Parkinson Medications

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Contact hours: 2.5

Course price: $19

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Course Summary

Overview of Parkinson's Disease (PD) and its affect on the human brain. Includes a description of genetic and protective factors, and characteristics that differentiate it from other neurological disorders. Summarizes current treatment options, medications, and surgical options including deep brain stimulation.

COI Support

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Criteria for Successful Completions

80% or higher on the post test, a completed evaluation form, and payment where required. No partial credit will be awarded.

Course Objectives

When you finish this course you will be able to:

- Discuss the long history of Parkinson's disease.
- Describe Parkinson's disease in detail.
- Explain what happens in the brain that results in PD.
- List both genetic and protective factors that impact PD.
- Spell out the characteristics of PD and differentiate it from other conditions.
- Summarize treatment options, including medications, surgical interventions, and other interventions still in the pipeline.
- Explain the rating scales and their relationship to prognosis of PD.

A History of Parkinson's Disease

Parkinson's disease is named for the English physician James Parkinson, who in 1817 published a comprehensive description titled *An Essay on the Shaking Palsy*. Though Parkinson's research was later recognized as a major work in the field, it received little attention for decades. The disease was only given its current name in the 1870s when the French neurologist Jean-Martin Charcot named it to honor Parkinson's studies, which had identified all of the symptoms as relating to a single disease. Charcot's studies between 1868 and 1881 also became a landmark in the understanding of Parkinson's disease when he made the distinction between rigidity, weakness, and bradykinesia as the disease progressed (Wikipedia, 2012b).

Early descriptions of people with symptoms of tremors while at rest, characteristic slowed movement, stooped posture, or drooling date back as far as the Egyptians and biblical times. Similarly, an Ayurvedic medical treatise from India of the 10th century B.C.E. describes a disease that evolves with tremor, lack of movement, drooling, and other symptoms of Parkinson's disease (PD). Galen also described in 175 A.D. the symptoms now associated with PD patients: tremors while at rest, postural stooping, and paralysis. Others through the centuries described one or several of the characteristic symptoms but without clear understanding of the cause or their progressive relatedness through time.

Some of the earliest treatments for PD involved plants of the mucuna family of tropical vines, some of which produce seeds now known to be rich in levodopa. Levodopa is a direct molecular precursor of the neurotransmitter dopamine. These *Mucuna pruriens* seeds have long been used in traditional Indian medicine to treat ailments including Parkinson's disease and are native to Africa, India, and the Caribbean.

Mucuna pruriens

Mucuna pruriens, also known as velvet bean, Cowitch, Cowhage, or Konch, in Kawal Wildlife Sanctuary, Andhra Pradesh, India. Courtesy of J.M. Garg, through Wikimedia Commons.

In Central America, for decades these "velvet beans" have been roasted and ground to make a coffee substitute that goes by the common name of *nescafé* in those regions and Brazil. Single portions, approximately one ounce of the seeds, have been shown to be as effective as single doses of modern medicines in the treatment of Parkinson's disease, but long-term efficacy and tolerability have not been determined. It appears likely that *nescafé* would have similar limitations with long-term use (see later section).

In addition to levodopa, the seeds contain other potent neuroactive and psychoactive compounds such as serotonin (5-HT), 5-hydroxytryptophan, nicotine, dimethyltryptamine (DMT), bufotenin, and 5-MeO-DMT, the last three being powerful psychedelic tryptamines also found in tropical frog skins. As such, extracts could exhibit strong psychedelic effects and they have reportedly been used in South American ayahuasca preparations.

Mucuna pruriens Seeds

Though numerous physicians had noted characteristic components of PD in older patients, not until 1817, when Parkinson published his studies of six cases, had anyone connected the characteristics of resting tremor, abnormal posture and gait, paralysis, and diminished muscle strength with disease progression in time. Positive effects to reduce tremor by blocking the body's nervous system with the anticholinergic alkaloids of the belladonna plant (Deadly Nightshade) were described during the nineteenth century by Charcot and others, and were used well into the 1950s.

Mucuna pruriens seeds of two different colors. Source: Wikimedia Commons.

The anatomical deficits of PD were described around 1900, when it was discovered that the subthalamus or cerebral peduncle of patient brains suffered from local cell death. In 1912 Frederic Lewy described a stainable protein marker, later referred to as **Lewy bodies**, in pathology slides made post mortem from affected brains. In 1919 the substantia nigra was found to be the main cerebral structure affected, but this was not widely accepted until confirmation by further studies published in 1938.

Early surgery aimed to ablate parts of the corticospinal pathway, resulting in paralysis as the alternative to tremors. Modern surgery for tremor, consisting of the destroying of some of the basal ganglia structures that control coordinated movement and balance was first tried in 1939 and was improved over the following twenty years. Otherwise, anesthetic anticholinergic agents to reduce nerve impulses to muscles were the only available drug treatments used to control tremors until the discovery of levodopa's efficacy.

The underlying biochemical changes in the brain were identified in the 1950s, due largely to the work of Swedish scientist Arvid Carlsson on the neurotransmitter dopamine and its role on PD. Carlsson was awarded a Nobel Prize in 2000 for this work showing that dopamine is not only a precursor of norepinephrine (noradrenaline) and epinephrine (adrenaline) but also a neurotransmitter.

Levodopa was first synthesized in 1910 but it received little attention for decades. Carlsson showed that administering levodopa (L-DOPA) to animals with parkinsonian symptoms would reduce their intensity. L-DOPA entered clinical testing and use and a year later, in 1968, the first large study on treatment with levodopa reported improvements in people with Parkinson's disease.

Levodopa brought about a true paradigm shift in the management and understanding of PD. At the same time, neurologist Oliver Sacks described levodopa treatment in human patients with encephalitis lethargica, detailed in his 1973 book (and later movie) *Awakenings*. However those patients—frozen motionless with post encephalitic parkinsonism* thought to result from a viral illness—lose benefit from L-DOPA medication far faster than do patients with Parkinson's disease.

***Parkinsonism** refers to any condition that causes Parkinson's-type abnormal movements.

By the late 1980s, deep brain stimulation (see later section) emerged as a possible treatment and was approved for clinical use by the FDA in 1997. It was also determined in 1997 that synuclein proteins were the main component of Lewy bodies. Stem cell therapies and other innovative treatments are currently being investigated.

What is Parkinson's Disease?

Parkinson's disease (PD), also known historically as paralysis agitans or shaking palsy, results from a disorder of the neurons in the brain that are responsible for production of the neurotransmitter dopamine. **Dopamine** is a signaling molecule to other neurons that manage the coordination of body movement. When these cells die or fail to work properly, the symptoms of PD begin to appear, often very gradually.

Most cases occur, apparently randomly, in about 1% to 2% of people more than 60 years old, and they occur twice as often in men as in women. Diagnosis of PD is based on medical history and neurologic examination because there are as yet no confirming blood or other markers. This may eventually change with more advances in understanding the role of genetics and with ongoing improvements in brain imaging techniques (Medline Plus, 2012).

PD is characterized clinically by tremor in the hands, arms, legs and jaw; muscle rigidity in the limbs and body; impaired balance, coordination, and stability; and bradykinesia (slowed movement). These impairments can lead to fatigue and sleep problems, writing and speech difficulties, and a characteristic stooped posture; they will eventually lead to difficulty with or loss of walking, communication, chewing and swallowing, and other activities of daily life (ADLs). The progression of symptoms can be unpredictable and somewhat different for each patient. Many symptoms can be ameliorated, sometimes near the point of vanishing, with various medications or other therapies, though none of the known therapies appear to be permanent solutions.

Many patients also have depression, irritability, and visual hallucinations, with eventual dementia developing in 20% of cases. There is some evidence for an increased risk of PD in people exposed to certain pesticides and a reduced risk in tobacco smokers, who may be protected by nicotine (see later discussion). The combined direct and indirect cost of Parkinson's disease is estimated to be $28 billion per year in the United States, and medication costs for an individual person with PD average $2500 a year. Therapeutic brain surgery can cost up to $100,000 per patient (NINDS, 2012).

About 65,000 Americans are diagnosed with Parkinson's disease each year, and there are now estimated to be 1.5 million Americans living with PD. These numbers are expected to increase as the population continues to age. Based on the age of onset of symptoms, PD has several classifications. Individuals with symptoms that start before the age of 20 years are said to have juvenile onset PD, those with adult onset before 50 years of age have early onset PD, and those whose symptoms start after age 50 have late onset PD. Only about 4% of all PD cases are juvenile or early onset PD. Diagnosis of typical cases is based on accumulating symptoms, with neuro-imaging or other tests used for confirmation of suspected disease, and to rule out other causes. Unfortunately there is still no cure for PD, though promising therapies are being actively researched and developed.

Public awareness campaigns make use of a red tulip as the symbol of the disease and include an annual Parkinson's disease day, April 11, the birthday of physician James Parkinson. Well-known people with Parkinson's disease include the actor Michael J. Fox and former boxer Muhammad Ali (Wikipedia, 2012a).

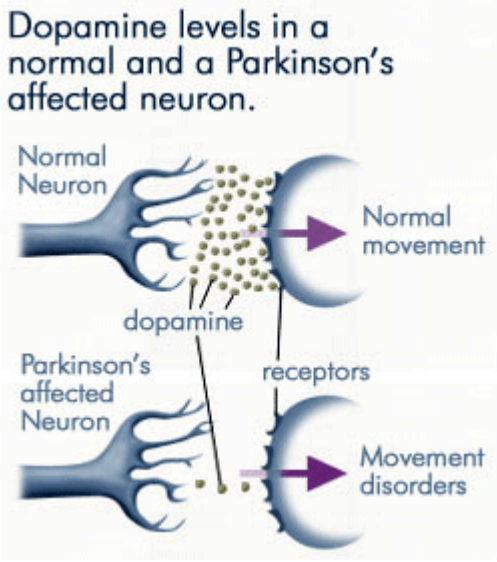
Causes of Parkinson's Disease

Parkinson's disease (PD) is caused by ongoing loss of dopamine-secreting neurons and the associated deficiency of dopamine in the brain's striatum, which is responsible for coordinating movement and balance. Parkinson's is the second most common neurodegenerative disease, behind Alzheimer's disease. PD affects 1% of those above 55 years old, and more than 3% of those over 75 years old. Some studies seem to indicate that PD occurs less often in African Americans and Asian Americans than in Caucasians.

On histopathology tissue slides at autopsy, PD is characterized by aggregation of the protein alpha-synuclein into clumps (Lewy bodies) in the neurons. This correlates with a loss of dopamine production in the neurons of the substantia nigra within the midbrain. The basal ganglia, innervated by the dopaminergic system, are the most seriously affected brain areas in PD. Cell death in the substantia nigra and the ventral (front) part of the pars compacta can affect almost all of the neurons by the time of patient death.

Dopamine Levels

Lewy bodies usually are found in the sporadic, idiopathic disorder, and their distribution throughout the affected brain varies substantially, although the density of occurrence of Lewy bodies is often reflective of the level of symptoms and severity in PD patients. In the rapidly induced parkinsonism discussed below, however, Lewy bodies are not present, though all of the other symptoms of PD do occur. This leads to the notion that Lewy bodies are not a *causative* factor of declining function, but instead an indicator of declining function over time.



Source: anti-agingfirewalls.com.

Some interesting clues as to the causes and development of PD arose in 1982 from the biologic responses to contaminated opiate that involved exposure to the chemical MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). A synthetic neurotoxin, MPTP is a precursor molecule that can cross into the brain and be metabolized to the toxic chemical MPP+ (1-methyl-4-phenylpyridinium). This conversion and toxicity in the brain can interfere with oxidative phosphorylation in mitochondria, the major chemical process that generates adenosine triphosphate (ATP) and energy for the cell. Inhibition of this pathway results in cell death (Martinez & Greenamyre, 2012).

This was evidenced quite starkly in the 1982 California incident when heroin addicts in their twenties and thirties were affected by a batch of a synthetic opiate contaminated with MPTP that unfortunately led to acquired symptoms of irreversible parkinsonism within days for all who took the drug.

This clinical case happened several years after a similar case in Maryland, where MPTP had been found as a contaminant in another opiate synthesis and the chemist who illicitly produced the drug also became parkinsonian. The Santa Clara neurologist J. William Langston, in collaboration with the National Institutes of Health (NIH), tracked down MPTP as the cause and documented the case in his 1995 book *The Case of the Frozen Addicts*, which was later featured in two NOVA productions by PBS.

The MPP+ chemical rapidly causes permanent clinical symptoms very similar to those of PD, with a high affinity and selective damage to the dopaminergic neurons in the substantia nigra of the brain. This implies that exposure to some types of chemicals over a lifetime may be involved in the development of idiopathic PD. Some pesticides (rotenone) and herbicides (paraquat, agent orange) have been correlated with an increased risk of developing PD in humans. The chloride version of MPP+ has been used as a herbicide under the trade name *cyperquat;* it is structurally similar to paraquat, which is sometimes used to kill illegal marijuana fields and is particularly dangerous if smoked.

MPTP as well as the herbicide paraquat and the pesticide rotenone are selective complex-I inhibitors of ATP production in the mitochondrial membrane and induce dopamine depletion and PD in animal studies. This correlates with the finding of complex I mitochondrial defects in the substantia nigra of patients with sporadic PD.

Dopaminergic nerve cell bodies in the substantia nigra tend to be pigmented due to the presence of melanin. It is posited that the toxic chemicals such as MPTP and rotenone have a higher binding affinity to the cells with this pigment, leading to their selective death and resulting PD.

Welding and exposure to heavy metals such as iron, manganese, copper, lead, amalgam, aluminum, or zinc have also been hypothesized to increase the risk of PD through the accumulation of metals in the substantia nigra and increased oxidative stress. Some reports have been published, but epidemiological evidence for an association between metal exposure and risk of PD is not yet conclusive.

Living in agricultural environments has been correlated with an increased the risk of PD, presumably due to exposure to these agents over time. Clearly any agents or injuries that accelerate damage and loss of the dopamine producing neurons of the substantia nigra are critical to development of parkinsonism and its related symptoms.

As discussed above, certain chemicals can induce parkinsonism that mimics most of the symptoms of PD. Additionally, lifetime exposure to head traumas has been correlated to parkinsonism. This is most notable among former boxers and others who have suffered numerous traumatic brain injuries or other repetitive trauma. Each of these patient histories may involve mitochondrial dysfunction as an underlying cause of cell stress and death, leading to eventual PD symptoms.

Factors Impacting Parkinson’s Disease

Protective Factors

Caffeine

What may be an additional relief to many coffee drinkers, caffeine consumption appears to protect against PD. Epidemiologic and pre-clinical data suggest that caffeine may confer neuroprotection against the underlying dopaminergic neuron degeneration, and may delay the onset and progression of PD. Caffeine is thought to be the responsible component, since total caffeine intake and intake of caffeine from non-coffee sources were found to be inversely correlated to PD risk, whereas no association was found between other components in coffee and the risk of PD.

Caffeine is an inhibitor of the adenosine A2 receptor and seems to improve motor function in a mouse model of PD. Caffeine may also improve the motor deficits of human PD, as adenosine A2A receptor antagonists such as istradefylline, reduces the "off" time and **dyskinesia** (impairment of voluntary movements) associated with standard dopamine replacement treatments at the end of a dose period. Finally, caffeine may help to alleviate some of the non-motor symptoms of PD, which are not benefited by dopaminergic drugs. Altogether, studies provide strong evidence that caffeine may represent a promising therapeutic tool for PD to alleviate both motor and non-motor early symptoms with its neuroprotective potential (Kalda et al., 2006).

Nicotine

Many epidemiologic studies have also shown a reduced risk of PD among cigarette smokers, to as low as 40% compared to non-smokers. Several mechanisms may explain the potential neuroprotective effect of cigarette smoking, and they likely involve nicotine, because nicotine may stimulate dopamine release, act as an antioxidant, or alter activity of the enzyme monoamine oxidase B. Tobacco smoke contains compounds that act as MAO inhibitors that also might contribute to this effect. Certainly tobacco smoking is a severe health hazard in its own right, though understanding its mechanistic relationship, probably through the actions of nicotine, to a diminished risk of developing PD may provide novel therapeutic avenues.

Antioxidants

Antioxidants, such as vitamins E and C, have been proposed to protect cells against oxidative damage by neutralizing free radicals. Clinical trials of vitamin E supplements for PD have shown no effect on primary endpoints, such as when there is need to start levodopa therapy. The results regarding fat and fatty acids have also been contradictory, with various studies reporting protective effects, risk-enhancing effects, or no effects. There are some indications of a possible protective role of estrogens (lower incidence in women) and anti-inflammatory NSAID drugs, though more study is needed to understand the mechanisms and scale of those effects.

Genetic Factors

Parkinson's disease is usually **idiopathic** (having no known cause). Many PD cases may also arise from environmental components and exposures. A small number of genes are known to be involved in up to 6% of PD cases, and there are probably other genes that increase the potential risk of PD without necessarily causing it. Though PD is not generally considered a genetic disease, up to 15% of patients have a direct family member who has also had PD. As genome technologies continue to improve and be reduced in cost, genetic links and associations may become more clear with time and greater sequence information from patients afflicted with PD. Entire genome sequence analysis can be performed on individual patients at a reasonable and ever-decreasing price.

Mutations in at least seven genes have been linked to either dominant or recessive early-onset familial forms of PD. Additional loci segregating with inherited PD have been identified, with the causative genes to be identified by further study. Known PD genes code for:

- alpha-synuclein (SNCA)
- parkin (PRKN)
- DJ-1 (PARK7)
- cation-transporting ATPase (ATP13A2)
- ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCHL1)
- PTEN-induced kinase-1 (PINK1)
- leucine-rich repeat kinase 2 (LRRK2, or Dardarin)

People with mutations in these genes will develop PD, though they only account for a small percentage of the total cases, with the largest component being the LRRK2 mutations in about 5% of cases. Genome studies have now revealed that mutations in these genes do show up in multiple cases of the sporadic PD. Most likely, mutations in these genes result in cellular alterations that are similar to those seen in sporadic PD and likely include impaired mitochondrial function and dynamics, increased oxidative stress sensitivity, and abnormal protein aggregation (Kumar et al., 2011).

Mutations in three known genes—SNCA (PARK1), UCHL1 (PARK5), and LRRK2 (PARK8)—and one mapped gene (PARK3) result in autosomal dominant Parkinson's disease (one bad copy of two is sufficient to cause disease). Mutations in three known genes—parkin (PARK2), DJ-1 (PARK7), and PINK1 (PARK6)—result in autosomal recessive Parkinson's disease (requires both gene copies to be mutated for disease) and have been linked to the early onset inherited forms of PD. These three autosomal recessive genes appear to form a protein complex that is important in the degradation of some proteins. Three susceptibility genes have been identified and more may become known as more complete DNA sequencing analysis of patients is performed. Molecular genetic testing is clinically available for the most common mutated alleles of PARK2, (the gene-encoding parkin), PINK1, PARK7, SNCA, and LRRK2.

Traditionally, the presence of Lewy bodies was required for pathologic confirmation of Parkinson's disease after death. However, with the discovery of new subtypes of Parkinson's (eg, PARK2 juvenile onset PD), it has been recognized that nigral pathology may occur in the absence of Lewy bodies, and that therefore the Lewy bodies may not be the primary cause of disease pathology.

Autosomal Dominant Genes

The SNCA gene (PARK1) encodes alpha-synuclein protein, the main component of Lewy bodies and the noted pathology marker in autopsy slides of PD brains. Mutations of the SNCA gene include single nucleotide changes, or duplications and triplications of the gene locus. Extra copies via duplication of the SNCA locus account for about 2% of familial cases, though not all persons where they are found have yet developed PD. Perhaps simple overexpression of the gene, via too many copies, is sufficient to cause it to precipitate into aggregated inclusion bodies, with subsequent triggering of damage control or apoptosis of the cell. The mean age of onset in individuals with mutations in this gene is 46 years.

The LRRK2 gene (PARK8) encodes for a protein called *dardarin*. Nearly a dozen different mutations have been reported in the LRRK2 gene. Most of these prevent LRRK2 from localizing properly in the cell and instead the protein pools inside the cell, possibly resembling inclusion bodies with reduced degradation. Mutations in LRRK2 are the most common known cause of familial and sporadic PD, accounting for approximately 5% of individuals with a family history of the disease and 3% of sporadic cases. Sergey Brin, a cofounder of Google, has a known mutation in this autosomal dominant gene for PD, with the resulting 20% to 80% chance of developing PD; his mother, carrying the same mutation, already has PD.

Autosomal Recessive Genes

The parkin (PARK2) type of juvenile-onset parkinson disease, originally described in Japanese individuals, is characterized by typical Parkinson's disease features, often with lower-limb **dystonia** (a movement disorder that causes the muscles to contract and spasm involuntarily) and onset between age 20 and 40 years. Disease progression is slow. Sustained response to levodopa is observed, as well as early, often severe, dopa-induced complications (fluctuations and dyskinesias). The parkin protein is found in a multi-protein E3 ubiquitin ligase complex which is part of the ubiquitin-proteasome system that mediates the targeting of cellular proteins for degradation. Most likely parkin helps degrade one or more proteins toxic to dopaminergic neurons, and when that process is defective, neurons are more susceptible to damage and early death.

Mutations in PARK2 include point mutations as well as exon coding-sequence rearrangements, including both deletions and duplications. Of the patients with onset of PD prior to age 40, 18% had parkin mutations, with 5% having two identical homozygous mutations. Patients with an autosomal recessive family history of parkinsonism are much more likely to carry parkin mutations if age at onset is less than 20 (80% vs. 28% with onset over age 40).

PARK7, (previously known as DJ-1) encodes a ubiquitous, highly conserved protein (protein DJ-1) that may play a role in defense against oxidative stress. Two mutations have been found: one with a deletion of several exons, which prevents any synthesis of the DJ-1 protein, and another that is a point mutation at a highly conserved residue (L166P). That mutation makes the protein less stable and promotes its degradation through the ubiquitin–proteasome pathway, thereby reducing the amount of DJ-1 protein to low or absent levels.

PINK1 (PARK6) encodes a protein called PTEN-induced putative kinase 1. This protein is found in cells throughout the body, with highest levels in the heart, muscles, and testes. Within cells, the protein is located in the mitochondria, the energy-producing centers that provide power for cellular activities. It appears to help protect mitochondria from malfunctioning during periods of cellular stress, such as unusually high energy demands.

More than seventy mutations that can cause Parkinson's disease have been found in the PINK1 gene. By studying these mutations, scientists hope to unravel the mechanisms underlying the disease process that may lead to new therapies. When fruit flies carrying PINK1 mutations were given vitamin K2, the energy production in their mitochondria was partially restored and the insects' ability to generate energy to fly was improved. Researchers were also able to determine that the energy production was restored because the vitamin K2 had improved electron transport in the mitochondria. This in turn led to improved ATP and energy production in the muscles used for flight.

Vitamin K2 plays a role in the energy production of defective mitochondria. Because defective mitochondria are also found in Parkinson's patients with a PINK1 or Parkin mutation, vitamin K2 potentially offers hope for a new treatment for PD.

PD Susceptibility Genes

For many years, it was thought that most forms of Parkinson's disease did not result from a genetic contribution; however, by the late 1990s, studies in different patient populations documented that the risk of Parkinson's disease among first-degree relatives of an affected individual is 2 to 14 times higher than the risk in the general population. With evidence of a genetic component for PD, families with two or more members who had PD were studied. Results suggest the presence of PD susceptibility genes that may increase the risk for familial PD.

A single mutation in GBA, the gene encoding glucocerebrosidase, may convey up to a 5-fold increased risk for PD. Individuals with two GBA mutations have Gaucher disease, which is also found at a high rate among Ashkenazi Jews. It remains to be seen if the risk for PD is as strong in other populations as it is in those heterozygous carriers of Gaucher disease.

Mitochondrial DNA

Mitochondrial impairment, particularly with regard to complex I of the electron transport chain, has been implicated as a cause of PD. Individuals that had one particular variant in the NADH complex I enzyme had a significantly lower risk of PD than others who had the most common form of the enzyme, suggesting that variation in complex I proteins is an important risk factor in PD susceptibility. Mitochondrial DNA deletions have also been found to be common in the substantia nigra neurons of individuals with Parkinson's disease, cells where mitochondrial dysfunction has been shown to be immediately causative of PD in the MPTP neurotoxin model discussed earlier.

Diagnosis of Parkinson's Disease

Characteristic Symptoms

Parkinson's disease is one of the most common neurologic disorders of older adults. The most common symptoms of PD include tremor, stiffness, poor balance even while seated, bradykinesia (slowed movement), and rigidity of the muscles. Walking may involve a **festinating gait**, in which the patient involuntarily moves with short, shuffling, accelerating steps, often on tiptoe, with the trunk flexed forward and the legs flexed stiffly at the hips and knees. Other symptoms may include fatigue, soft speech, writing problems, stooped posture, constipation, and sleep disturbance.

Diagnosis of clinical PD is made by observation of the characteristic symptoms. The tentative diagnosis can be confirmed by a regimen of levodopa that results in relief of motor impairment, especially if initial early symptoms occurred on one side. Presence of resting tremor, asymmetric onset of symptoms, and response to levodopa or similar agents are currently the best confirmation, if no other unusual symptoms are present; nevertheless, a variety of tests and brain scans should be done to rule out other causes or explanations of symptoms. The progress of the illness over time may reveal that it is not Parkinson's disease, so any diagnosis should be reviewed periodically (Brunton et al., 2011).

Front and side views of a man with a festinating gait characteristic of Parkinson's disease. Drawing after St. Leger, first published in Wm. Richard Gowers' *Diseases of the Nervous System*, in London, 1886. Source: Wikipedia.

Onset of PD is gradual and slowly increases in intensity. It often begins with a coarse tremor in one hand while it is at rest, but the tremor is diminished when a purposeful move is initiated or is absent at night while sleeping. The tremor may progress to the other hand, arms, legs, jaws, and face. For some patients, the tremor becomes less pronounced with time, and for some it never becomes a major feature of PD.

Parkinson's disease is classically a movement disorder with dystonia, where sustained muscle contractions cause twisting and repetitive movements or abnormal postures. Problems often develop with walking, and facial expressions become less active or expressive. Muscles of the limbs can tighten, restricting free and fluid motion. Muscles of the hands are less responsive, so daily activities become more difficult, as does handwriting. Often, taking a first step is difficult and, as noted earlier, walking motion resembles a shuffling motion, with little or no arm swinging and a characteristic stooped posture. With reduced flexibility, control, balance, and reaction, falling becomes more of a danger in later stages.

Parkinson's disease usually exhibits the presence of Lewy bodies in the brain cells, whereas Alzheimer's disease shows accumulation of tau protein in the brain with extracellular neurofibrillary tangles; however, dementia along with neurofibrillary tangles often occurs in advanced stages of PD. A person with PD has 2 to 6 times the risk of suffering dementia compared to the general population, and the chances increase with a lengthy duration of the disease. Dementia is associated with a reduced quality of life for people with PD and their caregivers, increased mortality, and a high likelihood of nursing home care.

Differential Diagnosis

Parkinson plus diseases are parkinsonisms with additional clinical disabilities that usually respond poorly to levodopa and can seem to degenerate relatively rapidly when compared to PD. These related diseases include multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration (CBD) and dementia with Lewy bodies (DLB). Antiparkinson medications are usually less effective at controlling symptoms in Parkinson plus syndromes. In addition, faster progression rates, early cognitive dysfunction or postural instability, minimal tremor, or symmetry at onset may indicate a Parkinson plus disease rather than PD itself. Genetic forms are usually classified as PD, although the terms *familial Parkinson's disease* and *familial parkinsonism* are used for disease entities with an autosomal dominant or recessive pattern of inheritance (see earlier discussion).

Dementia with Lewy bodies (DLB) is another synucleinopathy that has similarities with PD, and especially with the subset of PD cases with dementia. Usually DLB exhibits dementia symptoms much earlier though, maybe even concurrent with the first movement symptoms, whereas PD shows a much longer time to progression of dementia (>1 year).

There are several non-motor types of symptoms that are common for PD, such as sensory deficits, cognitive difficulties, or sleep problems. Behavior and mood alterations often include depression, apathy, and anxiety. Impulse control behaviors such as medication overuse, binge eating, hypersexuality, or pathological gambling can appear in PD and have been related to the long exposure to dopamine replacement therapy. Psychotic symptoms such as hallucinations or delusions occur in 4% of patients, most likely from side effects of levodopa treatment, and more common with increasing age and net levodopa intake.

Medical organizations have created diagnostic criteria to ease and standardize the diagnostic process, especially in the early stages of the disease. The criteria require slowness of movement (bradykinesia) plus either rigidity, resting tremor, or postural instability. Other possible causes for these symptoms need to be ruled out. Finally, three or more of the following features are required during onset or evolution: unilateral onset, tremor at rest, progression in time, asymmetry of motor symptoms, response to levodopa for at least five years, clinical course of at least ten years, and appearance of dyskinesias induced by the intake of excessive levodopa over time.

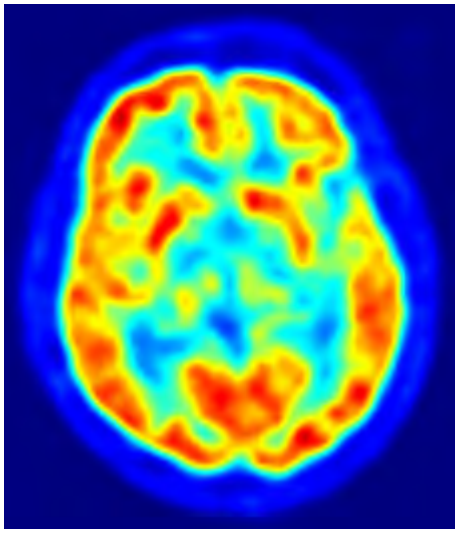
Imaging

Functional imaging techniques such as positron emission tomography (PET) or single photon computed emission tomography (SPECT) using radioactively labeled ligands of the presynaptic dopaminergic neurons can support the diagnosis but are usually limited to a research setting.

Computed tomography (CT) and magnetic resonance imaging (MRI) brain scans of people with PD usually appear normal. These techniques are, however, useful to rule out other diseases such as basal ganglia tumors, vascular pathology, and hydrocephalus. A specific technique of MRI, diffusion MRI, has been reported to be useful at discriminating between typical and atypical parkinsonism, although its exact diagnostic value is still under investigation.

PET Scan of a Healthy Brain

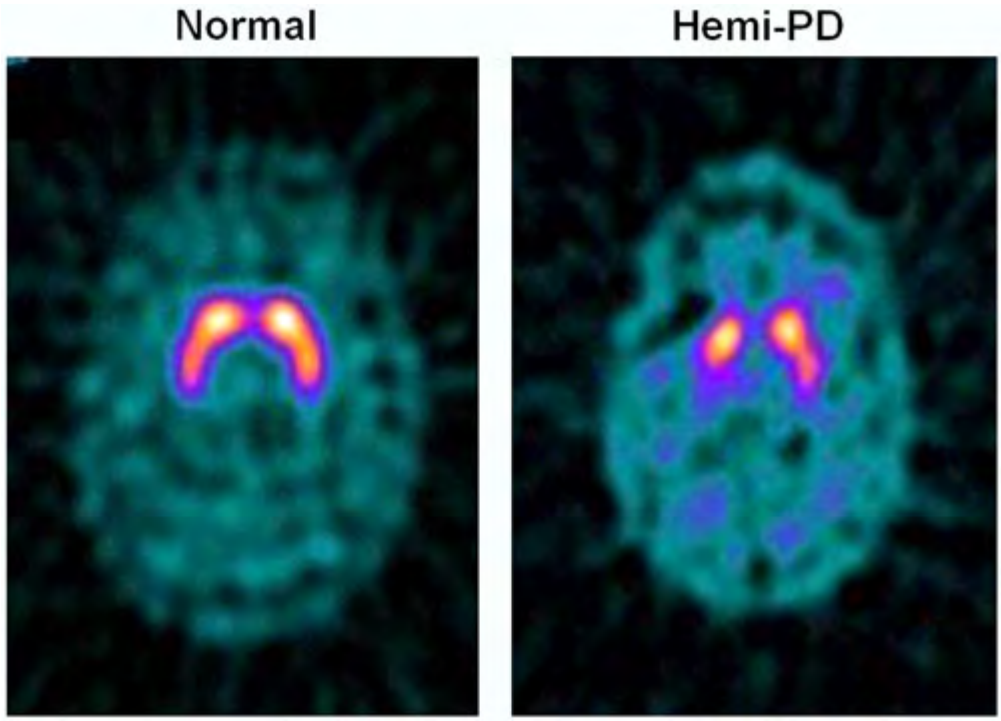
Dopaminergic function in the basal ganglia can be measured with PET and SPECT radiotracers. Examples for SPECT are ioflupane ^{123}I (trade name DaTSCAN) and iometopane (Dopascan); for PET, fluorodeoxyglucose (^{18}F). The DaTSCAN technique has the potential to predict the course of the disease for patients. By measuring the number of dopamine DAT transporters when compared to normal levels at an early point of PD, there is predictive value in how advanced the disease will be in 5 years. Generally a pattern of reduced dopaminergic activity in the basal ganglia can aid in diagnosing PD (Cummings et al., 2011).



Fludeoxyglucose (^{18}F) (FDG) PET scan of a healthy brain. Hotter (red) areas reflect higher glucose uptake and healthy metabolic activity. A decrease of activity in the basal ganglia can aid in diagnosing Parkinson's disease.

Fluorodopa, also known as FDOPA, is a fluorinated form of (^{18}F) L-DOPA primarily synthesized as a radiotracer for PET. Current studies employing the use of FDOPA PET scanning have focused on analyzing the efficiency of neurons in the striatum that utilize the neurotransmitter dopamine. This characteristic is useful in distinguishing corticobasal degeneration CBD from the similar PD, as individuals diagnosed with PD were more likely to have a lower uptake of dopamine than patients with CBD. As these noninvasive imaging techniques are improved, it is possible that therapeutic treatments can be followed more closely in time to demonstrate efficacy for individual patients.

One-Sided Deficit in Parkinson's Disease



^{123}I-FP-CIT SPECT images of healthy volunteer and patient with early hemi-PD. PD patient shows asymmetric bilateral loss of putamen DAT binding.

With new developments in preclinical studies, a recent technique has been devised to look inside living cells in tissue culture and see the insoluble fibrillar deposits associated with Parkinson's disease. A molecular probe was designed based on the metallic element *ruthenium*. Testing it inside live neuroglioma cells, the color probe binds to misfolded alpha-synuclein proteins that clump together and form fibrils that disrupt the cell's functions (Lewy bodies). The ruthenium complex lit up as a red color when triggered by a laser, but only when it was bound to the fibril, allowing alpha-synuclein aggregation to be tracked using photoluminescence spectroscopy. A molecular detector like this can be used to monitor the formation of aggregates inside live cells while screening for drugs that break up fibrils or prevent them from ever forming. The ruthenium complex itself has no therapeutic benefit at this time (Cook et al., 2012).

Treating Parkinson's Disease

There is no cure for Parkinson's Disease, so therapies are designed to alleviate symptoms and delay the progressive effects of the disease, and its treatments, for as long as possible. With that goal in mind, best treatment may vary for each patient and should be re-evaluated as symptoms change. Current treatments are effective at managing the early motor symptoms of the disease, though the patient should be encouraged to continue as many daily activities as possible and consider physical therapy to maintain motor skills and range of motion.

The antiparkinson drugs that are often employed to alleviate motor symptoms in early stages are levodopa (usually combined with a dopa decarboxylase inhibitor (DDCI) or COMT inhibitor), dopamine agonists, and MAO-B inhibitors. Initial drug treatment may start with MAO-B inhibitors and dopamine agonists to see if symptoms are sufficiently controlled. Levodopa (L-DOPA) plus a DOPA decarboxylase inhibitor (DDCI, such as carbidopa) are used sparingly at first to delay as long as possible the side effects resulting from cumulative exposure of systemic dopaminergic function.

As the disease progresses and dopaminergic neurons continue to be lost in the substantia nigra, these drugs eventually become ineffective for treating the motor symptoms, and at the same time cause a complication known as **dyskinesia**, marked by involuntary writhing movements. As medication becomes less effective, "off" periods may occur when the medication has worn off and movement is again difficult until a new dose is given. Medications to treat non-movement-related symptoms of PD, such as sleep disturbances and emotional problems, are also considered as needed (Brunton et al., 2011).

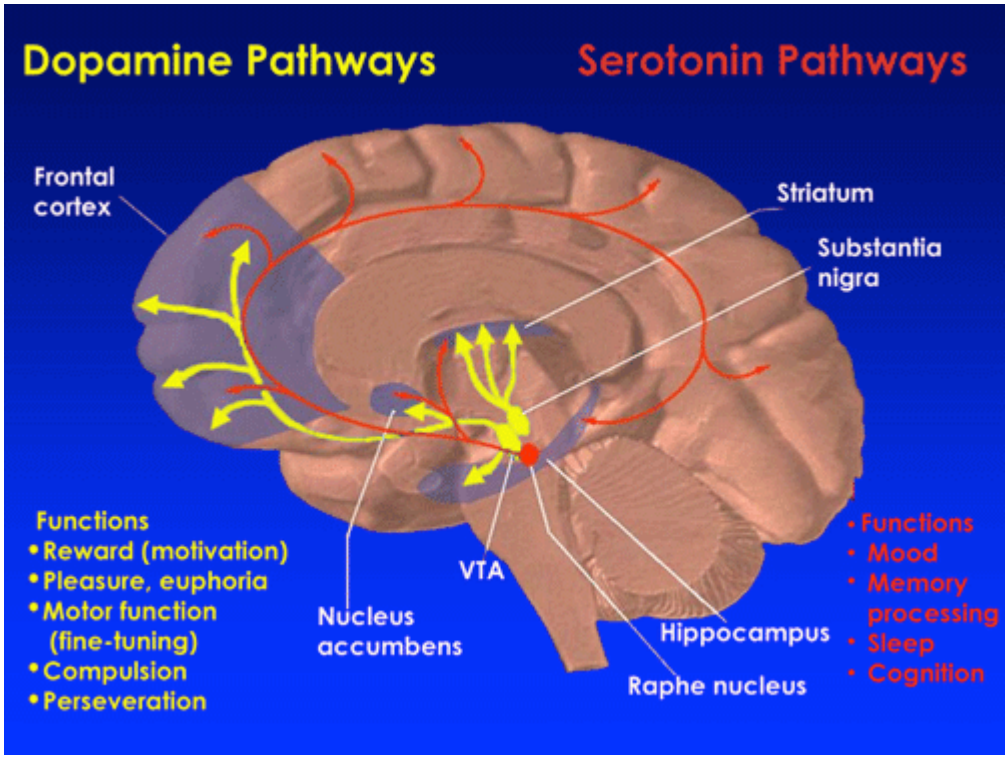
Diet and some forms of rehabilitation have shown some effectiveness at alleviating symptoms. Surgery and deep brain stimulation have been used to reduce motor symptoms when drugs are no longer effective or have too many side effects. Palliative care is given to enhance the quality of life in the final stages of disease.

Research is active to find better animal models of the disease and to advance new techniques using real-time, non-invasive imaging of the brain, stem cell, and gene therapies. New possibilities are being developed to reprogram cells, derived from the patient to avoid immune rejection, for tissue or functional replacement of some deficit.

The Dopamine Pathway

Dopamine is a neurotransmitter, conveying messages from one nerve cell to another. The nigrostriatal pathway in the midbrain, associated with motor control, is an information network for dopamine signaling.

Dopamine Pathways in the Brain



The nigrostriatal pathway makes use of dopamine signaling from the substantia nigra to the striatum. Source: NIDA, 2013.

Dopamine is secreted from membrane storage vesicles in the presynaptic neuron and binds to and activates dopamine receptors on the postsynaptic neuron to mediate its physiologic effects (Brunton et al., 2011). After dopamine has signaled from one neuron to another at the synapse, it is removed via re-uptake back into the presynaptic cell by either the high-affinity dopamine transporter (DAT) or the low-affinity plasma membrane monoamine transporter (PMAT). Once back inside the cytosol, it is eventually repackaged into vesicles for new signaling.

Alternatively, dopamine is directly broken down into inactive metabolites by two enzymes, monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT). In most areas of the brain, including the striatum and basal ganglia, dopamine is inactivated by re-uptake via the DAT, then enzymatic breakdown by MAO. MAO inhibitor drugs help to retain dopamine for a longer time, allowing more synaptic signaling where dopamine is helping to alleviate PD symptoms.

Insufficient dopamine biosynthesis due to loss of the substantia nigra dopaminergic neurons can cause Parkinson's disease and loss of ability to execute smooth, controlled movements; thus, one net effect of dopamine depletion is to produce hypokinesia, an overall reduction in motor output. Drugs that are used to treat PD may, however, produce *excessive* dopamine activity, allowing motor systems to be activated excessively and producing dyskinesias (jerky motions, spasms, tics).

Levodopa is the precursor to dopamine used for various forms of Parkinson's disease and dopa-responsive dystonia (twisting muscle contractions and postures). Dopamine is unable to cross the blood-brain barrier (BBB) directly. It is usually co-administered with an inhibitor of peripheral decarboxylation enzymes such as carbidopa or benserazide, to allow more levodopa to survive long enough to cross the BBB. Inhibitors (entacapone or tolcapone) of COMT—an alternative metabolic route for dopamine—are also used.

The long-term use of levodopa in Parkinson's disease has been linked to dopamine dysregulation syndrome—hence the attempt to delay and minimize use for as long as possible.

Medications

The mainstay of the treatment of Parkinson's disease is pharmacologic replacement of dopamine, most commonly accomplished with the precursor of dopamine, levodopa—usually combined with a DDCI or COMT inhibitor (see below), dopamine agonists, and MAO-B inhibitors. Initial drug treatment may start with MAO-B inhibitors and dopamine agonists to see if symptoms are sufficiently controlled (Brunton et al., 2011).

Levodopa (L-DOPA)

The most widely used drug for PD is levodopa (L-DOPA). Nerve cells can use levodopa to make dopamine and replenish the brain's dwindling supply. L-DOPA is converted to dopamine in the dopaminergic neurons by the enzyme dopa decarboxylase, temporarily diminishing motor symptoms of PD. Although levodopa helps in at least three-quarters of parkinsonian cases, not all symptoms respond equally to the drug. Bradykinesia and rigidity respond best, while tremor may be only marginally reduced. Problems with balance and other symptoms may not be alleviated at all.

Only about 10% of a dose of L-DOPA actually crosses into the brain while the rest is susceptible to conversion to dopamine in the periphery, leading to side effects such as nausea, dyskinesias, and joint stiffness. For that reason, peripheral dopa decarboxylase inhibitors (DDCI), such as carbidopa and benserazide, are given in combination with levodopa to reduce peripheral conversion that would otherwise devour most of the dose given. This also maximizes bioavailabilty for the brain, decreases side effects, and allows a lower dose of levodopa to be used.

Controlled-release versions of levodopa in the form of intravenous and intestinal infusions spread out the medication but have not shown a better control of motor symptoms or complications than standard forms.

Tolcapone inhibits the catechol-O-methyltransferase (COMT) enzyme, which degrades dopamine, prolonging the effects of levodopa, though its usefulness is limited by possible liver toxicity. A similar drug, entacapone, has not shown the liver complications and is used alone or in combination with carbidopa plus levodopa (Sinemet).

After prolonged therapy with levodopa, a person with PD can alternate from phases with good response to medication and few symptoms (the "on" state), to phases with no response to medication and significant motor symptoms (the "off" state); therefore, levodopa doses are kept as low as possible after using alternatives such as dopamine agonists and MAO-B inhibitors. Most people with PD will eventually require levodopa and hence later develop motor side effects such as involuntary movements (dyskinesia), painful leg cramps (dystonia) and a shortened response to each dose (motor fluctuations) (Huot et al., 2013).

Carbidopa Plus Levodopa

Carbidopa (Lodosyn) is used with levodopa (Sinemet, Parcopa, Atamet) to prevent the peripheral conversion of levodopa to dopamine before it can reach the brain and take effect. It also reduces the side effects of peripheral dopamine. Carbidopa is only effective if it is taken with levodopa; it has no effect if used alone. Carbidopa inhibits dopa decarboxylase (DDC), an enzyme important to converting L-DOPA to dopamine. Recall that dopamine itself cannot cross the blood brain barrier. DDC is found in the periphery and in the brain, but carbidopa does not cross the BBB so it does not inhibit conversion of L-DOPA to dopamine there.

Entacapone (Comtan), a COMT inhibitor, is used in combination with Sinemet for times when levodopa stops working at the end of a dose—the "off" times. This drug prevents breakdown of dopamine by inhibiting the enzyme catechol-O-methyltransferase (COMT).

Dopamine Agonists

Dopamine agonists are molecules that bind to the postsynaptic dopamine receptors and mimic the role of dopamine in the brain, causing a response similar to dopamine itself. These were initially used to help alleviate the "off" state of late PD when the benefits of levodopa doses were wearing off. Now they are used as an early alternative to levodopa so that later complications and dyskinesias are postponed for as long as possible. Dopamine agonists include

- Bromocriptine (Parlodel, Cycloset)
- Pramipexole (Mirapex)
- Ropinirole (Requip)
- Piribedil (Pronoran, Trivastal Retard, Trastal, Trivastan)
- Cabergoline (Dostinex, Cabaser)
- Apomorphine (Apokyn, Ixense, Spontane, Uprima)
- Lisuride (Dopergin, Proclacam, Revanil)

Ropinirole (Requip) and Pramipexole (Mirapex) are nonergot dopamine agonists also used for restless legs syndrome.

Dopamine agonists produce significant, though usually mild, side effects including drowsiness, hallucinations, insomnia, nausea, and constipation. If side effects appear even at a minimal effective dose, another of this class of drugs can be tested as an alternative. These drugs are less able to control motor symptoms than levodopa, but they are usually sufficient in the earliest stages of the disease.

Agonists have been related to impulse control disorders (such as compulsive sexual activity and eating, and pathological gambling and shopping) more strongly than levodopa.

Apomorphine may be used to reduce "off" periods and dyskinesia in late PD, though it requires injections or continuous subcutaneous infusions and may cause confusion and hallucinations. Apomorphine treatment obviously requires close attention from caregivers. Two other dopamine agonists are available as skin patches (lisuride and rotigotine) and have benefit in early stages and for the "off" state in advanced stages of PD.

MAO-B Inhibitors

Selegiline (Eldepryl, Deprenyl, or Selgene) and rasagiline (Azilect) are MAO-B inhibitors that increase the level of dopamine in basal ganglia synapses by blocking its metabolism. They inhibit the monoamine oxidase-B (MAO-B) enzyme responsible for breaking down dopamine secreted by the dopaminergic neurons. Like dopamine agonists, MAO-B inhibitors alone can improve motor symptoms and delay the need for levodopa use in early disease but they are less effective than levodopa. In the advanced disease, they can be used to reduce fluctuations between "on" and "off" periods. None of these treatments slow the progression of the disease.

Other Drugs

Amantadine (Symmetrel) is a weak antagonist of NMDA-type glutamate receptors, increases dopamine release, and blocks dopamine re-uptake in the synapse. It can be taken with Sinemet to treat motor response fluctuations in advanced disease.

Anticholinergics that block the neurotransmitter acetylcholine in the central and peripheral nervous system may be useful as treatment of motor symptoms by essentially anesthetizing the muscle/ nerve connections to reduce unwanted motor symptoms and rigidity.

Several drugs have been used to treat other symptoms common to PD patients, such as the use of clozapine (Clozaril, FazaClo) for psychosis, cholinesterase inhibitors for dementia, and modafinil for daytime sleepiness. Some studies have implied that regular users of nonsteroidal anti-inflammatory drugs (NSAIDs, apart from acetaminophen and aspirin), have a lower risk of ever developing PD.

Other medications may also include:

- Memantine (Namenda), rivastigmine (Exeleon), galantamine (Razadyne) for cognitive difficulties; these are NMDA-receptor antagonists or acetylcholinesterase inhibitors
- Antidepressants for mood disorders
- Gabapentin (Neurontin, Gralise, Fanatrex) to treat certain types of seizures or restless legs syndrome
- Duloxetine (Cymbalta) treats depression, anxiety, peripheral neuropathy (nerve pain), fibromyalgia (muscle pain and stiffness), or chronic pain related to muscles and bones. This is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI).
- Fludrocortisone, midodrine, botox, sidenafil for autonomic dysfunction
- Armodafinil (Nuvigil), clonazepam (Klonopin), zolpidem (Ambien) for sleep disorders and daytime wakefulness

Surgical Intervention

Deep Brain Stimulation

Surgery may be an option for some patients with Parkinson's disease. These surgeries do not cure Parkinson's but may help ease symptoms. Deep brain stimulation (DBS), using high-frequency stimulating electrodes, was approved by the FDA in 1997 and has been a promising avenue for treatment of movement disorders. DBS is recommended for people who have PD and suffer from motor fluctuations and tremor inadequately controlled by medication or for those who are intolerant of medication, as long as they do not have severe neuropsychiatric problems (Okun, 2012).

Stimulation of the ventral intermediate nucleus of the thalamus (VIM) can show marked reduction in the tremors associated with PD. Stimulation of the subthalamic nucleus (STN) or the internal segment of the globus pallidus (GPi) can greatly reduce tremor, rigidity, bradykinesia, and difficulty with walking and controlled movement.

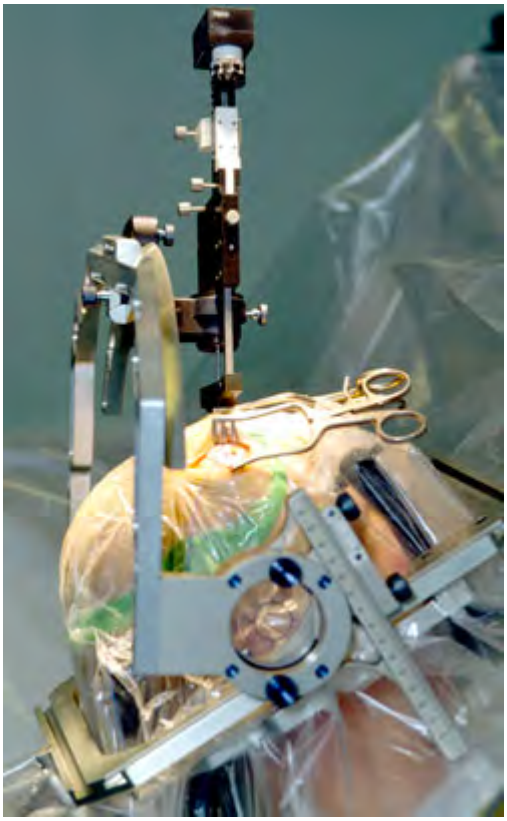
The results of stimulation for PD depends on which region receives DBS. VIM stimulation primarily reduces limb tremor. Targeting the GPi appears to reduce all of the major motor problems with PD, including those dyskinesias that arise after extended use of levodopa. It does not appear to alleviate other issues with drug side effects such as psychosis or cognitive impairment. Subthalamic nucleus DBS also appears to reduce most of the motor symptoms and, if performed on both sides of the brain, may allow reduction in dopaminergic medications and their associated side effects.

While the effects of DBS are not more effective than a dose of levodopa, it does seem to reduce the time spent in the "off" state when the medication has worn off and symptoms reappear, and it does allow a reduction in levodopa so that those side effects are pushed further into the future. The benefits of DBS are typically maintained for at least four years before other complications arise.

The best candidates for DBS are those who are exhibiting negative effects from levodopa exposure yet had been having motor benefit from the oral drugs. However, memory, disorientation, and other cognitive problems may be increased by DBS and may be sufficient reasons for not using it if these are already a clinical concern. There are still major questions as to the mechanisms of action for DBS, and research to improve it are ongoing.

Patient Undergoing DBS Surgery

Clinically, DBS is a two-stage procedure involving in the first stage a stereotactic frame, with the patient under sedation yet awake, for a 30-minute, three-dimensional MRI to locate the coordinates of the deep brain target. After determining the target, while still in the operating room a path for the very fine metal electrodes is planned that will reach the target. The DBS electrode is placed to the target, and electrical impulses are sent to see which placement gives the best reduction in tremors, while monitoring for other unwanted side effects in speech or numbness.



Placement of an electrode into the brain. The head is stabilized in a frame for stereotactic surgery. Source: Wikimedia Commons.

Once an effective place is found, the electrode is left in and clipped into place on the skull, and the exterior wound is closed. A second operation is performed under general anesthesia to place a small battery pouch containing the stimulator pulse generator under the collarbone. From there, a wire is passed under the skin up the neck to behind the ear, where it re-emerges and is attached to the stimulator wire into the brain.

After observation for several weeks, the unit will be turned on and tested further. Depending on the targeted region of the brain, a neurologist will be involved with the delicate electrode placement, and one or both sides of the brain may be targeted, in similar but separate operations.

The expected result of DBS is to relieve some or most of the motor dysfunction. This can often result in an improvement of the “off” state, when medication has had less benefit and motion is again stiff or slow. The “on” state, when medication is effective, is not further improved by DBS. Followup exams can allow externally programmed modifications of the stimulation frequency or intensity to optimize the benefit for each particular patient and the brain region targeted.

Pallidotomy

Some people with Parkinson's disease benefit from other types of neurosurgical procedures such as pallidotomy. **Pallidotomy** is a procedure whereby a tiny electrical probe is placed in the globus pallidus (GPi, one of the basal ganglia of the brain), which is then heated to 80°C for 60 seconds to ablate a small area of brain cells. Pallidotomy is an alternative to deep brain stimulation for the treatment of a condition known as levodopa-induced dyskinesia, the involuntary movements that can become a problem in people with PD after long-term treatment with levodopa. It can be an alternative to DBS for treating difficult cases of essential tremor.

Animal Models

It is thought that no other species than humans naturally develop PD, although animal models have been developed for research. In the early 1980s the appearance of parkinsonian symptoms in a group of drug addicts who consumed a contaminated batch of the synthetic opiate MPPP led to the discovery of the chemical MPTP as an agent that causes a parkinsonian syndrome in nonhuman primates as well as in humans. Other toxin-based models of PD employ the insecticide rotenone, the herbicide paraquat, or the fungicide maneb. Models based on toxins are most commonly used in primates. Transgenic rodent models that replicate various aspects of PD have also been developed for understanding or testing treatments for specific components of PD symptoms.

Gene and Stem Cell Therapies

There is consensus that new treatments move from treating symptoms to modifying the disease pathology, while also aiming to reduce the nonmotor disease symptoms such as loss of balance, autonomic dysfunction, and cognitive impairment that come with time and diminish quality of life.

Gene therapy involves the use of DNA in a noninfectious virus to shuttle a gene into a part of the brain. The gene used is meant to increase the production of an enzyme that helps to manage PD symptoms or protects the brain from further damage. In 2010 there were four clinical trials using gene therapy in PD and none of them have had serious adverse effects, though the clinical benefit is also undecided.

Clinical studies have focused on the therapeutic potential of neurotrophic factors, including GDNF and neurturin, and enzymes that produce dopamine. One trial is using adenovirus-associated virus (AAV2) to deliver the gene for the enzyme that converts levodopa to dopamine, hoping to make this more abundant and thereby allowing a lower dose to be used. Another trial is using AAV2-mediated delivery of neurturin, a functional analog of glial cell-derived neurotrophic factor (GDNF), which aims to provide neuroprotective benefits in addition to symptomatic improvement. Neurturin provides neuroprotection and upregulation of dopamine function in a variety of rodent and nonhuman primate models. One of the human trials using gene transfer of glutamic acid decarboxylase (GAD) enzyme to improve GABA production in the subthalamic nucleus reported positive results for PD patients in 2011.

Since the 1980s, fetal porcine carotid body cells or immature retinal tissues have been used in cell transplants, in which dissociated cells are injected into the substantia nigra hoping that they incorporate themselves into the brain and replace the dopamine-producing cells that have been lost. Though mesencephalic dopamine-producing cell transplants were initially positive, further trials did not show benefit beyond other types of current therapy. In some cases the new cells were secreting more dopamine than was necessary, leading to the dystonias common in advanced PD.

Stem cell transplants are a recent research target, because stem cells are easy to grow and manipulate, and when transplanted into the brains of rodents and monkeys they have been found to survive and reduce abnormalities. New possibilities are recently available to re-program cells by using induced pluripotent stem cells, derived from the patient to avoid immune rejection, for tissue or functional replacement cells.

Several molecules have been proposed as potential treatments for neuroprotection in PD patients. However, none of them have been convincingly shown to reduce degeneration. Currently promising molecules include:

- Anti-apoptotics (omigapil, CEP-1347)
- Antiglutamatergics
- Monoamine oxidase inhibitors (selegiline, rasagiline)
- Promitochondrials (coenzyme Q10, creatine)
- Calcium channel blockers (isradipine)
- Growth factors (GDNF)

Oral supplementation with co-enzyme Q10, a mitochondrial complex I electron-accepting antioxidant, reduced dopaminergic neuron loss in MPTP-toxin treated mice. A vaccine that primes the human immune system to destroy alpha-synuclein, the main component of Lewy bodies, has entered clinical trials in humans. Whether this will help PD patients remains to be seen. Stem cell transplant and other clinical trials are currently ongoing in the United States. For more, click here.

Lifestyle Recommendations

[This section taken primarily from NIH, 2012.]

Individuals with Parkinson's disease may benefit from physical, occupational, and speech therapy. Several major organizations promote research and improving quality of life for those with the disease and for their families.

Lifestyle changes that you can recommend for the person with Parkinson's disease:

- Good general nutrition and health. Changes in food or drink are needed if there are swallowing problems.
- Exercising every day, but adjusting the activity level to meet changing energy levels
- Regular rest periods and avoiding stress
- Physical therapy, speech therapy, and occupational therapy. A physiotherapist can suggest appropriate stretches and exercises.
- Keeping informed on specific medical conditions.
- Joining a support group.
- Talking to your physician about when and what type of medication you can take.
- Railings or banisters placed in commonly used areas of the house. Other changes may be needed around the home to prevent falls and make the bathroom safe.
- Assistive devices, such as special eating utensils, wheelchairs, bed lifts, shower chairs, walkers, and wall bars
- Social workers or other counseling services to help you cope with the disorder and get assistance (eg, Meals-on-Wheels)
- Continue doing what makes you happy.

A wide variety of complementary and supportive therapies may be used for Parkinson's disease. Among these therapies are standard physical, occupational, and speech therapies, which help with gait and voice disorders, tremors and rigidity, and decline in mental functions. Other supportive therapies include diet and exercise.

Diet

At this time there are no specific vitamins, minerals, or other nutrients that have any proven therapeutic value in Parkinson's disease. Some early reports have suggested that dietary supplements might protect against PD. Also, a preliminary clinical study of a supplement called coenzyme Q10 suggested that large doses of this substance might slow disease progression in people with early-stage Parkinson's. This supplement is now being tested in a large clinical trial.

Other studies are being conducted to find out if caffeine, antioxidants, nicotine, and other dietary factors may help prevent or treat the disease. 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 Parkinson's disease, just as it would for anyone else. Eating a fiber-rich diet and drinking plenty of fluids can help alleviate constipation. A high protein meal, however, may limit levodopa's effectiveness because for a time afterwards less levodopa passes through the blood-brain barrier while competing with other amino acids. Therefore, when levodopa is introduced, excessive protein consumption is discouraged and a well-balanced Mediterranean diet is recommended. In advanced stages, additional intake of low-protein products such as bread or pasta is recommended for similar reasons. To minimize interaction with proteins, levodopa should be taken 30 minutes before meals.

Exercise

Exercise can help people with Parkinson's disease improve their mobility and flexibility. Some doctors prescribe physical therapy or muscle-strengthening exercises to tone muscles and to put under-used 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 Parkinson's disease, and it may improve the brain's dopamine synthesis or increase brain levels of beneficial compounds called neurotrophic factors. Although structured exercise programs help many patients, more general physical activity, such as walking, gardening, swimming, calisthenics, and using exercise machines is beneficial. People with Parkinson's disease should always check with their doctors before beginning a new exercise program.

In terms of improving flexibility and range of motion for patients experiencing rigidity, generalized relaxation techniques such as gentle rocking have been found to decrease excessive muscle tension. Other effective techniques to promote relaxation include slow rotational movements of the extremities and trunk, rhythmic initiation, diaphragmatic breathing, and meditation.

Strengthening exercises have shown improvements in strength and motor function for patients with primary muscular weakness and weakness related to inactivity with mild to moderate PD. However, reports show a significant interaction between strength and the time the medications was taken, so it is recommended that patients should perform exercises 45 minutes to 1 hour after medications, when the patients are at their best. Also, due to the forward flexed posture and respiratory dysfunctions in advanced Parkinson's disease, deep diaphragmatic breathing exercises are beneficial in improving chest wall mobility and vital capacity.

A common treatment for speech disorders associated with Parkinson's disease is the Lee Silverman voice treatment (LSVT). Occupational therapy (OT) aims to promote health and quality of life by helping people with the disease to participate in as many of their daily living activities as possible.

Other Therapies

Other complementary therapies include massage therapy, yoga, tai chi, hypnosis, acupuncture, and the Alexander technique, which improves posture and muscle activity. There have been limited studies suggesting mild benefits from some of these therapies, but they do not slow Parkinson's disease. However, this remains an active area of investigation.

Parkinson's Disease in the Long Term

Prognosis

Parkinson's disease is both **chronic**, meaning it persists over a long period of time, and **progressive**, meaning its symptoms grow worse over time. Although some people become severely disabled, others experience only minor motor disruptions. 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 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. There are national organizations that can help patients locate support groups in their communities. Individual or family counseling also may help people find ways to cope with Parkinson's disease (FDA, 2010).

Tremor is the major symptom for some patients, while for others tremor is only a minor complaint and other symptoms are more troublesome. No one can predict which symptoms will affect an individual patient, and the intensity of the symptoms also varies from person to person. Most people respond to medications. How much the medications relieve symptoms, and for how long, varies with each person. The side effects of medications may be severe. Untreated, the disorder will get worse until a person is totally disabled. Parkinson's may lead to a deterioration of all brain functions and an early death.

People with Parkinson's disease 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 cope with the disease.

With appropriate treatment, most people with Parkinson's disease can live productive lives for many years after diagnosis.

Palliative care is often required in the final stages of the disease when all other treatment strategies have become ineffective. The aim of palliative care is to maximize the quality of life for people who have the disease and for those surrounding them. Some central issues of palliative care are: reducing or withdrawing drug intake to reduce drug side effects, preventing pressure ulcers by management of pressure areas of inactive patients, and facilitating end-of-life decisions for the patient as well as involved friends and relatives.

Rating Scales

The progression of symptoms in Parkinson's disease may take twenty years or more. In some people, however, the disease progresses more quickly. There is no way to predict what course the disease will take for an individual person. One commonly used system for describing how the symptoms of Parkinson's disease progress is called the Hoehn and Yahr scale.

Hoehn and Yahr Staging of Parkinson's Disease

Hoehn and Yahr (1967) devised a system for describing the progression of Parkinson's disease that comprises five stages:

- **Stage one.** Symptoms on one side of the body only.
- **Stage two.** Symptoms on both sides of the body. No impairment of balance.
- **Stage three.** Balance impairment. Mild to moderate disease. Physically independent.
- **Stage four.** Severe disability, but still able to walk or stand unassisted.
- **Stage five.** Wheelchair-bound or bedridden unless assisted.

Unified Parkinson's Disease Rating Scale (UPDRS)

Another commonly used scale is the Unified Parkinson's Disease Rating Scale (UPDRS). This much more complicated scale has multiple ratings that measure mental functioning, behavior, and mood, activities of daily living, and motor function. Both the Hoehn and Yahr scale and the UPDRS are used to measure how individuals are faring and how much any treatments are helping them.

Research

The National Institute of Neurological Disorders and Stroke (NINDS) conducts PD research in laboratories at the National Institutes of Health (NIH) and also supports additional research through grants to major medical institutions across the country. Current research programs funded by the NINDS are using animal models to study how the disease progresses and to develop new drug therapies. Scientists looking for the cause of PD continue to search for possible environmental factors, such as toxins, that may trigger the disorder, and study genetic factors to determine how defective genes play a role. Other scientists are working to develop new protective drugs that can delay, prevent, or reverse the disease (NINDS, 2012).

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Post Test

Use the answer sheet following the test to record your answers.

1. Velvet beans (*Mucuna pruriens*), long used in traditional medicine to treat symptoms of Parkinson's, contain:

    a. Anti-oxidants.
    b. Vitamin K.
    c. Levodopa.
    d. Carbidopa.

2. A pathological marker found post mortem in the brains of those with PD is:

    a. Substantia nigra.
    b. Striatum.
    c. Cerebral peduncle.
    d. Lewy bodies.

3. Parkinson's disease results from a disorder of the neurons in the brain that are responsible for the production of:

    a. Serotonin.
    b. Dopamine.
    c. Carbidopa.
    d. Adenosine.

4. PD is characterized by all but one of the following:

    a. Tremors.
    b. Bradykinesia.
    c. Kinesthesia.
    d. Impaired balance.

5. Classification of PD is by:

    a. Age of onset.
    b. Length of disability.
    c. Brain scan.

d. Prognosis.

6. Parkinson’s disease is caused in the midbrain by:

a. Amyloid plaques.
b. Loss of dopamine-secreting neurons.
c. Tau tangles.
d. Anomaly in chromosome 17.

7. The level of symptoms and their severity in PD patients is related to:

a. Presence of Lewy bodies.
b. Lack of certain necessary proteins.
c. Presence of amyloid tangles.
d. Inadequate thyroid function.

8. Living in agricultural areas has been correlated with increased risk of PD related to damage from exposure to chemicals found in certain pesticides and herbicides:

a. True
b. False

9. Protective factors against PD include all but one of the following:

a. Nicotine.
b. Antioxidants.
c. Alcohol.
d. Caffeine.

10. Of the seven genes known to be associated with PD, mutations likely include all but one of the following:

a. Impaired mitochondrial function and dynamics.
b. Insulin-receptor mutations.
c. Increased oxidative stress sensitivity.
d. Abnormal protein aggregation.

11. A common symptom of PD is a **festinating gait**, which involves:

a. Long, shaky steps with arms swinging erratically.

b. Abnormally pronounced flexion in the legs and hips.

c. Backward leaning short, shaky steps.

d. Short, shuffling steps with trunk flexed forward.

12. Differential diagnosis of PD is generally confirmed by:

a. Genetic testing.

b. Response to levodopa.

c. Response to muscle relaxants.

d. Deep brain stimulus.

13. Established criteria for diagnosis of PD include:

a. History of awkwardness.

b. Aphasia.

c. Unilateral onset.

d. History of alcohol/drug abuse.

14. Imaging techniques used on people with PD are usually normal but are used merely to rule out other causes of the presenting symptoms.:

a. True

b. False

15. Antiparkinson drugs often employed to alleviate motor symptoms are delivered initially:

a. In a bolus.

b. At high doses for maximum early effect.

c. In small doses repeated throughout each 24-hour period.

d. Sparingly at first to delay side effects.

16. Levodopa (L-DOPA), is usually co-administered with an inhibiter of peripheral enzymes to:

a. Modify its long-term side effects.

b. Allow more L-DOPA to cross the blood-brain barrier.

c. Facilitate uptake in the substantia nigra.

d. Prevent it from crossing the blood-brain barrier.

17. Carbidopa is best used on its own when levodopa has ceased to be effective:

a. True
b. False

18. Dopamine agonists mimic the role of dopamine in the brain and are used:

a. Throughout for a more alert mental state in the PD patient.
b. As needed to prevent nausea and constipation.
c. Early to postpone the complications of levodopa as long as possible.
d. As a last resort when dopamine has ceased to be effective.

19. Deep brain stimulation for PD patients can be effective in:

a. Reducing motor fluctuations and tremors.
b. Alleviating cognitive impairment.
c. Addressing psychosis related to antiparkinson medications.
d. Ending hallucinations and delusions.

20. Deep brain stimulation (DBS) not only improves the “off” state but also enhances the “on” state for PD patients:

a. True
b. False

21. While PD is both chronic and progressive, with treatment most people can live productive lives for many years after diagnosis:

a. True
b. False

Answer Sheet

Parkinson Medications

Name (Please print your name): _____

Date: _____

Passing score is 80%

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____
11. _____
12. _____
13. _____
14. _____
15. _____
16. _____
17. _____
18. _____
19. _____
20. _____
21. _____

Course Evaluation

Please use this scale for your course evaluation. Items with asterisks * are required.

- 5 = Strongly agree
- 4 = Agree
- 3 = Neutral
- 2 = Disagree
- 1 = Strongly disagree

* Upon completion of the course, I was able to:

a. Discuss the long history of Parkinson's disease.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

b. Describe Parkinson's disease in detail.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

c. Explain what happens in the brain that results in PD.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

d. List both genetic and protective factors that impact PD.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

e. Spell out the characteristics of PD and differentiate it from other conditions.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

f. Summarize treatment options, including medications, surgical interventions, and other interventions still in the pipeline.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

g. Explain the rating scales and their relationship to prognosis of PD.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

* The author(s) are knowledgeable about the subject matter.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

* The author(s) cited evidence that supported the material presented.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

* This course contained no discriminatory or prejudicial language.

○ Yes ○ No

* The course was free of commercial bias and product promotion.

○ Yes ○ No

* As a result of what you have learned, do you intend to make any changes in your practice?

○ Yes ○ No

If you answered Yes above, what changes do you intend to make? If you answered No, please explain why.

* Do you intend to return to ATrain for your ongoing CE needs?

- ○ Yes, within the next 30 days.
- ○ Yes, during my next renewal cycle.
- ○ Maybe, not sure.
- ○ No, I only needed this one course.

* Would you recommend ATrain Education to a friend, co-worker, or colleague?

- ○ Yes, definitely.
- ○ Possibly.
- ○ No, not at this time.

* What is your overall satsfaction with this learning activity?

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

* Navigating the ATrain Education website was:

- Easy.
- Somewhat easy.
- Not at all easy.

* How long did it take you to complete this course, posttest, and course evaluation?

- 60 minutes (or more) per contact hour
- 50-59 minutes per contact hour
- 40-49 minutes per contact hour
- 30-39 minutes per contact hour
- Less than 30 minutes per contact hour

I heard about ATrain Education from:

- Government or Department of Health website.
- State board or professional association.
- Searching the Internet.
- A friend.
- An advertisement.
- I am a returning customer.
- My employer.
- Other
- Social Media (FB, Twitter, LinkedIn, etc)

Please let us know your age group to help us meet your professional needs.

- 18 to 30
- 31 to 45

- ○ 46+

I completed this course on:

- ○ My own or a friend's computer.
- ○ A computer at work.
- ○ A library computer.
- ○ A tablet.
- ○ A cellphone.
- ○ A paper copy of the course.

Please enter your comments or suggestions here: _____

_____

_____

_____

Registration Form

Please print and answer all of the following questions (* required).

* Name: _____

* Email: _____

* Address: _____

* City: _____ * State: _____ * Zip: _____

* Country: _____

* Phone: _____

* Professional Credentials/Designations:

_____

Your name and credentials/designations will appear on your certificate.

* License Number and State: _____

* Please email my certificate:

○ Yes ○ No

(If you request an email certificate we will not send a copy of the certificate by US Mail.)

Payment Options

You may pay by credit card or by check.
Fill out this section only if you are **paying by credit card.**
2.5 contact hours: $19

Credit card information

* Name: _____

Address (if different from above): _____

* City: _____ * State: _____ * Zip: _____

* Card type:

○ Visa ○ Master Card ○ American Express ○ Discover

* Card number: _____

* CVS#: _____

* Expiration date: _____