxyzine (Vistaril), trimethobenzamide (Tigan), or domperidone (Motilium) usually prevents or alleviates levodopa-related nausea. Hallucinations and other psychiatric complications of levodopa can be managed effectively with a class of medications known as the atypical neuroleptics, such as quetiapine (Seroquel) and clozapine.
(Clozaril), however these medications have a risk of worsening PD symptoms.
Pimavanserin (Nuplazid) is the first and only FDA approved medication shown to reduce hallucinations and psychosis in Parkinson’s disease without affecting motor function. Drug-induced drowsiness can be effectively treated with modafinil (Provigil).

**Neuroprotective Therapy**

Despite intensive search for neuroprotective therapies, thus far no medication, vitamin or any nutritional supplement has been shown to protect the dopamine-producing neurons. Some drugs, such as the MAOB-I and dopamine agonists, however, have been found to delay the need for levodopa, although there is controversy whether they favorably modify the disease through any neuroprotective effect.

In the age of digital technology and social media, patients may be subjected to medical news information and disinformation. There are often “new discoveries” and “miracle cures” within this medical news that can attract mainstream media and social attention. It is important for patients and physicians alike to maintain vigilance when interpreting these often exaggerated health claims and for patients to discuss questions and concerns with their physicians.

**Surgery**

Patients who continue to be troubled by their PD symptoms and experience levodopa-related motor complications, particularly fluctuations and dyskinesias, may be considered candidates for surgery. Deep brain stimulation (DBS) has replaced the older, ablative, procedures, such as thalamotomy and pallidotomy, as the surgical treatment of choice in patients whose symptoms cannot be adequately controlled despite optimal medical therapy. See [Deep Brain Stimulation](#) for additional information about the role of surgery in the treatment of PD.

**Role of Physical Therapy and Exercise**
Any discussion of management of PD would not be complete without emphasizing the importance of physical therapy and improved conditioning of patients with PD. Regular exercise program, combined with appropriate medical management, has been shown to delay the onset of physical disability associated with PD. Many studies have shown that exercise improves stamina and prevents fatigability, constipation, depression, sleep, osteoporosis, and memory loss. Exercise also decreases the risk of stroke and heart attacks by reducing body weight, blood pressure, and risk of diabetes, and increasing the HDL ("good") cholesterol. For these and many other reasons ongoing vigorous exercise and physical fitness, which should include stretching, range of motion and conditioning exercises should be highly encouraged, particularly if there are no physical contraindications. Many patients wrongly assume that the "exercise" they get during their daily routines at work or at home, such as housecleaning, climbing stairs, and even mowing the lawn are sufficient forms of exercise. While these activities are encouraged, regular exercise program, tailored to the needs of the individual patient, is critical for continued well being. The exercises should be designed to improve strength (e.g. using free weights, weight machines, and elastic bands) and overall fitness (e.g. walking, swimming). Water aerobics and dancing have been found particularly effective and safe.

Incorporation of external sensory cues in the rehabilitation protocol has been shown to extend short-term benefits of physical therapy. For example, a visual cue provided by an inverted L-shaped cane, horizontal beam on a walker, or by rhythmical sound, such as listening to a marching music, can significantly help overcome gait freezing. Also, instructing the patient to take high steps or exaggerate their arm swing (e.g. simulating marching) may improve their gait and balance. Swimming or otherwise exercising in the water has the additional advantage in that there is very little stress on the joints and the resistance improves muscle strength. This low impact activity also increases endurance and balance. Some patients prefer stretching and muscle relaxing exercises such as Pilates, tai chi, and yoga and they are clearly useful additions but should not
replace the various conditioning exercises. Recent animal research has provided strong evidence that exercise can increase resistance to brain insult or injury and can improve learning, mental, and motor performance. Patients should always check with their physicians before launching into new exercise program. All precautions should be taken to prevent injuries.

Experimental Treatments

The Parkinson's Disease Center and Movement Disorders Clinic at Baylor College of Medicine, is engaged in clinical trials testing cutting-edge, innovative therapies designed to improve symptoms of PD or to favorably modify its progression. Please discuss your interest and willingness to participate in the therapeutic trials with one of our physicians or research coordinators. As new trials are being continuously approved, please consult ClinicalTrials.gov for the most up to date listing of available clinical trials for PD. Please use the following link, which will automatically insert the "Parkinson's disease and Baylor" search terms for you.

Selected References


Rousseaux MWC, Shulman JM, Jankovic J. Progress toward an integrated understanding of Parkinson's disease. *F1000Research*. 2017;6(0):1121


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