Parkinson’s Disease: Moving Forward

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Contact hours: 10

Course price: $55

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Course Summary

A thorough review of Parkinson’s comprising its history, genetics, biomarkers, and rating scales, with particular emphasis on preserving gait and other motor and cognitive functions over the course of the disease. Includes a personal narrative by a patient who has Parkinson’s.

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:

1. Trace the history of "shaking palsy" in Western medicine.
2. Discuss the role of dopamine and Lewy bodies in Parkinson's disease.
3. Spell out the role of gene therapy in the treatment of PD.
4. Explain biomarkers and appraise commonly used PD rating scales.
5. Specify the most common motor symptoms found in PD.
6. Evaluate risk factors for fall and the various clinical tests for balance.
7. Describe non-motor aspects and symptoms associated with PD.
8. List common cognitive changes that occur as PD progresses.
9. Identify current strategies and those in development for the treatment of PD.
10. Evaluate rehabilitation treatment approaches for PD.
11. Discuss the issues related to providing excellent hospital care for patients who have PD.
12. Relate the difficulties associated with caring for a person with PD.
13. Describe the complications that arise in those with advanced PD.

The Story of Parkinson's Disease

The symptoms associated with Parkinson's disease have been observed throughout human history. Early descriptions of people with symptoms date back thousands of years. An Ayurvedic medical treatise from India of the tenth century B.C.E. describes a disease that evolves with tremor, lack of movement, drooling, and other symptoms characteristic of PD.

Galen of Pergamon
(A.D. 129–C. 200)

In A.D. 175 the medical researcher Galen described the symptoms now associated with PD: 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 the progression of the disease.

Early treatments for PD involved plants of the mucuna family of tropical vines. *Mucana pruriens* seeds, also known as the tropical legume "velvet bean" or "cow itch," are rich in levodopa, a direct molecular precursor of the neurotransmitter dopamine. The seeds are native to Africa, India, and the Caribbean, and have long been used in traditional Ayurvedic Indian medicine for the treatment of Parkinson's and other diseases.

Also known as Aelius Galenus, roman physician from Pergamon, Turkey, the most famous medical researcher of classical antiquity. Lithograph by Pierre Roche Vigneron.

Left: The *mucuna pruriens*, a hand-colored engraving after a drawing by Miss S.A. Drake, from Vol. 24 of the Botanical Register (1838), edited by John Lindley. Public Domain. Right: *Mucuna pruriens* seeds of two different colors, each about the size of a chicken egg. Source: USDA, 2012.

In Central America and Brazil, velvet beans have been roasted and ground for decades to make a coffee substitute with the common name of nescafé. Single portions, approximately 1 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.

Mucuna seeds also contain several other potent neuroactive and psychoactive compounds. These include serotonin, 5-hydroxytryptophan (5-HTP), nicotine, dimethyltryptamine (DMT), bufotenin, and 5-MeO-DMT, the last three being powerful psychedelic tryptamines. Extracts can exhibit strong psychedelic effects, and are reportedly used in the South American *ayahuasca* (medicinal tea) preparations.

Early Clinical Descriptions

Although the physical symptoms and rudimentary medical descriptions were around for many centuries, one of the earliest *clinical* descriptions identifying PD as a neurologic syndrome is found in *An Essay on the Shaking Palsy*, published in 1817 by the London physician James Parkinson. He described six individuals, each with similar clinical features:

> So slight and nearly imperceptible are the first inroads of this malady, and so extremely slow is its progress, that it rarely happens that the patient can form any recollection of the precise period of its commencement. The first symptoms perceived are a slight sense of weakness with a proneness to trembling in some particular part; sometimes in the head, but most commonly in one of the hands and arms.
>
> These symptoms gradually increase in the part first affected; and at an uncertain period, but seldom in less than twelve months or more, the *morbid influence* is felt in some other part. After a few more months the patient is found to be less strict than usual in preserving the upright posture: this being most observable whilst walking, but sometimes whilst sitting or standing. (Parkinson, 1817)

James Parkinson (1755–1824)

Source: Courtesy of allaboutParkinsons.com

With the publication of his essay, James Parkinson provided the first formal clinical description the disease, which focused on tremor, weakness, rigidity, and postural and gait changes. Parkinson wrote that patients with the shaking palsy exhibited:

- Involuntary, tremulous motion with lessened voluntary muscle power, in parts, not in action, and even supported
- A propensity to bend the trunk forwards, and to pass from walking to a running pace

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.

Building on Parkinson's work, in 1871 Theodor Meynart, a German-Austrian neuropathologist, recognized that a part of the brain called the *basal ganglia* was involved with abnormal movements. Shortly after Meynart's discovery and more than seventy years after Parkinson published his essay, Jean-Martin Charcot, in his *Clinical Lectures on Diseases of the Nervous System* (Charcot, 1889), refined Parkinson's clinical description of shaking palsy (or "paralysis agitans") by adding bradykinesia or slowness of movement as a defining feature of the disease. Charcot wrote:

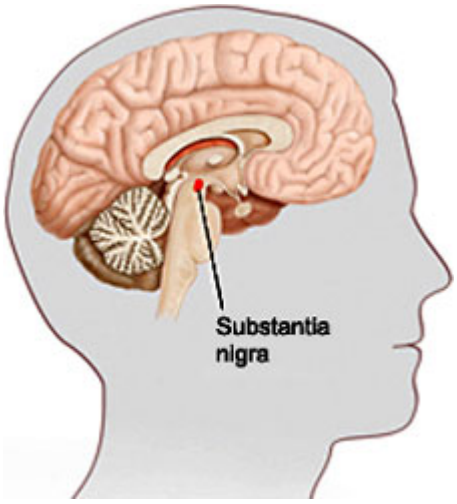
> Long before rigidity actually develops, patients have significant difficulty performing ordinary activities: this problem relates to another cause. In some of the various patients I showed you, you can easily recognize how difficult it is for them to do things even though rigidity or tremor is not the limiting feature. Instead, even a cursory exam demonstrates that their problem relates more to slowness in execution of movement rather than to real weakness.
>
> In spite of tremor, a patient is still able to do most things, but he performs them with remarkable slowness. Between the thought and the action there is a considerable time lapse. One would think neural activity can only be effected after remarkable effort.

Jean-Martin Charcot (1825–1893)

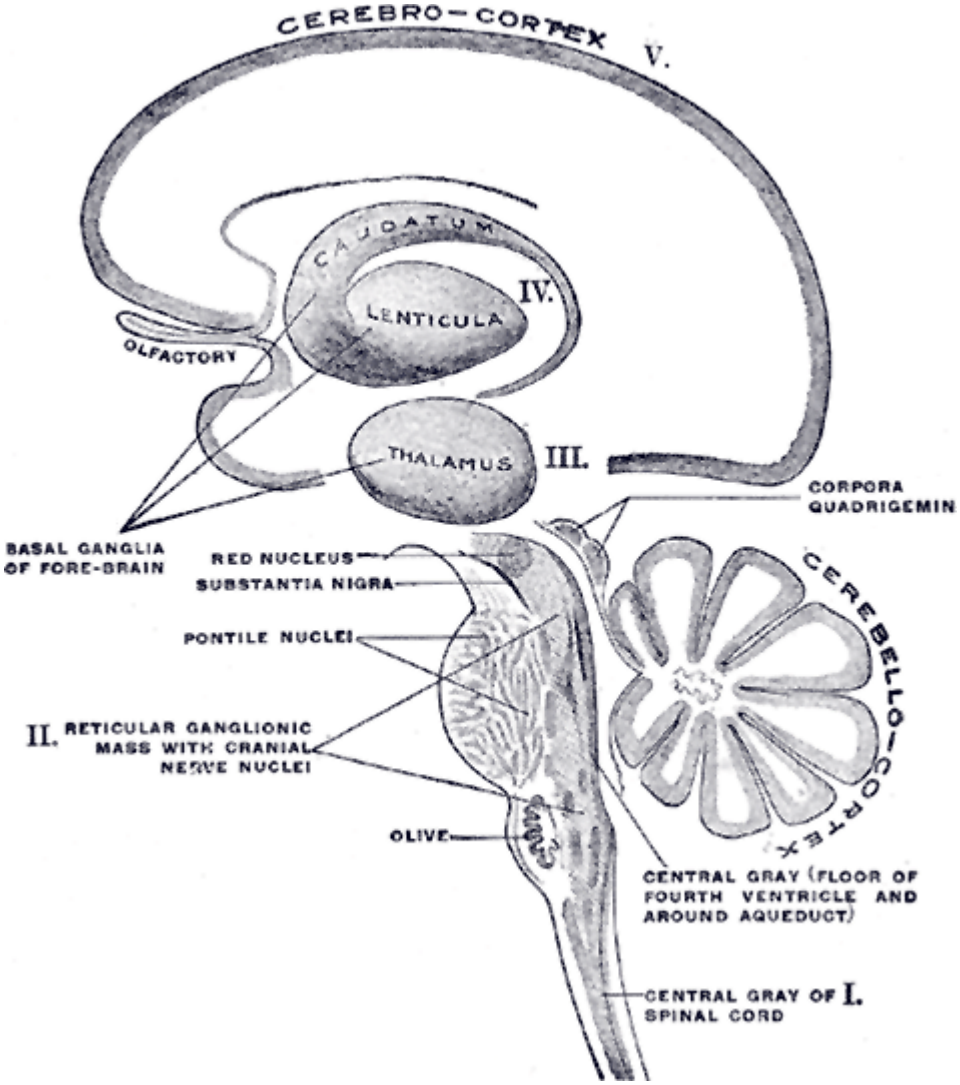
Source: Wikimedia Commons

The addition of bradykinesia as one of the cardinal features led Charcot to suggest a new name honoring James Parkinson's early work. He was the first to call it "Parkinson's disease," rather than shaking palsy or paralysis agitans, arguing that tremor was not always present, nor was paralysis.

Just a few years later, in 1895, Edouard Brissaud, a student of Charcot, became the first researcher to suggest that damage to a part of the midbrain called the **substantia nigra**—so named because it appears darker than neighboring areas—was the cause of Parkinson's disease. Then, in 1912, in a breakthrough that was to have lasting implications, Frederic Lewy identified what he called "spherical neuronal inclusions" on a pathology slide from the brain of a deceased Parkinson's patient. Seven years later Konstantin Tretiakoff, a Russian neuropathologist, named the inclusions *corps de Lewy* or **Lewy bodies** (Kasuga et al., 2012). Further research confirmed Brissaud's observations that the substantia nigra was the main cerebral structure affected in people with Parkinson's disease, but this was not widely accepted until confirmation by further studies published in 1938.



An illustration showing the location of the substantia nigra. Source: veteranshealthlibrary.org.



Schematic representation of the chief ganglionic categories by Henry Gray. Note the location of the basal ganglia above the thalamus and the substantia nigra at the top of the brainstem just below the thalamus. From *Gray's Anatomy*, 1918. Source: courtesy bartleby.com.

The Poskanzer and Schwab Hypothesis

[This section taken largely from Estupinan et al., 2013.]

In the long history of research into the cause of Parkinson's disease, one important hypothesis should be noted. In 1956 two Harvard-based neurologists, David C. Poskanzer and Robert S. Schwab, put forth a bold hypothesis that Parkinson's disease was caused by influenza and that the disease would die out by 1980. Their hypothesis linked influenza infection during the 1918 influenza pandemic with "Parkinsonism."

According to Poskanzer, one of the original inspirations for his hypothesis was derived from a 1956 study that reported Parkinson's disease prevalence shifting toward an older age group when compared to a previous seven-year period. Sixty percent of the older patients interviewed—all but one born before 1927—recollected a history of influenza infection. Poskanzer was struck by the possibility that a viral infection could be the underlying cause of Parkinson's disease.

In 1961, at the Eighty-sixth American Neurological Association meeting held in Atlantic City, New Jersey, Poskanzer and Schwab presented a paper, "Studies in the Epidemiology of Parkinson's Disease Predicting Its Disappearance as a Major Clinical Entity by 1980." Their paper formally presented the hypothesis that Parkinson's disease was caused by previous influenza viral infection. The paper and the hypothesis were both received with skepticism. The hypothesis received public attention in a 1962 *New York Times* article that linked "palsy to virus" and the prediction that some researchers believed "Parkinsonism" would die out in 20 to 40 years.

Bulletin

October 19, 1962 (*The New York Times*). **New Theory Links Palsy to a Virus**; Two Researchers Believe Parkinsonism May Vanish in 20 to 40 Years (By John A. Osmundsen, Special to *The New York Times*)

In 1963 Poskanzer and Schwab published more studies postulating a direct link between viral exposure and Parkinson's disease. The two neurologists reported that the cohorts of Parkinson's patients exposed to influenza during two successive pandemics (1920–1924 and 1955–1959) had the greatest incidence of Parkinson's disease. As a result of these collective observations, the two neurologists asserted that the incidence of Parkinson's disease would dramatically tail off and perhaps even disappear with the death of all influenza sufferers.

Poskanzer was so confident of his theory that, in a 1974 *Time* magazine article entitled "The Parkinson's Puzzle," he famously challenged: "I offer a bottle of scotch to any doctor in the U.S. who can send me a report of a clearly diagnosed case of Parkinson's in a patient born since 1931. So far it's cost me 14 bottles—just 14 of these younger patients identified since 1961."

Although Parkinson's disease is currently defined as an **idiopathic** disease—no specific cause has been identified—influenza may provide the first "hit" that leads to the later development of Parkinson's disease, suggesting a possible mechanism for viral infection in disease manifestation. More important, despite discounting Poskanzer and Schwab's initial hypothesis, the association between virus exposure and Parkinson's disease is still being actively studied (Estupinan et al., 2013).

The Development of Levodopa (L-dopa)

In the first half of the twentieth century, many medical and surgical strategies were used in an attempt to alleviate the tremors and other symptoms associated with Parkinson's. Surgery—such as ablating part of the basal ganglia to reduce tremor—was first tried in 1939 and was improved over the following twenty years. Anesthetic anticholinergic agents (used to reduce nerve impulses to muscles) were the only available drug treatments available for tremors until the discovery and widespread use of levodopa.

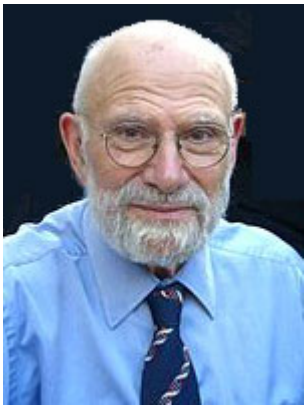
Arvid Carlsson (b. 1923)

Source: nobelprize.org

Dopamine was first identified as an independent neurotransmitter in 1957, a discovery that had a profound impact on the field of neuroscience. The work, by Arvid Carlsson and his colleagues in Sweden, quickly led to the discovery of the first dopamine receptor. The understanding that Parkinson's disease was associated with the depletion of dopamine led to the development of the first drug treatment for Parkinson's disease: L-3,4-dihydroxyphenylalanine (L-dopa, levodopa), which is still used today (Meiser et al., 2013). Carlsson demonstrated that administering L-dopa to animals with parkinsonian symptoms reduced the intensity of their symptoms.

L-dopa entered clinical testing and use in 1968 after a large study reported that people with Parkinson's disease showed significant improvement following treatment with levodopa. Levodopa brought about a true paradigm shift in the management and understanding of PD. Carlsson was awarded the Nobel Prize in 2000 for his work with dopamine.

Oliver Sacks (b. 1933)



Levodopa was famously used by neurologist Oliver Sacks in his patients with encephalitis lethargica (detailed in his 1973 book and later movie, *Awakenings*). Sacks' patients were frozen motionless with post-encephalitic parkinsonism, a form of Parkinson's that causes degeneration of the nerve cells in the substantia nigra and is thought to be viral in origin. Unfortunately, the post encephalitic patients lost the benefits of L-dopa treatment far faster than do patients with Parkinson's disease.

Neurologist and writer Oliver Sacks at the 2009 Brooklyn Book Festival. Copyright © Luigi Novi/Wikimedia Commons.

Alan: Living with Parkinson's

In late 1995 I learned that I might have Parkinson's disease.

Several years earlier, I had noticed some changes in my body when playing first base in the men's softball league. The last game I played, I missed three throws from the shortstop. I didn't just drop the ball—I never even got a glove on it. This hesitation in reaching for the ball may have been my first indication of Parkinson's.

The next thing I noticed is that suddenly I began having extra a's in my news copy when I typed. Then one day I tripped going up the stairs to the restroom at the paper. The tripping became more frequent and began happening when I was just walking across the carpet.

It was at the Chamber's summer mixer in 1995 that I first heard the "P" word. I was talking to a realtor who had previously been a nurse. I told her that I was having some shaking in my left arm. I thought it had something to do with a shoulder injury sustained several years earlier while playing softball.

"Have you ever been checked for Parkinson's?" she asked.

"Isn't that an older person's disease?" I shrugged. I was 47 years old.

Several weeks later, a friend had emergency surgery to remove a brain tumor. After she recovered, I asked her what symptoms had preceded the seizure that sent her to the hospital. She said she had had some minor headaches, but two weeks before the seizure she was putting her makeup on and started drooling from the left side of her mouth. I told her I was experiencing the same things.

"Go get it checked," she echoed the earlier advice.

I made an appointment at the local health center. From the exam my doctor suspected something was going on so he scheduled me for an MRI. I went back to see him several days after the test.

"We scanned your brain and didn't find anything," said the doc.

"Maybe that's why I'm having memory loss—there isn't any brain up there," I quipped.

"No this is a good thing, there are no tumors. But I'm going to send you to a neurologist."

This neurologist turned out to be very thorough, and knowledgeable about Parkinson's.

He tried me on Sinemet and the symptoms went away.

"This is a good thing, right?"

"I'd say you are in the early stages of Parkinson's."

By this time it was February 1996.

Pathophysiology of Parkinson's Disease

Although we are learning more each day about the pathophysiology of Parkinson's disease, it is still considered largely idiopathic (of unknown cause). It likely involves the interaction of host susceptibility and environmental factors. A small percentage of cases are genetically linked and genetic factors are being intensely studied.

Physiologically, the symptoms associated with Parkinson's disease are the result of the loss of a number of neurotransmitters, most notably dopamine. Symptoms worsen over time as more and more of the cells affected by the disease are lost. The course of the disease is highly variable, with some patients exhibiting very few symptoms as they age and others whose symptoms progress rapidly.

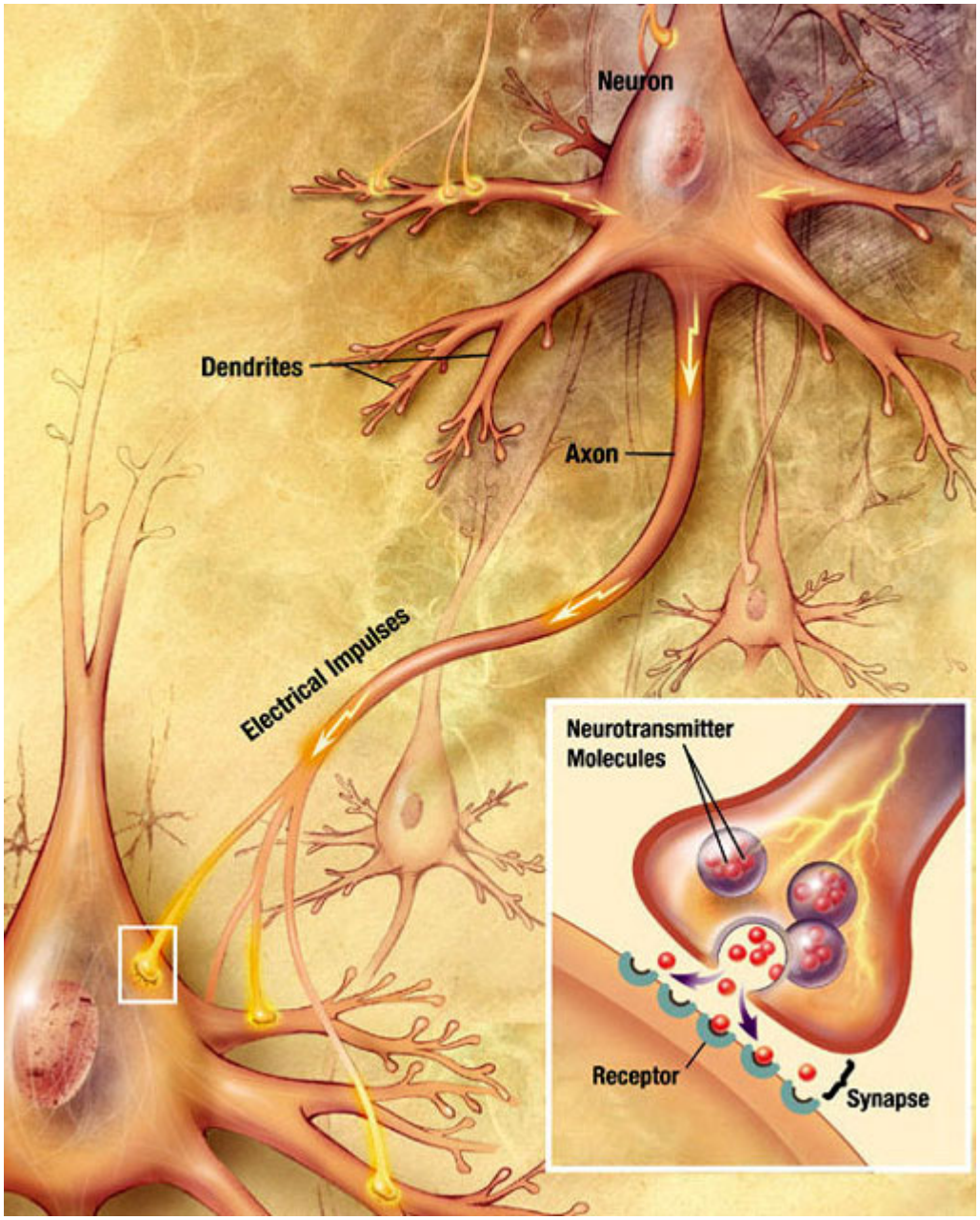
Parkinson's is increasingly seen as a complex neurodegenerative disease with a sequence of progression. There is strong evidence that it first affects the dorsal motor nucleus of the vagus nerve and the olfactory bulbs and nucleus, then the locus coeruleus, and eventually the substantia nigra. Cortical areas of the brain are affected at a later stage. Damage to these various neuronal systems account for the multi-faceted pathophysiologic changes that cause impairments not just to the motor system but also to the cognitive and neuropsychological systems (Kwan & Whitehill, 2011).

The Role of Dopamine

Dopamine, like other neurotransmitters, transmits chemical messages from one nerve cell to another across the **synapse**, a space between the presynaptic cell and the postsynaptic receptor. Dopamine is secreted into the synapse from membrane storage vesicles in the presynaptic membrane. It crosses the synapse and binds to the postsynaptic membrane, where it activates dopamine receptors. Unused dopamine remaining in the synapse is absorbed back into the presynaptic cell; once back in the presynaptic cell, the excess dopamine is repackaged into storage vesicles and released once more into the synapse.

Within the synapse, as dopamine travels from one cell to another, it can be broken down and rendered inactive by two enzymes, MAO (monoamine oxidase) and COMT (catechol-O-methyl transferase). One therapeutic strategy introduces a MAO inhibitor into the synapse, which interrupts the action of the MAO enzyme and prevents the breakdown of dopamine. This allows more dopamine to remain in the synapse and increases the likelihood that it will bind to the postsynaptic membrane.

Chemical Synaptic Transmission

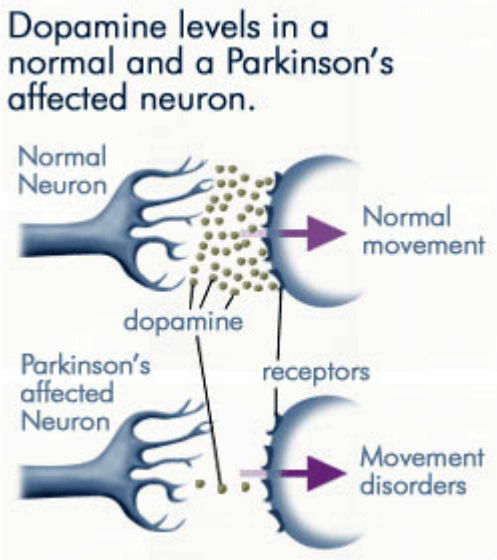


An electrochemical wave called an action potential travels along the axon of a neuron. When the action potential reaches the presynaptic terminal, it provokes the release of a small quantity of neurotransmitter molecules, which bind to chemical receptor molecules located in the membrane of the postsynaptic neuron, on the opposite side of the synaptic cleft. Source: Wikimedia Commons.

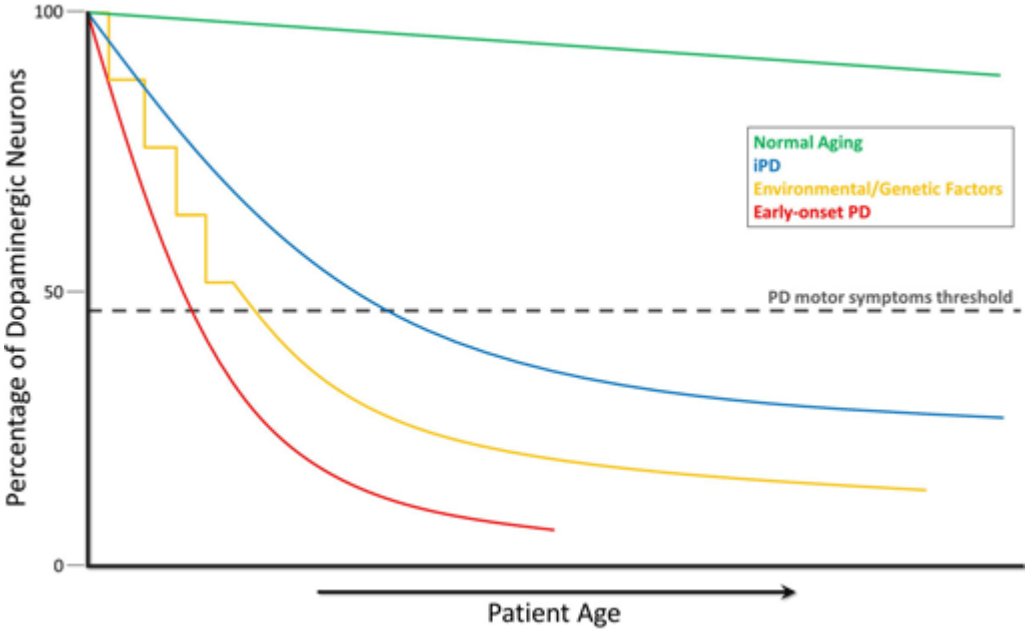
Progressive Loss of Dopamine

Although dopamine cell loss cannot be measured directly, measurements in neurologically normal people and in nonhuman primates reveal a slow progressive loss of dopamine with age. In Parkinson's disease the loss occurs at a much greater rate and both biochemical measures and imaging studies suggest there is a significant decrease in dopamine by the time motor symptoms appear. In this view, Parkinson's disease is an accelerated version of the cell death seen with normal aging (Cookson, 2009). This is illustrated in the graph below, which shows the decline of dopaminergic neurons during normal aging, in idiopathic PD, in PD caused by environmental or genetic factors, and in early-onset PD.

Evolution of Dopamine Depletion in Parkinson's Disease



As less and less dopamine is produced by the neurons affected by Parkinson's disease, far less dopamine is available to bind to the dopamine receptors on the post-synaptic membrane. Source: anti-agingfirewalls.com.



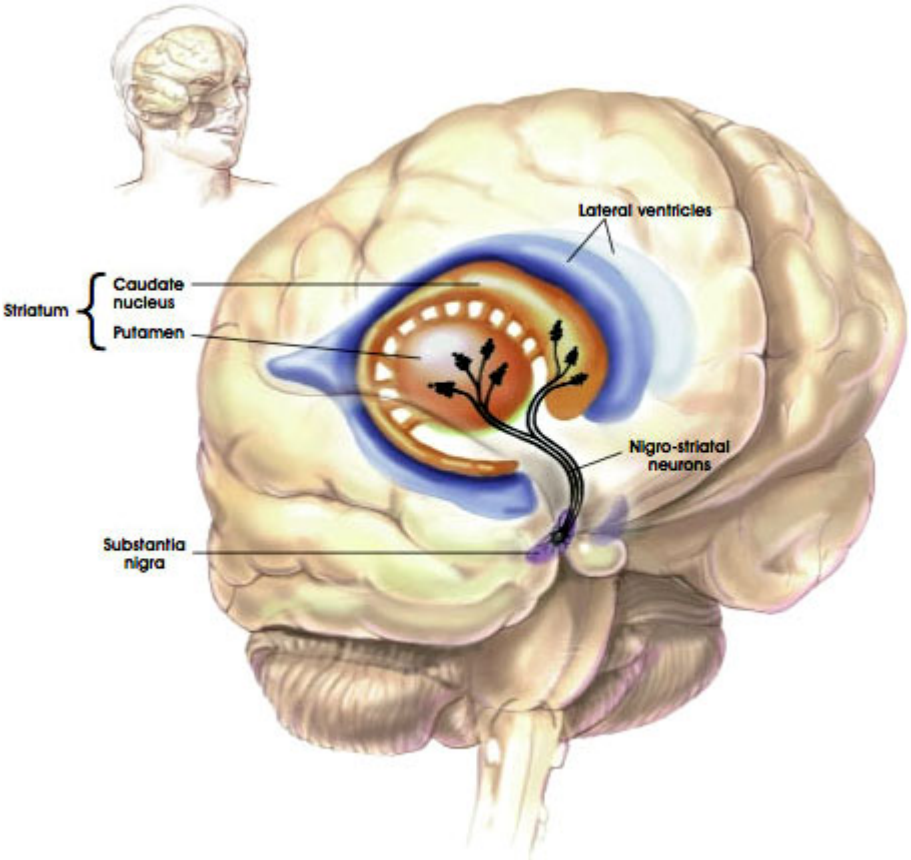
During the course of normal aging (green line), small but slow dopaminergic degeneration occurs without any motor symptoms. Idiopathic PD (IPD, blue line) is of unknown origin but is thought to develop gradually, with a slow degeneration of dopaminergic neurons leading to the classic PD motor symptoms later in life. Another model of dopamine neurodegeneration leading to PD motor symptoms involves repeated exposure to environmental toxicants over time in combination with a genetic predisposition to dopaminergic neuron loss (yellow line). Early-onset PD (red line), as caused by mutations in the PARKIN gene, involves a precipitous decline in dopaminergic neurons, and PD motor symptoms can present decades prior to those in idiopathic PD. One more scenario (not shown) of PD motor symptom development involves possible *in utero* environmental toxicants or genetic factors leading to an atypically low number of dopaminergic neurons at birth and increased susceptibility to PD development (Haas et al., 2012).

Degeneration of dopamine neurons is particularly evident in a part of the substantia nigra called the *pars compacta*. Significantly, the loss of dopamine in the pars compacta increases the overall excitatory drive in the basal ganglia,* disrupting voluntary motor control and causing the characteristic symptoms of PD. Normalization of motor function is seen initially with levodopa treatment (Gasparini et al., 2013).

*The main components of the basal ganglia are the striatum (caudate nucleus and putamen), the globus pallidus, the substantia nigra, the nucleus accumbens, and the subthalamic nucleus.

As the severity of PD increases, the depletion of dopamine leads to further changes in the basal ganglia pathways, including altered function of other basal ganglia neurotransmitters such as glutamate, GABA, and serotonin (Gasparini et al., 2013). Although there is relative vulnerability of dopamine-producing neurons in the substantia nigra, not all dopamine cells are affected in Parkinson's disease; in some parts of the brain the dopamine-producing neurons are relatively spared (Cookson, 2009).

The Nigrostriatal Pathway

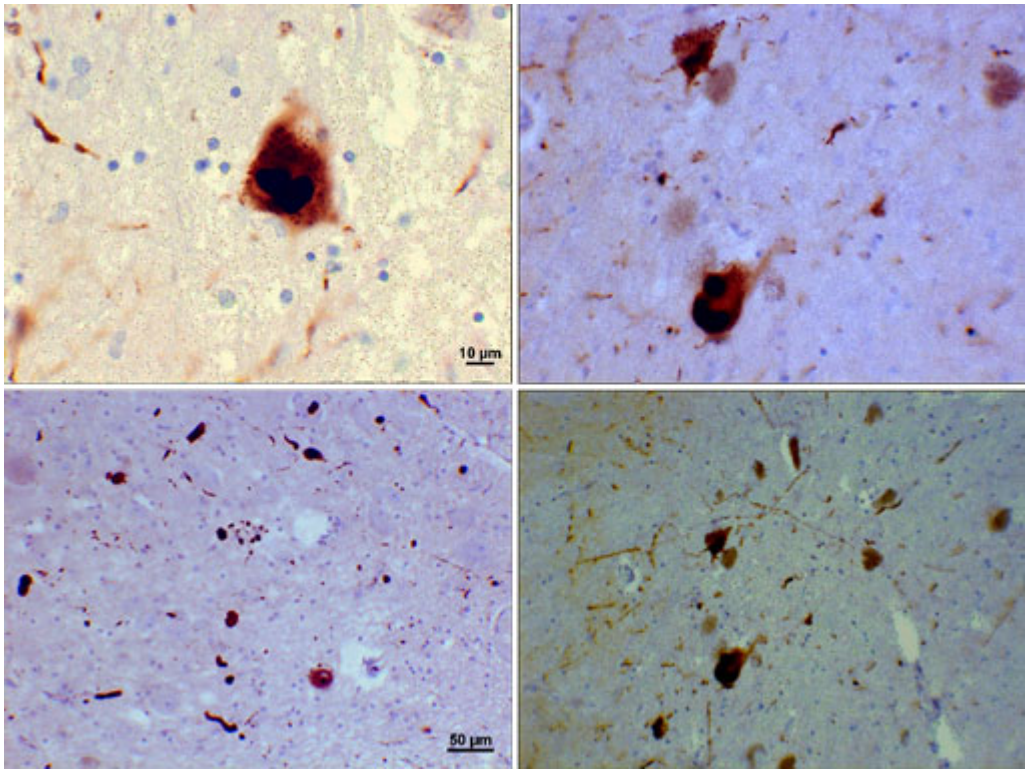


Source: NIH, n.d.

Lewy Bodies and Alpha-Synuclein

Lewy bodies are abnormal aggregates and inclusions of protein that develop inside nerve cells in people with Parkinson's disease. The aggregations usually consist of insoluble fibrillary aggregates containing misfolded proteins. A large number of molecules have been identified in Lewy bodies but a protein called alpha-synuclein is the main component.

Lewy Bodies (Alpha-Synuclein Inclusions)



Photomicrograph of regions of substantia nigra in a Parkinson's patient showing Lewy bodies and Lewy neurites in various magnifications. Top panels show a 60x magnification of the alpha-synuclein intraneuronal inclusions aggregated to form Lewy bodies. The bottom panels are 20× magnification images that show strand-like Lewy neurites and rounded Lewy bodies of various sizes. Images courtesy of Suraj Rajan.

Lewy pathology encompasses many regions of the brain and some reports have suggested that the substantia nigra is **not** the first place where Lewy bodies form in Parkinson's disease. Inclusions and aggregates likely symbolize the end stage of a cascade of complicated events. An earlier stage may be more directly tied up to the pathogenesis of the disorder than the inclusions themselves, which may or may not represent diagnostic hallmarks.

Lewy bodies are also seen in "dementia with Lewy bodies," suggesting that these conditions are related to one another by shared pathology and possibly by shared etiology. Neither cell loss nor the formation of Lewy bodies is absolutely specific for PD but both are required for a diagnosis of PD under current definitions (Cookson, 2009).

Neurodegenerative disorders such as Alzheimer's disease, frontal-temporal degeneration, prion disease, Huntington's chorea, and motoneuron diseases are increasingly being realized to have common cellular and molecular mechanisms, including protein aggregation and inclusion body formation in certain areas of the nervous system (Jellinger, 2011).

Inflammation and Immune Response

The trigger of dopaminergic degeneration seems to be multifactorial—affected by both endogenous and environmental elements. Inflammation and immune responses are increasingly being considered as important mediators of dopaminergic degeneration. Large population studies have suggested that individuals taking nonsteroidal anti-inflammatory drugs (NSAIDs) have less risk of developing idiopathic PD, which suggests that anti-inflammatory drugs may be a promising disease-modifying treatment for parkinsonian patients (Barcia, 2013).

New trial phases have involved anti-inflammatory treatments—specifically looking for an objective biomarker in treatments aimed at reducing inflammatory changes in patients with PD. Researchers are using neuroimaging tools to develop a relevant biomarker with the intention of testing this in large clinical imaging trials. The outcome of these trials will provide data to test and monitor the progression of anti-inflammatory treatments for PD and will help to identify the timely therapeutic window to stop, or at least slow, inflammatory-mediated dopaminergic degeneration (Barcia, 2013).

Parkinsonism

Parkinsonism, also known as "atypical Parkinson's," "secondary Parkinson's," or "Parkinson's syndrome," is a neurologic syndrome in which a patient exhibits some of the symptoms associated with Parkinson's disease—tremor, rigidity, bradykinesia, and postural instability. But **parkinsonism is not Parkinson's disease.** Parkinsonism is not thought to be caused by Parkinson's disease and patients typically respond poorly to pharmacologic intervention. Parkinsonism often has an identifiable cause, such as exposure to toxins, methamphetamine, trauma, multiple strokes, other nervous system disorders, or illness. Generally, Lewy bodies are not seen in parkinsonism.

The term *parkinsonism* is also associated with disorders such as progressive supranuclear palsy, multiple system atrophy, Lewy body dementia, corticobasal degeneration, vascular parkinsonism, drug-induced parkinsonism, and parkinsonism secondary to infection and other causes (Hohler et al., 2012). A form of reversible parkinsonism can occur from the use of certain neuroleptic drugs, particularly reserpine, antipsychotics (haloperidol), and metoclopramide. Exposure to certain toxins, severe carbon monoxide poisoning, and mercury poisoning can also lead to parkinsonism.

The appearance in the early 1980s of parkinsonism symptoms in a group of drug addicts who had consumed a contaminated batch of a synthetic opiate led to the discovery of the chemical MPTP as an agent that causes parkinsonism syndrome in nonhuman primates as well as in humans. MPTP can be produced when making a form of heroin (MPTP is converted to a neurotoxin that selectively destroys dopamine cells in the substantia nigra). These cases are rare and have mostly affected long-term drug users.

Methamphetamine abuse has also been linked to parkinsonism. In experimental animals, exposure to methamphetamine damages dopaminergic fibers in the striatum* as well as the cell bodies in the substantia nigra, echoing the degeneration observed in human patients with PD. Selective damage to dopaminergic terminals in the striatum has also been observed in human methamphetamine users, although there is no evidence so far that methamphetamine abuse damages dopaminergic cell bodies in the substantia nigra (Granado et al., 2013).

*The largest nucleus of the basal ganglia, the striatum consists of the caudate nucleus and the putamen.

It has been hypothesized that methamphetamine use may predispose users to future development of PD. This hypothesis has been supported by recent epidemiologic work indicating that methamphetamine users have an increased risk of developing PD. This is consistent with the persistent neurotoxic effects of methamphetamine in experimental animals (Granado et al., 2013).

Patients with parkinsonism are often difficult to manage as outpatients. The complexity of their symptoms, the added cognitive and autonomic deficits, the poor response to most PD medications, and the relatively rapid decline in status contribute to the challenges in managing these patients, particularly as the disease progresses (Hohler et al., 2012).

Genetic Factors in Parkinson’s Disease

For many years, it was thought that most forms of Parkinson’s disease did not have a genetic basis. But by the late 1990s, studies in a number of 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. As genome technologies have become more cost-effective and precise, genetic linkage maps have improved dramatically, allowing more research into the genetic cause of disease. Entire genome sequence analyses are now being completed on individual patients at a reasonable and ever-dropping price.

There are a small number of genes that are known to be involved in up to 6% of total PD cases, and there are probably other genes that increase the potential risk of Parkinson's, without necessarily causing it. Up to 15% of PD patients have a direct family member who has also had PD.

PARK Family of Genes

A **gene family** is a group of genes that share important characteristics. The PARK gene family has been of particular interest and is the focus of widespread research. Mutations in PARK genes affect the function and survival of nerve cells critical for normal movement, balance, and coordination (NIH, 2013a).

Mutations in three known genes (SNCA, UCHL 1, and LRRK 2) have been reported in families with **dominant** inheritance. Mutations in three other genes (PARK 2, PARK 7, and PINK 1) have been found in affected individuals who had siblings with the condition but whose parents did not have Parkinson's disease (**recessive** inheritance). There is some evidence to suggest that these genes are also involved in early-onset Parkinson's disease (diagnosed before the age of 30) or in dominantly inherited Parkinson's disease but it is too early to be certain (genome.gov, 2011).

The following table lists the genes in the PARK family with their approved symbol in the first column and their previous names in the middle column. The approved symbols are used in this section of the course.

Genes in the PARK Family		
Approved Symbol	Previous Name	Comments
SNCA	PARK 1, PARK 4	Provides instructions for making alpha-synuclein.
PARK 2 (parkin)	---	Provides instructions for making a protein called parkin.
PARK 3	---	---
UCHL 1	PARK 5	Provides instructions for making an enzyme called ubiquitin carboxyl-terminal esterase L1, which is probably involved in the cell machinery that breaks down unneeded proteins.
PINK 1	PARK 6	Provides instructions for making a protein called PTEN induced putative kinase 1. Appears to help protect mitochondria from malfunctioning during periods of cellular stress, such as unusually high energy demands.
PARK 7	---	Provides instructions for making the DJ-1 protein. One of the protein's functions may be to help protect cells, particularly brain cells, from oxidative stress.
LRRK 2	PARK 8	The LRRK 2 gene provides instructions for making a protein called dardarin.
ATP13A2	PARK 9	May play a role in intracellular cation homeostasis and the maintenance of neuronal integrity.
PARK 10	---	---
PARK 11	---	---
PARK 12	---	---
HTRA2	PRSS25	Also known as PARK 13
PLA2G6	---	Provides instructions for making a type of enzyme called an A2 phospholipase. This type of enzyme is involved in metabolizing fats called phospholipids.

Genes in the PARK Family		
Approved Symbol	Previous Name	Comments
FBXO7	---	Also known as PARK 15
PARK16	---	---
VPS35	---	Also known as PARK 17
EIF4G1	EIF4G, EIF4F	Also known as PARK 18

Source: National Institutes of Health, 2013.

Dominant Genes in PD

Mutations in a group of genes that encode alpha-synuclein and LRRK 2 are transmitted in a **dominant** fashion and generally lead to Lewy body pathology, with alpha-synuclein being the major component of these pathologic protein aggregates (Greggio et al., 2011). Although genetic tests can test for the presence of the LRRK 2 mutation, they cannot be used to make a definitive diagnosis of PD.

SNCA

The discovery of mutations in the SNCA gene was the first evidence of a genetic cause for PD. This gene encodes the protein alpha-synuclein, the main component of Lewy bodies and the noted pathology marker in autopsy slides of PD brains. Mutations of the SNCA gene, including nucleotide changes, and duplications, triplications, and extra copies of the SNCA gene, account for about 2% of familial cases, though not all persons with these changes have developed PD. The mean age of onset in individuals with mutations in this gene is 46 years (Greggio et al., 2011).

Recent studies have demonstrated that alpha-synuclein regulates the release of neurotransmitters at the presynaptic terminal. In addition, alpha-synuclein seems to modulate intracellular dopamine concentration through interactions with proteins that regulate dopamine synthesis and uptake (Greggio et al., 2011).

LRRK 2 (PARK8)

The LRRK 2 gene (formerly PARK8) is a signaling protein that becomes toxic when it mutates (Greggio et al., 2011). The LRRK 2 gene encodes for a protein called **dardarin**. One segment of the dardarin protein contains a large amount of an amino acid called leucine. Proteins with leucine-rich regions appear to play a role in activities that require interactions with other proteins, such as transmitting signals or helping to assemble the cell's structural cytoskeleton. Other parts of the dardarin protein are thought to be involved in protein-to-protein interactions (NIH, 2013a).

Nearly a dozen different mutations have been reported in the LRRK 2 gene. Mutations in LRRK 2 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, one of the two noted co-founders 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, Genia Brin, carrying the same mutation, was diagnosed with PD in 1998 at the age of 50.

Recessive Genes in PD

Mutations in PARK2 (parkin), PINK1 (PARK 6), and DJ-1 (PARK7) cause recessive Parkinson's, with a variable pathology often lacking the characteristic Lewy bodies in the surviving neurons. Intriguingly, recent findings highlight the role of these genes in mitochondria function, suggesting a common molecular pathway for recessive Parkinson's (Greggio et al., 2011).

PARK2 (Parkin)

The PARK2 gene, one of the largest human genes, provides instructions for making a protein called **parkin**, which plays a role in the breakdown of unneeded proteins. It does this by tagging damaged and excess proteins with molecules called **ubiquitin**. Ubiquitin serves as a signal to move unneeded proteins into specialized cell structures known as **proteasomes**, where the proteins are degraded (NIH, 2013a).

The ubiquitin-proteasome system acts as the cell's quality control by disposing of damaged, misshapen, and excess proteins. This system also regulates the availability of proteins that are involved in several critical cell activities, such as the timing of cell division and growth. Because of its activity in the ubiquitin-proteasome system, parkin belongs to a group of proteins called **E3 ubiquitin ligases** (NIH, 2013a).

Parkin also appears to be involved in the maintenance of mitochondria, the energy-producing centers in cells. Genetic and cell biologic work in the last decade have uncovered essential roles of parkin and PINK1 in mitochondrial quality control. PINK1 senses damaged mitochondria and recruits and activates parkin to degrade and recycle damaged mitochondria. Much evidence suggests that defects in this pathway may cause PD (Wauer & Komander, 2013).

A great deal of research has focused on the Parkin gene. In early 2013, in a significant breakthrough, the crystal structure of parkin was identified, providing new insight into the function of this important gene. According to Jennifer Johnson, one of the researchers involved with the discovery of the crystal structure of parkin, "The crystal structure acts as a sort of blueprint for parkin's function. Scientists can see exactly how it works, and then begin to develop compounds to target areas of dysfunction, and then better see if compounds applied to trouble areas are making a difference" (MJFF, 2013).

Studies of the structure and activity of parkin have led researchers to propose several additional roles for this protein. Parkin may act as a tumor suppressor protein, which means it prevents cells from growing and dividing too rapidly or in an uncontrolled way. Parkin may also regulate the supply and release of synaptic vesicles from nerve cells.

The parkin type of juvenile-onset Parkinson's disease, originally described in Japan, is characterized by typical Parkinson's disease features with onset between age 20 and 40 years. Disease progression is slow and lower-limb dystonia is often present, which causes muscles to contract and spasm involuntarily. Sustained response to levodopa is observed, as well as early, often severe dopa-induced complications (e.g., fluctuations, dyskinesias).

PINK1 (PARK6)

More than seventy mutations that can cause Parkinson's disease have been found in the PINK1 (PARK6) gene. Interestingly, when fruit flies carrying PINK1 mutations were given vitamin K2, the energy production in their mitochondria was partly restored and the insects' ability to generate energy to fly was improved. Researchers have been 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 adenosine triphosphate (ATP) and energy production for flight. Vitamin K2 plays a role in the energy production of defective mitochondria. Because defective mitochondria are also found in some Parkinson's patients, vitamin K2 potentially offers hope for a new treatment for Parkinson's (NIH, 2013a).

DJ-1 (Park7)

The PARK7 gene provides instructions for making the DJ-1 protein. This protein is found in many tissues and organs, including the brain. One of the protein's functions may be to help protect cells, particularly brain cells, from oxidative stress. Oxidative stress occurs when unstable molecules called free radicals accumulate to levels that can damage or kill cells. Additionally, the DJ-1 protein may serve as a chaperone molecule that helps fold newly produced proteins into the proper three-dimensional shape as well as helping refold damaged proteins (NIH, 2013a).

The DJ-1 protein may also assist in delivering selected proteins to proteasomes, which are structures within cells that break down unneeded molecules. Researchers suggest that the DJ-1 protein may also play a role in activities that produce and process RNA, a chemical cousin of DNA (NIH, 2013a).

Genetic Testing

The term **genetic testing** covers an array of techniques including analysis of human DNA, RNA, and protein. Genetic tests are used to detect gene variants associated with a specific disease or condition, as well as for nonclinical uses such as paternity testing and forensics. In the clinical setting, genetic tests can be performed to:

- Confirm a suspected diagnosis
- Predict the possibility of future illness
- Detect the presence of a carrier state in unaffected individuals (whose children may be at risk)
- Predict response to therapy

Genetic tests are also performed to screen fetuses, newborns, or embryos used in *in vitro* fertilization for genetic defects (NHGRI, 2013).

Genetic testing has recently become available for the parkin and PINK1 genes. But because parkin is such a large gene, testing is difficult. At the current stage of understanding, testing is likely to give a meaningful result only for people who develop the condition before the age of 30 years (NHGRI, 2011).

PINK1 appears to be a rare cause of inherited Parkinson's disease. About 2% of those developing the condition at an early age appear to carry mutations in the PINK1 gene. Genetic testing for the DJ-1 (PARK7), SNCA and LRRK2 genes is also available (NHGRI, 2011).

Individuals and families who are interested in genetic testing can learn more about their risk for Parkinson's disease and the availability and accuracy of genetic testing by contacting a genetics specialist. Genetics professionals provide information and support to individuals or families who have genetic disorders or who may be at risk for inherited conditions, and can discuss the risks, benefits, and limitations of available genetic testing for Parkinson's disease (NHGRI, 2011).

Gene Therapy

Gene therapy is "the use of genes as medicine" involving the transfer of a therapeutic or working copy of a gene into specific cells in order to repair a faulty gene or to give the cell a new function (Centre for Genetics Education, 2012). The most effective vector or carrier of a therapeutic gene is a very small virus that does not cause inflammation or an immune response.

Before a therapeutic gene can be inserted into a patient, the gene's viral genetic material is removed and replaced with the therapeutic gene. The altered virus is then injected into a specific part of the brain where it deposits its genetic material. Once in the brain, it infects the target cells and releases its gene (Aminoff, 2010).

In Parkinson's disease, which is related to the deficiency of dopamine and treated with an oral medication, injecting a gene into a discrete area of the brain may allow the cells in that area to produce more of the missing neurotransmitter. Gene therapy has two advantages over oral medications:

1. It reduces side effects associated with dopamine replacement, which when taken orally stimulates dopamine receptors all over the brain, leading to unwanted side effects.
2. It has the potential to provide a steady supply of the missing neurotransmitter, an improvement over an oral tablet, whose levels increase when the medication is taken and then decrease as the medication wears off (Aminoff, 2010).

Surgical Insertion of Inhibitory Neurotransmitters

In PD, it has been long observed that the subthalamic nucleus—the part of the brain targeted by deep brain stimulation, is overactive. This has become the focus of a gene therapy study at the University of California at San Francisco (UCSF), in which an inhibitory neurotransmitter is surgically inserted into the subthalamic nucleus to calm the activity in that area of the brain. This UCSF gene study was first done in experimental animals and then in a small group of PD patients in a phase 1 trial (safety study). Results were encouraging and participants showed significant improvement, which was maintained for a year. Although it appeared the treatment had helped, critics claimed that the improvement was due to a placebo effect. The study did, however, show that gene therapy was feasible and safe (Aminoff, 2010).

AADC Enzyme: Converting Levodopa to Dopamine

Other gene therapy trials have focused on an enzyme that converts levodopa to dopamine. Researchers have known that the effectiveness of dopamine-replacement diminishes after several years—not because the medication no longer works but because the substantia nigra is slowly losing its ability to make the enzyme that converts levodopa to dopamine. In a gene therapy study at UCSF (the second gene therapy study ever done for patients with Parkinson's disease), researchers focused on an enzyme called aromatic acid decarboxylase (AADC), an enzyme that converts levodopa to dopamine.

This AADC study sought to restore the brain's ability to convert levodopa to dopamine by inserting a gene containing the AADC enzyme into a virus, then injecting the virus into the brain of study participants. This was done in 10 patients with fairly severe PD who were good candidates for deep brain stimulation but elected instead to participate in the AADC clinical trial. Researchers used various scales to measure response to treatment, including the United Parkinson's Disease Rating Scale (UPDRS), which showed approximately 30% improvement at 6 months. There was also an improvement in medication fluctuations—improved "on" times and reduced "off" times. Enzyme activity also appeared to increase (Aminoff, 2010).

Neurturin Gene Therapy

A third gene therapy technique using neurturin hopes to "rescue" sick dopaminergic nerve cells by injecting a growth/trophic factor. The goal is to help damaged nerve cells repair themselves. In this gene therapy study, the viral genes were removed and the genes to make neurturin were inserted. The altered virus was then injected into the brains of study participants. The phase 1 study involved 12 patients who were followed for 1 year. Over the course of a year their UPDRS showed significant improvement. Although the phase 1 trial seemed to improve the patient's symptoms, researchers were unable to replicate the positive results in a larger, phase 2 study (Aminoff, 2010).

Parkinson's Biomarkers and Rating Scales

Recall that in James Parkinson's 1817 *Essays on the Shaking Palsy* he made the following observation:

> So slight and nearly imperceptible are the first inroads of this malady, and so extremely slow is its progress, that it rarely happens that the patient can form any recollection of the precise period of its commencement.

New research is shedding light on what James Parkinson's called "the precise period of its commencement." In this emerging field of study, the classic clinical symptoms of PD are increasingly thought to be preceded by a wide variety of symptoms that may manifest years before the onset of motor symptoms and may serve as possible "premotor" or "preclinical" biomarkers for PD.

Biomarkers for PD

Biomarkers are biologic indicators of disease or therapeutic effects that can be measured by *in vivo* biomedical or molecular imaging as well as laboratory methods (Clarke, 2006). Biomarkers can include changes in body chemistry or physiology or changes in genes and how they are regulated. Even subtle changes in a persons behavior may be a biomarker. Currently, there are no proven biomarkers for Parkinson's disease. Biomarkers are used, however, in the successful detection of many other diseases (NIH, 2013b).

Finding a biomarker that aids in the early detection of PD may provide information about the cause of PD and its progression, and lead to treatments that delay the progression of the disease. As with any biomarker, one for PD must be **specific** for Parkinson's disease and **sensitive** to every person who has the disease. A good PD biomarker should identify someone who is beginning to undergo metabolic changes associated with PD before substantial injury has occurred. It should measure disease activity and progression and assist in determining the benefit of treatments and neuroprotective therapies (Christine, 2011a).

The range of potential biomarkers for Parkinson's is vast, and there have been some promising leads. For example, researchers are investigating the use of noninvasive imaging to detect changes in brain function or brain biochemistry. This is a promising area for research because several studies have tentatively linked PD with changes in proteins or other molecules in blood, urine, or the cerebrospinal fluid (NIH, 2013b).

There is a pressing need for an accurate, relatively noninvasive, and affordable PD diagnostic test or biomarker. This is particularly true given widespread recognition that early detection and early treatment helps to slow the progression of the disease, minimize symptoms, and improve the patient's overall quality of life. Currently, there is no one imaging technique or test that can provide a conclusive primary diagnosis of PD. There are also no laboratory tests utilizing blood, cerebrospinal fluid, or urine samples that have proven to be effective in primary diagnosis or confirmation of PD (Han et al., 2012).

Imaging Biomarkers

Functional imaging techniques such as positron emission tomography (PET) and single photon computed emission tomography (SPECT) can support the diagnosis of PD 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.

Current imaging techniques are used mostly to exclude other diseases, such as basal ganglia tumors, vascular pathology, and hydrocephalus. A specific technique, **diffusion MRI**, has been reported to be useful at discriminating between typical and atypical Parkinson's, although its exact diagnostic value is still under investigation.

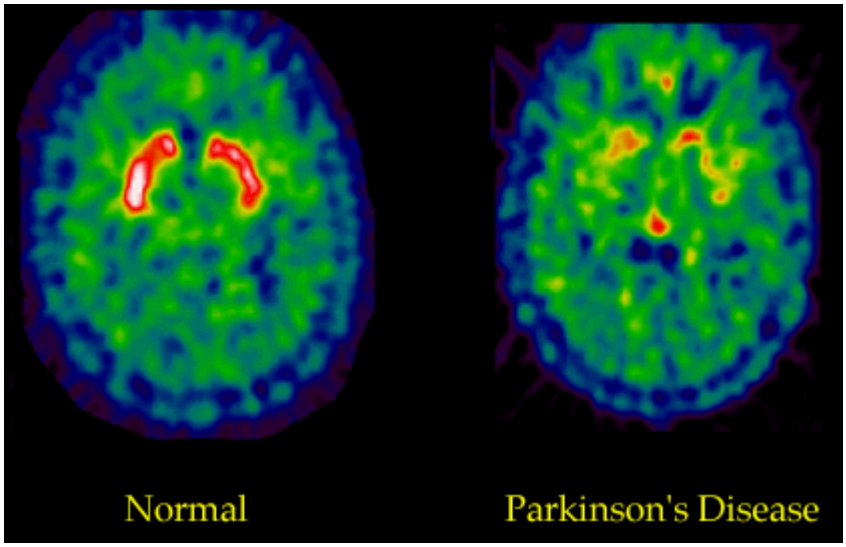
Two widely-used imaging techniques, fluorodopa PET and DaTSCAN focus on dopamine, using radiotracers to measure dopamine function in the basal ganglia. Unfortunately, dopamine biomarkers only detect changes in dopamine after the disease is well established. A substantial fraction of patients with early idiopathic Parkinson's disease have normal scans, and the costs and use of intravenous radioactive tracers are seen as important disadvantages of this technique (Bouwmans et al., 2013). In addition to these two types of scans, transcranial sonography is showing promise as a diagnostic tool.

Fluorodopa PET Scan

Fluorodopa (FDOPA) is a fluorinated form of L-dopa that is synthesized for use as a radiotracer in PET scans. Current studies employing the use of FDOPA PET scanning have focused on analyzing the efficiency of neurons in the striatum that utilize dopamine. This test is useful in distinguishing PD from other types of neurodegeneration.

The pictures below are examples of a PET scan that has utilized fluorodopa as a radiotracer. The bright orange areas in the scan on the left show a robust uptake of fluorodopa in the striatum—indicating normal dopamine function. The image on the right shows much less uptake of the fluorodopa, indicating a significant loss of dopamine receptors in a person with PD.

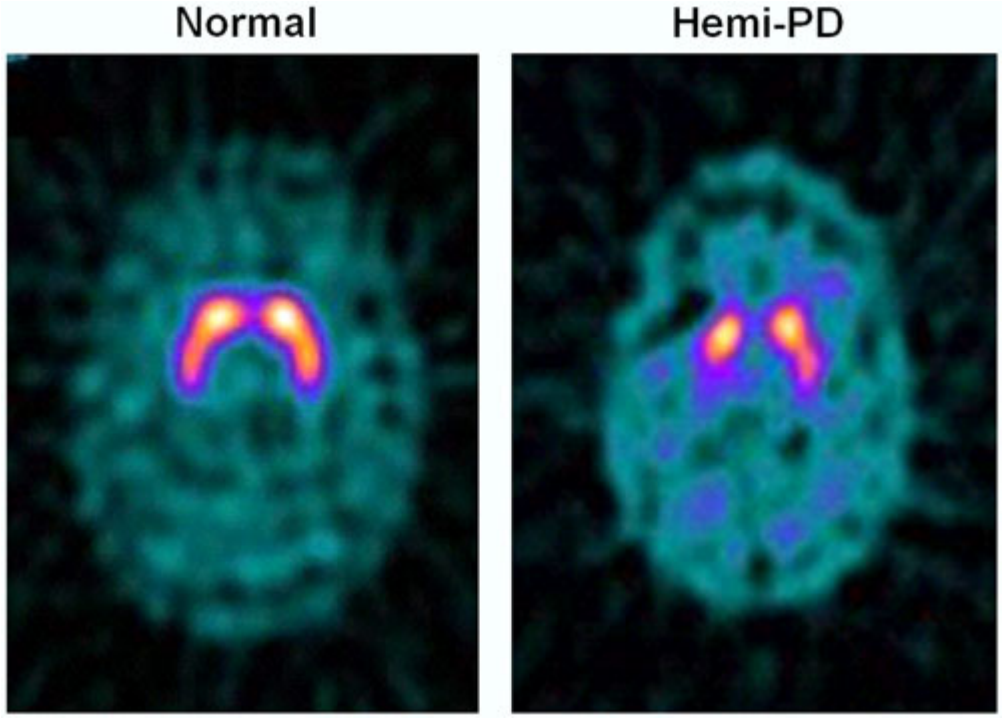
Fluorodopa PET Scan



DaTSCAN

DaT (dopamine transporter) imaging scans look at the function of presynaptic dopamine transporters. The DaTSCAN technique has the potential to predict the course of the disease by measuring the number of dopamine transporters when compared to normal levels at an early point of PD. This may be predictive of how advanced the disease will be in five years. Generally a pattern of reduced dopaminergic activity in the basal ganglia can aid in diagnosing PD (Cummings, 2011).

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.

Transcranial Sonography

The search for a cheap and patient-friendly technique to diagnose PD has continued, and over the past ten years transcranial sonography of the substantia nigra has emerged as a promising tool. Numerous ultrasound studies have found that a significant percentage of patients with idiopathic PD have a typical enlarged area in the substantia nigra, which is thought to be associated with increased iron concentrations (Boewmans, 2013).

Among the new techniques, transcranial B-mode duplex sonography has been drawing a lot of attention as an easily accessible and inexpensive imaging method. Transcranial sonography shares some features of the functional imaging methods, which is thought to detect very early dysfunction of the nigrostriatal pathways. This probably demonstrates an increased vulnerability of the extrapyramidal system, or even an increased risk of PD development (Laučkaitė, et al., 2012).

Hyperechogenicity* of the substantia nigra, both in echo intensity and size of area, has been repeatedly reported as a characteristic transcranial sonography finding in PD patients. It can be also detected in some other neurodegenerative and even in non-neurodegenerative disorders, or just related to aging. Therefore, the issue regarding sensitivity and specificity of transcranial sonography is still disputable. While many studies have estimated specificity of transcranial sonography comparing PD patients to healthy controls or essential tremor group, to date very few case control studies involved patients with atypical Parkinson's syndromes, neurodegenerative hereditary, or secondary Parkinson's (Laučkaitė, et al., 2012).

*Hyperechogenicity is an increased response (echo) during the ultrasound examination of an organ, usually as a result of fatty deposits.

Transcranial sonography has also shown brainstem abnormalities in approximately 90% of patients with PD but the size of the abnormality does not correlate with disease severity and does not change over five years despite progression of symptoms (Christine, 2011a).

Genetic Biomarkers

Genetic testing can identify a trait or susceptibility for Parkinson's disease but it is not used to determine the presence or progression of the disease. The presence of a certain gene does not definitively indicate that PD will develop. Genetic tests can be used to test for the presence of certain gene mutations but cannot be used to make a diagnosis of PD because the presence of the gene is not definitive. Recessive gene testing provides information but is not ideal for biomarkers because the onset and progression of the disease is so slow (Christine, 2011a).

Alpha-Synuclein Biomarkers

The alpha-synuclein protein is a major component of Lewy bodies and its accumulation likely precedes a diagnosis of PD by many years. The ability to identify a biomarker for the presence of alpha-synuclein is the subject of intense research.

One technique uses a molecular probe based on the metallic element *ruthenium* to look inside living cells in tissue culture and see the insoluble fibrillar deposits associated with Parkinson's disease. In tests using live neuroglioma cells, the color probe binds to misfolded alpha-synuclein proteins that clump together and form Lewy bodies. The ruthenium complex lights 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 (Cook, 2012).

It is hoped that a molecular detector can be used to monitor the formation of aggregates inside live cells while screening for drugs that break up fibrils or prevent them from forming. The ruthenium complex itself has no therapeutic benefit at this time (Cook, 2012).

Abnormal alpha-synuclein aggregation may begin in the peripheral nervous system, possibly in the nerves of the gastrointestinal submucosa many years before motor symptoms appear. In one study, colon tissue extracted during a colonoscopy was analyzed in patients in the early stages of PD but who had not been treated for PD. Tissue samples showed that 9 out of 10 had alpha-synuclein inclusions in the tissue (Christine, 2011a).

A vaccine that primes the human immune system to destroy alpha-synuclein has entered clinical trials in humans. Considered a **disease-modification strategy** (as opposed to symptomatic treatment), the two-year study involves four injections intended to stimulate an immune system response to alpha-synuclein. Removing alpha-synuclein may have the potential to modify the course of the disease.

Screening for Biomarkers

Screening for biomarkers employs techniques that look for patterns of variation in genes, proteins, and small molecules using a biologic sample such as saliva, blood, urine, or spinal fluid. The Michael J. Fox Foundation is using these techniques in an ongoing study of biomarkers called the Parkinson's Progression Markers Initiative (PPMI). They are looking at movement, cognitive, and brain biomarkers in addition to blood, urine, DNA, and spinal fluid sampling in 400 newly diagnosed PD patients over a 3- to 5-year period (Christine, 2011a).

Rating Scales for PD

In clinical practice the diagnosis of idiopathic Parkinson's disease, delineating it from the atypical parkinsonism, vascular parkinsonism, drug-induced parkinsonism, essential tremor, other neurodegenerative and movement disorders is still difficult. Especially in the early stage of these diseases, a large group of patients is erroneously diagnosed, even by experienced movement disorder specialists, when compared to postmortem findings (Bouwmans et al., 2013).

Parkinson's disease is clinically classified according to the age of onset. If symptoms begin after age 50 it is usually referred to as late-onset disease. The condition is described as early-onset disease if signs and symptoms begin before age 50. Cases that begin before the age of 20 are sometimes referred to as juvenile-onset Parkinson's disease. The late-onset form is the most common type of Parkinson's disease, and the risk of developing it increases with age.

There are several rating scales used to determine the presence of Parkinson's disease, assess its severity, and monitor its progression. One of the most commonly used is the Unified Parkinson's Disease Rating Scale (UPDRS), which was first developed in 1987 and is used extensively throughout the world. The International Classification of Functioning, Disability, and Health (ICF) is another rating scale that looks at body structure and function, activity and participation, and environment. The Hoehn and Yahr scale, in use since it was developed in 1967, is also widely used to describe how symptoms progress. The Hoehn and Yahr Rating Scale measured progression of the disease but has been largely replaced by the UPDRS. The Schwab and England ADL scale is used to determine levels of independence.

Unified Parkinson's Disease Rating Scale

Currently the Unified Parkinson's Disease Rating Scale (UPDRS) and its most recent version, the MDS-UPDRS, are considered the gold standards for determining the severity and progression of Parkinson's disease. However, the UPDRS focuses primarily on measuring impairments associated with PD, with fewer items addressing specific functional limitations or perceptions of quality of life. The MDS-UPDRS is divided into four main areas: (I) non-motor experiences of daily living, (II) motor experiences of daily living, (III) motor examination, and (IV) motor complications (Dibble et al., 2012).

The motor examination section (part III) of the UPDRS is the most widely used measure to assess motor symptoms and signs in PD; it is the only part of the UPDRS scored by the healthcare provider rather than by patient self-report. However, examining motor abnormalities may not reveal the beneficial effects of treatments that target certain motor components or enable identification of subsets of patients with different motor profiles and prognoses (Vassar et al., 2012).

Because the UPDRS is organized according to motor and non-motor aspects of PD, it has limited focus on the assessment of disability. As a result, PD is commonly understood more in terms of **disease progression** (ie, the predictable evolution of signs, symptoms, and impairments) rather than in terms of the potentially diverse paths through which persons with PD becomes disabled (Dibble et al., 2012).

International Classification of Functioning, Disability, and Health (ICF)

In contrast to the UPDRS, the International Classification of Functioning, Disability, and Health (ICF) was developed to provide an underlying framework for understanding the consequences of a disease from body, individual, and societal perspectives. The effects of a disease are considered across three domains of human function: (1) body structure and function, (2) activity and participation, and (3) environmental factors.

In the ICF, *disability* is used to denote a decrement at each level (ie, a body structure or functional impairment, an activity limitation, a participation restriction). Underscoring the value of this approach, the World Health Organization (WHO) endorsed the use of the ICF in 2001 as the international standard to describe and measure health and disability (Dibble et al., 2010).

The ICF puts the notions of "health" and "disability" in a new light. It acknowledges that every human being may experience a decrement in health and thereby some degree of disability; that is, disability is not something that only happens to the few. The ICF "mainstreams" the experience of disability and recognizes it as a universal human experience.

By shifting the focus from cause to impact, the ICF places all health conditions on an equal footing, allowing them to be compared using a common metric—the ruler of health and disability. Furthermore, ICF takes into account the social aspects of disability and does not see disability only as a medical or biologic dysfunction. By including environmental factors to provide context, the ICF examines the impact of the environment on the person's functioning (WHO, 2013).

Body Structure and Function

Body structure, in ICF terms, is defined as an anatomical part of the body, such as organs, limbs and their components, while **body function** is defined as the physiologic function of body systems. Applied to PD, motor signs such as bradykinesia, tremor, and rigidity represent impairments in body structure and body function (Dibble et al., 2010).

Impairments in body structure and body function are rated using a scale, which describes the extent of impairment from no impairment (no problems) to complete impairment (problem is present more than 95% of the time, with an intensity that is totally disrupting the persons day-to-day life and happened every day over the last 30 days).

Body structure includes:

- The nervous system
- Eyes, ears, and related structures
- Structures involved with voice and speech
- Structures of the cardiovascular, immunologic, and respiratory systems
- Structures related to the digestive, metabolic, and endocrine systems
- The genitourinary and reproductive systems
- Structures related to movement
- Skin and related structures
- Any other body structures

Body function includes:

- Mental functions
- Sensory functions and pain
- Voice and speech functions
- Functions of the cardiovascular, hematologic, immunologic, and respiratory systems
- Functions of the digestive, metabolic, and endocrine systems
- Genitourinary and reproductive functions
- Neuromusculoskeletal and movement-related functions
- Functions of the skin and related structures
- Any other body functions

Activity and Participation

Activity is defined as the execution of a task or action by an individual. Activity limitations are the difficulties an individual may have in executing such tasks. Activity limitations common in PD are those affecting gait, balance, dressing, bathing, and other activities of daily living (Dibble et al., 2010).

Participation is defined as the involvement in a life situation. Participation restrictions are the problems an individual may experience in involvement in life situations. Participation restrictions may affect leisure activities, work, and social aspects of life in both the household and community settings (Dibble et al., 2010).

Activity limitation and participation restrictions are rated using a scale, which describes the extent of participation restriction and the extent of activity limitation from no difficulty (no problem) to complete difficulty (problem that is present more than 95% of the time, with an intensity that is totally disrupting the person's day-to-day life and which happened every day over the last 30 days).

Activity and participation domains include:

- Learning and applying knowledge
- General tasks and demands
- Communication
- Mobility
- Self-care
- Domestic life
- Interpersonal interactions and relationships
- Major life areas
- Community, social, and civic life
- Any other activity and participation

Environmental Factors

Environmental include the physical, social, and attitudinal environment in which people live and conduct their lives. This section of the ICF uses a scale to rate **barriers** (no barriers to complete barriers) and **facilitators** (no facilitator to complete facilitator).

Environmental factors include:

- Products and technology
- Natural environment and human-made changes to the environment
- Support and relationships
- Attitudes
- Services, systems, and policies
- Any other environmental factors

For a detailed and current version of the ICF at the World Health Organization's website, click here.

Hoehn and Yahr Staging Scale

The Hoehn and Yahr scale describes how symptoms progress in PD. It has been widely used because it is simple and identifies patterns of progressive motor impairment. It does not provide information about non-motor aspects of PD. It was first published in 1967 and has largely been replaced by the more thorough UPDRS scale. A modified version of the original scale is available (shown here).

Modified Version of Original Hoehn and Yahr Staging Scale	
Stage	Description
1	Unilateral involvement only.
1.5	Unilateral and axial involvement
2	Bilateral involvement without impairment of balance.
2.5	Mild bilateral disease with recovery on pull test.
3	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severe disability; still able to walk and stand unassisted.
5	Confinement to bed or wheelchair unless aided

Schwab and England ADL Scale

The Schwab and England Activities of Daily Living scale assesses daily activities in terms of speed and independence. It uses a scale divided into 10% increments starting at 100% (complete independence in all activities without slowness, difficulty, or impairment) and moving to 0% (vegetative functions such as swallowing, bladder and bowel are not functioning; bedridden).

Motor Symptoms, Postural Instability, and Gait

In Parkinson's disease, the loss of dopaminergic cells in the substantia nigra affects the basal ganglia's ability to coordinate inhibitory and excitatory neural motor signals (Kwan & Whitehall, 2011). The net effect is an overall reduction in motor output, referred to as *hypokinesia*. Unfortunately, drugs used to treat PD can introduce too much dopamine, causing over-activation of the motor system and producing *dyskinesias* (fragmented or jerky motions, spasms, or tics). The motor symptoms associated with PD affect all aspects of daily activities, gait, postural stability, and mobility.

Tremor, Rigidity, Bradykinesia, and Dyskinesia

One of the first visible motor symptoms to emerge in PD is **resting tremor** of a limb that is supported and at rest. Tremor typically begins on one side of the body (frequently in one hand) with a tremor rate of 3 to 7 cycles per second. Tremors are usually less severe or even absent with voluntary movement and can increase during times of emotional stress. Tremor is considered one of the cardinal symptoms of Parkinson's disease—some studies report it to be present in up to 80% of patients with autopsy-proven PD (Dovzhenok & Rubchinsky, 2012).

Rigidity is another common visible motor symptom associated with PD. It is a type of increased muscle tone generally defined as an increased resistance to passive movement of a joint. Rigidity tends to be more prominent in the flexor muscles of the trunk and limbs, causing a characteristic stooped posture. There are two types of rigidity: lead pipe and cogwheel. Lead pipe rigidity is defined as a constant resistance to motion throughout the entire range of movement. Cogwheel rigidity refers to resistance that stops and starts as the limb is moved through its range of motion.

Bradykinesia, another cardinal motor feature of PD, is of unknown cause and remains the subject of debate. It is defined as slowed *voluntary* movement, although we now know that rigidity also affects automatic movements such as arm and leg swing during gait.

One theory suggests that bradykinesia is a compensatory response, intended to slow voluntary movements and improve movement accuracy. Another hypothesis suggests that it is caused by a deficit in force production. The force production theory has been contested by studies demonstrating that people with PD are able to achieve adequate muscle contractions on neurophysiologic testing. Some researchers have suggested that bradykinesia, rather than being simply a manifestation of motor slowness (movement speed and initiation), might reflect a specific neural deficit originating in the striatum (Shiner et al., 2012).

One of the striking clinical characteristics of bradykinesia is its variability, with the same patient being able to achieve perceivably different movement speeds in different contexts. An extreme manifestation of this variability is *kinesia paradoxica*, in which patients are suddenly able to move at near normal speeds, that can occur in extreme, aversive contexts (Shiner et al., 2012).

Among the major complications in PD is the presence of dyskinesia. **Dyskinesias** consist of abnormal movements (e.g., movement of the head, neck, limbs) that are debilitating, physically tiring, and embarrassing. Several reports have shown that the rate of this problem varies, ranging from 19% to 80% in PD patients (Lokk & Delbar, 2012).

Balance, Orientation, and Postural Control

Balance is the ability to automatically and accurately maintain your center of mass over your base of support. **Postural orientation** is the ability to control the segments of your body in relation to one another and to gravity, taking into account the environment and whatever task is being performed. **Postural control** involves both balance and postural orientation.

Control of posture has both musculoskeletal components (range of motion, flexibility, muscle function, and the biomechanical relationship between body segments) and motor processes, which organize the muscles into neuromuscular synergies. Balance also involves neural components—sensory and perceptual processes—that integrate input from the somatosensory, visual, and vestibular systems, as well as higher level processes that contribute to anticipatory and adaptive aspects of postural control (Shumway-Cook & Woollacott, 2012).

Poor balance and unstable posture are commonly observed motor symptoms in those with PD. Until recently, it was thought to occur relatively late in the course of the disease. This is reflected by the Hoehn and Yahr scale, in which postural instability is represented only in the advanced stages of the disease (stages 3 to 5). However, there is significant evidence that changes in postural control occur even in the early stages of Parkinson’s and, although there is fluctuation, generally increase over time (Maetzler et al., 2012).

In early-stage Parkinson’s there may be only minimal levels of functional impairment. Walking may be slowed and stride length reduced during simple movement and gait tasks. However, altered postural control is often evident during standing tasks along with difficulty in turning. Turning difficulty becomes a sensitive indicator of a higher prevalence of freezing and falling in persons with advanced PD (Song et al., 2012).

Gait Impairment

Gait changes are a hallmark of PD, with reductions in speed, decreased step length, altered cadence, and increased gait variability. While gait abnormalities are not pronounced in the early stages, their prevalence and severity increase with disease progression. Within 3 years of diagnosis, more than 85% of people with clinically probable PD develop gait problems. The potential consequences of gait impairments in PD are significant and include increased disability, increased risk for falls, and reduced quality of life (Kelly et al., 2012).

As the disease progresses, people with PD typically exhibit shuffling gait with a forward-stooped posture and asymmetrical arm swing (**festinating gait**). These characteristics use a lot of energy, so that routine walking places a person at or near their maximum metabolic capacity (Hass et al., 2012). Gait impairments are compounded by the presence of bradykinesia, rigidity, and postural instability (Shumway-Cook & Woollacott, 2012).

In kinematic studies of those with Parkinson's disease, these gait alterations are commonly observed:

- Lack of heel strike—foot lands either flat or forefoot lands first
- Incomplete knee extension during stance phase
- Inability to extend the knee and flex the ankle in terminal stance
- Forward trunk lean
- Lack of motion in the trunk
- Reduced or absent arm swing
- Decreased toe clearance
- Reduced speed and amplitude (Shumway-Cook & Woollacott, 2012)

Single-task walking deficits, in which no other task besides walking is required, have been associated with a variety of motor symptoms in PD. For example, increased rigidity is associated with poorer performance on single-task measures of balance and functional mobility. Rigidity may contribute to reduced lower-extremity joint excursions and a forward flexed posture when walking. Bradykinesia can lead to shortened step length and reduced gait speed during walking. Postural instability may contribute to gait impairments such as increased stride-to-stride variability and double limb support (Kelly et al., 2012).

Balance and gait abnormalities can lead to reduced quality of life. In fact, people with PD consider mobility and walking limitations to be among the worst aspects of the disease (Kelly et al., 2012). Patients consistently identify improvement in walking as the most relevant outcome when rating the success of a Parkinson's treatment (Hass et al., 2012).

Freezing of Gait

Freezing of gait (FOG) is the periodic inability to generate effective stepping. It is consistently seen as one of the most disabling and distressing symptoms of PD. Patients often describe FOG as a feeling that their feet are “stuck to the floor”; or “glued to the ground” despite attempts to force themselves to walk. FOG increases with duration of disease; approximately 30% of PD patients experience FOG within 5 years, and nearly 60% after 10 years (Lo et al., 2010).

FOG is chiefly triggered at the onset of walking and during turning, but also when confronted with narrow spaces (such as doorways) or when approaching targets. Its duration is usually less than 10 seconds and rarely longer than 30 seconds. Administration of L-dopa can reduce FOG, which is more common when medications wear off, suggesting dopamine deficiency as a cause (Arias & Cudeiro, 2010).

Clinical management of FOG is limited in large part by the difficult nature of assessing its severity, and subjective measures have dominated the field. Item 14 (part III) of the Unified Parkinson’s Disease Rating Scale (freezing when walking), rates patients on a scale from 0 (none) to 4 (frequent falls from freezing) based on clinical history. This was the primary outcome measure (UPDRS 14 ≥1) used in a large study of selegiline* as a prophylactic treatment for FOG in early PD (Moore et al., 2013).

*Selegiline (a MAO inhibitor) is used to help control the symptoms of Parkinson’s disease in people who are taking levodopa and carbidopa combination (Sinemet). Its use is discussed in detail later.

A number of prediction studies have shown that postural control deficits and freezing of gait (FOG) are powerful determinants of recurrent falls. A FOG episode can present itself by a significant step size reduction (shuffling gait), knee trembling, or complete akinesia, all leading to a sudden arrest of walking. During freezing, the center of gravity may continue to move forward while the feet stop moving; this leads to imbalance that cannot be corrected by compensatory steps and therefore increases the risk of falling. In one study, patients with PD failed to initiate compensatory stepping and exhibited FOG-like trembling knee movements when balance was challenged using a sudden forward platform movement. These findings suggest a postural control deficit and, more specifically, a failure to couple balance and voluntary locomotor synergies (Vervoort et al., 2013).

Postural control deficits in those with FOG can also occur during voluntary weight shifts. As part of a repetitive stepping task, freezers show rapid, small, and inefficient weight transfers between legs that are associated with freezing episodes. In addition, both peripheral proprioceptive feedback and central sensory processing abnormalities have been attributed to postural control deficits in PD (Vervoort et al., 2013).

A Freezing of Gait Questionnaire (FOG-Q) and the new FOG-Q (NFOG-Q) have recently been proposed as sensitive tools to identify FOG behavior and assess the efficacy of interventions. However, neither the FOG-Q nor NFOG-Q score correlated with the severity (frequency or duration) of freezing episodes during actual walking in a recent study of PD patients with self-reported FOG (Moore et al., 2013).

Evaluation of video recordings of ambulating patients has been used to identify the number of FOG events utilizing one, two, or three observers. This technique has emerged as a *de facto* gold standard in the past decade. A recent study utilizing ten experienced raters across four leading PD centers who assessed videos from "freezers" found only moderate inter-rater agreement for number of FOG events, and intra-rater reliability was remarkably low (Moore et al., 2013).

Current treatment options for FOG are largely ineffective. Increased prevalence of freezing is observed in advanced disease and in the clinical "off" or un-medicated state, highlighting the key role of striatal dopamine depletion in its pathogenesis. Increasing levodopa dosage can reduce the frequency of off-state freezing without altering the underlying pathophysiology, likely by increasing the threshold for FOG to occur. However, FOG commonly shows only partial response to levodopa, and the benefits of increasing levodopa dosage in reducing FOG must be balanced with the increased likelihood of levodopa-induced dyskinesias, also associated with a greater fall risk (Moore et al., 2013).

Patients may undergo deep brain stimulation surgery to relieve symptoms of off-state FOG, although these surgical interventions are currently viewed as a treatment option only in the later stages of PD. Clinical management of dopaminergic therapy to minimize FOG, as well as the evaluation of new targeted interventions, would benefit from the development of objective, standardized FOG measures capable of monitoring this debilitating symptom in a community setting (Moore et al., 2013).

Alan: Living with Parkinson's

Initially the Sinemet took care of the tremors but as the disease advanced I started experiencing new problems. I needed assistance cutting my food, and once it was cut I didn't know if I could keep it on my fork.

In 2004 I traveled to Costa Rica to visit some friends who had retired there. Getting off the plane in San Jose, I experienced for the first time the "Parkinson's freeze."

I couldn't move my feet. It was as if they were glued to the floor.

A stranger came up to me and asked if I had Parkinson's. I told him yes, and he said he would take care of me. He ordered me a wheelchair and took me to the baggage claim, through customs, and to my friends, who were waiting outside the terminal.

I had a rough week in Costa Rica. I was having great difficulty walking, and for the first time I felt afraid of this disease.

Unbelievably, the same man who had assisted me in the San Jose airport was a passenger on my return flight, and he assisted me at the end of the trip until we found my wife Diane. The man told me that his boss has Parkinson's, and he had recognized the symptoms in the way I was trying to take a step.

I went back to my neurologist, who put me on Stalevo and Requip.

At the suggestion of a friend, I also visited an acupuncturist, who started inserting needles in my hands each day. He suggested a routine of stretching exercises and changes in my diet. To this day I don't know which helped the most, but the medications helped for a long time.

Difficulty with Dual-Task Walking

[This section taken largely from Kelly et al., 2012.]

Several studies have looked at gait impairment when walking is performed simultaneously with another task, referred to as **dual-task walking**. Dual-task walking requires the simultaneous performance of walking and another physical or cognitive task. Concurrent cognitive tasks can include mental tracking, arithmetic calculations, conversational tasks, and memory tasks. Concurrent motor tasks can include carrying objects or manipulating objects while walking.

People with PD report that walking while performing another task is one of the greatest challenges of daily mobility. They also describe the need to use concentration to monitor and correct walking, consistent with James Parkinson's original observation that "walking becomes a task that cannot be performed without considerable attention."

Several mechanisms specific to PD may contribute to dual-task walking deficits. One such mechanism is referred to as *reduced movement automaticity*. **Automaticity** is the ability to perform a skilled movement without conscious or executive control or attention directed toward the movement.

The basal ganglia are proposed to play a key role in the automatic control of movement. Basal ganglia dysfunction may lead to reduced movement automaticity and the need for increased reliance on cognitive resources to control movements. If reduced movement automaticity contributes to dual-task walking deficits in people with PD, rehabilitation strategies designed to improve the automatic control of walking should improve dual-task walking.

Dopamine-mediated dysfunction of the basal ganglia may also contribute to dual-task walking deficits in PD. Degeneration of dopaminergic neurons in PD appears to affect both motor and cognitive circuits within the basal ganglia. Dual-task walking deficits are improved by antiparkinson medications, supporting the idea that motor and cognitive impairments are due in part to dopaminergic pathways. The impact of antiparkinson medications may be limited to those impairments mediated by dopamine dysfunction, and many studies demonstrate dual-task walking deficits in people with PD in the "on" medication state.

The presence of non-dopaminergic pathology, which may affect both gait and cognition, may also contribute to dual-task walking deficits in PD. It is increasingly thought that the pathology of PD is not limited to dopamine but includes other neurotransmitter systems such as serotonin, norepinephrine (noradrenaline), or acetylcholine. Dysfunction in multiple neurotransmitter systems may contribute to gait and cognitive impairments. Consistent with this idea, dual-task walking deficits persist even when people with PD are optimally medicated.

Community Walking

[This section is based on Lamont et al., 2012.]

People who have Parkinson's disease face a variety of challenges in the community. Independent functioning is related to our ability to walk efficiently, and community walking enables us to participate in a range of societal, work, and leisure activities. This includes the ability to negotiate public and private venues, both indoors and outdoors, that present a variety of environmental demands. People with PD often find environmental barriers to walking in the community but tend not to report disability; rather, they modify their behavior.

Current clinical methods of assessing community mobility that focus on gait speed or distance may not provide sufficient information to accurately reflect a person's ability to walk in the community. A deeper understanding of preclinical walking disability may allow therapists to provide more timely assessment and therapy, delaying the onset of disability rather than attempting to reverse disability after it presents.

A recent Australian study looked at factors that contribute to a person's ability to walk in the community. Eighteen participants with PD were asked which factors help or hinder their community mobility. Participants considered several factors associated with successful community ambulation, including walking speed, planning and preparation, traveling on holiday, medication management, the role of a partner, pedestrian crossings, and barriers to community walking.

Paying Attention to Walking Speed

A common strategy reported by study participants was the need to consciously pay attention to walking speed, step length, and toe clearance. Most people reported that they either concentrated on their walking or took extra care with walking. Consciously taking long, rhythmical steps was commonly used to aid walking in the community but several participants reported that using this strategy in a community environment was less automatic than when at home (Lamont et al., 2012):

> "If you walk slower, and lift your feet and concentrate, that helps."

> ". . .you've got to try and think and remember to do it, like, think and make sure you do it. . . try and step it out and lift your feet more."

Planning and Preparation

Study participants noted that planning and preparation played a key role in the success of community ambulation. Almost everyone reported planning outings to coincide with times of high medication effectiveness ("on" times). Being prepared for outings and making a plan and keeping to that plan reduced the chance of running late, feeling rushed, and making errors such as forgetting to take medications. Errands were also carefully organized to ensure the shortest walking distance. Study participants reported feeling less stress when these strategies were employed (Lamont et al., 2012).

Traveling on Holiday

Community walking related to a novel or enjoyable situation was discussed by several of the study participants and supported by their partners. Specifically, participants described reduced symptoms and less fatigue while traveling on holiday than they generally experienced at home, a change which could last for a number of weeks after their return (Lamont et al., 2012):

> "Going back three years when [my wife], I'd say, had full-blown Parkinson's, she was very, very bad. We took an overseas trip and. . . [my wife] just kept going and going. By the time we got to France I flaked. . . She still kept going. . . Something kept her going because as soon as we got home, boom, she got Parkinson's again, but while we were away it didn't seem to affect her."

Optimal Medication Management

The reported effects of antiparkinson medications on walking were variable. Medications improve some aspects of single-task walking, including gait speed and stride length, but may not influence other aspects, such as stride-to-stride variability, festination, and freezing of gait. Optimal medication management was related to a more efficient gait pattern and less fatigue, making long-distance walking more feasible. A positive response to surgical intervention allowed one study participant freedom from a schedule of medication, permitting community outings to occur at times convenient for reasons other than medication effectiveness (Lamont et al., 2012):

> "I love it, I love the independence and I love being able to go to the shops and not be dictated by the medication."

The Role of a Partner

Several of the study participants and their partners reported that the partners played a crucial role in mobility by encouraging the participant to go out, promoting the importance of walking, providing physical assistance to overcome barriers in the environment, and supporting the use of attention or cueing strategies. Effective cueing strategies were discrete, mutually agreed upon, and practiced to avoid using a counterproductive cue (Lamont et al., 2012).

Pedestrian Crossings

Only one aspect of the physical environment was described as a facilitator to community walking, but this was reinforced by most of the study participants: pedestrian crossings with signals. Participants reported that signaled pedestrian crossings reduced the attention required to monitor traffic and decide when to cross safely and therefore facilitated walking in the community. For a number of participants, this had become a habit, now done without compromise (Lamont et al., 2012):

> ". . .you never try to run a light, you always wait for the lights, and you don't cross any road if there is not a light."

Barriers to Community Walking

Participants reported a number of external barriers when walking in the community. Crowded environments were overwhelmingly disliked. Participants described that the need to change direction and avoid obstacles when walking in cluttered or heavily populated environments was a trigger for short, shuffling steps and more frequent episodes of freezing (Lamont et al., 2012):

> "I find it more difficult when there are a lot of people around, it means you have to take shorter steps. I like taking long steps, I can balance myself better."

Characteristics of the walking surface, such as uneven footpaths, hills, ramps, moving walkways, and slippery surfaces, were reported as a cause of increased fatigue, fear of falling, and more frequent freezing episodes. Even the camber of the footpath, designed to allow water to drain, was commonly reported to make walking more difficult (Lamont et al., 2012):

> "My greatest difficulty when I'm walking is going downhill. Can't handle it. I can go uphill flat out, but I can't handle going downhill. Even with a trolley my feet get stuck on top of a ramp and I can't get going."

Alan: Living with Parkinson's

Another condition I am dealing with is burning and tingling in my feet. It's a strange sensation that tends to get worse when I sit or stand for an extended period of time. Periodically I also experience my feet feeling very heavy.

On the burning and tingling sensations and "heaviness" in my feet, my doctor suspected neuropathy or restless legs syndrome and prescribed gabapentin.

The foot symptoms made it uncomfortable to walk, so I stopped my daily outings to the park about a month ago. That was not a good thing to have done. I started dragging my feet and once again developed a hesitation when I took a step.

Well, to make a long story short, I started walking at Target with my friend Frank last week. I'm already walking better and I'm through with excuses.

Fall Risk and Tests of Balance

It is not surprising that falls are common in those with Parkinson's disease nor that injuries from falls are the most common reason for hospital admission. The estimated prevalence of falls in those with PD ranges from 40% to 90%, with about half of those falls occurring when walking (Kelly et al., 2012).

There are many significant consequences associated with falling, including fractures (particularly hip fractures), head trauma, head injuries, and even death. Falling may also cause fear of new falls, which can in turn reduce mobility and lead to osteoporosis, loss of independence, social isolation, and depression (Contreras & Grandas, 2012).

Because falls are associated with such serious complications for people with PD, healthcare providers should be familiar with practical and accurate measures for assessing and predicting falls as well as with interventions to decrease future falls (Duncan & Earhart, 2012). This is particularly important because numerous studies have shown that a wide range of healthcare providers are reluctant to incorporate fall prevention into their practice (Tinetti et al., 2008). In an attempt to discern why, Mary Tinetti and her colleagues at the Connecticut Collaboration for Fall Prevention surveyed healthcare providers near Yale University. The respondents (physical and occupational therapists, emergency department physicians and nurse managers, and primary and home care providers) gave the following reasons:

- Ignorance of falling as a preventable condition
- Competing time demands
- Perceived lack of expertise
- Insufficient reimbursement
- Inadequate referral patterns among clinicians (Tinetti et. al., 2008)

The Tinetti researchers recommended evidence-based fall prevention strategies to the healthcare providers that included a reduction in medications, management of postural hypotension, management of visual and foot problems, hazard reduction, and balance, gait, and strength training. Healthcare providers were encouraged to incorporate assessments, treatments, and referrals into their practice, as appropriate to their discipline and setting. Following these interventions, a 9% decrease in fall-related injuries and an 11% decrease in fall-related use of medical services were noted in the intervention group (Tinetti et al., 2008).

Risk of Falls in Those with PD

Preventing falls is one of the most important unmet needs in PD, and strategies to prevent falls should focus on those at high risk for falling. A **risk factor** is something that increases a person's risk or susceptibility for falling. The presence of one or more risk factors should prompt a referral to a healthcare provider familiar with assessment and treatment of balance disorders and to a physician or nurse practitioner familiar with medications that increase the risk of falling. Increased risk of falling is closely associated with certain pre-existing conditions, and fall risk increases proportional to the number of pre-existing conditions.

In fall intervention studies focusing on older adults, **age** and **history of falls** are the two risk factors most commonly used to define high risk. Also considered are gender, impaired balance and gait, visual impairment, and use of multiple medications or medications known to increase fall risk (Moyer, 2012). Musculoskeletal problems, neurologic diseases, psychosocial characteristics, functional dependency, and drug and alcohol abuse all contribute to an increased risk of falling (Baranzini et al., 2009).

For people with Parkinson's disease, there are risk factors specific to PD. These include changes in posture, postural instability, freezing of gait, dyskinesias, gait changes, medication side effects, and decreased ability to react automatically to a loss of balance. Health and cognitive factors such as cognitive decline and depression can also greatly increase the risk of falling.

A Spanish study of 160 people with Parkinson's disease who were being seen at a movement disorders clinic in Madrid found that fallers were older and had longer disease duration. They also had increased disease severity according to the UPDRS (part III) and the Hoehn and Yahr scale, and lower scores on the Schwab and England ADL test. In addition, fallers scored worse in the Mini-Mental State Examination and experienced a higher frequency of motor fluctuations, dyskinesia, and freezing of gait (Contreras & Grandas, 2012).

Recurrent Falls

In the general population of elders, a fall is considered recurrent when it occurs more than once in a given time period (usually 12 months). Using this definition, about 15% of people in the general older population are classified as recurrent fallers. Among people with PD, recurrent falls are more frequent, with one study reporting that more than 50% of the study participants fell recurrently. In another study involving a survey of 100 people with PD, 13% reported falling more than once a week, with most of these people falling multiple times a day (Allen et al., 2013).

Several risk factors for falls have been found to be more strongly associated with recurrent falls than single falls. Some of these factors are potentially modifiable, including cognitive impairment, freezing of gait, fear of falling, reduced mobility, reduced physical activity, and balance impairments. There is substantial variability in the falling rates reported in various studies, with the proportion of fallers (single and recurrent) ranging from 35% to 95%. Differences in the method of monitoring falls could contribute to this variability (Allen et al., 2013).

Despite the fact that recurrent falls are a substantial problem for people with PD, the scope of, and risk factors for, recurrent falls in PD are not clearly understood. Improving our understanding of recurrent falls is the first step toward developing effective interventions designed to reduce and manage these falls (Allen et al., 2013).

Cognitive Decline and Fall Risk

Several studies have examined the role of specific cognitive domains on fall risk. Lower scores on cognitive screening tests. such as the Mini-Mental State Examination and the Montreal Cognitive Assessment, were associated with an increased risk of falls. Lower scores on tests of attention, executive function, memory, and visual-spatial function have all been reported to be associated with an increased risk of falls in both cognitively intact and cognitively impaired individuals (Buracchio et al., 2011).

Difficulty with dual-task walking, a measure of divided attention and executive function in which individuals are given a secondary mental task while walking, has consistently been shown to be associated with an increased risk of falls (Buracchio et al., 2011). Impaired cognition may cause these problems because of a limited ability to perform either task or because of problems associated with allocating attention efficiently between the two tasks (Shumway-Cook & Woollacott, 2012).

An Israeli study looked at executive function, attention, and other cognitive domains in 256 community-living older adults with an average age of 76 years. Participants were free of dementia and had good mobility upon entrance into the study. Baseline cognitive function was established using computerized cognitive tests. Gait was assessed during single and dual-task conditions. Falls data were collected prospectively, using monthly calendars. The researchers found that among community-living older adults, the risk for future falls was predicted by executive function and attention tests conducted 5 years earlier, indicating that screening executive function will likely enhance fall risk assessment, and that treatment of executive deficits may reduce fall risk (Mirelman et al., 2012).

Fear of Falling

Fear of falling (FOF) has emerged as an important health concern in all older adults given its demonstrated association with restrictions in daily activity and in many cases activity avoidance. The substantial body of literature that has emerged addresses prevalence, risk factors, and consequences. Reported prevalence of FOF in the general population of elders is as high as 85%. Identified risk factors include having had a previous fall, increasing age, female gender, dizziness, depression and anxiety, and balance and gait disorders. Documented consequences of FOF include a decline in physical and mental performance, activity avoidance, and a loss of health-related quality of life (Foran et al., 2013).

A consequence of FOF is an increased risk of falling and there is a likelihood of additional falls, given reported rates of 29% and 92% of FOF among recent fallers with previous falls. Studies suggest that FOF is a psychological experience resulting in reduced physical activity leading to poor balance, mobility impairment, and social isolation. Such consequences may lead to increased likelihood for falling in the future (Foran et al., 2013).

Fear of falling is a common and potentially serious problem in people with Parkinson's disease. Studies have consistently reported that community-dwelling individuals with PD have a greater FOF than age-matched healthy subjects. The level of fear is further increased in those who have had a fall history. Fear of falling is also a significant risk factor for predicting future falls. While some level of FOF has a protective role against falls, irrational fear—either too much or too little—may increase fall risk. One recent study noted that only those with excessive FOF had a higher risk of injurious falls (Mak et al., 2012).

Repeated falls may lead to avoidance of activity, physical deconditioning, and increased institutionalization. Therefore, interventions aiming to enhance balance confidence have the potential to reduce fall risk in appropriately targeted individuals with PD (Mak et al., 2012).

Depression and Falls

Depression is common and treatable in older adults, and outcomes improve with effective antidepressant therapy, which could lead to a decrease in the morbidity associated with falls. Older people who fall are twice as likely to be depressed compared with those who do not fall (Kerse, 2008). However, antidepressant use can also increase the risk of falls, both for those in the community and in residential care (Kerse et al., 2008).

A cross-sectional survey of Australians aged 60 and over investigated the association between depressive symptoms, medication use, falls, and fall-related injury. Both depression and the treatment for depression were independently associated with an increased risk of falls. Selective serotonin reuptake inhibitor (SSRI) use was associated with the highest risk of falls and injurious falls of all psychotropic agents (Kerse et al., 2008).

Polypharmacy and Falls

Polypharmacy is the use of multiple medications at one time, including over-the-counter (OTC) medications, dietary supplements, and herbal remedies. Polypharmacy includes prescribing more medications than are clinically indicated, using inappropriate medications, and using the correct medication for an inappropriate length of time. Polypharmacy is regarded as an important risk factor for falling, and several studies and meta-analyses have shown an increased fall risk in users of diuretics, type 1a anti-arrhythmics, digoxin, and psychotropic agents (Baranzini et al., 2009).

Due to concurrent prescription of several drugs, the risk of inappropriate drug combinations is increased in older adults. In addition, medication metabolism is affected by age-related changes, which increase both drug half-life and drug free fraction. Co-existing illnesses can also interact with medications. For all these reasons, older adults are at higher risk of experiencing adverse drug effects (Berdot et al., 2009).

Medication management in those with Parkinson’s disease is complicated by the number and schedule of medications, which can change dramatically as the disease progresses. One strategy is to use alternate treatment strategies such as transdermal patches and intestinal gel formulations.

Predicting Falls in Those with PD

Despite the relatively high prevalence of falls in the PD population, accurate and useful methods for predicting an impending future fall, especially during the early stages of the disease, remain elusive. Fall history, a well-known fall risk factor among older adults, has limited utility as a solitary predictive indicator. Although a meta-analysis of prospective studies of falling in PD found that 57% of individuals who had a history of falls in the past year fell during a 3-month surveillance period, so did 21% of individuals with no history of falls (Duncan et al., 2012).

Of perhaps more concern, fall incidence alone does not help to identify underlying contributors to postural instability specific to PD. People with PD, for example, may demonstrate impairment in areas of movement control such as sensory integration, keeping their center of mass within their base of support, coordination of anticipatory postural control tasks, as well as medication side effects such as dyskinesias (Duncan et al., 2012).

Falling in the Previous Year

In a meta-analysis of studies of falling in those with PD, the best predictor of falling was experiencing two or more falls in the previous year. Fallers scored worse in the Balance and Gait subscales of the Tinetti functional test and were slower in the Timed Get-Up-And-Go test (discussed later). There were no statistically significant differences in gait velocity, step length, and cadence between fallers and non-fallers (Contreras & Grandas, 2012).

The independent variables most associated with falls were the Tinetti Balance score and Hoehn and Yahr staging. The Tinetti Balance test predicted falls in patients with 71% sensitivity and 79% specificity, and Hoehn and Yahr staging predicted falls with 77% sensitivity and 71% specificity. No differences were observed between fallers and non-fallers in other drug treatments, age at onset of PD, symptoms of orthostatic hypotension, and cerebrovascular disease (Contreras & Grandas, 2012).

Most PD fallers had scored at Hoehn and Yahr stage III, or more. The transition from stage II to III, with the emergence of postural instability, appears to play a crucial role in the appearance of falls and is related to increased disability in many gait-dependent activities. Fallers had longer disease duration and increased disease severity based on the UPDRS, Hoehn and Yahr, and Schwab-England activities of daily living scores, and more frequently experienced motor fluctuations and dyskinesia. For the same reasons, fallers were treated with higher doses of levodopa and more frequently used COMT inhibitors (Contreras & Grandas, 2012).

A meta-analysis, conducted by Pickering and colleagues, noted that the best predictor of falls in individuals with PD is a history of 2 or more falls in the previous 6 months. However, simply asking about fall history does not provide information about factors associated with the cause of the falls (Duncan & Earhart, 2012).

Factors such as postural instability, gait difficulty, and other facets of mobility are significantly associated with falls in people with PD. As such, it is imperative that rehabilitation clinicians employ assessments that test mobility-related constructs in an effort to detect deficits in mobility prior to a fall. Gaining information about future fall risk allows for the implementation of effective rehabilitation programs to reduce fall risk and possibly prevent falls in people with PD (Duncan & Earhart, 2012).

Screening for Falls

Screening is a method for detecting dysfunction before an individual would normally seek medical care. Screening tests are usually administered to individuals who are without current symptoms but who may be at high risk for certain adverse outcomes. The purpose of screening is early diagnosis and treatment. Screening tools that address fall risk have been developed for use in various populations, including hospitalized older adults, adults in residential care, and community-dwelling older people.

Screening is an effective tool for quickly identifying patients at high risk for falling; however, finding an agreed-upon definition for *screening* is fraught with problems. For example, if a patient is asked "Have you fallen in the last year?" and the answer is no, the screen leads nowhere, even in the case of an older adult patient who has real risk factors for falls. It is important to observe the patient and have a screening tool that is quick and easy but also provides guidance about fall risk.

A practical approach for screening high-risk persons is to **ask and assess**: ask about history of falls, frequency and circumstances of falls, and mobility problems, then assess using a quick test such as the Timed Up and Go (TUG) test. The TUG test is performed by observing the time it takes a person to rise from an armchair, walk 10 feet, turn, walk back, and sit down again. The average healthy adult older than 60 years can perform this task in less than 10 seconds (Moyer, 2012).

Using Balance Tests to Predict Falls

The ability to predict future falls has improved through use of assessments that include measurements of postural stability during static and dynamic tasks. However, these assessments have some limitations when used in a clinical setting. Balance assessment tools often require special training of the tester, who must make subjective ratings of participant's performance. In addition, administration of balance assessments can be time consuming. Because of these limitations, there is a need for measures that are objective, quick, and easy to administer. Adopting a measure with these qualities for clinical use must be based on the knowledge that such a measure is equally as accurate as more involved measures at predicting falls in people with PD (Duncan & Earhart, 2012).

A study at the Washington University School of Medicine's Movement Disorders Center sought to determine how well four commonly used balance tests predicted falls in community dwelling adults over the age of 40 who had idiopathic PD. Participants were evaluated at baseline utilizing four balance tests (Berg Balance Test, Functional Gait Assessment, BESTest, and Mini-BESTest). Participants were followed for 12 months, with fall incidence determined through a participant's report at 6 months and 12 months. Individuals were considered fallers if they reported two or more falls over the surveillance period of interest (0–6 months or 0–12 months). Individuals were considered non-faller s if they reported 0 or 1 fall during the surveillance period (Duncan et al., 2012).

Data from the study confirmed that a shorter followup period (6 months) consistently produced more accurate predictions than a longer followup period (12 months). In addition, at the 6-month followup all of the balance assessments studied provided clinically useful predictive accuracy. Comparisons suggested that the BESTest produced the greatest predictive accuracy. However, it is unclear whether the differences between the BESTest and the other balance measures are sufficiently large to merit use of one test over another in a clinical setting (Duncan et al., 2012).

Clinical Tests of Balance

A number of clinical tests are available for testing balance in patients with Parkinson's disease. The Berg Balance Scale, the BESTest, the Tinetti Test, and the Timed Up and Go (TUG) are commonly used in hospitals and long-term care settings. The Pull Test, part of the UPDRS, is also used to test postural reactions in those with PD.

The Berg Balance Scale (BBS)

One of the most commonly used clinical tests of balance in people with PD is the Berg Balance Scale. The BBS, originally designed for use in the frail elderly, is a 14-item test that focuses on a variety of self-initiated tasks related to everyday function, such as sit-to-stand and functional forward reach. The Berg does not include tests of postural reactions or dynamic gait.

The Berg has excellent reliability and is somewhat correlated with severity of PD, as measured with the Unified Parkinson's Disease Rating Scale. However, the Berg is not necessarily a good predictor of falls in those with neurologic impairment (Shumway-Cook & Woollacott, 2012). These particular limitations are important considerations when evaluating patients with mild neurologic deficits, who are easy to under-identify and therefore less likely to receive rehabilitation (King et al., 2012).

The Berg Balance Scale includes the following activities:

- Sit to stand
- Stand unsupported
- Sit unsupported
- Stand to sit
- Transfers
- Stand with eyes closed
- Stand with feet together
- Reach with outstretched arm
- Retrieve object from floor
- Turn to look behind
- Turn 360 degrees
- Alternate stepping on stool
- Standing with one foot in front of the other
- Standing on one foot

The BESTest

Documented limitations of the Berg have led many clinicians to do more than one validated balance assessment in order to identify deficits that may respond to treatment. A more comprehensive clinical balance test, the Balance Evaluation Systems Test (BESTest), is essentially a battery of balance and mobility tests borrowed from other validated tests such as the Berg and Dynamic Gait Index. The BESTest is a comprehensive clinical tool for evaluating six different balance control systems:

- Biomechanical
- Stability limits/verticality
- Anticipatory
- Reactive
- Sensory orientation
- Stability in gait

Such system-specific assessment is helpful in directing treatment and to ensure that a meaningful deficit is not overlooked. The BESTest has good inter-rater reliability and good validity in discerning fallers from nonfallers in patients with PD (King et al., 2012).

The BESTest, though comprehensive, valid, and reliable, is lengthy to administer and may not always be practical in a busy clinical setting. A shorter version of the BESTest—the Mini-BESTest—was developed using psychometric techniques to reduce redundancy and simplify scoring. This shorter version has excellent inter-rater and test-retest reliability and is similar in length to the Berg. However it is currently unknown how the Mini-BESTest compares with the Berg in detecting balance deficits in the PD population (King et al., 2012).

The items tested in the Mini-BEST examine one of four categories of balance: anticipatory, dynamic gait, reactive control, and sensory orientation. The Berg was not designed with such systems in mind but, if a system categorization were assigned to each item, the Berg items primarily evaluate anticipatory and sensory contributions to balance (King et al., 2012).

The following table compares individual items on the Berg and the Mini-BESTest. Items are ranked from most difficult to least, along with the percentage of participants with PD who did not have normal scores. Difficulty with the test was determined if the participant did not receive a perfect score.

Berg Test and Mini-Best Comparing Items by Difficulty				
Berg Test item	% with difficulty	Mini-BESTest item	% with difficulty	System (Mini-BEST)
Turning to look behind	70.1	Rise to toes	86.6	Anticipatory
Standing with 1 foot in front	42.3	Single leg	81.4	Anticipatory
Reaching forward with outstretched arms	40.2	TUG (Timed Up and Go) with cognitive task	54.6	Gait
Standing on 1 foot	39.2	Pivot turn	51.5	Gait
Turn 360 degrees	30.9	Eyes closed/foam	46.4	Sensory
Placing alternate foot on stool	27.8	Obstacle during gait	46.4	Gait
Standing to sitting	11.3	Turn head with gait	41.2	Gait
Retrieving object from the floor	9.3	Incline eyes closed	33	Sensory
Sitting to standing	5.2	Backwards recovery	29.9	Postural
Standing with feet together	4.1	Lateral recovery	29.9	Postural
Transfers	4.1	Change pace gait	13.4	Gait
Standing with eyes closed	3.1	Forward recovery	13.4	Postural
Standing unsupported	3.1	Sit to stand	6.2	Anticipatory
Sitting unsupported	0	Eyes open stance	2.1	Sensory

There are two additional systems that the Mini-BESTest evaluates—dynamic gait and reactive postural control—providing more detail when analyzing balance and gait deficits.

Because dynamic gait (cognitive task with gait) and reactive postural control (response to perturbation) are the most difficult items for people with PD, clinicians may add additional tests such as the Dynamic Gait Index and the Pull Test (tested within the UPDRS).

The Tinetti Test

The Tinetti test is another commonly used balance assessment tool. It is a simple, widely used, qualitative test comprising two subscales, one to assess clinical balance and another to assess gait. The balance subscale consists of nine items, where lower scores indicate poor balance. The Tinetti test is a reliable and valid clinical test to measure balance and gait in elders and in patients with PD (Contreras & Grandas, 2012).

The first part of the tool, the Tinetti *Balance* Test, is scored on a scale of 0 to 16, and assesses:

- Sitting balance
- Sit to stand
- Standing balance
- Standing balance when nudged
- Standing balance with eyes closed
- Balance while turning, and stand to sit

The second part to the tool, the Tinetti *Gait* Test, is scored on a scale of 0 to 12, and assesses:

- Initiation of gait
- Step length and height
- Step symmetry
- Step continuity
- Deviation from a straight path when walking
- Trunk sway and stance when walking

When taken together, the maximum score on the Tinetti tests is 28; a client who scores between 19 and 24 is at risk for falls and a client who scores below 19 is at high risk for falls.

The Timed Up and Go (TUG)

The Get Up and Go test, the predecessor of the Timed Up and Go test (TUG), was developed by Mathias and Nayak as a tool to screen for balance problems, primarily in the frail elderly. The test measures how long it takes for a person to rise from a chair, walk 3 meters (about 10 feet) to a line on the floor, and return to the chair. The test correlates well with the Berg Balance Scale, the Barthel Index of activities of daily living, and gait speed tests. The Timed Up and Go modified the earlier version of the test by adding a timing component. An adult who is independent in balance and mobility can perform the TUG in less than 10 seconds (Shumway-Cook & Woollacott, 2007).

In a study of older adults with a range of neurologic pathologies, people taking 30 seconds or more to complete the TUG were more likely to need an assistive device, walk too slowly for community ambulation, and score lower on the Berg Balance scale. In contrast, a person completing the test in less than 20 seconds was more likely to be independent in daily living activities, score higher on the Berg Balance scale, and walk at a speed sufficient for community mobility (Podsiadlo & Richardson, 1991).

Shumway-Cook and Woollacott (2012) noted that the TUG can be used to predict the risk of falls in older adults. In a study, 30 community-dwelling frail elderly adults were tested using the TUG, and researchers found that those taking longer than 14 seconds to complete the task were at high risk for falls.

In the same study, the TUG was modified by adding a cognitive task (counting backward by threes) and a manual task (carrying a full cup of water). The addition of a secondary task increased the time need to complete the TUG by 22% to 25% (Shumway-Cook & Woollacott, 2012).

The Pull Test

The Pull Test is a measure of postural instability that is done in part III of the UPDRS. In the Pull Test, the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. The tester stands behind the patient and applies a sudden, strong pull on the shoulders to see how well he or she compensates for a sudden imbalance. The Pull Test is positive if the person takes more than two steps back or would fall if not caught by the tester. A positive Pull Test indicates progression from Hoehn and Yahr stage II to stage III.

Nonmotor Aspects of Parkinson’s Disease

Nonmotor symptoms of Parkinson's disease are common, but unfortunately **are often under-recognized in clinical practice**. This may be because of the lack of spontaneous complaints by the patients or the absence of systematic questioning by healthcare professionals (Bonnet et al., 2012).

At the time of diagnosis, pain, urinary symptoms, depression, and anxiety are present in about 20% of patients. After about seven years, the occurrence of these nonmotor symptoms increases to 88%. Additionally, symptoms such as sleep disturbances, bowel disruptions, gastroesophageal reflux, and olfactory changes occur in a large percentage of patients with PD.

In a recent international study, nonmotor symptoms such as constipation, bladder dysfunction, and feeling of sadness were reported by more than half of the patients, significantly more prevalent among PD patients than controls, and correlated with the duration of the disease (Bonnet et al., 2012).

Major Nonmotor Symptoms in Parkinson's Disease*

Neuropsychiatric symptoms	▪ Depression, anxiety, apathy ▪ Hallucinations, delusions, illusions ▪ Delirium (may be drug induced) ▪ Cognitive impairment (dementia, MCI) ▪ Dopaminergic dysregulation syndrome (usually related to levodopa treatment) ▪ Impulse control disorders (related to dopaminergic drugs)
Sleep disorders	▪ REM sleep behavior disorder ▪ Excessive daytime somnolence, narcolepsy type "sleep attack" ▪ Restless legs syndrome, periodic leg movements ▪ Insomnia ▪ Sleep disordered breathing ▪ Non-REM parasomnias (confusional wandering)
Fatigue	▪ Central fatigue ▪ Peripheral fatigue
Sensory symptoms	▪ Pain ▪ Olfactory disturbance ▪ Hyposmia (reduced ability to smell and detect odors) ▪ Functional anosmia ▪ Visual disturbance (blurred vision, diplopia; impaired contrast-sensitivity)
Autonomic dysfunction	▪ Bladder dysfunction (urgency, frequency, nocturia) ▪ Sexual dysfunction (may be drug-induced) ▪ Hyperhydrosis (sweating abnormalities) ▪ Orthostatic hypotension

Major Nonmotor Symptoms in Parkinson's Disease*	
Gastrointestinal symptoms	▪ Dribbling of saliva ▪ Dysphagia ▪ Agueusia (loss of taste) ▪ Constipation ▪ Nausea, vomiting
Dopaminergic drug-induced nonmotor symptoms	▪ Hallucinations, psychosis, delusions ▪ Dopamine dysregulation syndrome ▪ Impulse control disorders ▪ Ankle swelling ▪ Dyspnea ▪ Skin reactions, subcutaneous nodules ▪ Erythematous
Nonmotor fluctuations	▪ Dysautonomia ▪ Cognitive/psychiatric ▪ Sensory/pain ▪ Visual blurring
Other symptoms	▪ Weight loss, weight gain

*Source: Bonnet et al., 2012.

Sleep Disturbances

It has been long observed that PD patients experience a variety of sleep disturbances, which can precede the clinical motor symptoms associated with PD by several years. Rapid eye movement sleep-behavior disorder (RBD), in particular, is strongly correlated with the development of synucleinopathies in which alpha-synuclein proteins form into fibrils that accumulate in dopamine cells, leading to the degradation and death of the cell (Haas et al., 2012). Sleep disturbances are estimated to occur in 60% to 98% of patients with PD (Swick, 2012).

REM Sleep Behavior Disorder (RBD)

Rapid eye movement sleep-behavior disorder (RBD) has long been associated with PD. This nonmotor symptom can start years, if not decades, before the development of the classical clinical motor symptoms. RBD is characterized by loss of skeletal muscle atonia during REM sleep with prominent motor and behavioral activity and dreaming (Swick, 2012). When loss of atonia occurs, a person is unable to suppress motor responses during REM sleep and may react to a dream by screaming, kicking, punching, or jumping out of bed. They may remember the dream but have no recollection of having engaged in any movement.

Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS)—inappropriate and undesirable sleepiness during waking hours—is one of the most commonly reported sleep complaints in patients with PD, affecting between 15% and 50% of patients (Swick, 2012). The degree of EDS has been shown to be a key determinant of a patient's quality of life.

EDS is a multifactorial issue—it can be caused by fragmented sleep resulting from a primary sleep disorder such as obstructive sleep apnea, periodic limb movement disorder, narcolepsy, idiopathic hypersomnia, or behaviorally induced insufficient nocturnal sleep. Medications, pain syndromes, and numerous medical and psychiatric disorders also have been associated with EDS (Swick, 2012).

Patients may start napping more often even before the diagnosis of PD. As the disease progresses this may increase, although tiredness may also be a side effect of the medications prescribed for PD.

Restless Legs Syndrome

There have been numerous cross-sectional studies examining the frequency of restless legs syndrome (RLS) symptoms in patients with PD. The generally accepted frequency is 10% to 20% association of RLS symptoms in patients with Parkinson's (Swick, 2012).

In a 2011 study, Gjerstad and colleagues looked at 200 patients with early untreated PD and compared them to appropriate community-based controls. They were unable to find a statistically significant association between RLS in patients with PD versus the controls. They found that the patients with PD complained of leg motor restlessness but did not have the "urge to move" that characterizes the sensory phenomenon in patients with RLS (Swick, 2012).

Alan: Living with Parkinson's

After going on the new meds I found I could walk again without using a cane. I began typing again, putting the voice recognition software back in the box. My voice, which had become weak, was getting stronger.

Both doctors recommended I reduce the amount of stress in my life and get more rest. That was a difficult challenge for a newspaper publisher. I love what I do. Volunteerism had been my way of giving back to the community that has been so good to me. In 2007 I spoke to the local Parkinson support group and told them my quality of life had improved over the previous two years.

In 2008, however, I started having trouble sleeping. I was never one to sleep very long. Even as a young boy I generally slept only five to six hours a night, Sleep was something I had to put up with. My attitude growing up was I would rather read an encyclopedia under the covers by flashlight than sleep. And I couldn't wait to hear the morning newspaper plop on the driveway. As an adult with my own business, I was often at the office by 6:15 to get my regular work done so I could work on volunteer activities in the afternoon.

Now I would go to bed, fall instantly asleep, but wake up two hours later. This went on for months. After falling asleep while driving on the freeway, I went to my GP to tell him about my sleep problems.

He sent me to the Mayo Clinic (fortunately the Arizona campus is only a few miles away), where I was tested for sleep apnea. The test was conducted during an overnight stay. I was wired up at points all over my body. It was very strange. But at least the test confirmed it was mainly stress keeping me awake.

My regular doctor let me try some sleep aids. Ambien made my head do weird things. We went through a number of over-the-counter drugs. But then he tried me on Lunesta and that was the magic pill for me. I've been sleeping much better since then and of course I feel much better after a full night's sleep.

To maintain my new sleep status, I wear a mask over my eyes and try to avoid bright lights during the night. Television is taboo after I go to bed. I changed my eating habits. No caffeine. No chocolate or other sweets in the evening.

Sometimes I try counting backward from 100, mentally drawing each number as I go. I precede each number by inhaling deeply through my nose, holding the air in my lungs for varying amounts of time, and exhaling through my mouth.

I also began practicing some relaxation techniques I read about in a flight magazine. I imagine a cabin in the woods with snow falling. Everything is seen in a light blue tint. I don't like snow or cold weather, but for some reason that scene is very peaceful to me.

I also envision a favorite beach in Cabo San Lucas. That is what I call relaxation. Warm, sunny, with a Corona in hand! Sadly, there are no vendors in my dreamland version.

Sleep Disordered Breathing

The reported frequency of sleep-disordered breathing (SDB) in patients with PD varies from 20% to 60%. This is an unexpected association because the usual patient with PD is not obese, a major factor in the development for SDB. Possible etiologic explanations include decrease in upper airway muscle tone because of degeneration of the brainstem, serotoninergic neurons that ennervate the muscles of the upper airway, deficient respiratory muscle coordination, or autonomic dysregulation (Swick, 2012).

In a cross-sectional survey, researchers assessed the risk of SDB in patients with PD versus controls in a university-based movement disorders clinic. They identified a high risk of SDB in 49% of the patients with PD compared to 35% of controls. After adjustment for age, gender, and body mass index, patients with PD showed a higher risk for SDB than controls did. The survey also found that quality of life was significantly decreased in patients with PD at high risk for SDB (Swick, 2012).

REM Sleep and Hallucinations

Treatment with dopaminergic agents has been associated with hallucinations in up to 40% of PD patients. Three factors have been shown to be independently predictive of visual hallucinations: severe cognitive impairment, duration of PD, and daytime sleepiness. The presence of RBD has been found to increase the risk of hallucinations by a factor of 3. The brainstem degeneration that is responsible for RBD may also be responsible for the intrusions of dream mentation into wakefulness that are then manifested as hallucinations. Parkinson’s disease hallucinations are best treated by the discontinuation of centrally acting anticholinergic agents, anxiolytics, antidepressants, and opiate pain medications. The use of the newer “atypical” antipsychotics has been shown to reduce the hallucinations without substantially worsening the motor symptoms of PD (Swick, 2012).

Bowel Disruptions

Disruptions in bowel function is another known co-morbidity of PD. Constipation affects most PD patients and can arise many years prior to the motor symptoms of PD. The frequency of bowel movements has been correlated inversely with PD risk, and constipation may be one of the first symptoms of PD. These findings were supported by an epidemiologic study involving women in Olmsted County, Minnesota, where an association between earlier life constipation and PD risk was well documented. Constipation may emerge as much as 20 years prior to a diagnosis of PD (Haas et al., 2012).

Gastroesophageal Reflex Disease (GERD)

Gastrointestinal dysfunction is one of the most common nonmotor features of Parkinson's disease, and was included in the original description by James Parkinson. Gastroesophageal reflux symptoms characterized by heartburn and regurgitation are generally recognized as clinical symptoms of GERD. Gastroesophageal reflux disease can also show dyspeptic manifestations other than reflux symptoms. In clinical practice, disappearance of these symptoms following treatment with proton pump inhibitors (PPIs) allows general physicians to reasonably conclude that the patient had acid-related dyspepsia (Maeda et al., 2013).

Variable abnormalities from the mouth through the rectum may contribute to the onset of GERD in those with PD. Dysphagia is relatively common, being observed in 29% to 80% of PD patients, and can be related to dyscoordination of various organs such as the mouth, pharynx, and esophagus. In addition to abnormalities of esophageal peristalsis, dysfunction in the lower esophageal sphincter can also produce clinical symptoms of gastroesophageal reflux (Maeda et al., 2013).

Olfactory Disruptions

Difficulties in detecting, discriminating, and identifying odors are observed in up to 90% of PD patients. As with other nonmotor symptoms, olfactory deficits can begin several years before motor impairments lead to a clinical diagnosis. In PD patients with mild symptoms, severity of olfactory deficits has been found to correlate with dopaminergic dysfunction (Haas et al., 2012).

To determine whether these early olfactory symptoms might prove useful as a premotor biomarker for PD, a number of studies have examined olfaction in early or asymptomatic patients. A recent prospective study showed that patients with poor olfaction were more likely to develop PD in the four-year followup period than those with normal olfaction (Haas et al., 2012).

Another study found that, when assessing asymptomatic first-degree relatives of PD patients, performance levels of odor discrimination robustly correlated with future PD risk. In addition, **olfactory identification dysfunction** on the University of Pennsylvania Smell Identification Test was able to distinguish PD from other movement disorders and is a strong candidate for a clinical premotor PD biomarker (Haas et al., 2012).

Olfaction in Differential Diagnosis of PD

Inexpensive olfactory probes may improve the diagnostic process in patients with PD. In contrast to imaging procedures, olfactory testing is quick and easy to perform. Validated tests can be used as reliable diagnostic tools even in non-specialized centers (Haehner et al., 2011). The American Academy of Neurology now recommends olfactory testing as an aid in diagnosing Parkinson's disease (Fornazieri et al., 2013).

In a study comparing a smell test with a dopamine transporter scan (DaTSCAN), researchers found that a basic smell test is just as sensitive. According to this study, the sensitivities of the University of Pennsylvania Smell Identification Test and DaTSCAN are high at 86% and 92%, respectively. Although DaTSCAN is superior for localization, a smell test is considerably cheaper. Structured and validated tests of olfactory function should be a mandatory part of the early and differential diagnosis of PD (Haehner et al., 2011).

UPSIT Smell Identification Test

Originally published only in English, the University of Pennsylvania Smell Identification Test (UPSIT) has been translated into more than a dozen languages. This widely used test is considered by many to be the gold standard to which other tests of olfactory function have been compared. It is sensitive to the influences of a wide range of variables, including age, gender, environmental pollution, and numerous diseases (Fornazieri et al., 2013).

The UPSIT consists of four booklets, each with ten pages. Microencapsulated "scratch and sniff" odorant strips are positioned on brown strips that are located at the bottom of each page, resulting in a total of 40 odorants. The subject releases the odor by scratching the strip with a pencil tip in a standardized manner. He or she then indicates the smell that is perceived by choosing a name from a set of four odor descriptors located just above the odorized strip. The number of correctly identified odors serves as the test score (Fornazieri et al., 2013).

A response is required for each odor even if no smell is perceived (i.e., it is a forced-choice test). This procedure enables the detection of malingering based on improbable responses and increases the likelihood that a subject will pay close attention to the released odorant. The UPSIT is strongly correlated with odor threshold tests, and the magnitude of these correlations is limited by the reliability of the threshold test that is being evaluated (Fornazieri et al., 2013).

Speech and Language Impairments

Nearly 90% of individuals with Parkinson's disease develop voice and speech disorders. Difficulties getting speech started and a quiet or weak voice are commonly noted changes. Patients report they are often asked to repeat their words because listeners have difficulty understanding, although patients themselves may self-estimate their speech as loud and sufficiently articulated (Skodda, 2012).

Changes in communication brought about by neurologic disorders are most often defined and described in terms of the individual's impairments of speech and voice (dysarthria) or language (aphasia). Different aspects of speech and language can be measured and quantified using clinical tests and instrumental analyses. The individual's perception of degree of impairment and its impact can also be assessed, using qualitative interviews or self-report questionnaires. However, communication is an interaction, a joint effort, which makes the conversational partner a key player. This is true in all types of everyday conversations, but especially so when one of the interacting persons has a communicative impairment (Hartelius et al., 2011).

The necessary prerequisites in communicative interaction are:

- Intact sensory-motor processes (auditory and visual perception, voice and speech function, ability to gesture, change posture, and so on)
- Linguistic ability (knowledge of the sound system, semantics, syntax, and discourse)
- Cognitive abilities (attention, memory, inference, executive function, affect, and the ability to infer mental states in others, ie, theory of mind)

These capacities interact to form a person's pragmatic ability. The occurrence of any type of neurologic damage can have a negative impact on the ability to communicate in several different ways. Of interest, some studies have indicated that those whose speech is affected by neurologic damage may be unaware of the extent of their communication problems (Hartelius et al., 2011).

There is a growing recognition that language impairments and pragmatic deficits occur in Parkinson's disease. There is increased interest in the role of basal ganglia and frontostriatal systems in the processing of complex language. Affected abilities include:

- Interpretation of the intentions underlying verbal irony and lies
- Theory of mind
- Comprehension of metaphors
- Ability to use vocal cues effectively to infer a speaker's emotions and attitudes (Hartelius et al., 2011)

Dysarthria

Dysarthria is a motor-speech disorder in which the muscles of the mouth, face, and respiratory system become weak. Dysarthria is fairly common in PD and can emerge at any stage of the disease. It generally worsens in the later stages, leading to a progressive loss of communication and social isolation.

Parkinsonian dysarthria has traditionally been considered a manifestation of rigor (stiffness) and hypokinesia of the speech effector organs. This leads to a multidimensional motor-speech impairment that alters speech respiration, phonation, articulation, and prosody.* Hypokinetic dysarthria is characterized by a breathy and harsh voice, monotony of pitch and loudness, reduced stress, variable speech rate with short rushes of speech, and imprecise articulation resulting in a reduction of overall speech intelligibility (Skodda, 2012).

*Prosody is the rhythm, stress, and intonation of speech.

From the therapeutic point of view, the effect of dopaminergic medication on various speech parameters and overall speech intelligibility in particular remains somewhat inconclusive. There are some reports of positive levodopa effects on tongue strength and endurance and of an improvement of speech intelligibility. However, the majority of studies have found no relevant effect of dopamine therapy on speech rate, prosody, and phonatory parameters, or on overall intelligibility (Skodda, 2012).

The results of medical, surgical, and deep-brain stimulation treatments of dysarthria in patients with PD have been variable and generally disappointing. Several studies have suggested that the pathophysiology of speech disorder may be different from the limb movement disorders of Parkinson's, including studies employing functional imaging, demonstrating a negative correlation between disease severity and impaired speech, and showing nonresponsiveness towards levodopa in people with PD-induced oral festination (Kwan & Whitehill, 2011).

Perception of Loudness

For some time, there have been anecdotal reports of a distorted perception of one's own loudness in individuals with PD. Speakers with PD tend to overestimate the loudness of their own voice and when asked to speak with "normal" loudness perceive that they are shouting or producing abnormally loud speech. Another common observation is the ability of individuals with PD to improve their loudness (and other aspects of speech production) when prompted to do so in a clinical or laboratory setting, but with a return to reduced loudness and poorer speech production upon leaving the clinical setting (Kwan & Whitehill, 2011).

Cognitive Changes in Parkinson's Disease

In recent years, there has been increasing interest in cognitive and behavioral changes associated with Parkinson's disease. Recent studies have identified deficits in cognitive function, neuropsychiatric status, and language. There has been a parallel development in the domain of speech, as researchers have turned from a focus purely on speech production deficits to an interest in possible deficits of speech perception (Kwan & Whitehill, 2011).

Cognitive and behavioral symptoms can appear at the earliest stages of the Parkinson's, before any treatment has occurred, and may even be biomarkers for PD. Cognitive profiles are variable and range from mild deficits in specific cognitive domains to severe dementia affecting multiple domains. It is estimated that 19% to 30% of people with early, newly diagnosed PD present with cognitive impairments and these impairments worsen with disease progression (Kelly et al., 2012).

Mild Cognitive Impairment and Dementia

Cognitive impairment and the development of dementia are increasingly being considered part of the course of Parkinson's disease. Of particular importance, nearly 90% of PD patients with dementia exhibit at least one neuropsychiatric symptom, and 77% have two or more neuropsychiatric symptoms. Risk factors for the development of mild cognitive impairment include older age at disease onset, male gender, depression, severity of motor symptoms, and advanced disease stage (Leroi et al., 2012).

The prevalence of dementia in PD is estimated at 26% to 44%, with over 80% developing dementia within 20 years of diagnosis. Mild cognitive impairment (MCI) in people with PD is associated with the development of dementia within 4 years (Kelly et al., 2012). Depression can exacerbate cognitive impairments in PD, and the frequency of depression in PD is estimated at 25% to 33% (Kelly et al., 2012).

In a study that examined clusters of neuropsychiatric symptoms and cognitive status in PD, it was found that in people suffering from hallucinations nearly 80% had dementia; in those with mixed neuropsychiatric symptoms nearly 58% had dementia; and in those with mild depression 31% had dementia. Patients experiencing hallucinations tended to have longer disease duration, more severe motor symptoms, and older age (Leroi et al., 2012).

Mood Alterations

Mood alterations such as depression, anxiety, and apathy are increasingly being thought of as a component of PD. Supporting this theory are findings of alterations in the serotonergic signaling pathways. As with sleep disorders, constipation, and olfactory disruption, anxiety and depression are nonspecific and do not stand alone as clinical premotor PD biomarkers (Haas et al., 2012).

Depression

The most frequently experienced and researched psychological difficulty in people with PD is depression. Some researcher has demonstrated that the pattern of depression varied in a nonlinear way over the course of PD and suggested that depression is not simply a result of increasing impairment. Other studies have suggested that disability and participants' perceptions of the personal and social impact of PD were stronger predictors of depression than impairment (Simpson et al., 2013).

Depression is detected in nearly a quarter of patients in the early stages of PD. Several groups have indicated that in the later stages of PD depression rates are approximately 40%, but that this rate is probably grossly underestimated (Haas et al., 2012). Depression and anxiety tend to be more frequent during medication off-periods and often improve when the dopaminergic treatment is optimized (Lokk & Delbari, 2012).

Antidepressants—especially serotonin reuptake inhibitors (SSRIs)—are widely used to treat PD patients with depression. Other drugs are less advisable because they carry more risk of cognitive side effects, which is especially true for tricyclic antidepressants (Lokk & Delbari, 2012).

Anxiety

Two-thirds of PD patients with motor fluctuations experience anxiety, often associated with irritability (Lokk & Delbari, 2012). Some researchers have even speculated about a possible "parkinsonian personality" that involves such traits as inflexibility, neuroticism, obsessive-compulsivity, uneasiness, and anxiety, among others. These characteristics may be present from childhood, leading to the possibility of long lasting biologic changes preceding PD motor symptoms, and possibly implying that the observed motor symptoms of PD are really characteristic of end-stage disease (Haas et al., 2012).

Apathy

The behavioral syndromes of apathy and impulse control disorders, and the symptoms that comprise them, have received much less attention and are less well understood than cognitive impairment and dementia (Ahearn et al., 2012).

Apathy is defined as a lack of goal-directed behavior, cognition, or emotion. It is closely linked to cognitive impairment and may even be a harbinger of conversion to dementia. A recent longitudinal study of a PD cohort without dementia found that after a median period of 18 months, the proportion of those who converted to dementia was significantly higher in those with apathy. In those who did not develop dementia, cognitive decline was still greater in the apathy sufferers (Leroi et al., 2012).

The Psychosocial Impact of Stigma

Several studies have found correlations between perceived stigma and depression in people with PD. Participants in qualitative studies have repeatedly reported embarrassment and shame about having PD. From a social relations perspective, it is argued that these feelings are, in part, a result of stigmatizing attitudes and actions of other people because PD is seen as breaking social rules. The shame experienced by people with PD can be considered "public shame," with their home and private world being experienced as safer, which highlights the social relational nature of shame (Simpson et al., 2013).

The socially created shame about having PD may be internalized and taken on as part of a person's self-identity. Some qualitative studies have explored the concept of self-identity in PD, and participants have described the challenges of living with PD and how it affects their sense of self and their social roles. People with chronic illness may feel discredited, which can be influenced by stigmatizing and disabling societal views of illness (Simpson et al., 2013).

A person may internalize the negative stereotypes of what it means to have PD. This may be particularly pertinent for people who acquired impairments as adults after they had earlier developed perceptions of impairment from a non-impaired perspective. They may impose their own non-impaired view of illness on themselves. For example, a person with PD may experience negative feelings about being a burden and strive to sustain independence (Simpson et al., 2013).

Changes in Social Contact

Changes in social contact are reported by many people with PD. In some studies, participants described choosing to spend time with people who were in a similar position to them rather than people without PD or impairment. Other people's lacking understanding or being uncomfortable with PD have been cited as a contributory factor to altered social contacts. People who have Parkinson's disease have reported benefits from spending time with other people with PD in nonstigmatizing contexts such as self-help and therapeutic groups. Moreover, studies have found that people with PD and their families often avoid social situations due to fear of negative judgment by others. As such, negative and stigmatizing public attitudes or action by others are considered to limit social opportunities for people with PD (Simpson et al., 2013).

Negative social experiences can contribute to psychological difficulties. For example, social rejection and reduced social contact have been found to be associated with depression in people with PD. Experiencing psychological difficulties may further fuel the stigma associated with PD, since mental health difficulties in themselves have been found to be stigmatizing. People with PD have reported being reluctant to take medication or engage in psychological therapy for depression because of the additional stigma associated with perceived mental health problems (Simpson et al., 2013).

The Stigma of Impaired Communication

People who have Parkinson's may be subject to negative actions and stigmatizing attitudes about their communication style. For example, there may be misunderstanding and lack of awareness about speech or **expressive masking**, reduced facial, body, and vocal expressions due to muscular difficulties. People with PD have been perceived by others as being less sociable, less happy, and less friendly due to their speech style and facial masking. **Some aspects of personality** (e.g., extroversion, neuroticism) **in people with facial masking are often inaccurately perceived by professionals, particularly by novice professionals.** Furthermore, studies have found that caregivers can often misinterpret how people with PD are feeling (Simpson et al., 2013).

Misinterpretation and inaccurate judgment about a person's character or feelings may affect social interactions. This may emotionally impact the person with PD. However, more experienced professionals were found to be less likely to misinterpret neuroticism than novice professionals, suggesting that experience and awareness of PD contributes to more accurate perceptions. Accordingly, raising public awareness about the lesser known features of PD, such as facial masking, may help reduce negative or misinformed perceptions (Simpson et al., 2013).

Medical Management of Parkinson's Disease

Because diagnosis is based on medical history, neurologic examination, and observation over time, a correct diagnosis is critical for effective management of the disease. Since many other diseases have similar features (especially when symptoms are mild), a timely and precise diagnosis is important so that patients can receive the proper and early treatment.

Brain scans and laboratory tests can be used to rule out other diseases but commuted tomography (CT) and magnetic resonance imaging (MRI) brain scans of people with PD usually appear normal. Cellular changes that occur on a microscopic, chemical level cannot be reliably detected by scans or blood tests.

Although there is progress on tests that can identify the presence of PD *in vivo*, Parkinson's can currently only be definitively confirmed through its pathologic hallmark of Lewy bodies and Lewy neurites upon postmortem analysis (Haas et al., 2012). **In the absence of confirming tests, the patient's response to levodopa is often used to confirm the presence of PD.**

There is a consensus among clinicians and researchers that new medical treatments for Parkinson's disease should move from treating symptoms to modifying the disease pathology. The ultimate goal is to find neuroprotective treatments that stop or even prevent neurologic degeneration.

Symptomatic Treatment

Symptomatic Parkinson's disease therapies are designed to alleviate motor and nonmotor symptoms, delay the progression of the disease, and manage the side effects of treatment. The challenge faced by clinicians is to find best treatments for each patient, re-evaluating as symptoms change. Among the many symptoms that occur in PD, cognitive changes, fatigue, anxiety and depression, sleep disturbances, and bladder and bowel dysfunction are usually treated successfully with a variety of drugs.

Early PD symptoms can be vague: increased clumsiness with the hands, mild gait irregularities, and intermittent tremor that is most obvious when the hand is resting or suspended when walking. Tremor, when present, is regular and rhythmic. A number of nonmotor symptoms such as loss of smell, sleep disturbances, sensory changes, and pain can occur well before motor symptoms are evident.

Dopamine Replacement

The pharmacologic mainstay for the treatment of Parkinson's disease is the replacement of dopamine with levodopa, a precursor of dopamine. Dopamine replacement poses many challenges because only about 10% of a levodopa dose actually crosses the blood–brain barrier and enters the brain. The remaining levodopa is susceptible to conversion to dopamine in the periphery, leading to side effects such as nausea, dyskinesias, and joint stiffness. To address this, inhibitors that reduce the breakdown of dopamine in the peripheral nervous system—called *peripheral dopa decarboxylase inhibitors* (carbidopa and benserazide) are given in combination with levodopa to reduce peripheral conversion that would otherwise devour most of the dose given. The addition of dopa decarbozylase inhibitors also maximizes bioavailabilty of dopamine in the brain, decreases side effects, and allows a lower dose of levodopa to be used.

Once in the brain, as dopamine travels from one cell to another, it can be broken down and rendered inactive by two enzymes, MAO (monoamine oxidase) and COMT (catechol-O-methyl transferase). One therapeutic strategy introduces a MAO inhibitor into the synapse, which interrupts the action of the MAO enzyme and prevents the breakdown of dopamine in the synapse. This allows more dopamine to remain in the synapse and increases the likelihood that it will bind to the postsynaptic membrane.

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. Controlled release versions of levodopa in the form of intravenous and intestinal gel infusions spread out the medication and are showing promise.

Initial drug treatment may start with MAO-B inhibitors and dopamine agonists. Levodopa plus a dopa decarboxylase inhibitor (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, L-dopa eventually becomes ineffective for treating the motor symptoms and may concurrently *cause* dyskinesias. As medication becomes less effective, "off" periods may occur when the levodopa dose has worn off and movement is again difficult until a new dose is given. Medications to treat nonmovement-related symptoms of PD, such as sleep disturbances and emotional problems, are also considered as needed (Goodman & Gilman, 2011).

After prolonged therapy with levodopa, a person with PD may alternate between phases with good response to medication and few symptoms (the "on" state) and phases with no response to medication and significant motor symptoms (the "off" state). Levodopa doses are therefore 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).

Transdermal Patches and Intestinal Gels

Transdermal dopaminergic patches is a recently developed therapy that has important advantages over pills and injectable medications. A patch formulation provides a more constant drug delivery, offers better compliance, avoids drug–food interactions, and offers the possibility of a once-a-day alternative. Additionally, pills may lose some clinical effectiveness when they are processed in the liver. The idea of a patch for a disease such as PD, where there are multiple drugs and multiple doses, is therefore very attractive to patients and to caregivers (Okun, 2012).

Duodopa is a new therapy recently out of clinical trials in the United States. Duodopa was approved for use in Europe in 2004. It may provide significant benefits by improving "on" time and reducing on-off fluctuations and dyskinesia. Duodopa is a pump-based therapy and requires the patient to wear a large external "box" in the belt region that is used to administer the intestinal gel preparation through a surgically placed intestinal tube.

Duodopa requires an attentive caregiver who must manage the device, the skin surrounding the tube, and medication refills. Early studies have revealed high rates of device-related problems with the intestinal tube (eg, clogging, kinking, moving out of the correct location). Despite these tube-related issues, Duodopa will likely be a great choice for many patients with on-off fluctuations, and will in most cases allow discontinuation of oral PD drugs (Okun, 2012).

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. Agonists were initially used to alleviate symptoms during the "off" state in patients with late PD when the benefits of levodopa doses were wearing off. Agonists are also used as an early alternative to levodopa so that later complications and dyskinesias are postponed for as long as possible.

Dopamine Agonists	
Generic name	Brand name
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 non-ergot dopamine agonists also used for restless legs syndrome.

Dopamine agonists produce significant, though usually mild, side effects such as drowsiness, hallucinations, insomnia, nausea, and constipation. Agonists have also been related to impulse control disorders such as compulsive sexual activity, compulsive eating, and pathologic gambling and shopping. If side effects appear even at a minimal effective dose, another drug from this class can be tried as an alternative. These drugs are less effective than levodopa in the control of motor symptoms but are usually sufficient in the earliest stages of the disease.

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. Like dopamine agonists, MAO-B inhibitors alone can improve motor symptoms and delay the need for levodopa early in the 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 PD Treatment

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

Anticholinergics that block the neurotransmitter acetylcholine in the central and peripheral nervous system may be useful to treat 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 non-steroidal anti-inflammatory drugs (NSAIDs, apart from acetaminophen and aspirin), have a lower risk of ever developing PD. Other medications are listed in the following table.

Other Drugs Used for Treating Parkinson's Disease	
Drug	Purpose
Memantine (Namenda), rivastigmine (Exeleon), galantamine (Razadyne)	Treatment of cognitive difficulties—these are NMDA receptor antagonists or acetylcholinesterase inhibitors.
Antidepressants	Treatment of mood disorders
Gabapentin (Neurontin, Gralise, Fanatrex)	Treatment of certain types of seizures or restless legs syndrome
Duloxetine (Cymbalta)	Treatment of depression, anxiety, peripheral neuropathy, fibromyalgia, or chronic pain related to muscles and bones. This is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI).
Fludrocortisone, midodrine, botox, sidenafil	Treat of autonomic dysfunction
Armodafinil (Nuvigil), clonazepam (Klonopin), zolpidem (Ambien)	Treatment of sleep disorders and daytime wakefulness

Treatment of L-dopa Induced Dyskinesia

Levodopa remains the most effective agent to improve motor symptoms in PD but, as noted earlier, chronic use is associated with the emergence of motor fluctuations. This is manifested by a loss of clinical benefit before the next levodopa dose (wearing off), dyskinesias (abnormal involuntary movements), and nonmotor complications, such as behavioral and cognitive changes (Tambasco et al., 2012).

In most patients, L-dopa treatment begins with a "honeymoon" period during which motor symptoms are well controlled. However, after 5 years of treatment, approximately 40% of patients develop fluctuations in symptom control in response to the drug, as well as involuntary movements known as "L-dopa-induced dyskinesias" (LID). These complications affect as many as 89% of PD patients after 10 years of L-dopa treatment (Aviles-Olmos et al., 2012).

Dyskinesias usually improve when dopaminergic therapy is reduced but the reduction often cause PD symptoms to worsen. As the "off" state gets longer, bradykinesia usually increases, motor performance worsens, and daily activities are adversely affected.

Three risk factors are associated with increased occurrence of dyskinesias—younger age at disease onset, longer disease duration, and longer duration of dopaminergic treatment. The first two factors are interrelated and almost all patients with early-onset PD develop dyskinesias, whereas they are less frequent in patients with late-onset PD. Other risk factors associated with increased risk of dyskinesias are female gender and the occurrence of specific polymorphisms for dopamine receptors or dopamine transporters (Tambasco et al., 2012).

Peak Dose Dyskinesia

Dyskinesias more commonly appear as choreiform,* but in some cases they may resemble dystonia, myoclonus, or other movement disorders. Peak dose dyskinesias are the most common type of dyskinesia, which occur during peaks of levodopa-derived dopamine in the brain, when the patient is otherwise experiencing a beneficial response (the "on" state). Peak dose dyskinesias worsen with increases in dopaminergic dose and lessen when dopamine dose is reduced (Tambasco et al., 2012).

*Involuntary, irregular, dance-like movements that appear to move from one muscle to the next.

Diphasic Dyskinesia

In certain cases, dyskinesias appear with an alternating pattern (dyskinesia-improvement-dyskinesia). This is termed **diphasic dyskinesia**, and it tends to occur when levodopa-derived dopamine concentrations are increasing or decreasing. Diphasic dyskinesias are typically displayed with large-amplitude stereotypic, rhythmic, and repetitive movements, more often of the legs, that may be associated with parkinsonian features in other body regions. In extreme cases, patients treated with levodopa can cycle between "on" periods, which are complicated by disabling dyskinesias, and "off" periods, in which parkinsonism is uncontrolled and the patient is akinetic and frozen (Tambasco et al., 2012).

Motor complications occur in about 50% of patients with PD who have been in therapy with levodopa for more than 5 years, and in almost 100% of patients with young-onset disease. Achieving an acceptable clinical control once these motor fluctuations have appeared is usually a relatively simple matter, increasing the frequency of the levodopa doses or adding medications that reduce "off" time. However, when a patient develops peak dose dyskinesias too, it becomes difficult to smooth the clinical response. Although for many patients dyskinesias are not disabling, they create a barrier to adequate treatment of fluctuations and parkinsonian symptoms (Tambasco et al., 2012).

Alan: Living with Parkinson's

My symptoms were worsening in 2010, and my quality of life was not what it had been. Dyskinesia, which is a common symptom of Parkinson's, was the main problem. I could barely sit in a chair—I was constantly tipping over. On several occasions I even twisted right out of my office chair while at work.

It was when I saw two videos of myself that I started thinking seriously about having deep brain stimulation (DBS) surgery. One video showed me dancing with my daughter at her wedding; the other showed me speaking to the local Parkinson support group in early 2011. I was not aware how much my head was twisting until I saw those videos.

I was also experiencing an increasing number of Parkinson's "spells." The medical people call it "down time," when your body does not respond to your medications. When I had a spell, I couldn't walk but had to shuffle from place to place using one or two canes. I also had a fear of falling, which was happening a lot more often.

I decided to talk with my neurologist about having the DBS procedure. We had talked about the surgery as an option several times over the years. He had never recommended it because of the risks involved, but when I brought it up this time his attitude had changed.

"They are having a very high success rate these days," he said.

Deep Brain Stimulation (DBS)

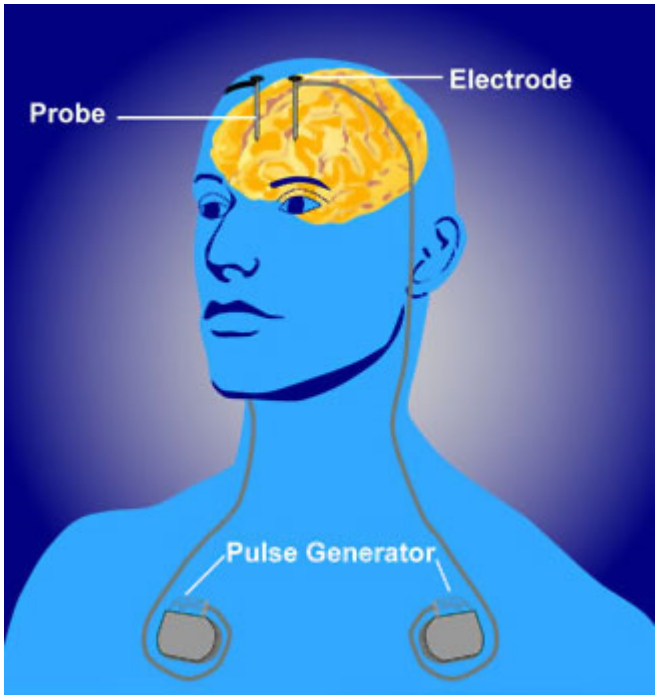
Deep brain stimulation (DBS) was approved by the FDA in 1997. It is recommended for people who have PD and suffer from motor fluctuations and tremor inadequately controlled by medication, or for those who are intolerant to medication, as long as they do not have severe neuropsychiatric problems (Okun, 2012). About 85,000 people worldwide have had DBS.

Deep brain stimulation is a surgical intervention that utilizes an implantable pulse generator (neurostimulator) as a waveform generator and power source. The neurostimulator controls the flow of current to specific brain regions through an attachment to an implantable DBS lead. Each DBS lead has multiple contacts and therefore many possible parameter configurations. The optimization of possible settings, which may number into the thousands when considering the range of pulse widths, frequencies, amplitudes, and configuration of anodes and cathodes, can provide a critical determinant for therapeutic success or failure (Fakhar et al., 2013).

Deep brain stimulation is a two-stage procedure involving 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 in the operating room, a path for the very fine metal electrodes is selected that will reach the target. The DBS electrode is placed, 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 (Fakhar et al., 2013).

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 anesthetic 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 in 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 (Fakhar et al., 2013).

Deep Brain Stimulation Diagram



Source: NIMH, n.d.

Determining Candidates for DBS

In deciding candidates for DBS, a good carbidopa/levodopa (Sinamet) profile is considered a key determinant for success. A person with a good Sinamet profile:

- Shows dramatic improvement in response to Sinamet
- Experiences a dramatic difference between "on" and "off" states
- Appears near normal in the "on" state
- Spends most of the day "off" (Larson, 2011)

Deep brain stimulation has shown good results with certain symptoms of PD while having little effect on other common symptoms. Dyskinesias and tremor are the symptoms most commonly helped. DBS can reduce on/off fluctuations (more "on" and less "off") and can also address:

- Dyskinesias
- Tremor
- Stiffness
- Slowness of movement, including freezing episodes
- Shuffling gait (Larson, 2011)

Deep brain stimulation does **not** help:

- Swallowing problems

- Softness of speech
- Constipation
- Drooling
- Memory difficulties (Larson, 2011)

Alan: Living with Parkinson's

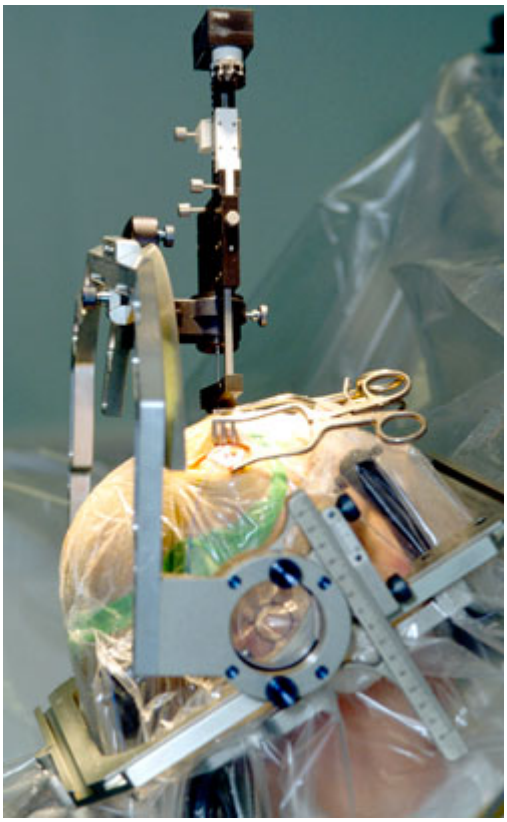
To see if I was a good candidate for DBS, I had to undergo a series of tests. They began by videotaping me doing a series of movements such as walking, touching each of my fingers with my thumb, and standing up from a chair with my arms crossed in front of me. They made a video of me with no medication in my system and again after being medicated. The difference was major, but not surprising to me.

Another session was with a voice therapist. Again a video was taken of me doing various vocal exercises. Next was a swallowing test where I swallowed a variety of items, both liquid and solid.

The final session was a three-and-a-half hour neuropsychology exam. Each exercise started out simple but became more difficult.

I was mentally drained when it was over.

Deep Brain Stimulation Surgery



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

My surgeries were scheduled for August 2011. There were three in all. The first two were to open holes in my skull and put the wiring in place and the third was to install the device that creates the electrical impulse and connects everything together.

During the first two surgeries I was conscious. My skull was placed in a halo device to hold it steady. During the surgery the neurologist asked me to do certain movements at his command.

Someone asked me how it was to be conscious while the procedure was going on. I said that the hard part was hearing the drill as it bore through my skull.

Complications in Deep Brain Stimulation

Deep brain stimulation is associated with certain complications. Because an electrode penetrates the brain, there is a slight risk of puncturing small or medium-sized blood vessels. This occurs in 2% to 3% of cases, although permanent brain damage occurs in only 0.6% of cases, or 1 in 200. Infections occur in 4% to 5% of cases and may require removal of the hardware, although the brain electrodes are usually left in place. The most common site of infection is in the chest where the battery pack is located (Larson, 2011).

In less than 2% of cases, DBS has no effect and symptoms fail to improve, either due to malpositioned electrodes or because of an incorrect diagnosis. The success of DBS depends on a confident diagnosis and the choice of a good candidate. "Garden variety" PD responds well to DBS (Larson, 2011).

If other movement disorders that mimic PD are present, DBS is not effective. Red flags for the presence of something other than PD include more brain atrophy on MRI than is expected for a person's age, evidence of severe vascular disease, or signs of other neurologic disease. A clinician should be suspicious of other neurologic disorders if these factors are present:

- Rapid onset of symptoms
- Rapid progression of symptoms
- Early onset of symptoms (early memory loss)
- Postural instability soon after diagnosis
- Autonomic failure soon after diagnosis
- Unusual findings on exam or on MRI (Larson, 2011)

Sinamet responsiveness is often used to determine the presence of PD, and a trial of this medication should clearly improve symptoms. Tests are performed before and after medication, and a 30% improvement after taking Sinamet is considered a good response and is usually correlated with a good response to DBS. Deep brain stimulation generally does not make symptoms better than a person's best "on" state; rather, it tends to make "off" periods more like the "on" periods.

Degree of disability is important when considering DBS. Generally, it is not recommended in the early stages of PD when a patient is doing well on a consistent amount of medication that is controlling symptoms throughout the day. These patients are encouraged to wait, partly because the technology is improving rapidly. At the other end of the spectrum patients should not wait until symptoms have progressed so far that medications are ineffective (Larson, 2011).

Impaired Memory and Cognitive Function

Parkinson's patients with impaired cognition generally do not do well with DBS, partly because the procedure is complicated and the patient must be able to reliably and clearly explain symptoms. Specific memory testing is now done on all patients to try to identify cognitive issues. If DBS is done in someone with memory problems, it is usually done only on one side of the brain and the patient is allowed to fully recover before the second implant is considered (Larson, 2011).

Age is also a consideration with DBS, although there is no cut-off age. Of concern is that with age the benefits associated with DBS decrease and the risk increases. Those over the age of 75 see only modest benefit and patients over the age of 80 are rarely offered DBS (Larson, 2011).

There are a number of other medical problems that increase risk of a poor outcome with DBS. Poorly controlled hypertension can make blood pressure difficult to control during surgery. Significant cardiac disease increases risk, especially in patients on blood thinners, which must be stopped a week before DBS surgery and remain stopped for a week after surgery. Other medical conditions such as diabetes or the use of steroid medications increase the risk of infection; however, this does not contra-indicate the DBS in many cases (Larson, 2011).

Long-Term Results Following DBS

Long-term results depend on which region of the brain receives DBS. Stimulation of certain areas of the brain primarily reduces limb tremor. Targeting other areas appears to reduce all of the major motor problems with PD, including those dyskinesias that arise after extended use of levodopa (Larson, 2011).

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 and it allows a reduction in levodopa use so that side effects are pushed further into the future (Larson, 2011).

A study in Italy, which followed 14 patients for several years after DBS surgery, showed a 56% improvement after 1 year, a 45% improvement after 5 years, and a 42% improvement after 9+ years. The symptoms varied, however: tremors had the best sustained improvement, gait improved significantly after 1 year but declined over the next 8 years. Posture, balance, and ADLs (eg, rising from a chair) improved significantly after 1 year with no further improvement after 9 years (Larson, 2011).

Alan: Living with Parkinson's

After the final surgery, I had to wait another week before the programming. That week seemed like an eternity.

But the day finally arrived. My neurologist turned on the device and started giving me the same commands he had given me in surgery. "Tap your foot, raise your leg, wave, turn the door knob, open and close your fist."

Then came the real test.

"I want you to go out the door and walk down the hall."

I did it without hesitation.

One of the nurses who had seen me wheeled in said, "It's a miracle, he can walk again!"

Pallidotomy

Pallidotomy is a procedure in which a tiny electrical probe is placed in the globus pallidus (part of the basal ganglia), which is then heated to 80°C for 60 seconds, to ablate a small area of brain cells. Pallidotomy is an alternative to DBS for the treatment of levodopa-induced dyskinesia, and it can be an alternative to DBS for treating difficult cases of essential tremor.

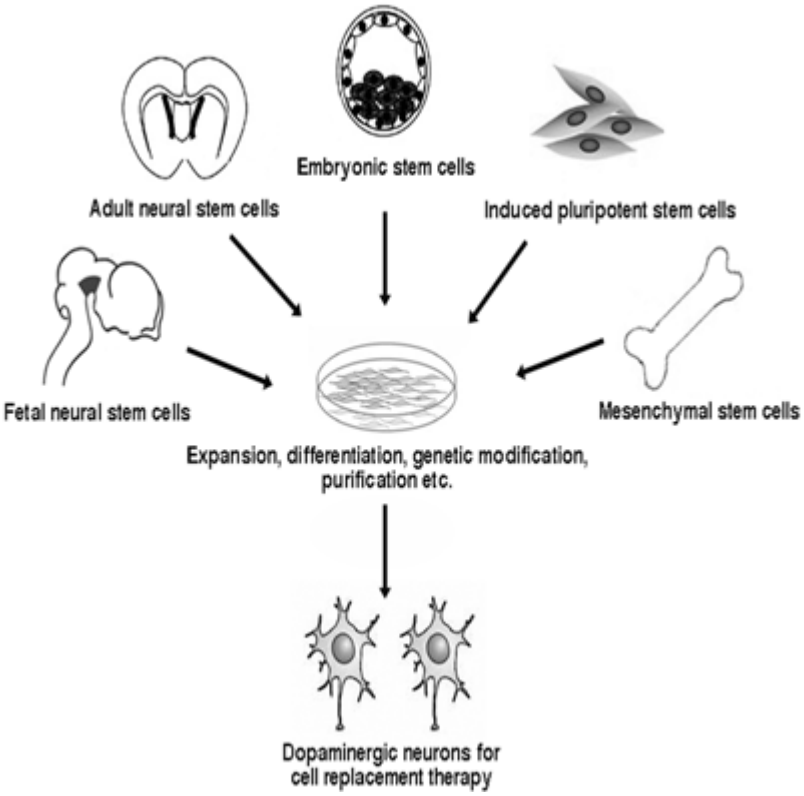
Stem Cell Therapies

Stem cells are undifferentiated cells without mature, tissue-specific characteristics that are able to reproduce themselves by division into identical daughter cells. In response to proper stimuli, stem cells are able to produce more specific progenitor cells that can further differentiate into one or more functional cell types. Stem cells represent a very promising source of cell replacement therapy in a number of diseases, including PD, due to these key properties, namely, self-renewal and multipotentiality as well as the possibility to manipulate these cells *in vitro* (Jensen et al., 2011).

Dopaminergic neurons can be generated from stem cells of different sources. **Embryonic stem cells (ESCs)** have unlimited self-renewal capacity and are *pluripotent*, since they are able to generate cells of all three germ layers. Somatic (tissue-derived) stem cells can be isolated from developing tissues of the fetus or in the newborn, juvenile, or adult organism. **Somatic stem cells** have a more limited proliferation capacity than ESCs and are termed *multipotent*, typically being able to differentiate into the different cell types of one germ layer. Potential groups of stem cells for PD cell therapy include embryonic stem cells, neural stem cells, mesenchymal stem cells, and, more recently, induced pluripotent stem cells (Jensen et al., 2011).

The most important question regarding using stem cells as a therapy for PD remains whether it is possible to generate a large number of cells with the capacity to survive and function as dopaminergic neurons following transplantation; in addition, to ensure that these stem cell-derived grafts do not show adverse effects such as tumor formation or immune rejection (Jensen et al., 2011).

Types of Stem Cells



Source: Intechopen.com.

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 in hope that they incorporate themselves into the brain and replace the dopamine-producing cells that have been lost. Though the results of dopamine-producing cell transplants were initially positive, further trials have not shown 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 continue to be a research target, because stem cells are easy to grow and manipulate, and when transplanted into the brains of rodents and monkeys they have been able to survive and reduce abnormalities. Reprogramming of cells using pluripotent stem cells derived from the patient is being actively studied.

Several molecules have been proposed as potential treatments aimed at reducing the rate of degeneration in PD patients. None of them have been convincingly shown to reduce degeneration.

Video (3:46): Parkinson's Progress and Promise in Stem Cell Research

California Institute for Regenerative Medicine, 2009.

Inhaled Levodopa

Clinical trials, partly funded by the Michael J. Fox Foundation, are underway on an inhaled formulation of levodopa. Called CVT-301, the therapy is designed to function as a sort of "rescue drug" to be taken in conjunction with the traditional pill form of levodopa/carbidopa (Sinemet). The idea is that patients taking CVT-301 could self-medicate by taking a puff from an inhaler should they feel an "off" period coming on. The medication is inhaled into the lungs and passes into the bloodstream much more quickly than oral medication.

In December 2018, the U.S. Food and Drug Administration (FDA) approved Inbrija™ (levodopa inhalation powder) for the intermittent treatment of "off" episodes in people with Parkinson's disease who are already treated with carbidopa/levodopa. Inbrija, an inhaled version of levodopa, provides a new method of delivery for this medication.

Rehabilitation

Because Parkinson's disease impairs speech, swallowing, limb function, gait, and balance, it affects all aspects of daily living. Even with optimal medical management these deficits cannot be controlled satisfactorily in the vast majority of individuals (Fox et al., 2013).

A growing body of evidence has emerged revealing significant and clinically meaningful benefits of exercise for addressing PD-related problems. A critical review of the literature identified 23 randomized controlled trials demonstrating that patients who participated in exercise programs had better quality of life, walking ability, balance, strength, flexibility, and cardiovascular fitness compared to those who did not exercise (Dibble et al., 2010).

Exercise studies of both rodent and primate models of PD have demonstrated increased survival of nigrostriatal dopaminergic neurons, suggesting a potential protective effect of exercise as well. Furthermore, a prospective epidemiologic study revealed significant decreased risk of developing PD in people who participated in moderate to vigorous exercise (Dibble et al., 2010).

The impact of exercise is being increasingly considered in studies that have explored **drive activity-dependent neuroplasticity** (modifications in the central nervous system in response to physical activity) such as specificity, intensity, repetition, and saliency (Fox et al., 2013). These findings have emphasized the important role of exercise and rehabilitation in the overall management of PD.

Unfortunately, rehabilitation programs have traditionally been offered in the later stages of PD or as reactive referrals for treatment of secondary impairments, such as aspiration due to swallowing dysfunction, or hip fracture due to falling. Today, such therapeutic options are increasingly being prescribed early in the course of PD and may potentially contribute to slowing of motor symptom progression.

Therapeutic Exercise and Motor Training

There are a number of randomized controlled trials that have assessed the effects of exercise and motor training in people with Parkinson's disease. Overall, these trials support exercise and motor training as beneficial in improving walking, balance, muscle strength, and the performance of functional tasks in people with mild to moderate PD (Allen et al., 2012).

Gait Training

Gait impairments in PD are an important target of therapeutic interventions because of their prevalence and consequences. The use of cognitive processes to consciously attend to and modify gait parameters is a key strategy for gait rehabilitation in PD. For example, people with PD can increase gait speed and stride length when instructed to focus on taking longer strides. Such cognitive strategies improve walking under single-task conditions, but the evidence for transfer to dual-task walking conditions is mixed. The ability to improve dual-task walking using cognitive strategies requires that people with PD focus on walking while also directing cognitive resources or processes to the performance of a concurrent cognitive or motor task (Kelly et al., 2012).

Progressive Resistance Strength Training

Progressive resistance strength training is an exercise therapy that can increase the ability of muscles to generate force. Strength is reduced in many people with PD, most likely because hypokinesia and aging lead to reduced physical activity and disuse. There is preliminary evidence that progressive resistance strength training for people with Parkinson's can result in increased muscle strength and hypertrophy, improved walking ability, and enhanced balance (Morris et al., 2012).

Movement Strategy Training

There are several approaches to physical therapy that can be delivered within the home. One effective method, known as movement strategy training (MST), teaches the individual to compensate for the disabling movement disorders that occur in PD. These approaches teach people to use attentional strategies to consciously bypass the basal ganglia instead using the frontal cortex to initiate and execute functional activities (Morris et al., 2012).

Motor performance is enhanced by the use of structured practice, which breaks down complex movement sequences into segments and focuses attention on each segment before practicing the activity as a whole. Additional components of movement strategy training are the mental rehearsal of forthcoming movements, conscious focus on the movement as it occurs, and the use of supplementary visual or auditory cues (Morris et al., 2012).

Agility Boot Camp

The theoretical basis for a novel, the sensorimotor Agility Boot Camp (ABC) exercise program is based on research from Oregon Health and Science University and others that identified the primary neurophysiologic constraints that limit balance and mobility in PD. The exercises are designed as a circuit with six types of sports skill activities focused on improving basic postural systems:

1. **Pre-Pilates**
2. **Kayaking** to improve biomechanical constraints on joint flexibility, muscle strength, and postural alignment
3. **Tai chi** to improve kinesthesia and increase functional limits of stability
4. **Boxing** to improve anticipatory postural adjustments prior to stepping in multiple directions
5. **Lunges** to improve the speed and size of automatic stepping for postural correction
6. **Agility course** to improve stability and coordination during gait that is challenged by quick changes in direction, avoiding or overcoming obstacles, and

simultaneously performing a secondary cognitive or motor task (King et al., 2013)

Each activity is engaged for 10 minutes with rest periods, and systematically progressed from beginning to intermediate to advanced levels by:

1. Challenging sensory integration (altering vision and/or surface conditions)
2. Adding a secondary, cognitive task
3. Limiting external cues
4. Increasing speed and resistance

Cool-down activities at the completion of the circuit included adapted floor Pilates: stretching of flexors and rotators, strengthening of extensors, and practice of transitional activities such as rising from a chair, getting onto the floor, rolling, and coming to stand from the floor (King et al., 2013).

Powering Forward: Boot Camp for People with Parkinson's (1:02)

Source: youtube.com

Treadmill Training

In study at Oregon Health and Science University, treadmill training was used to address gait and mobility. The training consisted of fast walking on a treadmill for up to 30–45 minutes as tolerated per session, with an additional 10 minutes of warm-up and cool-down of adapted Pilates. Treadmill intensity was started at 80% of each participant's natural over-ground gait velocity and increased to 90% after a week. Natural gait velocity was measured at the beginning of each week with a stopwatch prior to each treadmill training by asking participants to walk 25 feet. From the third week of training, the treadmill speed was gradually increased to reach a goal of 5% to 10% above that week's over-ground walking speed. Participants are allowed to hold onto the railing to focus on gait training. Therapists encouraged participants to increase stride length and height and to keep their upper body erect during the training period but were not allowed to work with the patient on any direct aspects of balance beyond that used for walking on a treadmill. Safety harnesses were worn at the discretion of the physical therapist and none of the participants used a body weight support harness (King et al., 2013).

Multi-Modal Exercise Programs

A Brazilian study looked at the effects on idiopathic PD patients of a multi-modal exercise program addressing functional mobility and cognitive parameters. The aim of the multi-modal exercise program was to develop the patients' functional capacity, cognitive functions, posture, and locomotion through a program that is primarily aerobic. It comprised a variety of activities that simultaneously focused on the components of functional capacity, such as muscular resistance (specific exercises for large muscle groups), motor coordination (rhythmic activities), and balance (recreational motor activities). These components were selected because they seem to be those most affected by PD (Gobbi et al., 2011).

The multimodal program took place over a 6-month period (72 sessions, 3 times a week, and 60 minutes per session). Each session consisted of five components (warm-up, pre-exercise stretching, the main exercise session, cool-down, and post-exercise stretching). All sessions were conducted in the morning, in the "on" medication state, between 1 and 1½ hours after participants' first morning dose of medication. The program was designed in six phases and each phase was composed of 12 sessions and lasted approximately one month (Gobbi et al., 2011).

At the end of each phase there was a progressive increase of load. Heart rate during the sessions remained between 60% and 80% of maximum heart rate, which characterizes training with aerobic predominance. The exercise program was supervised by at least three physical education professionals at any one time. Each participant was required to attend at least 70% of the sessions in order to be included in the data analysis (Gobbi et al., 2011).

A clinical assessment was performed using the Unified Parkinson's Disease Rating Scale, Mini-Exam of Mental Status, and Hoehn and Yahr. Higher scores on the UPDRS and Hoehn and Yahr indicate more severe disease. Conversely, higher scores on the Mini-Exam of Mental Status indicate a more preserved cognitive function. Basic functional mobility and cognitive function was assessed using standardized tests (Gobbi et al., 2011).

The purpose of the study was to demonstrate the effectiveness of a long-term multi-modal exercise program in improving clinical parameters, functional mobility, and cognitive function in people with PD. The results showed a clear maintenance level in disease stage and severity, with an increase on both balance control and functional mobility. Also observed was the maintenance of both the executive functions and the short-term memory (Gobbi et al., 2011).

LSVT LOUD and LSVT BIG

One rehabilitation approach for those with Parkinson's disease is the Lee Silverman Voice Treatment (LSVT) Programs—LSVT LOUD for speech and LSVT BIG for motor systems. These programs focus on increasing the amplitude of movements, use an intensive mode of treatment delivery, and teach individuals with PD to recalibrate their sensorimotor systems using self-cueing and attention to action, which may be important for generalization and long-term maintenance of treatment effects (Fox et al., 2012).

LSVT LOUD and Speech Therapy

Recent investigations consistently report speech symptoms in the early stages of PD. Self-report data from individuals with PD has indicated that voice and speech changes are associated with inactivity, embarrassment, and withdrawal from social situations. Nearly 90% of individuals with PD have speech and voice disorders that impact communication. This includes:

- Reduced vocal loudness
- Monotone, hoarse, breathy voice quality
- Imprecise articulation (perceived as mumbling)

- Rate-related features, such as hesitations and short rushes of speech (Fox, et al, 2012)

LSVT LOUD is a standardized, research-based speech treatment protocol with established efficacy. LSVT LOUD, which focuses on increasing vocal loudness, was developed for the treatment of voice and speech impairment in individuals with PD. The treatment protocol involves intensive treatment delivery (a 1-hour session, 4 days a week for 4 weeks). Positive changes have been noted not only for vocal loudness but also for many other speech dimensions, including intonation (Whitehall et al., 2011).

LSVT LOUD targets vocal loudness in order to enhance the voice source. It uses vocal loudness as a trigger for distributed effects (eg, improved articulation, vocal quality and intonation, reduced rate) across the speech production system. It also seeks to recalibrate sensorimotor perception of improved vocal loudness. Finally, it trains a single self-cue and attention to action to facilitate generalization of treatment effects into functional communication.

Although LSVT LOUD is a standardized treatment protocol, the materials used during treatment and the homework and carryover exercises are tailored to each individual to facilitate motivation, engagement, and the potential to drive neuroplasticity (Fox et al., 2012).

Alan: Living with Parkinson's

Another positive is that I have been accepted in a voice therapy program at Mayo Clinic. It is an hour session four days a week for four consecutive weeks and is specifically designed for Parkinson's speech problems.

When I have completed the sessions, you should be able to hear me better. That's a good thing, since many of my boomer friends have hearing problems! Maybe it was listening to Jimi Hendrix, the Stones, and Iron Butterfly all those years ago when we were young.

LSVT BIG and Physical/Occupational Therapy

In LSVT BIG, training of amplitude rather than speed is the main focus of treatment to overcome bradykinesia and hypokinesia. Training of velocity can induce faster movements but does not consistently improve movement amplitude and accuracy. Training to increase velocity of limb movements may result in hypokinetic (reduced) movement amplitude. In contrast, training of amplitude not only results in bigger but also faster and more precise movement (Fox et al., 2012).

In LSVT BIG, individuals perform movements that are hesitant (akinesia), slow (bradykinesia), and with reduced amplitude (hypokinesia). Changing from one motor program to another (set-shifting) may be disturbed and sequencing of repetitive movements may occur with prolonged and irregular intervals and reduced and irregular amplitudes. External cues may exert disproportionate influences on motor performance and can trigger both motor blocks and kinesia paradoxica (Fox et al., 2012).

The goal of LSVT BIG is to overcome deficient speed-amplitude regulation leading to underscaling of movement amplitude at any given velocity. Continuous feedback on motor performance and training of movement perception is used to counteract reduced gain in motor activities resulting from disturbed sensorimotor processing (Fox et al., 2012).

Most current therapies rely on compensatory behavior and external cueing in order to bypass deficient basal ganglia function. Other protocols focus on retraining of deficient functions. Task-specific, repetitive, high-intensity exercises for individuals with PD include treadmill training, training of compensatory steps, walking, and muscle strengthening. LSVT BIG belongs to the latter restorative approaches and is aiming to restore normal movement amplitude by recalibrating the patient's perception of movement execution. LSVT BIG differs from other forms of physiotherapy in PD in its training of movement amplitude as a single treatment parameter through high effort and intensive treatment, with a focus on recalibrating sensory perception of normal amplitude of movements (Fox et al., 2012).

Therapeutic Exercise and Dyskinesia

A considerable number of studies have shown that exercise is effective in improving gait, balance, freezing, and motor performance in PD. In particular, recent studies on animals allow hypothesizing a direct action of physical activity on the mechanisms responsible for dyskinesias (Frazzitta et al., 2012).

In an Italian study, 10 parkinsonian patients underwent a 4-week intensive rehabilitation treatment. Patients were evaluated at baseline, at the end of the rehabilitation treatment, and at 6-month followup. Outcome measures were the Unified Parkinson's Disease Rating Scale—parts II, III, and IV—and the Abnormal Involuntary Movement Scale. At the end of the intensive rehabilitation treatment, levodopa dosage was significantly reduced, dropping from 1016 mg/day to 777 mg/day. All outcome variables improved significantly by the end of intensive rehabilitation treatment. At followup, all variables still maintained better values with respect to admission. In particular, Abnormal Involuntary Movement Scale scores improved decreasing from 11.90 at admission to 3.10 at discharge and to 4.27 at followup. The results suggest that it is possible to act on dyskinesias in parkinsonian patients with properly designed rehabilitation protocols. Intensive rehabilitation treatment, the acute beneficial effects of which are maintained over time, might be considered a valid noninvasive therapeutic support for parkinsonian patients suffering from dyskinesia, allowing a reduction in medication dosage and related adverse effects (Frazzitta et al., 2012).

The Stigma of Impaired Movement

Given the nature of some symptoms of PD, people with the disease may be subject to stigmatization and discredited because of negative societal perceptions of bodily movement. The more visible and less "normal" the symptoms of PD are, the more likely they are to be judged as socially unacceptable or threatening by people who do not have PD (Simpson et al., 2013).

Research findings offer insights into the nature of stigma associated with movement difficulties. For example, in one study researchers found that women who experienced PD reported discomfort during social interactions because "involuntary movements of arms and legs make them feel especially conspicuous." Participants reported that friends and family could be uncomfortable because they lacked understanding of the physical symptoms and so would make comments and ask questions (Simpson et al., 2013).

Such experiences extended to public situations; studies have found that participants with PD experienced other people staring at them or directly expressing irritation at PD symptoms. Furthermore, people with PD movement difficulties can be viewed as less socially desirable, and this may manifest as hurtful comments or avoidance (Simpson et al., 2013).

In addition, movement difficulties may be misinterpreted by people who are not aware that they are due to PD (eg, mistaken for being drunk). Furthermore, research has demonstrated that judgments about the unacceptability of movement difficulties may be influenced by the age of the person experiencing PD. One study suggested that PD may be viewed as socially unacceptable because it involves a presentation, such as slowness of movement, that is suggestive of older age. Indeed, aging alone can be a source of stigma, with discrimination occurring toward people when they are seen as less competent (Simpson et al., 2013).

Additionally, people may try to conceal an illness due to fear of stigma. Indeed, some research participants have described trying to hide symptoms of PD by not talking or by trying to control body movement. "Passing" in this manner can have negative psychological consequences; hiding the effects of impairment to pass as normal takes physical and emotional effort, and the person is always at risk of exposure if disability status is suddenly revealed (Simpson et al., 2013).

Alan: Living with Parkinson's

I was taking 39 pills a day for the various Parkinson's conditions at the time of my surgeries. I am now down to four.

What I was not prepared for was the withdrawal from all that medication! A friend gave me an article comparing the withdrawal from Sinemet—the main drug used for Parkinson's—to that from cocaine. I felt confused and foggy headed.

I mentioned these conditions to my neurologist at my six-month surgical followup.

As for the confusion and fogginess, he said, "After all, you had brain surgery. You just have to give it time!"

Don't get me wrong, for all of these inconveniences I have experienced, the benefits of DBS surgery far outweigh the negatives. My wife says I laugh more and have more expression in my face. The tremors and dyskinesia are gone or very minor. And I am eating more protein, which makes me happy.

Hospitalization and Parkinson's Disease

Numerous studies have shown that people with PD are hospitalized at higher rates and experience longer stays than those without PD, and as a group accumulate more inpatient days over their lifetime after the PD diagnosis (Aminoff et al., 2011). This was confirmed by an influential Canadian study, in which people with PD were hospitalized at a frequency 44% higher and for longer periods of time (21 days vs. 18 days) than people without PD (Christine, 2011b). However, little is known about what interventions may reduce the need for hospitalization or reduce complications related to hospitalization (Aminoff et al., 2011).

One issue with hospitalization of the PD patient is related to healthcare providers themselves. Because Parkinson's disease is largely managed on an outpatient basis, often by specialists familiar with the course of the disease and its medical management, hospital-based healthcare providers may not have experience treating someone with PD. They may be unfamiliar with the symptoms of PD, with its complex medication regimens and medication contraindications. Additionally, the specialist responsible for a person's outpatient care may not have privileges at the admitting hospital or may not be contacted by the hospital when their patient is admitted.

Confounding the picture, people with Parkinson's disease are usually admitted to a hospital with medical problems unrelated or only partly related to their PD. An Australian study indicated that, among 716 parkinsonian patients admitted to the hospital, only 16% were admitted for reasons related to PD. The remaining admissions were for falls, pneumonia, cardiac disorders, genitourinary infections, gastrointestinal disorders, neoplasia, encephalopathy, syncope, stroke, and dementia (Aminoff et al., 2011).

Whether admitted for a reason directly related to PD or for another reason, the underlying medical and medication complications associated with PD can affect outcomes. A Danish study found that a substantial fraction of hospitalized PD patients deteriorate during their hospital stay (Gerlach et al., 2012).

Despite many hospital's concerns about the quality of care provided to PD patients, most hospitals do not have proper guidelines in place to prevent worsening of PD symptoms and complications during hospitalization (Gerlach et al., 2012). Several studies have highlighted the need for better Parkinson's disease training and, alarmingly, this is true even at hospitals designated as a National Parkinson's Foundation Center of Excellence.

Hospitalization-Related Issues

So what are the issues that affect outcomes for a patient with a PD? Among the most important is medication management, particularly related to dosages, schedule, and contraindications. Failure to follow the required medication schedule and regimen for PD patients can cause delirium, anxiety, or depression, and can profoundly and quickly affect mobility and increase the risk of falls. Medical issues related to PD also arise including increased risk of aspiration, hypotension, venous thrombosis, and infections.

In an emergency, PD patients are encouraged to go to the hospital where they are receiving care on an outpatient basis. But even when a PD patient is admitted to a hospital with a PD center, communication with the PD specialist is not always consistent (Chou et al., 2011). Only one-quarter of the participating National Parkinson's Foundation Centers have a policy *in their own hospital* that triggers a contact from the hospital alerting the PD specialist a patient has been admitted. Moreover, many NPF Centers have yet to implement a systematic process of patient education and engagement in the hospitalization process. Only 61% of NPF Centers reported that they instructed patients to contact their PD Center if presenting to an ED (Chou et al., 2011).

Risk Factors for Deterioration in Hospital

A survey of 684 PD patients in the Netherlands sought to assess the prevalence and risk factors associated with deterioration during hospitalization. Of the patients surveyed, almost one-fifth had been hospitalized in the past year. Traumatic injury, infections, direct PD-related problems, and problems with circulatory and digestive systems were the main admission reasons, which accords with the literature. As in previous studies, confusion and infections were the most common complications during hospitalization (Gerlach et al., 2012).

Several studies have documented high rates of incorrect medications given to hospitalized PD patients—some as high as 74%—and this was found to be associated with deterioration to varying degrees. In the Netherlands survey, having had surgery or not did not matter in terms of medication distribution problems or complications. Somewhat unexpectedly, neurology wards do no better than other wards; there was no statistically significant difference among wards regarding problems with medication distribution, complications, and PD deterioration. Second to medication distribution problems, infections were significantly related to PD deterioration (Gerlach et al., 2012).

Medication Issues

[This section taken largely from Aminoff et al., 2011.]

The failure of hospital staff and hospital pharmacies to provide Parkinson's medications on the precise schedule needed for the medications to be effective is one of the most pressing problems facing those with PD when admitted to the hospital. Hospitals often place PD patients on standard medication order sets without consideration of contraindications. As a result, a person with PD is at higher risk for complications and even death due to issues that arise from their care in the hospital.

Certain medications should be avoided because they are contraindicated in those with PD. If a PD patient becomes confused while in the hospital, consider urinary or lung infections, pain medications, or benzodiazepines as the potential cause. In cases of prolonged confusion, where an antipsychotic is necessary:

Best Options for Prolonged Confusion

- Quetiapine (Seroquel)
- Clozapine (Clozaril)

These two drugs minimally affect Parkinson's symptoms.

Drugs to Avoid

- Haloperidol (Haldol)
- Risperidone (Risperdal)
- Olanzapine (Zyprexa)
- Aripiprazole (Abilify)
- Ziprasidone (Geodon)

Safe Options for Nausea

- Trimethobenzamide (Tigan)
- Ondansetron (Zofran)

Drugs to Avoid

- Prochlorperazine (Compazine)
- Promethazine (Phenergan)
- Metoclopramide (Reglan)

These drugs can worsen PD symptoms.

Do not mix selegiline or rasagiline (MAO-B inhibitors) with meperidine because the combination can cause a serious reaction characterized by blood pressure fluctuations, respiratory depression, convulsions, malignant hyperthermia, and excitation. **Do not stop carbidopa/levodopa or amantadine abruptly**—this can lead to neuroleptic malignant-like syndrome.

In cases of PEG or NG tube administration of crushed medication, give at least 1 hour prior to meals, and be aware that controlled-release (CR) formulations may not work as well due to reduced bioavailability and other factors.

Protein may interfere with carbidopa/levodopa absorption. There is a dissolvable form of carbidopa/levodopa (Parcopa) that may be useful in some patients, but despite its ability to dissolve in the mouth it is not orally absorbed. To avoid or reduce protein interference with absorption, give levodopa 1 hour prior to meals or 2 hours after.

Patients and family members are urged to be proactive by bringing a copy of their medication schedule and dosages when they are admitted to the hospital and to make sure this information is included in the doctor's orders. Patients and family members are also encouraged to talk to the nursing staff about the importance of adhering to the schedule provided and to remind the staff that failure to keep to the schedule of medications can result in motor and cognitive problems.

Patients should bring their medications from home in their original bottles, so they can be used if the hospital pharmacy does not stock a full spectrum of PD medications. The medications brought from home should be given to the nursing staff so they can administer the medications according to the orders provided by the doctor.

Increased Risk for Aspiration

Aspiration is an issue in the hospitalized PD patient and can be exacerbated when medications are not given on time (Christine, 2011b). Aspiration increases the risk of pneumonia, which is the most commonly reported cause of death in those with PD (Aminoff et al., 2011). Aspiration can be reduced by:

- Changing the consistency of food
- Teaching chin-down swallowing
- Teaching expiratory muscle strength training (Aminoff et al., 2011)

Mobility, Falls, and Fractures

A physical therapy evaluation should be initiated so that hospitalized PD patients can be up and moving as quickly as possible. Interdisciplinary training is critical to improve outcomes through prevention and better management (Christine, 2011b).

Falls and fractures may be the reason for admission to the hospital but can also occur after admission. People with PD often have limited mobility and are at increased risk for falls. Poor medication management in the hospital can lead to increased tremors and rigidity and adversely affect balance.

Other Medical Issues

[This section taken largely from Aminoff et al., 2011.]

There are a number of medical issues that affect the hospitalized PD patient more acutely than those without PD. Delirium and encephalopathy (can occur as a result of hospitalization itself—being in an unfamiliar place), infections, changes in medications, changes in the environment, the lingering effects of anesthesia, or pre-existing dementia.

Orthostatic hypotension is common in those with PD and should be closely monitored. Orthostatic hypotension can be treated with reductions of anti-hypertensives, increases in circulating blood volume via intravenous fluids, oral intake, increases in salt intake (salt tablets, diet changes) or fludrocortisone, or increases in arterial pro-contraction drugs such as midodrine or possibly pyridostigmine. Nighttime head elevation and tight thigh-high stockings should also be considered.

A person with PD may be hospitalized as a result of psychiatric problems, including psychosis, anxiety, or depression. For psychotic patients with PD, only two medications—quetiapine (Seroquel) and clozapine (Clozaril)—have been shown in double-blind placebo-controlled trials to **not** worsen motor dysfunction in PD.

Anxiety should be evaluated to determine if it is generalized anxiety or anxiety related to the wearing off of medications. Depression in PD has been shown in double-blind placebo-controlled studies to benefit from tricyclics as well as SSRIs. Tricyclics in low dose were better tolerated than expected in the PD population (Aminoff et al., 2011).

Perceptions of Hospital Care

A 2010 online survey of fifty-four National Parkinson's Foundation Centers of Excellence asked a respondent from each center about his or her perception of care when a patient being followed on an outpatient basis is admitted to their hospital. Survey respondents reported several key issues associated with the care provided to PD patients who are hospitalized. Respondents reported a lack of understanding and awareness of Parkinson's disease, even in the best hospitals, and, somewhat surprisingly, reported that many hospital pharmacies do not stock the full array of PD medications (Okun & Hassan, 2012).

Respondents also noted a lack of awareness among hospital-based healthcare providers that medication timing is critically important in PD. According to the respondents, healthcare providers also lacked the understanding that many common medications for pain, nausea, depression, and psychosis are contraindicated therapies and unsafe for people with PD. For example, anti-emetics such as metoclopramide (Reglan, Metozolv ODT) and prochlorperazine (Compazine) can worsen the symptoms of PD; and, that Clozapine (Clozaril) and quetiapine (Seroquel) are preferred over other antipsychotics. Finally, in the opinion of the survey respondents, hospital-based healthcare providers lacked awareness that poorly managed PD patients might experience mental confusion and other serious symptoms (Okun & Hassan, 2012).

NPF Aware in Care Program

The National Parkinson's Foundation has designed a program to guide people with PD who are admitted to the hospital. Called *Aware in Care*, the program promotes best practices by supporting both the patient and the healthcare organization. They recommend that patients create a hospitalization kit that contains:

- *Aware in Care* materials and extra bottles of Parkinson's medications
- A hospital action plan that provides instructions for a hospital stay
- A Parkinson's disease ID bracelet
- A Medical Alert card
- A list of medications currently in use

Caregivers of PD Patients Weigh In

The impact of maintaining a caregiving role for people with Parkinson's disease has been largely restricted to the assessment of caregiver burden and caregiver strain. Several studies have suggested that increased burden and strain are associated with the duration of caring; the physical health of the patient, including their increasing disability and propensity to falls; patient psychiatric symptoms, including behavioral disturbances (eg, impulse control disorders, apathy); the age of the caregiver; and caregiver mood (Morley et al., 2012).

In a recent British study, Morley and colleagues (2012) assessed the factors influencing the quality of life of those caring for a person with PD. The study identified a number of factors that significantly influence the caregiver's quality of life:

- Female caregivers reported significantly inferior quality of life compared to male caregivers.
- Caregivers with a long-term condition themselves experience significantly inferior quality of life when compared with healthy caregivers.
- Caregivers are significantly affected if the person they are caring for has cognitive impairment and impaired mobility.
- Duration of caring and the age of the caregiver affect caregivers, with older caregivers experiencing inferior quality of life.

Caregivers and Medication Adherence

Although a person in the early stages of PD may be completely independent, in the advanced stages a considerable amount of support is usually needed and many people with PD receive support through informal caregivers such as a spouse or family member. This often extends to medication management, particularly aid in taking medications (Daley et al., 2011).

For a caregiver, the responsibility for the timely management of a relative's antiparkinson medication is essential, and the consequences of non-adherence are substantial. Poor adherence results in the wearing off of the treatment effect, which can significantly increase motor dysfunction. Over-medicating, particularly with dopamine, can result in severe dyskinesia, potentially leading to the development of impulse control disorder and even to psychosis (Daley et al., 2011).

Not surprisingly, medication adherence can be poor in people with PD, especially when cognitive impairment, anxiety, and depression are present. Reported medication adherence in PD was as low as 10% in one study, with 76% acknowledging mistimed or missed doses. For management of drugs with multiple daily doses, only 3% fully adhered to medication regimens (Daley et al., 2011).

Levodopa remains the most efficacious and widely used treatment for Parkinson's disease, with the majority of patients requiring levodopa therapy at some point during the course of their disease. As the disease progresses it can become increasingly difficult for patients to achieve clinical benefits, and they require increasingly higher doses of levodopa. This may lead to adherence-related issues as a result of the increased pill burden and complex dosing schedules. Failure to manage the medication regimen effectively can contribute to functional impairment, decreased quality of life, and increased motor symptoms. Maintaining patients on their therapy is a key issue for the management of PD (Sethi et al., 2009).

Hospital Failures in Medication Management

To try to understand the reasons for poor medication adherence, a structured survey of 20 people with PD and their caregivers in New Zealand turned up five themes that accounted for possible adherence errors both at home and during hospitalization. Survey participants reported particular problems with abrupt withdrawal of PD medications, wrong or vague instructions from healthcare providers, failure of hospital staff to listen to the caregiver's knowledge, lack of knowledge of PD on the part of healthcare providers, and caregiver difficulty remembering to give medications at the required time.

Causing Abrupt Withdrawal

One caregiver described how the benign hallucinations her husband suffered with PD worsened when he was admitted to the hospital for hip fractures. She attributed this sudden change to the morphine administered for his two broken hips. However, the hospital ascribed the exacerbation to his amantadine and "made him go cold turkey." Amantadine was reinstated only when she reminded staff that the abrupt withdrawal of amantadine could aggravate PD and its mental manifestations. Other participants spoke of medication "omissions for several days" in hospital, even though it is "imperative that none of the Parkinson's medications be halted" (Buetow et al., 2012).

Instructions Wrong, Vague, or Misread

One patient stated that for two years her community pharmacy, despite "a lot of the staff changing all the time," had dispensed two PD medications (Sinemet and entacapone) to her with the labeled instruction: "Take 6 tablets once daily as directed." Recognizing this instruction as a dangerous mistake, she reported instead taking 1 tablet of each medicine every 3 hours (Buetow et al., 2012).

Other wrong instructions were given in non-neurological hospital wards through the mischarting of dosing frequencies. According to one participant, herself a practice nurse, this error led to her father receiving doses at wrong times over 2 days. Another patient described how "the charting would change (for her husband with PD). They would have 8.00, 8.30, and I would say, "He is supposed to get his pergolide on a full stomach." "Oh, no, no, it's charted for. . ." (Buetow et al., 2012).

In other instances, information was not wrong but misread: one caregiver indicated that hospital staff "just glanced down" at her partner's chart, getting "in the routine of giving him one without checking it thoroughly." She reported that the neurologist had assured her that the chart was correct, and that "human error" accounted for her daily observation that the Sinemet dosage was short and given "late, anything up to three-quarters of an hour" (Buetow et al., 2012).

In community settings, however, the problem was sometimes the vagueness of dispensing instructions. One caregiver reported how her family had misunderstood instructions to take a medication "4 times a day." They had thought this indicated a need "to time the (PD) medicine to 4 tablets over 24 hours" even though this led to "big lows and big highs" and interrupted their sleep for several months. Based on advice from the prescriber, the Parkinson's Society field officer explained to the family that "you need to give them during the daytime" (Buetow et al., 2012).

Devaluation of the Caregiver and Family

Several participants suggested that hospital staff wanted to take control of the PD medications and did not seek or respect the insights or perspective of the person with PD or their family. According to one caregiver, timing errors could have been avoided "if they (hospital staff) had only asked me—I had the latest scrip." And when patients or caregivers offer information, "nobody listens, like you try and tell them something and they think they know better all the time." This was despite people with PD having experience of what worked best for them: "if you are taking them every day, you know when you need to take them; your body tells you", so "it is not really a sort of arranging it at the same time every day" (Buetow et al., 2012).

It was felt that staff commitments to change the timing could not be relied upon: "They would say, "Oh yes, we will do that tomorrow" but it never happened." Another participant concurred: "They are good at talking on, rather than listening. They did not like being corrected, any of them. I felt that they would have been happier if I had not been there and chased them up on times." Indeed, some staff were perceived to be patronizing. One caregiver said that her partner with PD "was dismissed" by a nurse who "was very abrupt and ignored him and virtually walked off." This was despite—and perhaps contributed to by—his PD making him "slightly slower to respond" and asking of "him quite a bit of courage to speak out." Another caregiver reported that "they will talk to him and they will ignore me" (Buetow et al., 2012).

Lack of Knowledge or Caring Behavior

Participants suggested that staff "do not always understand the way the (PD) medications work" and "were not aware, I think, of the need for Parkinson's people to have their medication at a given time"; they "regard the times as a suggestion, an indication of when you might get them." One participant, a nurse, acknowledged that she was similarly inclined until she developed PD: "I nursed a lot of [PD patients] in the rest homes and hospitals that I have worked in and I was not aware really of the importance." She added that staff "admitted afterwards that it was different for them—having a Parkinson's patient—and a big learning curve" (Buetow et al., 2012).

"Part of the problem," suggested one caregiver, "is they are short staffed they are rushing round all over the place and medication times fall by the wayside." As a consequence, "If they were busy, it [the charted times] did not matter and there was no check whether he [her husband] took the pill." One survey participant, however, questioned the attribution to staff shortages: "There were numerous staff standing around—you could hear conversation and it was not medical conversation, it was more casual talk—so it seems that they could not have given a damn" (Buetow et al., 2012).

Lay Forgetfulness

Timing errors were commonly ascribed to lay error, both by people with PD and their caregivers: forgetting to administer the PD medication on time, for example, because "I am busy doing [something]"; forgetting to use the timer that reminds them when to take their medication; and forgetting "whether I have taken it or not." These memory errors were reported to take place only occasionally.

Consequences included taking late or extra doses of Sinemet to manage motor fluctuations (and then adjusting the timing of the remaining doses) but tending to miss the forgotten doses of other, less potent antiparkinson medications: "I often do forget the ropinirole and that is not such an issue—I just skip that dose" and "I would suddenly think 'Oh, I forgot the amantadine and the pergolide and it is now 3.30, there is no point in having it'" (Buetow et al., 2012).

Managing Advanced Parkinson's Disease

Advanced Parkinson's disease, stage 4 or 5 of the Hoehn and Yahr Scale, is characterized by very limited mobility without assistance, severe motor deficits, risk of falls, and cognitive and psychotic problems. With the advent of L-dopa and other dopaminergic treatments, the progression of PD has become markedly slower; however, over the years treatment loses its efficacy, while a number of complications—such as motor fluctuations and dyskinesia—develop, probably due to the progressive loss of dopaminergic neurons and their striatal and cortical connections. These complications are observed in 50% of patients after 5 years of disease and in 80% of patients after 10 years of treatment (Varanese et al., 2010).

Treatment of the advanced stages of PD is entirely different from earlier stages. Early treatment is geared towards symptom relief and prevention of motor symptoms. During the later stages, the palliative care model is introduced to provide the patient with comfort and support. In the advanced stages, the focus of treatment shifts to treating nonmotor symptoms using a more supportive and palliative approach (Lokk & Delbari, 2012).

Complications in Advanced PD

While worsening of motor function and drug-induced motor complications represents a major challenge in patients with mid-stage to advanced disease, in the advanced stage of PD the most troublesome and distressful complications are usually nonmotor symptoms, including psychiatric and cognitive disorders, autonomic disturbances, and sleep disorders that significantly increase the need for supportive care. Unfortunately, these symptoms are frequently neglected in clinical practice due to limited consultation time, perception of the patient and caregivers that their symptoms are unrelated to the disease, or insufficient awareness of the clinicians, who generally focus on motor symptoms (Varanese et al., 2010).

Proper supporting care becomes increasingly important in advanced PD. Rehabilitative and support services for patients and family become key interventions as the disease reaches its more debilitating stages and pharmacologic or surgical treatment becomes less relevant. Management of motor and nonmotor complications in advanced PD requires careful and ongoing assessment of whether symptoms are a side effect of medication or related to the progression of the disease (Varanese et al., 2010).

Medication Issues

The progressive degeneration of the nigrostriatal dopaminergic transmission means fewer and fewer receptors are capable of taking up L-dopa and converting it to dopamine for subsequent storage and release. Unlike early and mid-stage PD, patients with advanced and end-stage PD experience an enhanced sensitivity to small changes in plasma L-dopa levels that narrow the therapeutic window and negatively impact motor function (Varanese et al., 2010).

As the dose requirements of levodopa increase, patients' functioning is increasingly inhibited in the period before their next dose of medication. This usually functioning deficit takes place 2 to 4 hours after a levodopa dose and may appear as sensory, psychiatric, or autonomic symptoms, or progression of motor symptoms or dystonia. This is called "end of dose wearing off" (Lokk & Delbari, 2012).

"End of Dose Wears Off" Symptoms in Advanced PD	
Systems affected	Symptoms
Sensory	Pain Paresthesias
Psychiatric	Paranoia Anxiety Hallucinations Depression
Autonomic	Sweating Belching Constipation Tachycardia Shortness of breath
Motor	Progression of motor symptoms Dystonia

On-off fluctuations are sudden unpredictable shifts between an over-treated state (on) and an under-treated state (off). Wearing-off and on-off fluctuations overlap in advanced PD. Wearing-off is generally predictable following the L-dopa administration, with the therapeutic window progressively narrowing over the years (Varanese et al., 2010).

Fragmentation of Dosing

Strategies used to address wearing off and on-off fluctuations include fragmentation of dosing—more frequent administration of lower doses—and use of a COMT inhibitor (entacapone and tolcapone), MAO inhibitor (selegiline and rasagiline), or dopamine agonists. Adjunctive therapy with a COMT inhibitor extends the duration of the L-dopa effect by blocking the COMT enzyme in the peripheral catabolism of L-dopa. Potential adverse events, however, may arise from the COMT inhibitors. Increasing synaptic dopamine levels may also be associated with dyskinesia and increased L-dopa toxicity, leading to worsening of dementia and psychosis (Varanese et al., 2010).

Fragmentation of oral therapy, with L-dopa administered up to 6-7 times a day at about 3-hour intervals is a commonly used and effective strategy. However, lowering individual doses of L-dopa may increase the risk of occasional drug failure or delayed response. Substitution of regular L-dopa with controlled-release L-dopa preparations may be particularly reasonable in end-stage patients, but the available extended-release formulations are not always effective and reliable (Varanese et al., 2010).

Dopamine Agonists Contraindicated

The use of dopamine agonists, although theoretically useful in regulating fluctuations by direct stimulation of the postsynaptic receptors, is generally contraindicated in late-stage disease in order to avoid hallucinations and psychosis, as well as worsening of autonomic dysfunction. The main challenge in controlling the on-off response is to improve the “on” time without increasing the dyskinesia. In very late-stage PD this may be achieved using liquid formulations of L-dopa, which can be prepared by dissolving ten 25/100mg standard-release carbidopa/levodopa tablets and 2g of ascorbic acid in 1 L of tap water (Varanese et al., 2010).

L-dopa and Dietary Proteins

The neutral aromatic amino acids contained in dietary proteins may compete with L-dopa for intestinal absorption and transport across the blood–brain barrier. This limits the efficacy of L-dopa and is responsible for the occurrence of motor fluctuations. Low-protein dietary regimens with protein redistribution by shifting protein intake to the evening are an effective strategy to ameliorate the response to L-dopa. Low-protein products designed for chronic renal failure patients are also a safe, well-tolerated, and useful option for end-stage patients (Varanese et al., 2010).

Motor Issues

Maintenance of independent motor function is the primary goal of treatment during the early and later stages of PD. Such a strategy allows the patient to remain independent and mobile for as long as possible and greatly improves quality of life. In end-stage PD the focus of treatment is to make the patient as independent as possible for as long as possible by increasing the time with no dyskinesias and decreasing occurrence of motor and nonmotor "off" times (Lokk & Delbar, 2012).

Dyskinesias

Dyskinesias in end-stage PD are more frequent and are likely to be a consequence of long-term levodopa therapy. A recent study showed that PD patients treated with levodopa for 4 to 6 years had a 40% likelihood of experiencing dyskinesia. Painful and debilitating dyskinesias are less common today than ten years ago due to more cautious, careful, and individualized anti-PD therapy. Lower doses of levodopa and earlier introduction of other anti-PD agents have contributed to this improvement. However, once dyskinesias occur, lowering of dopaminergic therapy, adding inhibitors of MAO-B or COMT, and adding amantadine may have some effect (Lokk & Delbar, 2012).

Debilitating hypokinesia is one of the most common signs of end-stage PD. Episodes of hypokinesia can occur many times a day and are typically associated with either a failure to respond or to the "off" phase of dopaminergic treatment. Frequent dosing of short-acting levodopa/carbidopa every 3 to 4 hours coupled with COMT inhibitors is currently the best therapy to minimize episodes of hypokinesia. This regimen causes the least variation of levodopa in blood levels, with less off-time, more on-time, and better quality of life (Lokk & Delbar, 2012).

The COMT-inhibitor tolcapone has both central and peripheral effects on the dopaminergic metabolism, in contrast to the COMT-inhibitor entacapone, which only acts peripherally. Tolcapone is particularly indicated in advanced patients where the otherwise most commonly used entacapone is no longer effective (Lokk & Delbar, 2012).

In end-stage patients, dyskinesia may appear in the “off” state as dystonic posture, especially in the lower limbs. Because of the narrow therapeutic window at this stage of the disease, it is not uncommon for patients to experience diphasic dyskinesia—repetitive alternating movements occurring at the beginning as well as at the end of the interval between two L-dopa doses (Varanese et al., 2010).

Controlled-release levodopa may worsen dyskinesias, especially later in the day, due to cumulative effect. Amantadine in doses between 100 mg and 400 mg can be effective, but side effects are frequent in more advanced patients and should be carefully monitored. These include edema, livedo reticularis, and confusional state or hallucinations and psychosis (Varanese et al., 2010).

Clozapine, an atypical dopamine receptor antagonist, has been found to be effective in reducing dyskinesia in advanced patients, and it may be particularly useful when hallucinations are also present. Advanced patients, however, are particularly prone to develop agranulocitosis, with high risks of infections, and thus the white cell count should be regularly monitored. Recent evidence suggests that memantine is also effective in reducing dyskinesia when other options are contraindicated (Varanese et al., 2010).

Despite limited evidence, high-frequency subthalamic DBS (DBS-HFS) has been shown by several reports to be surgically safe and able to produce improvements in dopaminergic drug-sensitive symptoms, and reductions in subsequent drug dose and dyskinesias are well documented. However, the procedure is associated with adverse effects, mainly neurocognitive, with side effects created by spread of stimulation to surrounding structures, depending on the precise location of electrodes.

The occurrence of cognitive complications limits the motor improvements induced by STN-HFS to a short period of time, because patients’ quality of life is greatly impaired by the progressing cognitive disorder. In the late stage of the disease, the number of patients eligible for surgical treatment of PD is extremely low, due to age and general debilitation that significantly increase the risks of short- and long-term complications (Varanese et al., 2010).

Dystonia

The treatment of dystonia varies based upon clinical presentation. Off-state dystonia is generally most troublesome upon awakening in the morning but in advanced disease patients may develop complex twisting dystonic movements during the day. Early morning dystonia, a symptom of overnight wearing off, may respond to nocturnal long-acting dopaminergic agents. In contrast, peak-dose dystonia, which occurs during the day, may respond to reduced dose of dopaminergic medications, given more frequently in smaller doses. Electromyography (EMG)-guided injections of botulinum toxins can be used to treat focal dystonia of a single muscle (Lokk & Delbar, 2012).

Anticholinergics, baclofen, and benzodiazepines are regularly used with caution due to possible cognitive side effects in the end-stage PD patient. The use of botulinum toxin (BT) is increasing in PD patients when treating dystonia, spasms, urinary bladder dysfunction, and drooling. Targeted injections of BT, often guided by EMG, can be tried in these conditions. Botulism toxin only starts having an effect after 3 to 4 days. This effect will gradually increase till about 3 weeks after treatment. There is no permanent effect and the treatment needs to be repeated after 3 to 4 months (Lokk & Delbar, 2012).

Freezing

Freezing can be the result of either too much or too little dopaminergic effect. "Off freezing" may react to changes in certain medications, while "on freezing" is often associated with end-stage disease and is typically difficult to handle. Nonpharmacologic treatments and tricks can be used in freezing conditions—auditory cueing by counting figures loudly or clapping hands can be tried, as well as visual cues like drawing lines on the floor and using a cane or the light of a laser pointer. These procedures might eliminate or diminish freezing episodes. However, these techniques may be associated with an increased risk of falling, for which PD patients are already at risk, and fall prevention is essential to avoid serious fractures or injuries to the head Lokk & Delbar, 2012).

Nonmotor Complications

At the end-stage of PD, nonmotor symptoms can become the most prominent medical problem, leading to increasing decline in quality of life for patient and increasing caregiver burden. Nonmotor symptoms occur in up to 50% of PD patients—especially in association with the medication "off" state—and may be made worse by anti-PD medications. Almost one-third of patients report their nonmotor symptoms to be at least as debilitating as their motor symptoms (Lokk & Delbar, 2012).

All patients with motor fluctuations face at least one nonmotor problem during the "off" phase. In the end-stage of PD, dementia, psychosis, and falls become more complex to manage than the motor complications; as a result, managing nonmotor aspects is important to increase quality of life and decrease the burden of illness. Some studies have noted noticeably high scores among PD patients for impaired taste and smell, impaired swallowing, weight loss, constipation, urinary urgency, forgetfulness, dribbling, sadness, hallucinations, anxiety, sexual dysfunction, falling, reduced concentration, daytime sleepiness, vivid dreams, and sweating (Lokk & Delbar, 2012).

Dopaminergic replacement does not improve cognition and may even worsen it, but cholinergic inhibitors can be helpful. They may not be well tolerated due to peripheral cholinergic adverse effects, and in some cases cholinergic inhibitors can worsen motor functions. Rivastigmine may be the most useful agent, while more controversial is the benefit produced by donepezil. Avoiding the medications that can possibly worsen dementia, like anticholinergics and dopamine agonists, as well as maintaining L-dopa at the lowest effective doses, is a key strategy to contain confusion, hallucinations, and psychosis in advanced patients (Varanese et al., 2010).

Hallucinations, Delusions, Psychosis

Behavioral disorders—especially hallucinations, delusions, and other psychotic symptoms—are frequent in advanced PD, with frequency rates ranging from 25% to 30%. Visual hallucinations, simple or complex in form, are the most common psychotic symptom in advanced PD patients, typically occurring in dim surroundings but often occurring through the entire day in late-stage patients (Varanese et al., 2010).

A range of factors contributes to the development of hallucinations and psychosis in PD, including intrinsic pathology and the effects of dopamine replacement therapy. In the treatment of these complications, the first step should always be to evaluate the role of drugs that can potentially induce or worsen psychosis, such as amantadine, anticholinergics, COMT-inhibitors, and dopamine agonists. These drugs should be tapered off, balancing the effect on psychosis with worsening of motor function (Varanese et al., 2010).

Precipitating events, such as urinary and pulmonary infections, cerebrovascular events, and metabolic dysfunctions, should also be carefully investigated and treated. Even mild metabolic imbalance or infection can profoundly affect the development of psychotic symptoms in those with advanced PD. Decreasing the dose of L-dopa should also be considered when severe psychosis persists, even though this action could worsen parkinsonism (Varanese et al., 2010).

All traditional antipsychotic drugs, such as haloperidol, aripriprazole, and chlorpromazine, should be avoided because of the high sensitivity of PD patients to the adverse motor effects induced through potent antagonisms of dopamine D2 receptors (Varanese et al., 2010).

Clozapine and quetiapine are the only two of the newest antipsychotics that should be considered atypical and thus safe in PD. There is a wealth of evidence demonstrating the efficacy and tolerability of clozapine in PD, but its use is limited by the need for weekly blood testing for the initial 6 months of treatment. Quetiapine is a more practical alternative. Unlike clozapine, quetiapine does not require monitoring of blood cell counts and it is effective in suppressing hallucinations and psychosis in the majority of patients at relatively low doses, ranging from 12.5 mg to 100 mg. Main side effects of quetiapine and clozapine are sedation and postural hypotension (Varanese et al., 2010).

In most cases, psychosis develops late in PD, often due to underlying dementia and as a result of anti-PD medication use. Around 40% of PD patients develop dementia in the late stages of the disease and, in these, psychosis is common. Patients suffering from PD dementia and psychosis are more likely to be placed in a nursing home and are also at an increased mortality risk (Lokk & Delbar, 2012).

The first step for treatment of psychosis is to discontinue or decrease likely offending agents in the hierarchical order of anticholinergics, MAO-B inhibitors, amantadine, dopamine agonists, and, eventually, levodopa. However, there is then a risk of the patient's having more motor problems. Healthcare providers should resort to atypical antipsychotics as the only remedy in the event psychosis persists despite best efforts to eliminate or decrease anti-PD drugs as being important contributors (Lokk & Delbar, 2012).

Depression and Anxiety

Depression and anxiety occur in up to 40% of all PD patients, possibly higher among end-stage patients with increasing motor complications. Anxiety also tends to be more frequent during "off" periods and often improves when dopaminergic treatment is optimized (Lokk & Delbar, 2012).

In late-stage PD it is essential to identify depression with the assistance of family and other caregivers. In addition to nonpharmacologic treatment, antidepressants are widely used—especially serotonin reuptake inhibitors (SSRIs). Other drugs are less advisable because they carry more risk of cognitive side effects; this is especially true for tricyclic antidepressants. Anxiety is closely related to depression, and it is found that 66% of PD patients with motor fluctuations experience anxiety, often associated with irritability (Lokk & Delbar, 2012).

More activating antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), are useful but significantly limited in advanced patients by the anticholinergic and orthostatic negative effects. SSRIs are also contraindicated in patients receiving selegiline, because of the potential drug-drug interaction leading to *serotonin syndrome*. S-adenosyl-methionine (SAMe) is reported to have an effective antidepressant effect without worsening of parkinsonism (Varanese et al., 2010).

Anxiety often occurs during "off" periods; it improves with better control of motor symptoms but can be a major source of distress for patients even during the "on" state. Low doses of benzodiazepines are effective when anxiety is persistent and debilitating, but may cause amnesia and confusion in advanced patients and are a risk factor for falls.

Other Medical Issues

Many other issues can arise in the advanced stages of PD. Some are the inevitable exacerbation of problems encountered earlier in the disease process while others emerge in advanced PD as a result of general decline, the long-terms side effects of medications, or medications that no longer work.

Sleep Disorders

Sleep disorders can occur to one degree or another at all stages of PD but by the time the disease progresses to the advanced stage they plague almost all patients. Sleep disorders in advanced PD consist of sleep fragmentation, REM sleep behavior disorders (RBDs), excessive daytime sleepiness, and altered sleep–wake cycle. Sleep fragmentation can be caused by difficulty turning in bed or nocturnal dystonia and can be ameliorated with controlled-release levodopa. Increased nocturnal urinary frequency can also affect sleep and can be controlled by reducing the amount of liquids in the evening when anticholinergic drugs are contraindicated (Valarese et al., 2010).

As mentioned earlier in this course, RBD is a disruption of the normal REM sleep cycle, in which the suppression of movement that normally occurs during REM sleep is incomplete or absent, causing patients to "act out" their dreams, which can be unusually vivid, intense, and violent. Dream behaviors may be complex, including talking, yelling, punching, kicking, jumping from bed, and grabbing, causing great distress for patients and their partners. RBD also prevents physiologic nocturnal restoration of dopamine reserve in cells, with worsening of parkinsonian symptoms. RBD improves when dopaminergic medications are reduced at bedtime. When RBD persists, low doses of clonazepam are effective and should be considered. Modafinil, a wake-promoting agent approved for narcolepsy, is effective without significant side effects in ameliorating daytime sleepiness induced by dopamine agonists and can be helpful in promoting alertness in advanced PD (Varanese et al., 2010).

Orthostatic Hypotension

Orthostatic hypotension is a fall of systolic blood pressure of at least 20 mm Hg or diastolic pressure of at least 10 mm Hg within 3 minutes of standing. Orthostatic intolerance related to orthostatic hypotension results from a reduction of cerebral perfusion when upright and presents in severe cases with lightheadedness or syncope, exposing the patient to high risk of fall. Careful education of patients and caregivers on factors that can trigger the orthostatic symptoms, like avoiding rapid changes of position or straining during micturition or defecation, is essential in the management of orthostatic hypotension (Varanese et al., 2010).

Fluid intake, particularly in the morning, should be maintained at around 2 L of water daily, and at least 8 g of sodium chloride is recommended to ensure adequate hydration. Antihypertensive therapy, when present, should be reconsidered and eventually discontinued. Thromboembolic elastic stocking and abdominal binders can be helpful and should be encouraged. When orthostatic hypotension becomes more severe, it is necessary to start pharmacologic agents such as a plasma volume expander like fludrocortisone, and vasoactive agents such as midodrine (Varanese et al., 2010).

Severe Dysphagia

Severe dysphagia occurs frequently at late stage of PD, causing weight loss, malnutrition, dehydration, and significantly increasing the risk of aspiration pneumonia and death. To make swallowing more effective, swallowing maneuvers such as the supraglottic swallow maneuver, the Mendelsohn maneuver, and the effortful swallow maneuver should be taught to patients (Varanese et al., 2010).

Dysphagia for fluid can be controlled by adding thickeners to liquids, which increases their viscosity without substantially modifying taste. Thickeners provide body, increase stability, and improve suspension of added ingredients. Some thickening agents form a gel that can be swallowed by patients, thus significantly reducing the risk of choking. When dysphagia becomes more severe, percutaneous endoscopic gastrostomy (PEG) should be considered. In the advanced phase, PEG can be a useful way to ensure adequate food and fluid intake as well as to provide a mechanism for giving dopaminergic therapy through infusion (Varanese et al., 2010).

Gastric Dysfunction

Gastrointestinal dysfunction, with erratic gastric emptying worsening over the years, is a common cause of poor absorption of L-dopa in PD. A liquid effervescent levodopa formulation called melevodopa (methyl-ester levodopa) plus carbidopa is a prodrug* with high solubility (about 250 times more than L-dopa) in a small amount of water. It is able to reach the small intestine quickly, where it is absorbed in a more regular and rapid way compared to solid formulations. The drug is approved in certain European countries and currently under phase 2 investigation in the United States (Varanese et al., 2010).

*A prodrug is a medication that is initially administered to the body in an inactive (or less than fully active) form and is converted to its active form through the normal metabolic processes of the body.

Continuous infusion of levodopa/carbidopa gel through portable duodenal systems (duodopa) using PEG can be a practical alternative. The infusion provides constant plasma levodopa concentration and continuous dopamine availability and receptor stimulation. This solution may be particularly reasonable in very advanced patients with severe dysphagia because the PEG may also be used for nutrition (Varanese et al., 2010).

Intrajejunal L-dopa/carbidopa gel infusion is effective in reducing “off” time and severity and duration of dyskinesia in advanced PD. Most important, a recent multicenter study demonstrated that intrajejunal L-dopa/carbidopa infusion provides a beneficial effect on several nonmotor complications, including cardiovascular, gastrointestinal, and urinary symptoms, sleep/fatigue, attention/memory, and pain. An adverse event can occur, however, from the procedure or from the dislocation or occlusion of the intestinal tube. Advanced patients may also experience local complications, particularly inflammation and infections at the site of entry (Varanese et al., 2010).

Apomorphine subcutaneous infusion is also an effective option for patients with severe fluctuations poorly controlled by oral treatment. Apomorphine infusion is often limited by the development of skin reaction at the site of injections after a few years of treatment (Varanese et al., 2010).

Constipation and Urinary Problems

Constipation is a common and early manifestation of PD but in late-stage can become particularly severe due to the combination of anti-PD medications, slowed intestinal motility, immobility, and dehydration. Constipation should be well managed in order to avoid bowel occlusion and to ensure proper absorption of L-dopa and other medications. Dietary supplementation of fibers that stimulate intestinal motility should be encouraged, as well as increased fluid intake. A conservative therapeutic option is administration of macrogol (polyethylene glycol), which can lead to marked improvement (Varanese et al., 2010).

Many late-stage PD patients face urinary problems such as urgency or frequency or stress incontinence, which can cause anxiety and feelings of social isolation. Overactive bladder is the result of loss of normal inhibition by the basal ganglia and the frontal cortex to the sacral spinal cord. Anticholinergics are commonly used to inhibit the overactive bladder, although their use should be discouraged in late-stage patients due to cognitive and other central anticholinergic adverse effects. Newer generation peripheral anticholinergics, like trospium, is better tolerated and can be used sometimes even in advanced patients (Varanese et al., 2010).

Recently, botulinum toxin injections in the detrusor muscle* have demonstrated marked efficacy in reducing urinary frequency with no side effects. Reduced mobility and difficulty toileting often lead to the use of urinary pads or catheters at the end stage of disease, exposing the patients to high risk of dangerous urinary infections when hygienic measures are not appropriate (Varanese et al., 2010).

*The detrusor muscle of the urinary bladder is smooth muscle found in the wall of the bladder. It remains relaxed to allow the bladder to store urine and contracts during urination to release urine.

Managing Falls

The incidence of falls in advanced PD is high (40%–70%), even when patients are optimally medicated. Falls occur because of very unstable gait, loss of center of gravity, poor balance, orthostatic hypotension, side effects of medications like antidepressants and benzodiazepines, and disturbances of posture. Falls lead to injuries and fracture that further reduce patient independence and increase the risk of nursing home admission. Patients with previous falls often develop fear of falling, which further limits their mobility, contributing to increased weakness and deterioration (Varanese et al., 2010).

Because of the devastating consequences, an assessment of falls risk should be completed in all advanced PD patients. A combination of both disease-specific and balance- and mobility-related measures is necessary to accurately predict falls in patients with PD (Varanese et al., 2010).

In those with advanced PD, full mobility should be encouraged and maintained as long as possible. Individual rehabilitative therapy sessions should be encouraged 2 to 3 times weekly for 30- to 40-minute durations, even at late-stage, when the patient is able to ambulate safely. Falls are perhaps the greatest concern for late-stage PD patients who are still mobile, and patients should be discouraged from standing or walking without assistance at very late stage of the disease. If patients are bedridden, residual mobility should be maintained through active and passive movement exercises, frequent position changes, and breathing exercises to prevent complications associated with being bedridden, such as decubitus, contracture, pain, and pneumonia (Varanese et al., 2010).

Malnutrition and Dehydration

Malnutrition is a common problem in advanced PD patients. It is caused by difficulty feeding, altered satiety mechanism, diminished gastric and intestinal motility, inactivity, lack of appetite, dysphagia, and metabolic syndrome. In patients still able to eat independently, meal and portion sizes should be monitored in order to provide sufficient nutrition. Any effort, including compensatory strategies, should be considered to delay PEG placement (Varanese et al., 2010).

Adequate hydration is another concern for late-stage PD patients, since even mild temperature change can lead to relative dehydration, exacerbate confusion and orthostatic hypotension, and cause syncope. Many patients become embarrassed when eating or drinking, and nursing assistance can ensure adequate nutrition and hydration through nonjudgmental caregivers who assist patients with the administration of meals (Varanese et al., 2010).

Impaired Communication

Difficulties with speech (severe dysarthria, hypophonia, tachylalia, freezing of speech) are associated with late-stage PD and can be a significant source of frustration for patients and families. Speech therapy should be encouraged whenever possible. The Lee Silverman Voice treatment has been shown, clinically and scientifically, to be a powerful method of improving speech and related functions such as swallowing and facial expression in PD, with documented improvement in vocal loudness, voice quality, prosody, and speech articulation, sustained at 1-year and 2-year followups. Simplified and codified communications—asking yes/no questions, using alphabet boards or speaking dictionaries—can become the only way of effective communication and should be considered (Varanese et al., 2010).

Palliative Care

Palliative care provides comfort and support for people who are facing life-threatening illnesses. In order to maximize quality of life, the palliative care should include a team of medical providers as well as additional caregivers. Such an approach provides traditional medical therapies and emotional and spiritual support while preserving patient autonomy and dignity (Lokk & Delbari, 2012).

As the patient approaches the end-stage of the illness, the main goal of both the patient and the healthcare provider becomes management of motor and nonmotor symptoms according to the principles of palliative care. It is important to take into account that symptomatic control includes the preserving of autonomy as well as stress relief. A holistic approach must be applied from the moment of diagnosis until the end of a patient's life (Lokk & Delbari, 2012).

Nursing home placement should be delayed as long as possible, because of the well-known risk of reduced survival. As death approaches for late-stage PD patients, it is important to provide them with the best care possible in a passionate environment. Many patients choose to do this through hospice care. Support to families, through social work and psychological counseling, should be offered at this time (Varanese et al., 2010).

Conclusion and Epilogue

Parkinson's disease has been plaguing humans for thousands of years and was described in detail in ancient medical writings. Early sufferers from it effects were treated with varying results by a variety of plant-based treatments, some of which are still in use today. With the discovery of dopamine in the twentieth century and the subsequent development of dopamine replacement therapy, plus surgical techniques such as deep brain stimulation (DBS), many of the debilitating symptoms are now successfully treated—at least for a time.

Despite the increased attention on Parkinson's, there is still no diagnostic test that is definitive. Diagnosis is made based on presenting symptoms and tested by medicating with levodopa. Only on postmortem can the diagnosis be confirmed.

There is an ever-increasing understanding that PD is more than a motor disorder. Research into the nonmotor symptoms of PD is the focus of intense research, and there is hope of developing treatments that not only arrest the progress of the disease but stop it in its tracks.

While research into the genetic basis of PD continues, pharmacologic treatment remains the mainstay. However, it is becoming more sophisticated as new delivery methods (such as inhaled dopamine and intestinal gel) are becoming available, allowing better control of symptoms. Rehabilitation therapy is showing promising results and may even affect the course of the disease by stimulating the production of protective neurotransmitters.

Despite these advances, the medical management of PD is complex, requiring knowledge of multiple medications that interact in sometimes unforeseen ways. Deep brain stimulation has helped some patients control some symptoms but does not provide across-the-board improvement. A number of gene therapy trials are under way and are showing promise, most focusing on the dopamine pathway. Stem cell therapy appears promising but results are currently inconclusive.

As PD progresses to the advanced stage, care becomes increasingly complicated. The side effects of years of PD medications begin to take their toll, requiring additional medications to address worsening sleep disorders, gastric dysfunction, and a host of other difficulties.

In light of these challenges, research into neuroprotective therapies is occurring at a feverish pace. The hope is to find the cause of PD, along with treatments that stop the disease from progressing. Of particular interest, PD research is uncovering what may turn out to be a common pathophysiologic mechanism underlying dementia and PD. For now, healthcare providers must continue to educate themselves about currently available treatments and hope for better alternatives in the near future.

Epilogue

Alan Cruikshank is a 65-year-old white male who has Parkinson's disease. He is the founder and publisher of the *Fountain Hills* (Arizona) *Times*, an award-winning weekly newspaper. Cruikshank himself is the 2013 recipient of the Amos Award for Excellence by the National Newspapers Association. Recognized as the highest tribute in community journalism, the Amos Award is presented annually to a working or retired newspaperman who has provided distinguished service and leadership to the press and to his community.

The personal narrative in this course is his story, in his own words. Cruikshank published a longer version in his newspaper in the spring of 2012. We are deeply grateful to Alan Cruikshank for allowing us to share his personal experience with Parkinson's disease.

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Post Test

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

1. The Poskanzer and Schwab Hypothesis that Parkinson's disease is linked to an earlier viral infection has been completely discounted.:

a. TRUE
b. FALSE

2. In the year 2000 the Nobel Prize was awarded to which one of the following for discovery of dopamine as an independent neurotransmitter:

a. Oliver Sacks.
b. Edouard Brissaud.
c. Arvid Carlsson.
d. James Parkinson.

3. Physiologically, the symptoms associated with the onset of Parkinson's disease are the result of:

a. Loss of neurotransmitters.
b. Amyloid tangles.
c. Cortical deterioration.
d. Damage to the brainstem.

4. The chemical messenger dopamine can be rendered inactive by:

a. Dehydration.
b. Presynaptic and postsynaptic synapses.
c. Earlier viral infection.
d. Monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT).

5. Dopamine depletion is significant because it is generally seen only in people who have Parkinson's disease.:

a. TRUE
b. FALSE

6. Lewy bodies are:

a. Clumps of extracellular material that impede dopamine function.
b. Abnormal aggregates of protein that develop in nerve cells.
c. Cyst-like sacs of fluid in the synapses.
d. Receptors for carbohydrate byproducts.

7. Parkinsonism:

a. Is symptomatically similar to PD but not responsive to dopamine.
b. Is different from PD in its proliferation of Lewy bodies.
c. Has not been associated with any external causation.
d. Can be successfully treated with MPTP.

8. With regard to the genetic basis of Parkinson's disease:

a. One gene was recently isolated as the cause of PD.
b. Genetic linkage maps have disappointed as a diagnostic tool.
c. Genome sequence analyses have shown no association to PD.
d. Up to 15% of PD patients have a direct family member with PD.

9. PARK is the identifier for:

a. Pathologic alpha-synuclein reuptake.
b. Parkinson-related kinesthesia.
c. A gene family with at least 18 gene members.
d. Parkinson-related karyotypes.

10. Gene therapy has what advantage over oral medications?:

a. It is cost-effective.
b. It reduces side effects.
c. It is readily available.
d. It is easy to use.

11. An enzyme called aromatic acid decarboxylase (AADC) converts levodopa to dopamine. A study that inserted a gene containing AADC into the brain of 10 patients with advanced PD:

a. Showed no measureable improvement.
b. Showed 30% improvement at 6 months.

c. Showed some improvement but none in on/off times.

d. Showed decreased enzyme activity over 6 months.

12. To be useful, a biomarker must be:

a. Identifiable by a blood test.

b. Able to be discerned by imaging.

c. Broad enough to encompass the array of a disease's symptoms.

d. Specific and sensitive to every person who has the disease.

13. Functional imaging techniques—including PET, SPECT, CT, and MRI—provide useful images only in the early stages of Parkinson's disease.:

a. TRUE

b. FALSE

14. Dopamine biomarkers detect changes:

a. Early enough to be regarded as a breakthrough in diagnosis.

b. When patients have been on medication for at least 3 months.

c. Only after the disease is well established.

d. For parkinsonism but not for PD.

15. Parkinson's disease is clinically classified according to age of onset. The age at which it is no longer called "early-onset" is:

a. 35 years old.

b. 40 years old.

c. 50 years old.

d. 60 years old.

16. Which one of the following is not a rating scale for Parkinson's disease?:

a. Unified Parkinson's Disease Rating Scale (UPDRS).

b. International Classification of Functioning, Disability, and Health (ICF).

c. Schwab and England ADL Scale.

d. Yale FICSIT.

17. The contribution of the ICF rating scale, endorsed by WHO as an international standard, is that it:

a. Separates human function into six domains and is thus more precise.
b. Clearly contrasts health and disability in each of its categories.
c. Mainstreams disability as a universal human experience.
d. Excludes environmental factors.

18. Which one is not a motor symptom typically signaling PD:

a. Resting tremor.
b. Dysphoria.
c. Rigidity.
d. Bradykinesia.

19. In the early stages of Parkinson's disease, altered postural control:

a. May be minimal except during standing tasks and when turning.
b. Becomes evident when "off" periods begin.
c. Can be seen with sporadic freezing episodes.
d. May be evident across all postural function if carefully monitored.

20. The shuffling gait of people with advancing PD is called:

a. Fenestrating gait.
b. Festinating gait.
c. Figurating gait.
d. Fimbriating gait.

21. Freezing of gait (FOG), where patients feel as if their feet are stuck to the ground:

a. Occurs mostly in mid-stride.
b. Is lessened when approaching a doorway or other target.
c. May be caused by dopamine deficiency.
d. Is most common when patients first go on medication.

22. A number of prediction studies have shown that powerful determinants of recurrent falls are:

a. Resting tremor.
b. Lack of adherence to medication.
c. Anti-inflammatory medications.

d. Postural control deficits.

23. The use of videos of ambulating patients has emerged as a de facto gold standard for assessing freezes, but a recent study found only moderate agreement among observers and even less reliability.:

a. TRUE
b. FALSE

24. One mechanism specific to PD that may contribute to dual-task walking deficits is:

a. Reduced movement automaticity.
b. Inability to multi-task.
c. Reduced mental tracking.
d. Increased movement automaticity.

25. When people with PD find environmental barriers to walking in the community they tend to:

a. Report the barrier to local government.
b. Complain to friends and family.
c. Try to fix the problem themselves.
d. Modify their behavior to avoid confronting the barrier.

26. In fall intervention studies focusing on older adults, which two risk factors were most commonly used to define “high risk”?:

a. Gender and fear of falling.
b. Age and history of falls.
c. Multiple medications and inattention.
d. Visual and hearing deficits.

27. Among the general population of elders, recurrent falls may be identified when they occur more than once a year. In a study of 100 people with Parkinson’s, 13% reported falling:

a. More than once a year.
b. More than once a month.
c. More than once week.
d. Many times per day.

28. Which one of the following is not a risk factor for falls in people with PD?:

a. Fear of falling.
b. Hearing deficits.
c. Depression.
d. Cognitive decline.

29. In a meta-analysis of studies of falling in those with PD, the best predictor of falling was having:

a. Fallen two or more times the previous year.
b. A deficit in gait velocity.
c. Problems with cadence in walking.
d. Inappropriate step length for body size.

30. A Washington University study show that fall incidence is predicted more accurately if the followup period is:

a. One month.
b. Three months.
c. Six months.
d. One year.

31. All but one of the following are characteristics of the Berg Balance Scale:

a. Excellent reliability.
b. Good predictor of falls in those with neurologic impairment.
c. Somewhat correlated with severity of Parkinson’s disease.
d. Focuses on a variety self-initiated tasks.

32. Although the BESTest is good at discerning fallers in patients with PD, the Mini-BESTest was created to:

a. Focus on specific neurologic deficits.
b. Be used in home as well as clinical settings.
c. Reduce redundancy and simplify scoring.
d. Address the shortcomings of the Berg Balance Scale.

33. The Tinetti test for balance assessment measures:

a. Dynamic gait and step length.

b. Gait velocity and cadence.

c. Turning and reactive control.

d. Clinical balance and gait.

34. Nonmotor symptoms of PD are common but are often under-recognized in clinical settings because:

a. Lack of spontaneous complaints and absence of questioning.

b. Inadequate ordering and administering of laboratory tests.

c. Imaging tests fail to reveal them.

d. Staff are overworked and distracted.

35. REM sleep behavior disorder (RBD):

a. Is often misdiagnosed in PD patients.

b. May begin decades before onset of clinical symptoms of PD.

c. Causes sleep so deep that movement is inhibited.

d. Is related to vivid dreams that are recalled clearly upon awakening.

36. The motor-speech disorder in which the muscles of the mouth, face, and respiratory system become weak is called:

a. Aphasia.

b. Bradykinesia.

c. Agnosia.

d. Dysarthria.

37. Cognitive and behavioral symptoms that appear at the earliest stages of PD, before any treatment:

a. Generally disappear as the disease progresses.

b. May affect as many as 60% of newly diagnosed PD patients.

c. May be biomarkers for Parkinson’s.

d. Are well controlled by medications following diagnosis of PD.

38. In treating the depression that often accompanies PD:

a. It is best to avoid the tricyclic antidepressants.

b. Tricyclic antidepressants have been found to be the most effective.

c. It is best to avoid SSRIs.

d. Any antidepressant is a risk when combined with other PD medications.

39. Misinterpretation and inaccurate judgment about the character or feelings of a person with PD by clinicians is most likely due to:

a. Impatience in busy settings.

b. Distraction because of erratic body movements.

c. Seeing the patient as "other."

d. Expressive or facial masking.

40. Although levodopa (L-dopa) is a mainstay of treatment for PD, it has a major drawback:

a. It is only available in intravenous form.

b. Only about 10% of it actually crosses the blood–brain barrier.

c. Its side effects make it undesirable from the patient's viewpoint.

d. There is a possibility of dependence or even addiction.

41. To alleviate the undesirable side effects of levodopa initially:

a. MAO-B inhibitors and dopamine agonists are added.

b. SSRIs and MAO inhibitors are recommended.

c. Bed rest is advised for the first six weeks.

d. Dopamine antagonists are administered.

42. Duodopa, a new therapy that reduces on/off fluctuations, is available as an intestinal gel administered:

a. Sublingually.

b. Via an intestinal tube.

c. Topically.

d. In a patch.

43. Dopamine agonists that mimic the role of dopamine in the brain:

a. Have been disappointing as a substitute for levodopa.

b. Do not cross the blood-brain barrier effectively.

c. Are used in early treatment to postpone levodopa complications.

d. Are ineffective in addressing the "off" state in patients with PD.

44. Despite its effectiveness in improving motor symptoms, chronic use of levodopa for PD is associated with all but one of the following:

a. Motor fluctuations.

b. Wearing off.

c. Dyskinesias.

d. Male gender.

45. Deep brain stimulation is an intervention sometimes effective in advanced PD that involves:

a. Surgical insertion of an electrode in the brain and a battery pouch under the collarbone.

b. Explorative insertion of a number of electrodes in the brain.

c. A PET scan while listening to calming music.

d. Insertion of one permanent electrode and a small battery pack behind the ear.

46. Deep brain stimulation generally does not made symptoms better than a patient's best "on" state but it does tend to make "off" periods more like the "on" periods.:

a. TRUE

b. FALSE

47. Stem cells are a promising source of cell replacement therapy in PD. Embryonic stem cells (ESCs) are pluripotent, since they can generate cells in all three germ layers. Somatic stem cells are multipotent because:

a. They can generate cells in every system in the body.

b. They are more potent than ESCs.

c. They are limited to differentiating in only one germ layer.

d. They are unlimited in terms of self-renewal.

48. Drive activity-dependent neuroplasticity means:

a. Changes due to the mind–body connection.

b. Modifications in the CNS in response to physical activity.

c. Exercise-related detriments in advanced PD.

d. Neurologic responses related to basic human drives.

49. The Agility Boot Camp addresses limitations of balance and mobility in PD by:

a. Pushing patients with PD to exceed their former limitations.

b. Using calisthenics in a patterned approach for greater results.

c. Offering a circuit of carefully monitored, graduated sports skills activities.

d. Presenting a motivational program that combines mental toughness with physical exercise.

50. LSVT LOUD (for speech) and LSVT BIG (for motor systems) are programs designed to:

a. Use training of very small movements for amplified results.

b. Aggravate body systems needing more stimulation for physical rehabilitation.

c. Provide DVDs for PD rehabilitation that can be used at home.

d. Teach patients to recalibrate their sensorimotor systems using self-cueing and attention to action.

51. In general, hospital staff are well informed about Parkinson's disease and the need for careful timing of medications.:

a. TRUE

b. FALSE

52. Mixing selegiline or rasagiline (MAO-B inhibitors) with meperidine is:

a. Commonly done to delay onset of dyskinesias.

b. Effective in treating prolonged confusion.

c. Unsafe because it can cause blood pressure fluctuations and other negative outcomes.

d. A good option for treatment of nausea.

53. The hospitalized PD patient may be more acutely affected by medical issues such as:

a. The lingering effects of anesthesia.

b. Lack of appetite due to unappealing menu items.

c. Diarrhea or irritable bowel syndrome.

d. Lack of stimulating activities.

54. As Parkinson's disease advances, caregivers become critical to:

a. Serve as doorkeepers who monitor the number of visitors.

b. Maintain an increasingly complicated medication dosing regimen.

c. Keep up the patient's spirits by remaining upbeat and optimistic.

d. Walking the patient for periods of time throughout the day.

55. Nonprofessional caregivers (eg, family members) reported having trouble with staff when the patient is hospitalized because the caregivers' knowledge of that particular patient was dismissed as unimportant.:

a. TRUE

b. FALSE

56. In the advanced stage of PD the most troublesome and distressful complications are usually:

a. Dyskinesias.

b. More frequent freezing of gait.

c. Festinating gait complications.

d. Nonmotor symptoms.

57. Because in advanced PD there are fewer and fewer receptors capable of taking up L-dopa:

a. Dopamine production increases but is not readily utilized.

b. The nigrostriatal pathway becomes nonfunctional.

c. Small changes in plasma L-dopa levels increasingly inhibit patient function between doses of medication.

d. Medication dosages need to be increased to make up for the deficit.

58. Dopamine agonists are generally contraindicated in late-stage PD:

a. Because they no longer control the on/off response.

b. To avoid hallucinations and worsening of autonomic functioning.

c. In an effort to preserve renal function.

d. Even though dyskinesias have generally disappeared by this stage.

59. Clozapine, an atypical dopamine receptor antagonist, has been found to be effective in reducing dyskinesia in advanced patients but it requires careful monitoring of:

a. White cell count.

b. Creatinine levels.

c. Electrolytes.

d. Heart, for arrhythmias.

60. In the end-stage of PD, motor complications are more easily managed than all but which one of the following?:

a. Dementia.

b. Visual deficits.

c. Psychosis.

d. Falls.

61. The first step for treatment of psychosis in late-stage PD is to:

a. Introduce tricyclics.

b. Increase protein in the diet.

c. Discontinue or decrease anticholinergics.

d. Give intravenous crystallines and colloids.

62. Treatment of the depression and anxiety in some advanced-stage PD patients with SSRIs is limited by:

a. The number of medications already being administered.

b. Patients' resistance to treatment.

c. Family and caregiver objections.

d. Anticholinergic and orthostatic negative effects.

63. REM sleep behavior disorders (RBDs) sometimes interferes with the suppression of movement that normally occurs during sleep, causing the patient to:

a. Be at risk for pressure ulcers.

b. Act out dreams with violent movements and actions.

c. Develop incontinence from failure to respond to signals during sleep.

d. Increase nocturnal restoration of dopamine reserve in cells.

64. In the end-stage of Parkinson's disease, the main goal becomes:

a. Preparing the family for loss and grief.

b. Medically induced coma.

c. Spiritual support.

d. Symptomatic control to preserve autonomy and relief of stress.

Answer Sheet

Parkinson's Disease: Moving Forward

Name (Please print your name): _____

Date: _____

Passing score is 80%

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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. Trace the history of "shaking palsy" in Western medicine.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

b. Discuss the role of dopamine and Lewy bodies in Parkinson's disease.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

c. Spell out the role of gene therapy in the treatment of PD.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

d. Explain biomarkers and appraise commonly used PD rating scales.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

e. Specify the most common motor symptoms found in PD.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

f. Evaluate risk factors for fall and the various clinical tests for balance.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

g. Describe non-motor aspects and symptoms associated with PD.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

h. List common cognitive changes that occur as PD progresses.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

i. Identify current strategies and those in development for the treatment of PD.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

j. Evaluate rehabilitation treatment approaches for PD.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

k. Discuss the issues related to providing excellent hospital care for patients who have PD.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

l. Relate the difficulties associated with caring for a person with PD.

○ 5 ○ 4 ○ 3 ○ 2 ○ 1

m. Describe the complications that arise in those with advanced 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: _____

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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.**
10 contact hours: $59

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: _____